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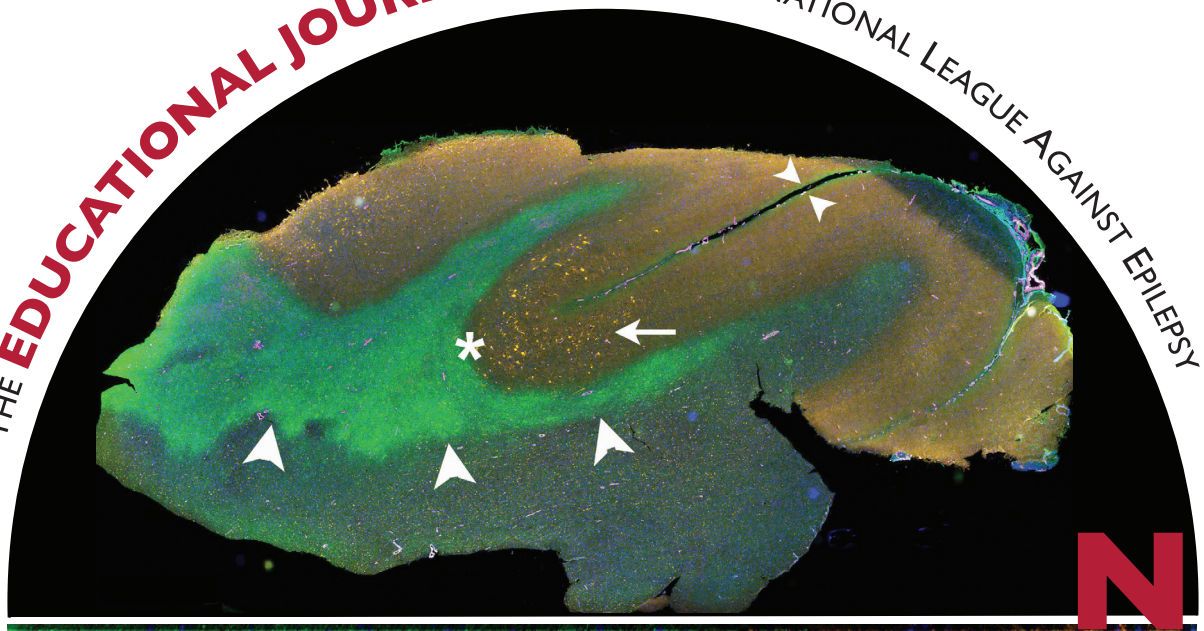

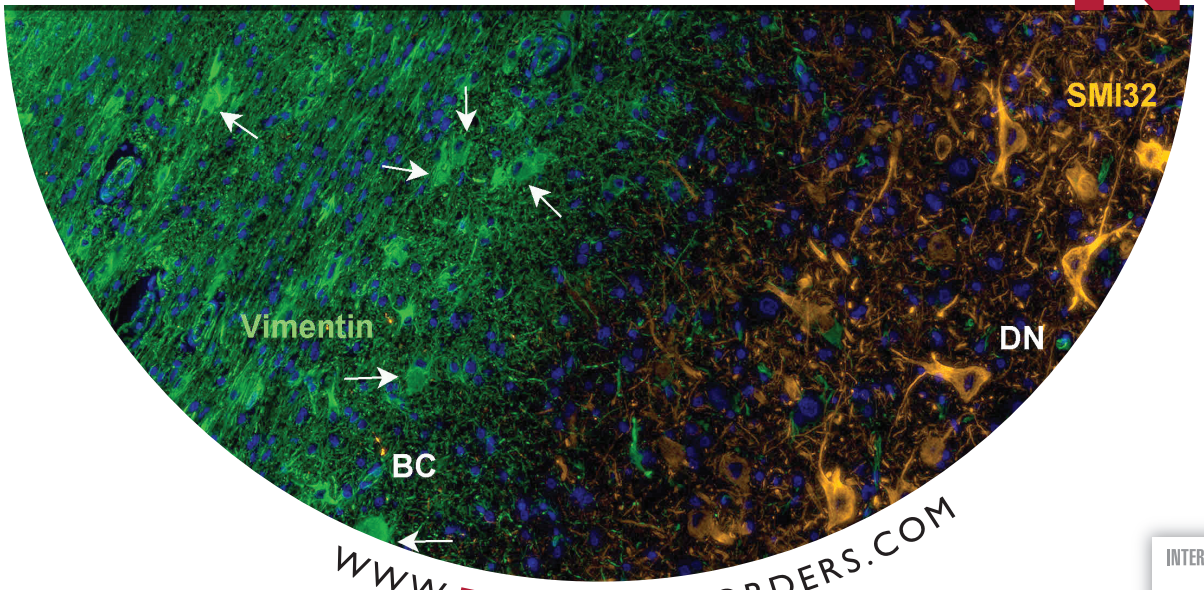

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Cover page figure: Cover figure is Figure 4 from the original article by Ying *et al*. on A comprehensive clinico-pathological and genetic evaluation of bottom-of-sulcus focal cortical dysplasia in patients with difficult-to-localize focal epilepsy (this issue, p. 65–77).

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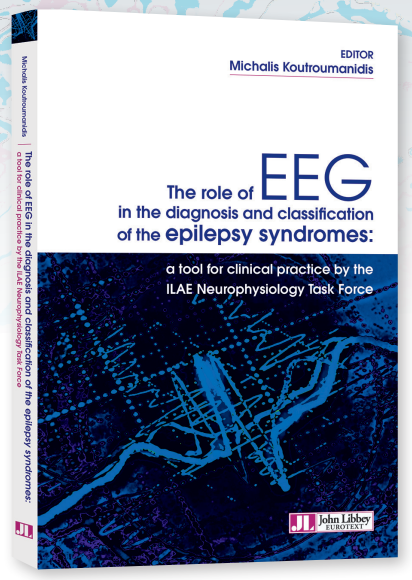

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EDITOR

- **Michalis Koutroumanidis**

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Review article

Epileptic Disord 2019; 21 (1): 1-29

Classification of paroxysmal events and the four-dimensional epilepsy classification system

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ABSTRACT – This educational review describes the classification of paroxysmal events and a four-dimensional epilepsy classification system. Paroxysmal events are classified as epileptic and non-epileptic paroxysmal events. Non-epileptic events are, in turn, classified as psychogenic and organic paroxysmal events. The following four dimensions are used to classify epileptic paroxysmal events: ictal semiology, the epileptogenic zone, etiology, and comorbidities. Efforts are made to keep these four dimensions as independent as possible.
The review also includes 12 educational vignettes and three more detailed case reports classified using the 2017 classification of the ILAE and the four-dimensional epilepsy classification. In addition, a case is described which is classified using the four-dimensional epilepsy classification with different degrees of precision by an emergency department physician, a neurologist, and an epileptologist. [*Published with video sequences on www.epilepticdisorders.com*]

Key words: classification, semiology, epileptogenic zone, etiology

Physicians are frequently called upon to see patients with paroxysmal events. We use the non-specific term ***"paroxysmal events"*** when we do not have sufficient evidence to diagnose with certainty whether a paroxysmal event is epileptic or non-epileptic. The paroxysmal events we evaluate as physicians, however, may be epileptic or non-epileptic. For this, we divide the paroxysmal events into ***epileptic paroxysmal events*** and ***non-epileptic paroxysmal events*** (*table 1*).

Once we have diagnosed that a paroxysmal event is ***epileptic*** in nature, we define the four dimensions that characterize epileptic paroxysmal events: ictal semiology, epileptogenic zone, etiology, and comorbidities.

On the other hand, if we diagnose ***non-epileptic paroxysmal events***, we classify these as psychogenic or organic paroxysmal events. Once we confirm that a non-epileptic paroxysmal event is ***psychogenic*** in nature, we define the following three dimensions: paroxysmal event semiology, etiology, and comorbidities. In this case, we use the same semiological seizure classification used for epileptic events (*see below*) but replace the expression "seizure" by "event" and the expression "aura" by "aura event." The classification of non-specific ***"paroxysmal events"*** (physician does not know if the event is epileptic or not) follows the same system as the classification of non-epileptic psychogenic paroxysmal events.

Finally, if we diagnose a patient with a ***non-epileptic organic paroxysmal event***, we also specify the three dimensions: semiology, etiology, and comorbidities. In this case, however, the semiology is defined by the type of non-epileptic, non-psychogenic event as, for example, syncope, resting tremor, cataplexy, *etc*.

Following a detailed description of the 4-dimensional epilepsy classification presented below, we also included 12 educational vignettes (*Appendix 1*) and three more detailed case reports (*Appendix 2*) classified using the 2017 classifications of the ILAE (Fisher *et al*. 2017; 2017b) and the four-dimensional epilepsy classification described below. In addition, a case is described (*Appendix 3*) which is classified using the four-dimensional epilepsy classification with different degrees of precision by an emergency department physician, a neurologist, and an epileptologist.

General organization of the classification system

(1) The dimensions that characterize all the paroxysmal events are independent and defined by different diagnostic methods. For example, a patient may have bilateral clonic seizures (defined by semiology), but the MRI shows an extensive left fronto-temporal tumor (epileptogenic lesion) and the epileptogenic zone is most likely the left frontal lobe (mainly defined by interictal and ictal EEG). The independence of the different dimensions allows precise correlations between the different dimensions. For example, the four-dimensional classification of the epilepsies permits us to calculate the percentage of patients who have no focal ictal findings by semiology but have a focal epilepsy. Because of the independence of the four dimensions, the classification system permits an almost infinite number of correlation studies between the different subgroups included in each dimension.

(2) The classifications of the paroxysmal events and the four dimensions that classify the epilepsies follow the same hierarchal system. The target parameter (namely one of the dimensions) is first subdivided into broad categories and each of them is again subdivided into more specific subcategories. In many cases, these again are subdivided into even smaller categories. In other words, as we move from "left to right", we find that the dimension is progressively defined more accurately.

The tables that follow provide a global overview of the 4-dimensional classification.

For example, in the classification of paroxysmal events (*table 1*), the broadest category is "paroxysmal event" that includes all the subcategories mentioned, and the second broadest category is epileptic vs non-epileptic paroxysmal events. Non-epileptic paroxysmal events are, in turn, subdivided into psychogenic and organic paroxysmal events.

The purpose of organizing the different categories into progressively smaller subgroups has the following objectives:

(i) Non-specialists who do not have the tools and knowledge to make a very precise classification of the epilepsies or other paroxysmal events can still use this classification system by just defining the broadest categories ("on the left hand of the table"). For example, if they just know that the patient was depressed and had a paroxysmal episode with generalized "twitching", unresponsiveness, and no memory for the event afterwards, they can classify the event as follows:

Paroxysmal event:
Semiology: *bilateral clonic event (LOC)*
Etiology: *unknown*
Co-morbidities: *depression*

The same patient seen by an expert might obtain a detailed history from a family member who witnessed the seizure. The expert could elucidate semiological details that make the probability of an epileptic seizure much more likely (initial ictal cry, tonic phase in decerebrate posture lasting 30 seconds followed by

Table 1. Paroxysmal event classification.

Paroxysmal events (PE)	Epileptic		Ictal semiology (*ie*. automotorseizure)
			Epileptogenic zone (*ie*. left temporal)
			Etiology (*ie*. hippocampal sclerosis)
			Co-morbidities (*ie*. anxiety)
	Non-epileptic	Psychogenic	Ictal semiology (*ie*. clonic event)
			Etiology (*ie*. post-traumatic stress disorder)
			Co-morbidities (*ie*. none)
		Organic	Ictal semiology (*ie*. cataplexy event)
			Etiology (*ie*. narcolepsy)
			Co-morbidities (*ie*. none)

a clonic phase lasting 1-2 minutes, "rolling back of the eyes", blood-tainted foaming at the mouth, postictal coma with gradual recovery of consciousness over 10-25 minutes, urinary incontinence, *etc*.) Besides, the expert could uncover that the patient was taking a high dose of bupropion. This would lead to the following diagnosis:

Epileptic paroxysmal event:
Semiology: *bilateral tonic-clonic seizure*
Epileptogenic zone: *generalized*
Etiology: *bupropion treatment*
Co-morbidities: *depression*

(ii) As mentioned above, this classification is organized first into broad categories that are subsequently subdivided into more specific subgroups. This strategy greatly simplifies the definition of the subgroups, as all subgroups must comply with the definition of the main group. This usually also implies similarities between the pathophysiology of all the subgroups. For example, all auras consist of purely subjective ictal symptoms that tend to occur at the beginning of a clinical seizure and with few exceptions are only seen in patients with focal epilepsy. The different subgroups (visual aura, auditory aura, somatosensory aura, *etc*.) differ according to the type of subjective symptom and the location of the symptomatogenic zone.

Four-dimensional epilepsy classification

Epilepsy is defined as an enduring condition in which brain regions in both hemispheres or part of the brain has an abnormally low threshold to trigger seizures. The part of brain with this characteristic is called the epileptogenic zone. The clinical manifestations of epilepsies are called epileptic seizures and symptomatology is determined primarily by the location of the epileptogenic zone. The impetus to classify epilepsy and seizures is to improve epilepsy management and prognosis and to facilitate communication and enhance epilepsy-related research.
Whenever we classify a disease, we should define the objective of the classification *a priori*. With the advent of objective medicine in the middle of the 19th century, brain diseases have usually been classified along the following four axes:
– Clinical semiology (Example: resting tremor, rigidity, *etc*. in Parkinson's disease);
– Location of the disease (Example: substantia nigra in patients with Parkinson's disease);
– Etiology (Example: degenerative disorder in Parkinson's disease);
– Co-morbidities (Example: dementia in Parkinson's disease).

A four-axis classification of a neurological disease gives an excellent overview of the disease, covering not only pathophysiology but also essential information necessary for its management and prognosis. In the specific case of epilepsy, the four axes refer to the following parameters:
– Clinical semiology = semiology of epileptic seizures;
– Location of the disease = epileptogenic zone;
– Etiology = etiology of the epilepsy;
– Co-morbidities = associated co-morbidities.

The ictal semiology is the clinical manifestation of the epilepsy. The seizure semiology and the frequency of the seizures will guide our diagnosis and management. In a patient with generalized epilepsy, clinical ictal semiology also dictates the antiepileptic drugs that will be most effective to control the epileptic

seizures. In a patient with focal seizures refractory to medical treatment, ictal semiology is an important piece of information to decide if a patient is a surgical candidate.

Definition of the epileptogenic zone is essential in the management of the epilepsy:
– Focal epilepsies and generalized epilepsies frequently respond best to different types of antiepileptic medication.
– For surgical treatment of epilepsy, precise definition of the location and extent of the epileptogenic zone is indispensable.

Etiology in most patients is another essential factor that guides treatment and prognosis.

Finally, knowledge of the main co-morbidities is essential to get a complete picture of the patient's disease, particularly cognitive impairment and psychiatric abnormalities. Besides, comorbidities such as severe renal, hepatic or psychiatric disease may greatly influence the type and dose of antiepileptic drug to use, or even the patient's candidacy for surgery.

As already mentioned above, it is essential that the different dimensions in a multi-dimensional classification system be as independent as possible. In other words, classifying one category in a dimension should not automatically define another dimension. For example, classifying the epileptogenic zone as "regional" should not force a classification of the seizure as "focal" and classifying the seizure as "focal" should not force classification of the epileptogenic zone as "regional." Ideally, to achieve independence in each dimension, the tests and criteria we use to define each dimension should not overlap. Independence of the different dimensions also allows us to evaluate correlations between them. Example: type of semiological seizures in patients with temporal or frontal epileptogenic zones. A typical example of violating this rule of independence is the latest version of the ILAE classification of epilepsies and seizures (Fisher *et al*., 2017a, 2017b; Berg *et al*., 2010). In this classification system, all test results are used to classify both seizures and epilepsies. Therefore, no correlation studies are possible, and defining the seizures already defines the type of epilepsy.

Classification of epileptic seizures (Refer to tables *2, 3, 4, 5, 6, 7*)

Investigators have taken the highly successful and biologically relevant classification of plants and animals as a template to create a similarly relevant classification of epileptic seizures. Plants and animals contain genetic evolutionary information that naturally leads to a biologically relevant classification. However, it is impossible to develop a "biologically relevant classification" system for objects, since the information contained within varies, for example, wooden boxes of different shapes, sizes, and colors. This fundamental difference in the subject matter largely explains why the ILAE's Committees have been unsuccessful in developing a biologically relevant classification of epileptic seizures that is similar to the classification of plants and animals by Linnaeus. On the other hand, the semiological characteristics of epileptic seizures contain highly relevant information regarding the origin and spread of epileptic discharges. Therefore, any classification of epileptic seizures should maximize the value of seizure semiology regarding the origin and spread of epileptic discharges.

Table 2. Semiology classification of low complexity.

Auras*
Autonomic seizures*
Dyscognitive seizures
Motor seizures*
Special seizures
Asymptomatic EEG seizure

The asterisk (*) indicates that a somatotopic modifier may be used to specify the category with more precision (see *Table 6*).

The following principles guide the semiological seizure classification:
– Epileptic seizures are broken down into "seizure components". Each seizure consists of 1-4 seizure components.
– Seizure components consist of sets of ictal symptoms that have semiological similarities and frequently a common pathophysiology, such as a common symptomatogenic zone. In other words, each seizure component tends to be triggered by a defined pathophysiology, *i.e*. activation of a defined symptomatogenic zone in most cases. For example: a left-hand somatosensory aura corresponds to a symptomatogenic zone in the right hemispheric hand S1 area.
– The different seizure components are linked in a sequence by arrows. The "sequence of seizure components", with each seizure component usually corresponding to a more or less clearly defined symptomatogenic zone, elucidate the most likely seizure spread. For example, the seizure of a patient having an aura of flashing lights in the left visual field, progressing to a sensation of nausea, chewing automatisms with loss of contact, and eventually becoming bilateral clonic, would be classified as follows:

Table 3. Semiology classification of moderate complexity.

Auras *	Auditory aura*	
	Autonomic aura	Abdominal Aura
	Gustatory aura	
	Olfactory aura	
	Psychic aura	
	Somatosensory aura*	
	Vestibular aura	
	Visual aura*	
Autonomic seizure*	Bradycardic seizure	
	Emetic seizure	
	Sialorrheic seizure	
	Tachycardic seizure	
	Urinary seizure	
Dyscognitive seizure	Aphasic seizure	
	Akinetic seizure	
	Dialeptic seizure	
Motor seizure*	Simple motor seizures*	Clonic seizure*
		Epileptic spasm*
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	Hypomotor seizure	
	Negative myoclonic seizure*	
Asymptomatic EEG seizure		

The asterisk (*) indicates that a somatotopic modifier may be used to specify the category with more precision (see *Table 6*).

Table 4. Semiology classification of high complexity.

Aura*	Auditory aura			
	Autonomic aura	Abdominal aura	Choking aura	
		Diaphoretic aura *		
		Dipsosic aura		
		Pilomotor aura *		
		Sialorrheic aura		
		Tachycardic aura		
		Urinary aura		
		Vasomotor aura*		
	Gustatory aura			
	Olfactory aura			
	Psychic aura	Affective aura	Pleasure aura	Ecstasy aura
				Religious aura
				Sexual aura
			Unpleasant aura	Anger aura
				Depression/Sadness aura
				Embarrassment aura
				Fear/Panic aura
				Guilt aura
		Cognitive aura		
		Experiential aura		
		Familiarity aura	Déjà-vu aura	
			Jamais-vu aura	
		Illusionary aura	Auditory aura	
			Body aura	
			Time aura	
			Visual aura	
	Somatosensory aura*			
	Vestibular aura			
	Visual aura* Ictal blindness*			
Autonomic seizures*	Abdominal seizure			
	Anisocoric seizure*			
	Bradycardic seizure			
	Emetic seizure			
	Fecal incontinence seizure			

Table 4. Semiology classification of high complexity. (*Continued*)

Autonomic seizure*	Hippus seizure		
	Hyperhydrotic seizure*		
	Hypertensive seizure		
	Lacrimatory seizure		
	Pilomotor seizure*		
	Sexual seizure		
	Sialorrheic seizure		
	Tachycardic seizure		
	Urinary seizure		
	Vasomotore seizure*		
Dyscognitive seizures	Amnestic seizure		
	Aphasic seizure		
	Akinetic seizure		
	Dialeptic seizure		
Motor seizures*	Simple motor seizure*	Clonic seizure*	
		Epileptic spasm*	
		Myoclonic seizure*	
		Nystagmoid seizure*	
		Tonic seizure*	
		Tonic-clonic seizure*	
		Versive seizure*	
		Vocalization seizure	
	Complex motor seizure	Alien limb seizure	
		Automotor seizure	
		Dacrystic seizure	
		Gelastic seizure	
		Hypermotor seizure	Emotional hypermotor seizure
		Kissing seizure	
		Singing seizure	
		Spitting seizure	
		Verbalization seizure	

Table 4. Semiology classification of high complexity. (*Continued*)

Special seizures	Astatic seizure
	Atonic seizure*
	Central apneic seizure
	Fear facies seizure
	Hypnopompic seizure
	Hypomotor seizure
	Negative myoclonic seizure*
	Water drinking seizure
Asymptomatic EEG seizure	

The asterisk (*) indicates that a somatotopic modifier may be used to specify the category with more precision (see *Table 6*).

(1) left visual aura → (2) abdominal aura → (3) automotor (LOC) → (4) bilateral clonic seizure

From this classification, we would assume that the seizure started in the right calcarine gyrus and then spread into the mesial temporal region before becoming generalized.
The concept that seizures spread and that the semiological evolution of epileptic seizures reflects the "march" of the epilepsy over the cortical surface was already applied first by Bravais in 1827 (Bravais, 1827) and was later adopted and expanded by Jackson (Taylor, 1958).

The semiological seizure classification assumes also that clinical seizures may sometimes remain limited to the first component (left visual aura in the example given above, under Point 3), occasionally spread to component 2 or 3 (left hand clonic component and left versive component in the example above), and become bilateral only rarely. If needed, this can be documented as follows:

Ictal semiology: *(1) left visual aura → (2) left hand clonic → (3) left versive → (4) bilateral clonic seizure*
Frequency: *(1) one/week; (2) one/month; (4) one/six months*

Exclusively subjective components are followed by the expression "aura" (examples: left visual aura, abdominal aura). All the objective components are expressed by adjectives (example: left hand clonic, right versive) except the last component that is followed by the expression "seizure" when classifying an epileptic paroxysmal event, or "event" when classifying a non-epileptic event or a paroxysmal event that could be epileptic or non-epileptic.

Table 5. Lateralizing signs.

Automotor seizures with no dialepsis	
Asymmetric ending seizure (1)	Clonic seizure*
	Versive seizure*
Early head deviation*	
Figure of 4*	
Ictal dystonia*	
Ictal speech	
Ictal unilateral automatisms*	
Ictal unilateral blinking*	
Immediate postictal speech	
M2e sign*	
Postictal aphasia	
Postictal hemiparesis*	
Postiictal nose wiping*	
Unilateral pupillary dilation*	

The asterisk (*) indicates that a somatotopic modifier may be used to specify the category with more precision (see *Table 6*).
(1) Asymmetric ending seizures refer to an asymmetric ending of bilateral tonic-clonic seizure or bilateral clonic seizure with either unilateral clonic jerks or a version.

In the semiological seizure classification, a total of four seizure components are allowed. This restriction avoids excessive detail that might make the classification impractical. However, additional signs that add lateralizing/localizing power may be added to the

Table 6. Somatotopic modifiers.

Bilateral
Bilateral asymmetric
Left
Right
Axial
Throat
Head
Face
Eyes
Eyelid
Lips
Tongue
Hand
Arm
Trunk
Abdomen
Leg
Foot

Table 7. Seizure triggering factors.

Alcohol withdrawal	
Auditory	Music
	Sounds
	Voices
Complex cognitive	
Eating	
Hypoglycemia	
Hyperventilation	
Movement	Active movement
	Passive movement
Reading	
Somatosensory	
Sleep	
Sleep deprivation	
Startle	
Visual	Flash
	Pattern evoked
	Eye closure
	Sensitivity-off

classification. In the example of Point 3 above, we could add a "left Todd's paralysis" as a lateralizing sign. Besides, if a seizure consists of more than four seizure components and some of the redundant seizure components have lateralizing value, they can be listed under "lateralizing signs". *Table 5* shows the lateralizing signs that can be identified during epileptic ictal events.

Ictal semiology: *(1) left visual aura → (2) left hand clonic → (3) left versive → (4) bilateral clonic seizure*
Frequency: *(1) one/week; (2) one/month; (4) one/six months*
Lateralizing signs: *left Todd's paralysis; left face tonic*

Loss of consciousness (LOC), defined as relative unresponsiveness associated with amnesia for the episode of unresponsiveness, is an essential semiological feature. In previous classifications, loss of consciousness was the main factor dividing focal seizures into simple or complex partial seizure (Bancaud *et al.*, 1981). In the semiological seizure classification, LOC is indicated by adding the notation "(LOC)" following the first seizure component for which the patient is relatively unresponsive and amnestic. In the example shown above a "(LOC)" will be inserted after the left hand clonic component if the patient was unresponsive during the clonic seizure component and does not remember the left clonic movements:

Ictal semiology: *(1) left visual aura → (2) left hand clonic (**LOC**) → (3) left versive → (4) bilateral clonic seizure*
Frequency: *(1) one/week; (2) one/month; (4) one/six months*

All epileptic seizures develop as the consequence of one or more triggers that lower the epileptic threshold. In most cases, these triggers are unknown. In some patients, however, a clearly defined trigger may be identified. Triggers that can elicit epileptic seizures are shown in *table 7*. Triggers are listed in the seizure classification; as shown below. The approximate percentage of seizures provoked by the trigger is listed following each trigger.

Table 8. Epileptogenic zone classification.

Generalized			
Focal	Hemisphere*	Temporal*	Lateral temporal*
			Mesial temporal*
			Temporal pole*
			Basal temporal*
		Frontal*	Prefrontal lateral*
			Prefrontal mesial*
			Basal frontal*
			Premotor lateral*
			Premotor mesial*
		Central*	Centro-temporal*
			Mesial central*
		Parietal*	Mesial parietal*
			Lateral parietal*
		Occipital*	Lateral occipital*
			Mesial occipital*
		Cingulate*	Anterior cingulate*
			Mid cingulate*
			Posterior cingulate*
		Insula*	Anterior insula*
			Posterior insula*
Multifocal			
Unknown			

The asterisk (*) implies that a left or right modifier can be added to the specified brain area (example: right mesial occipital).

Table 9. Etiology classification.

Structural*
Genetic
Inflammatory
Infectious
Unknown

The asterisk (*) indicates that a brain region may be defined to specify the category with more precision (see *Table 8*).

Example:
Ictal semiology: *automotor seizure (LOC)*
Frequency: *one/month*
Trigger: *music (100%)*

Tables 2, 3, 4 show the seizure classification. *Table 2* shows the broadest categories, which are less precise and more useful to non-neurologists. *Table 3* shows more detailed seizure components that can be seen during epileptic ictal events. General neurologists should have enough ictal semiology training to apply this degree of semiological precision. Finally, *table 4* shows the maximum semiological detail and should be used primarily by epileptologists.
Like other dimensions, the seizure components are grouped in major sets that share similar semiological features and frequently also a similar pathophysiology (example: auras that all consist of subjective symptoms tend to occur at the beginning of a seizure and are the result of epileptiform dysfunction of a relatively limited cortical territory). As we move from left to right within the table, we find that the dimension is progressively defined more accurately. Having "seizure components" that cover all possible ictal semiological manifestations has significant advantages:
– By design of the seizure components, any epileptic seizure can be classified semiologically.
– Breaking down the seizure symptoms into seizure components and expressing the seizure evolution by joining different seizure components by an arrow makes it possible not only to classify the seizure symptomatology, but also to express the infinite possible patterns of evolution.
– The same semiological seizure classification can be applied to classify newborns, children, and adults. Epileptologists only need to be aware that certain seizure components do not occur or cannot be diagnosed for certain age groups (for example, automotor seizures do not occur until age three years, and auras are not, or cannot, be reported until age 3-5 years) (Fernandez-Baca Vaca *et al*., 2018).
– The same classification system can also be used to classify other paroxysmal episodes and non-epileptic psychogenic paroxysmal episodes. However, in this case, the expression "aura" is replaced by "aura event", and the expression "seizure" is replaced by "event" at the end of the sequence of components (example: *visual aura (bilateral clonic event*).

Many of the auras, seizure components or seizures require a somatotopic modifier to define the semiology precisely. Examples include left visual aura, right hand somatosensory aura, and bilateral asymmetric tonic seizure component. Auras, seizure components, or seizures that may be modified by a somatotopic

modifier are indicated by an asterisk in *tables 2, 3, 4*. *Table 6* shows the somatotopic modifiers that are used. For some auras, seizure components or seizures, "left" or "right" may only be used as a somatotopic modifier (example: left auditory aura). Other auras, seizure components or seizures allow a detailed somatotopic modifier (example: left hand somatosensory aura).

Tables 2, 3, 4 also include a sixth category, labelled as "*asymptomatic EEG seizures*." In the epilepsy classification, the "epileptogenic zone" will essentially define the location of the EEG seizure. This category also allows specification of the frequency of the EEG seizures.

Classification of the epileptogenic zone (*table 8*)

The epileptogenic zone is defined as the minimal cortical region that must be resected, disconnected, thermo-coagulated, thermo-ablated or desynchronized by multiple transections to produce seizure freedom. It cannot be determined directly but it is deduced by outlining related cortical areas, including the irritative zone, the seizure onset zone, the epileptogenic lesion, the symptomatogenic zone, and the functional deficit zone.
The epileptogenic zone can also be defined with different degrees of precision; for example, by just listing the abnormal hemisphere (left or right), one or two lobes (left fronto-temporal, right occipital) or subdivision of one lobe (left mesial temporal lobe, right fusiform gyrus, *etc.*). Obviously, without performing surgery, the exact location of the epileptogenic zone cannot be determined with certainty. Besides, if a patient becomes seizure-free after surgery, it only indicates that the epileptogenic zone is a subset of the resected cortex; it does not mean that all the resected tissue is part of the epileptogenic cortex.

Etiological classification (*table 9*)

In this classification system, special attention is given to classification of the etiology of each epilepsy with maximum precision depending on the available information. The etiology is subdivided into five broad categories, as suggested by the ILAE (Scheffer *et al.*, 2017). For each patient, however, the most detailed etiology is indicated in parenthesis. It is the detailed etiological classification that permits the clinician to associate a specific etiology with a specific medical therapy or epilepsy surgery.
Structural refers to causes for which the seizures are the direct result of an abnormal underlying brain anatomy. Structural lesions are usually diagnosed by neuroimaging, commonly high-resolution MRI.
Genetic refers to causes for which the seizures are a direct result of a known or presumed genetic error.
Infectious refers to causes for which the development of seizures is the result of post-infectious processes.
Inflammatory refers to causes for which the development of seizures is immune-mediated central nervous system inflammation.
Unknown.

General principles guiding the etiology of epileptic seizures:
– In all patients, the etiology of the seizures is multifactorial, including at least one (and sometimes more than one) main etiological factor (example: left parietal ganglioglioma) and a number of contributing factors, such as susceptibility genes. As genetic testing becomes routine, the multi-etiological nature of epilepsy will become more evident.
– In general, for patient management, just specifying the broad main etiological category is of no or only minimal value. Therefore, we encourage the specification of the most precise category in each case (example: left middle cerebral artery infarction; *SCN1A* mutation).

Epileptic syndromes
Epilepsy syndromes consist of specific constellations of:
– semiologies
– EEG abnormalities
– comorbidities
– etiologies

Syndromes were defined by astute epileptologists who realized that the correct identification of an epilepsy syndrome was often helpful to determine prognosis and treatment. Syndromes, however, are, by definition, empirical and artificial. Modern diagnostic techniques including MRI and genetic testing now allow precise diagnosis of epilepsy causes, therefore identification of syndromes is less important than it once was (Kellinghaus *et al.*, 2004), although several still impact therapy decisions (*e.g.* West syndrome, self-limited Rolandic epilepsy, juvenile myoclonic epilepsy) or have relevance to genetic research (*e.g.* Dravet syndrome).
As diagnostic technology and knowledge about epilepsy improve, it is likely that more syndromes will become obsolete in the near future. The emphasis of a classification scheme should not be to preserve a set of increasingly archaic conventions, but rather to define, as precisely and objectively as possible, the characteristics of each individual case of epilepsy in order to facilitate discovery of new etiologies.
However, for many decades, classic epileptology assumed that identification of an epilepsy syndrome

was the diagnostic gold standard. Besides, there are innumerable publications on study treatment and prognosis for different epileptic syndromes. This information is useful for management of epileptic patients who have a well-defined epilepsy syndrome. This is the reason why we decided to include the syndrome as an option in parenthesis following the definition of the epileptogenic zone.

Example:
Epileptic paroxysmal event
Semiology: *bilateral myoclonic → bilateral clonic → bilateral tonic-clonic seizure*
Trigger: *sleep deprivation, alcohol withdrawal*
Epileptogenic zone: *generalized (juvenile myoclonic epilepsy)*
Etiology: *genetic*
Comorbidities: *none* □

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Legend for video sequences

– Video Case 1 (Appendix 2)
– Video Case 2 (Appendix 2)
– Video Case 3 (Appendix 2)

Key words for video research on www.epilepticdisorders.com

Video case 1

Phenomenology: bilateral tonic-clonic seizure
Localisation: insula (right)
Syndrome: focal structural
Aetiology: unknown

Video case 2

Phenomenology: hypermotor, emotional
Localisation: frontal (left)
Syndrome: focal (structural and genetic)
Aetiology: cortical dysplasia

Video case 3

Phenomenology: tonic (bilateral asymmetric); clonic (bilateral)
Localisation: unknown
Syndrome: neonatal (familial); generalised
Aetiology: genetic

References

Bancaud J, Henriksen O, Rubio-Donnadieu F, Seino M, Dreifuss FE, Penry JK. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1981; 22: 489-501.

Berg AT, Berkovic SF, Brodie MJ, *et al*. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010; 51: 676-85.

Bravais F. *Recherches sur les symptomes et le traitment de l'epilepsie hemiplegique*. Faculte de Medicine de Paris, 1827.

Fernandez-Baca Vaca G, Mayor C, Garcia Losarcos N, Park J, Lüders HO. Seizure semiology in different age groups. *Epileptic Disord* 2018; 20: 179-88.

Fisher RS, Cross JH, D'souza C, *et al*. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia* 2017a; 58: 531-42.

Fisher RS, Cross JH, French JA, *et al*. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017b; 58: 522-30.

Kellinghaus C, Loddenkemper T, Najm IM, *et al*. Specific epileptic syndromes are rare even in tertiary epilepsy centers: a patient-oriented approach to epilepsy classification. *Epilepsia* 2004; 45: 268-75.

Scheffer IE, Berkovic S, Capovilla G, *et al*. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58: 512-21.

Taylor J. *Selected Writings of John Hughlings Jackson*. New York: Basic books, Inc, 1958.

Appendix 1. PRACTICAL EXERCISE: CLASSIFICATION USING THE ILAE AND PAROXYSMAL EVENT FOUR-DIMENSIONAL EPILEPSY CLASSIFICATION

In this exercise, we replicate the 12 vignettes that Fisher *et al*. (2017a) included in their "Instructor manual for the ILAE operational classification of sensory types". The exercise consists of classifying the epilepsy in each case using the ILAE system and the paroxysmal event and four-dimensional system.

When classifying using the ILAE system, the following four levels must be specified:
a. Seizure type
b. Epilepsy type
c. Epilepsy syndrome
d. Etiology

When classifying using the paroxysmal event and four-dimensional epilepsy classification, the following dimensions must be defined:
Paroxysmal event type:
I. Ictal semiology
II. Epileptogenic zone
III. Etiology
IV. Co-morbidities

The answers for each case, under both systems of classification, with comments can be found after each vignette.

CASE 1: Unknown-onset tonic-clonic

A woman awakens to find her husband having a seizure in bed. The onset is not witnessed, but she is able to describe bilateral stiffening followed by bilateral shaking. EEG and MRI findings are normal. This seizure is classified as *unknown-onset tonic-clonic*. There is no supplementary information to determine whether the onset was focal or generalized. Under the old classification, this seizure would have been unclassifiable with no further qualifiers.

ILAE classification

a. Seizure type: unknown onset tonic-clonic seizure
b. Epilepsy type: unknown
c. Epilepsy syndrome: N/A
d. Etiology: unknown

Paroxysmal event and four-dimensional epilepsy classification

Paroxysmal event
I. Event semiology: bilateral tonic-clonic event
II. Etiology: unknown
III. Co-morbidities: none

Comments

The vignette does not contain sufficient information to reliably diagnose epilepsy. A detailed anamnesis most likely would have been sufficient to make a reliable diagnosis if the patient had an epileptic seizure or not. The interview should provide an answer to the following questions:

- Duration of "stiffening" and of "bilateral shaking"?
- Eyes open or closed?
- Did the eyes "roll back"?
- Was there foaming at the mouth?

- Was there blood anywhere?
- Did he wet himself?
- What happened after the shaking was over? Was there stertorous hyperventilation? How long did it take him to recover consciousness?
- Did he complain of muscle ache the following day? Did his tongue hurt? Where did he bite his tongue?

CASE 2: Focal-onset bilateral tonic-clonic

In an alternate scenario of Case 1, the EEG shows a clear right parietal slow-wave focus. The MRI shows a right parietal region of cortical dysplasia. In this circumstance, the seizure can be classified as *focal to bilateral tonic-clonic*, despite the absence of an observed onset, because a focal etiology has been identified, and the overwhelming likelihood is that the seizure had a focal onset. According to the old classification, this seizure would have been classified as partial onset, secondarily generalized.

ILAE classification

a. Seizure type: focal to bilateral tonic-clonic seizure
b. Epilepsy type: focal
c. Epilepsy syndrome: N/A
d. Etiology: genetic and structural

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: bilateral tonic-clonic seizure
II. Epileptogenic zone: right parietal
III. Etiology: right parietal cortical dysplasia
IV. Co-morbidities: none

Comments

Now even without a detailed clinical history, the chances that the patient has an epileptic seizure are extremely high. Therefore, we now classify the event as an *epileptic paroxysmal event*.

CASE 3: Absence

A child is diagnosed with Lennox-Gastaut syndrome of unknown etiology. EEG shows runs of slow spike-waves. Seizure types include absence, tonic, and focal motor seizures. The absence seizures are prolonged, have indistinct onset and cessation, and sometimes result in falls. In this case, the absence seizures are classified as *atypical absence* due to their characteristics, the EEG pattern, and underlying syndrome. The absence seizures would have had the same classification in the old system.

ILAE classification

a. Seizure type: atypical absence, tonic seizure, focal motor seizure
b. Epilepsy type: combined generalized and focal
c. Epilepsy syndrome: Lennox-Gastaut syndrome
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: tonic seizure, dialeptic seizure, motor seizure
II. Epileptogenic zone: generalized (Lennox-Gastaut syndrome)
III. Etiology: unknown
IV. Co-morbidities: intellectual disability

Comments

Again, the amnestic information provided in the vignette is inadequate to properly classify the epilepsy.

❖ Duration and somatotopic distribution of the tonic seizure.

❖ What do you mean by "focal motor seizure"? In the ILAE classification, a focal motor seizure means that the epileptogenic zone for the motor seizure is focal (or regional). Besides, motor may imply automatisms or atonic, tonic, clonic, hyperkinetic, myoclonic manifestations as also epileptic spams! A good anamnesis certainly can resolve this dilemma.

❖ In the vignette, it is mentioned that the patient has Lennox-Gastaut syndrome. This is the reason why we added intellectual disability as a comorbidity.

❖ As we mentioned in the main text, selected syndromes can be useful in the management of epileptic patients. Therefore the four-dimensional classification leaves the option open to include it in parenthesis after listing the epileptogenic zone.

CASE 4: Tonic

A child has brief seizures with stiffening of the right arm and leg, during which responsiveness and awareness are retained. This seizure is a *focal aware tonic seizure* (the words "motor onset" can be assumed). In the old system, the seizure would have been called *tonic*, with a perhaps incorrect assumption of generalized onset.

ILAE classification

a. Seizure type: focal aware tonic seizure
b. Epilepsy type: focal
c. Epilepsy syndrome: N/A
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: right tonic seizure
II. Epileptogenic zone: left hemisphere
III. Etiology: unknown
IV. Co-morbidities: none

Comments

❖ The information provided in the vignette is insufficient to establish the epileptic nature of the symptomatology. With the available information listed in the vignette, we would classify this as a "paroxysmal event", before additional data may confirm that the symptoms are epileptic. The classification listed above is based on the assumption that the epileptic nature of the symptoms has been provided.

❖ Above is a preliminary classification. Neurological examination and neuroimaging would be essential to properly classify the epilepsy.

CASE 5: Focal impaired awareness

A 25-year-old woman describes seizures beginning with 30 seconds of an intense feeling that "*familiar music is playing*". She can hear other people talking, but afterwards realizes that she could not determine what they were saying. After an episode, she is mildly confused, and has to "*reorient herself*". The seizure would be classified as *focal impaired awareness*. Even though the patient is able to interact with her environment, she cannot interpret her environment, and is mildly confused. Prior classification would have been complex partial seizure.

ILAE classification

a. Seizure type: focal impaired awareness seizure
b. Epilepsy type: focal
c. Epilepsy syndrome: N/A
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: *déjà-vu* aura→ dialeptic seizure
II. Epileptogenic zone: temporal lobe
III. Etiology: unknown
IV. Co-morbidities: unknown

Comments

❖ The information provided in the vignette is insufficient to establish the epileptic nature of the symptomatology. With the available information listed in the vignette, we would classify this as a "paroxysmal event", before additional data may confirm that the symptoms are epileptic. The classification listed above is based on the assumption that the epileptic nature of the symptoms has been provided

❖ The temporal lobe was identified as the epileptogenic zone because *déjà-vu* aura(dialeptic seizures almost always originate in the temporal lobe.

CASE 6: Autonomic

A 22-year-old man has seizures during which he remains fully aware, with "*hair on my arms standing on edge*" and a feeling of being flushed. These are classified as *focal aware nonmotor autonomic seizures*, or more succinctly, *focal aware autonomic seizures*. Based on the old classification, these would have been referred to as simple partial autonomic seizures.

ILAE classification

a. Seizure type: focal aware autonomic seizures
b. Epilepsy type: focal
c. Epilepsy syndrome: N/A
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: vasomotor aura → pilomotor aura
II. Epileptogenic zone: temporal lobe
III. Etiology: unknown
IV. Co-morbidities: none

Comments

❖ The information provided in the vignette is insufficient to establish the epileptic nature of the symptomatology. With the available information listed in the vignette, we would classify this as a "paroxysmal event" before additional data may confirm that the symptoms are epileptic. The classification listed above is based on the assumption that the epileptic nature of the symptoms has been provided

❖ The temporal lobe was identified as the epileptogenic zone because vasomotor aura (pilomotor auras almost always originate in the temporal lobe. In many cases, the epileptogenic zone is an inference from the semiology, until additional investigations provide more information. This may not be accurate as the epileptogenic zone may be a non-eloquent area from where the seizure spreads to a symptomatogenic zone.

CASE 7: Focal clonic

A one-month-old boy has rhythmic jerking of the left arm that does not remit when repositioning the arm. Corresponding EEG shows right frontal ictal rhythms. These seizures are *focal motor onset clonic seizures*, or more parsimoniously, *focal clonic seizures*. Because the level of awareness cannot be ascertained, awareness is not involved in classifying this seizure. No appropriate term exists under the old classification.

ILAE classification

a. Seizure type: focal aware tonic seizure
b. Epilepsy type: focal
c. Epilepsy syndrome: N/A
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: right tonic seizure
II. Epileptogenic zone: left hemisphere
III. Etiology: unknown
IV. Co-morbidities: none

Comments

None

CASE 8: Sequential seizure manifestations

A seizure begins with tingling in the right arm of a 75-year-old man. The patient says that it then progresses to rhythmic jerking of the right arm, lasting for about 30 seconds. He retains awareness and memory for the event. This seizure is a *focal (non-motor-onset) sensory seizure*. Additional description would be useful, namely *focal sensory seizure* with somatosensory features progressing to right arm clonic activity. If the sensory and motor events were to be discontinuous or the clinician had reason to consider the event to be two separate (bifocal or multifocal) seizures, then each component would be classified as a separate seizure. Under the old classification, this would have been called a *simple partial sensorimotor seizure*. An advantage of the 2017 classification is specification of the sensory onset, which may have clinical importance.

ILAE classification

a. Seizure type: focal impaired awareness seizure
b. Epilepsy type: focal
c. Epilepsy syndrome: N/A
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: *déjà-vu* aura→ dialeptic seizure
II. Epileptogenic zone: temporal lobe
III. Etiology: unknown
IV. Co-morbidities: unknown

Comments

❖ The information provided in the vignette is insufficient to establish the epileptic nature of the symptomatology. With the available information listed in the vignette, we would classify this as a "paroxysmal event", before additional data may confirm that the symptoms are epileptic. The classification listed above is based on the assumption that the epileptic nature of the symptoms has been provided

❖ The left parietal lobe was identified as the epileptogenic zone because right arm somatosensory aura → right arm clonic seizures almost always originate from the left parietal lobe.

CASE 9: Myoclonic-atonic

A four-year-old boy with Doose syndrome has seizures with a few arm jerks and then a rapid drop with loss of tone. These are now classified as *myoclonic-atonic seizures*. Based on prior unofficial usage, these would have been called *myoclonic-astatic seizures*.

ILAE classification

a. Seizure type: focal aware autonomic seizures
b. Epilepsy type: focal
c. Epilepsy syndrome: N/A
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: bilateral myoclonic axial atonic seizure
II. Epileptogenic zone: generalized (Doose syndrome)
III. Etiology: unknown
IV. Co-morbidities: none

Comments

None

CASE 10: Myoclonic-tonic-clonic seizures

A 13-year-old with juvenile myoclonic epilepsy has seizures beginning with a few jerks, followed by stiffening of all limbs and then rhythmic jerking of all limbs. These would be classified as *myoclonic-tonic-clonic seizures*. No corresponding single seizure type exists in the old classification, but they might have been called myoclonic or clonic seizures followed by tonic-clonic seizures.

ILAE classification

a. Seizure type: myoclonic-tonic-clonic seizures
b. Epilepsy type: generalized
c. Epilepsy syndrome: juvenile myoclonic epilepsy
d. Etiology: genetic

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: bilateral myoclonic → bilateral tonic-clonic seizures
II. Epileptogenic zone: generalized (juvenile myoclonic epilepsy)
III. Etiology: genetic
IV. Co-morbidities: none

Comments

None.

CASE 11: Focal epileptic spasms

A 14-month-old girl has sudden extension of both arms and flexion of the trunk for about 2 seconds. These seizures repeat in clusters. EEG shows hypsarrhythmia with bilateral spikes, most prominent over the left parietal region. MRI shows a left parietal dysplasia. Resection of the dysplasia terminated the seizures. Because of the ancillary information, the seizure type would be considered as *focal epileptic spasms* (the term "motor onset" can be assumed). Based on the previous classification, these would have been called infantile spasms, with information on focality not included. The term "infantile" can still be used when spasms occur in infancy.

ILAE classification

a. Seizure type: focal epileptic spasm
b. Epilepsy type: focal
c. Epilepsy syndrome: West syndrome
d. Etiology: genetic and structural

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: bilateral epileptic spasm
II. Epileptogenic zone: left parietal (West syndrome)
III. Etiology: left parietal dysplasia
IV. Co-morbidities: none

Comments

None.

CASE 12: Unclassified

A 75-year-old man, known to have epilepsy, reports an internal sense of body trembling and a sense of confusion. No other information is available. EEG and MRI are normal. This event is *unclassified*.

ILAE classification

a. Seizure type: unclassified
b. Epilepsy type: unknown
c. Epilepsy syndrome: unknown
d. Etiology: unknown

Four-dimensional epilepsy classification

Paroxysmal event
I. Event semiology: aura → dialeptic event
II. Etiology: unknown
III. Co-morbidities: unknown

Comments

❖ The vignette is very confusing. It indicates that the patient has epilepsy but does not indicate the seizure semiology of "known" epileptic seizures.

❖ The paroxysmal events are very non-specific and could well be non-epileptic paroxysmal events.

❖ The patient requires additional testing to elucidate the nature of the symptomatology (MRI and video EEG)

Appendix 2. CASE STUDIES: AN EXAMPLE OF THREE PATIENTS WITH PAROXYSMAL EVENTS

CASE 1

A 20-year-old, right-handed woman presents for evaluation of paroxysmal events. Onset of the events was at age 15.

(1) ANAMNESIS
Per patient: The last thing she remembers before her events is a "*weird feeling*", which she cannot further describe, and then she knows that the seizure is coming. This feeling just lasts for few seconds (~20 seconds). The next thing she remembers is laying on the floor, being surrounded by people and feeling confused. She feels tired and she goes back to sleep until the next day. She does not recall any particular difficulty talking or understanding after her events. She denies any particular pain, such as muscular pain, jaw pain or tongue soreness. She does not recall any episode with urinary incontinence.
Per witness: The mother hears a loud cry at the onset of the episode. Then the patient is unresponsive and turns her head to one side (the mother recalls "to the left"), while her eyes are open and "rolled back". This is followed by bilateral shaking with arms and legs extended; lasting for about a minute. She does not recall any foaming at the mouth. After the episode, the patient is unresponsive and her breathing is deep and stertorous for several seconds. She is then confused for about 20-30 minutes. No urinary incontinence. When asked, the patient denies recalling any pulling of her head towards one side or the other.
She is currently having 1-2 events a month.

Classification after clinical history

2017 ILAE classification system

a. Seizure type: focal to bilateral tonic-clonic seizure
b. Epilepsy type: focal
c. Epilepsy syndrome: NA
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: aura → left versive (LOC) → bilateral tonic-clonic seizure
II. Epileptogenic zone: right hemisphere
III. Etiology: unknown
IV. Co-morbidities: none
Comment: The description of the mother is consistent with generalized tonic-clonic seizures. This is also consistent with the history obtained by the patient; no recollection of the generalized convulsions. These facts support the conclusion that the patient has "epileptic paroxysmal events". Not infrequently, the observers are relatively inaccurate when lateralizing versions. Therefore, after obtaining the clinical history, the seizures could also be classified as follows:
Aura→versive (LOC) →bilateral tonic-clonic seizure.
The epileptogenic zone would be "focal".

(2) EMU EVALUATION (*figure 1A, B and video 1*).
Interictal: sharp waves, left frontal (F3-C3)
Ictal: right versive (LOC)→ right face tonic → bilateral asymmetric tonic clonic seizure
Lateralizing signs: right M2e, right sign of 4

(3) NEUROIMAGING (*figure 2*).
Small focus of abnormal signal in the left frontal periventricular white matter.

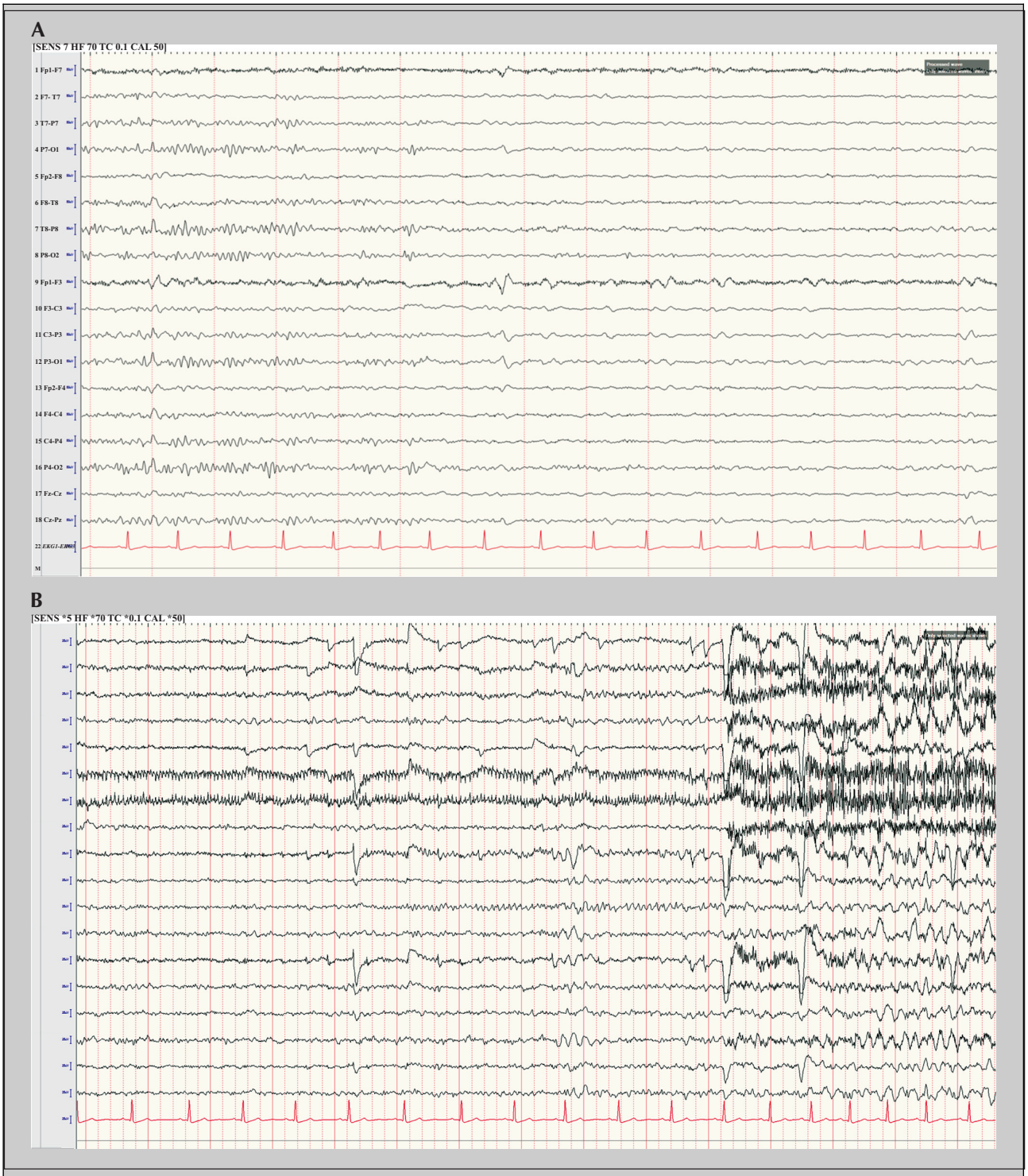

Figure 1. (A) Sharp waves, left fronto-central. (B) EEG seizure pattern, left fronto-central.

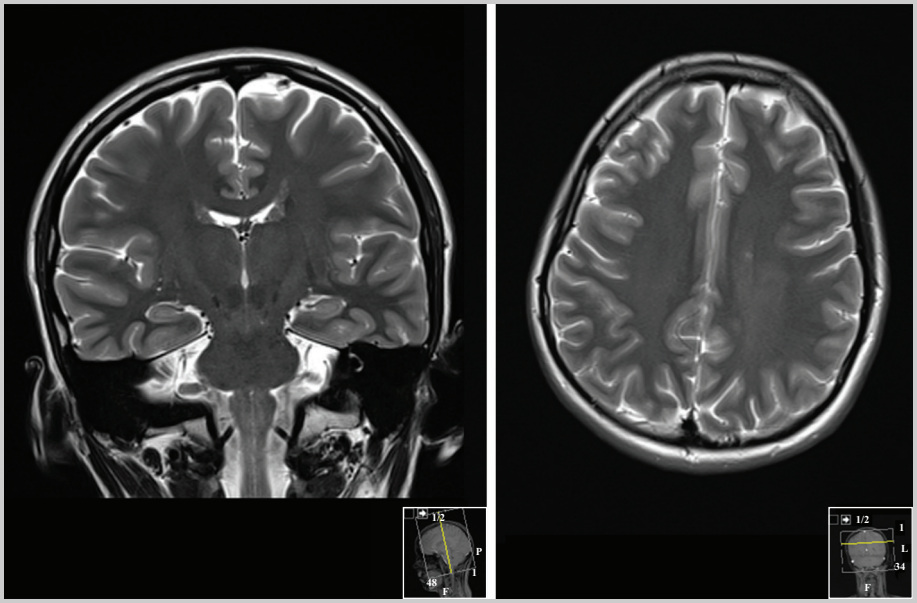

Figure 2. Small focus of abnormal signal in the left frontal periventricular white matter.

(4) FINAL CLASSIFICATION

2017 ILAE classification system

a. Seizure type: focal to bilateral tonic-clonic seizure
b. Epilepsy type: focal
c. Epilepsy syndrome: NA
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: aura→ right versive (LOC) → right face tonic → bilateral asymmetric tonic clonic seizure
II. Epileptogenic zone: left frontal
III. Etiology: unknown
IV. Co-morbidities: MRI shows a small focus of abnormal signal in the left frontal periventricular white matter

CASE 2

(1) ANAMNESIS
A 53-year-old, left-handed woman with dyslipidemia and hypothyroidisms presents to the epilepsy clinic for evaluation of paroxysmal events that started at age eight.
Per patient: Her episodes are nocturnal. She wakes up with a feeling "*the seizure is coming and I am losing control*". This feeling last for just "a second". Then, she remembers her left arm shakes uncontrollably. She tries to stop it by grabbing her left arm with the right hand, but she cannot control it. Occasionally, she also feels her legs moving up and down. The episodes last 2-3 minutes. After the seizure, she feels slightly confused, tired, and she has difficulty talking, but she feels she is able to understand. She denies biting her tongue and she only recalls urinary incontinence on one occasion. She feels she is probably aware during the entire episode, but she is not totally sure.
Per witness (husband): The patient suddenly wakes up and yells "*help*". Then, she starts moving uncontrollably all over. Her eyes are open. Her arms and legs move up and down. There is no foaming at the mouth, nor eye or head deviation that he recalls. Eyes do not roll up. After the seizure, she seems awake but confused and tired. He is not sure whether she would be able to follow any commands during this time, but she would know that she just had an episode.
On presentation, she was having one episode per week while on two AEDs.

Classification after clinical history

2017 ILAE classification system

a. Seizure type: focal aware non-motor onset
b. Epilepsy type: focal
c. Epilepsy syndrome: N/A
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal event
I. Ictal semiology: aura → left arm clonic → hypermotor seizure
II. Epileptogenic zone: right frontal
III. Etiology: unknown
IV. Co-morbidities: none
Comment: The duration and stereotypy of the episodes strongly suggests an epileptic paroxysmal episode. Besides, in this case, the patient herself lateralized the clonic seizure. This is usually a reliable lateralizing sign.

(2) EMU EVALUATION (*figure 3A, B, C and video 2*)
Interictal: sharp waves, maximum at right temporal electrodes (F8 and Sp2) (*figure 3*).
Ictal:
-Seizure semiology: emotional hypermotor seizure (*video 2*)
-EEG seizure pattern: right temporal (*figure 3*).
Comment: After the EMU evaluation, the seizure semiology classification was adjusted. The "aura" and the "left arm clonic" components were removed from the classification. Her subjective sensation started at the same time as the emotional hypermotor seizure, therefore it was felt to be most likely caused by it. Also, her left arm never moved in a clonic fashion, but rather exhibited complex movements, as expected in a hypermotor seizure. This exemplifies how the four-dimensional epilepsy classification may change overtime as the patient may undergo further investigations.

(3) NEUROIMAGING (*figure 4*)
Axial and coronal FLAIR MRI shows a "comet-like" high signal in the right anterior insula, consistent with a cortical dysplasia. The main juxtacortical lesion has a "tail", tracking along the expected course of the radial glial fibers to the subependimal margin.

(4) FINAL CLASSIFICATION

2017 ILAE classification system

a. Seizure type: focal aware hyperkinetic seizure
b. Epilepsy type: focal
c. Epilepsy syndrome: NA
d. Etiology: structural and genetic

Four-dimensional epilepsy classification

I. Ictal semiology: emotional hypermotor seizure
II. Epileptogenic zone: right insula
III. Etiology: structural and genetic (right insular cortical dysplasia)
IV. Co-morbidities: none

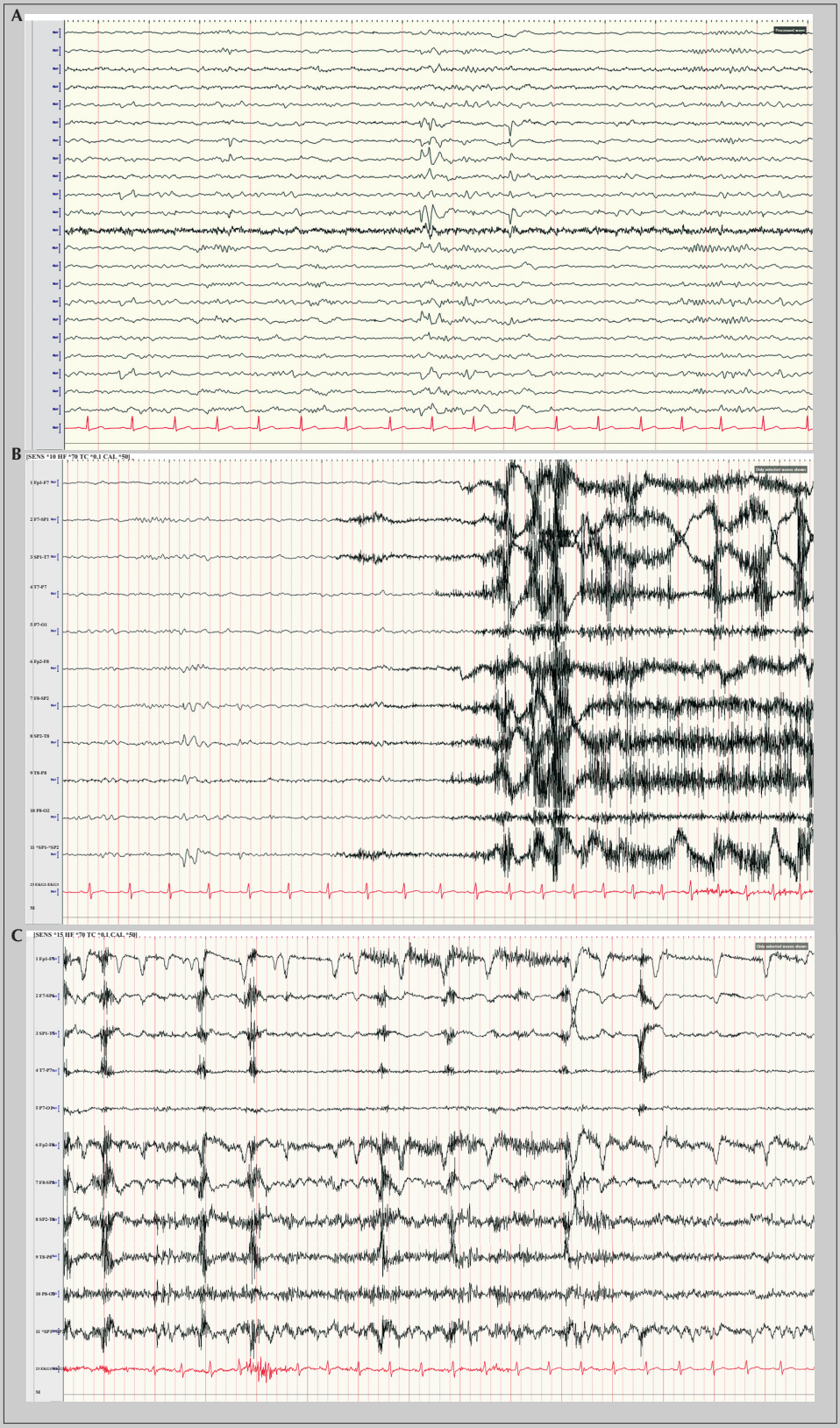

Figure 3. (A) Sharp waves, F8 Sp2. (B) EEG seizure onset. (C) EEG seizure evolution (1 minute from onset). EEG seizure pattern, right temporal.

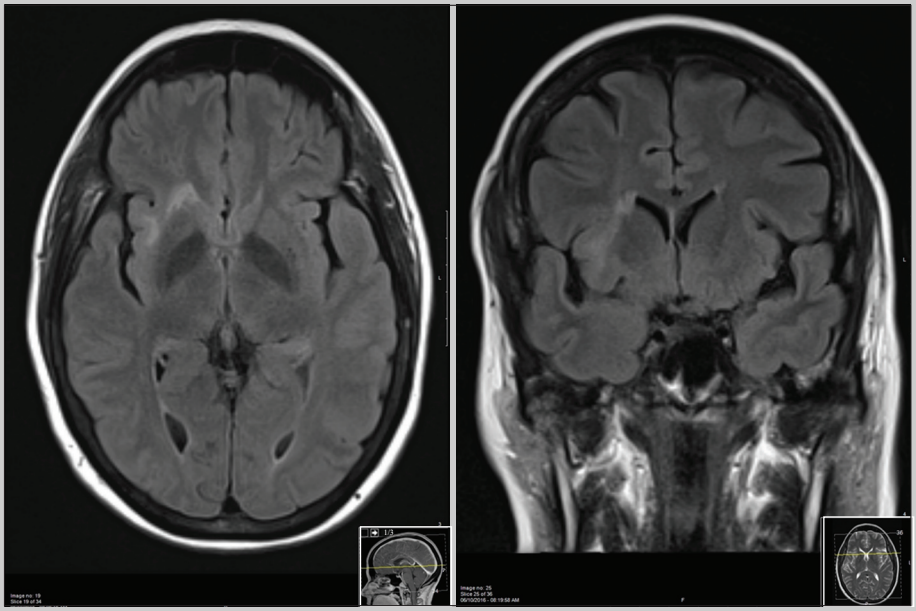

Figure 4. Axial and coronal FLAIR MR. High signal in the right anterior insula consistent with a cortical dysplasia.

CASE 3

(1) ANAMNESIS
An 11-day-old boy, born full-term, with no complications at birth presents with a five-day history of paroxysmal episodes.
Per witness (parents): Episodes of bilateral shaking of arms and legs which may be preceded by episodes of stiffening. These last for about one minute and are stereotypic. Initial frequency was once a day, but for the last days, the frequency has increased to four episodes a day. The patient's uncle had epileptic seizures during the newborn period which he outgrew during his first year.

Classification after clinical history

2017 ILAE classification system

a. Seizure type: sequential
b. Epilepsy type: NA
c. Epilepsy syndrome: unknown
d. Etiology: unknown

Four-dimensional epilepsy classification

Epileptic paroxysmal events
I. Ictal semiology: bilateral tonic → bilateral clonic seizure
II. Epileptogenic zone: unknown
III. Etiology: unknown
IV. Co-morbidities: none

Comment: Again, the duration and stereotypy of the episodes strongly suggests an epileptic paroxysmal episode.

(2) EMU EVALUATION (*figure 5 and video 3*)
Ictal: bilateral asymmetric tonic → bilateral clonic → left clonic seizure
EEG seizure pattern: generalized.

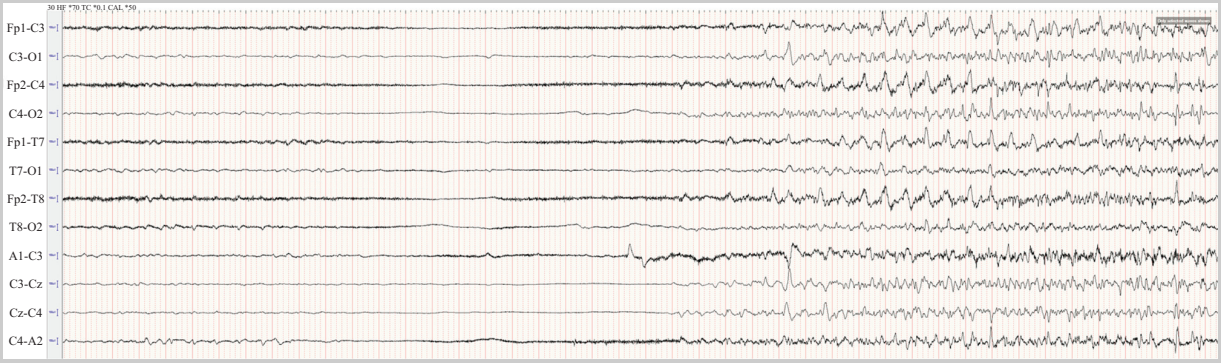

Figure 5. Case 3. EEG seizure pattern, generalized. Diffuse suppression followed by generalized rhythmic delta maximum over frontal and central regions.

(3) EVOLUTION

During his initial evolution, blood and urine and metabolic work-up was negative. Lumbar puncture was normal. Seizures responded to phenobarbital. At seven months, he had developed normally and no further seizures were noticed. Therefore, phenobarbital was stopped.

He is currently eight years old. He has growth and development appropriate for his age. He has been seizure-free, off phenobarbital, since age seven months old.

(4) FINAL CLASSIFICATION

2017 ILAE neonatal classification system

a. Seizure type: sequential seizure
b. Epilepsy type: NA
c. Epilepsy syndrome: self-limited neonatal or familial neonatal epilepsy
d. Etiology: genetic

Four-dimensional epilepsy classification

Epileptic paroxysmal event

I. Ictal semiology: bilateral asymmetric tonic → bilateral clonic → left clonic seizure
II. Epileptogenic zone: generalized (self-limited neonatal or familial neonatal epilepsy)
III. Etiology: genetic
IV. Co-morbidities: none

Appendix 3. CASE STUDY: A PRACTICAL EXAMPLE OF USING THE EPILEPSY CLASSIFICATION WITH DIFFERENT DEGREES OF PRECISION

Case study
A 35-year-old man presents to the emergency department (ED) for a new-onset paroxysmal event that occurred earlier that day. The ED physician gathers some information from the patient's wife who describes the patient having violent shaking of all limbs. The patient now feels that his condition corresponds to baseline. He has also had anxiety and depression for the last five years.
Based on the information gathered by the ED, the physician could try to classify the patient's epilepsy using the epilepsy classification and semiological classification with low or moderate complexity.

Paroxysmal event
Ictal semiology: bilateral motor event
Frequency: one event, hours ago
Etiology: unknown
Comorbidities: anxiety and depression

The patient is seen by a junior neurology resident who has rotated in the epilepsy service a few times. He asks additional questions to the patient's wife. The resident finds out the patient has been having brief episodes of staring and unresponsiveness for the last year, with an approximate frequency of one every month. In addition, he had urinary incontinence and has bitten his tongue today.
Based on the additional information, the resident suspects an epileptic paroxysmal event and he can further develop the epilepsy classification using the more complex semiological classification. At this moment, he is unsure whether the patient may have a focal vs a generalized epileptogenic zone.

Epileptic paroxysmal event
Ictal semiology: (1) dialeptic → (2) bilateral clonic seizure
Frequency: (1) one/month; (2) once today
Epileptogenic zone: unknown.
Etiology: unknown.
Comorbidities: anxiety and depression

The patient is later seen by the epilepsy faculty who accompanies the resident to see the patient again. The part of the interview that focuses on the ictal semiology is outlined below:
Epilepsy doctor: *Mr. S, what is the last thing you remember before the episode? I would like you to tell me only your own experience, not what you have been told.*
Mr. S: *I just recall waking up this morning feeling fine and the last thing I remember is going into the kitchen to get some coffee.*
Epilepsy doctor: *Anything else unusual preceding the episode that you may remember?*
Mr. S: *I may have felt nauseated for a second, but I am not sure.*
Epilepsy doctor: *What is the next thing you remember?*
Mr. S: *I just remember hearing my wife, asking me questions, like "How are you feeling? Can you stand up?"*
Epilepsy doctor: *How were you feeling at that point?*
Mr. S: *I was feeling confused, but otherwise OK.*
Epilepsy doctor: *Any particular pain?*
Mr. S: *Not that I can recall.*
Epilepsy doctor: *What about now? Any particular pain now?*
Mr. S: *Well... yes, my tongue, my tongue feels swollen and painful. My jaw is sore and I have some muscle aches around my shoulders, but overall, I feel fine. Just tired.*
Epilepsy doctor: *Your wife has mentioned you may have been having other episodes where you would stare. Were you aware of these?*
Mr. S: *She has told me before, but I am really not sure what she means.*
Epilepsy doctor: *Have you been feeling anything else unusual?*

Mr. S: *Now that you mention... I have been getting this feeling in my stomach... It is like an anxiety or nausea feeling or like being in a roller coaster. And I get this sensation of déjà vu or familiarity, as if I am experiencing something that has happened before. I mentioned this because lately it has gotten quite strong, and makes me even a little scared.*
Epilepsy doctor: *For how long does it last and how often do you get these sensations?*
Mr. S: *It is just a matter of seconds. I get these maybe once or twice a week, but for the last few days, I have them almost daily. It was really striking.*
Epilepsy doctor: *Mrs. S, I would like to ask you a few questions regarding the episodes you have seen. Can you start by describing these staring spells? Can you give me an example?*
Mrs. S: *Well, the last one I saw, we were seating on the couch, just watching TV, and I just saw him staring.*
Epilepsy doctor: *But what caught your attention? Anything in particular that made you look towards your husband while watching TV?*
Mrs. S: *He makes these chewing sounds with his mouth. And I try calling him, but he does not respond.*
Epilepsy doctor: *For how long does it last for? And what happens afterwards?*
Mrs. S: *It usually lasts for 1-2 minutes and afterwards he is somewhat confused.*

After further questioning the patient's wife, the Epilepsy doctor can gather additional information that is convincing for a generalized tonic-clonic seizure: ictal cry, blood-tainted foaming at the mouth, "eyes rolled back", tonic phase in decerebrate posture lasting 15 seconds followed by a clonic phase lasting approximately one minute, all followed by postictal coma for 5-10 minutes and gradual recovery.
Based on the additional information, the epilepsy faculty can further develop the epilepsy classification using the semiological classification of moderate complexity.

Epileptic paroxysmal event
Ictal semiology: (1) abdominal aura→ (2) psychic aura → (3) automotor (LOC) → (4) bilateral clonic seizure
Frequency: (1) (2) one/day; (3) one/month; (4) once today
Epileptogenic zone: temporal lobe
Etiology: unknown
Comorbidities: anxiety and depression

We know now that the patient has focal epilepsy, and among the focal epilepsies that can cause this seizure type, the most likely is temporal lobe epilepsy. This maybe correct for now, nevertheless this classification can be further developed and confirmed over time with additional testing, such as EEG, epilepsy monitoring unit (EMU) admission, and MRI of the brain.

Original article

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EEG of asymptomatic first-degree relatives of patients with juvenile myoclonic, childhood absence and rolandic epilepsy: a systematic review and meta-analysis

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ABSTRACT – *Aims*. Rolandic (RE), childhood absence (CAE) and juvenile myoclonic (JME) epilepsy encompass centrotemporal sharp waves, 3-Hz spike waves and >3-Hz spike or polyspike waves, respectively. Evidence abounds for genetic roles in all three syndromes, yet involved genes for the vast majority of patients remain unknown. It has long been proposed that while each disease is genetically complex, its specific EEG trait may represent a genetically simpler endophenotype. This meta-analysis of the literature focuses on the frequency of EEG traits in clinically unaffected first-degree relatives towards determining inheritance patterns of the EEG endophenotypes.

Methods. We used the Preferred Reporting Items for Systematic Review and Meta-Analysis for protocols (PRISMA-P) and searched Medline, EMBASE, CINHAL and the Cochrane Central Register of Controlled Trials.

Results. Following extensive screening, 15 studies were included with a total of 3,858 asymptomatic relatives. The prevalence of 'abnormal' EEG waves was 21%, 42% and 33% for JME, CAE and RE, respectively, close to what would be expected based on Mendelian inheritance.

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However, breaking down the reported EEG abnormalities, most consisted not of the respective EEG signature traits -prevalences of which were as low as 5%- but of non-specific EEG 'abnormalities'/variants.
Conclusions. Prevalence of non-specific EEG 'abnormalities'/variants in the general population ranges from 0.1 to 10%. Underlying this 100-fold-wide range is a spectrum of what is considered 'abnormal' or variant. The prevalences of 'abnormalities'/variants in asymptomatic siblings in RE, CAE and JME significantly exceed even the highest value in the general population and fall within Mendelian expectations. These results suggest that EEG 'abnormalities'/variants shared with the general population are enriched in the three syndromes and are endophenotypes inherited in a genetically simple near-Mendelian fashion. Future work with modern EEG variant definitions should uncover genetic variants contributing to neuronal hypersynchrony in epilepsy.

Key words: Rolandic epilepsy, childhood absence epilepsy, juvenile myoclonic epilepsy, endophenotype, EEG trait, spike wave, sibling, unaffected

The three most common childhood epilepsies are Rolandic (RE), childhood absence (CAE) and juvenile myoclonic (JME) epilepsy, accounting for 15%, 10-15% and 5-10% of cases, respectively (Avanzini and Noebels, 2009; Panayiotopoulos, 2010; Berg and Millichap, 2013; Camfield *et al.,* 2013; Pal *et al.,* 2016; Verrotti *et al.,* 2017). There is abundant evidence that genetic factors play important roles in each of these conditions though none (in the vast majority of families) is inherited in a Mendelian fashion, and all three are therefore genetically complex (Anderman and Metrakos, 1969; Delgado-Escueta, 2007; Panayiotopoulos, 2010; Panayiotopoulos *et al.,* 2012). Despite the genetic and genomic revolutions of the last three decades, only a few genes have been associated with these very common diseases, and then only in a small minority of patients.

The genetic complexities of CAE and JME were already recognized even prior to the two being carved out of what was called in the early 1950s, 'centrencephalic' epilepsy (Penfield, 1952). In their seminal work, Metrakos and Metrakos (1961a) reported that approximately 50% of clinically unaffected, age-matched first-degree relatives of patients with centrencephalic epilepsy had the same age-dependent generalized EEG abnormalities as the latter, and suggested that while the epilepsy itself was not inherited in a Mendelian fashion, the EEG trait, present as it is in nearly 50% of young adolescent relatives, may well be (Metrakos and Metrakos, 1961a). Following the spinoff of CAE and JME from the parent 'centrencephalic' concept, EEG studies of relatives of these patients continued to be carried out, but results usually showed rates substantially lower than 50%.

A decade following the work of Metrakos and Metrakos, studies in RE also reported a rate of EEG abnormality in clinically unaffected siblings of approximately 50% when the siblings were studied during the range of childhood years in which RE occurs (Bray and Wiser, 1964; Heijbel *et al.,* 1975). More recent work, however, questioned the role of genes in RE, based on the rate of non-concordance for the clinical syndrome in monozygotic twins (Valdamudi *et al.,* 2006). Meanwhile, ongoing EEG studies of relatives of RE patients continued to show rates of EEG abnormalities substantially higher than in children in the general population. RE, CAE and JME are not only common, they also are 'pure' epilepsies in which the CNS is otherwise grossly morphologically and functionally intact. As such, understanding the pathogeneses of these benign conditions will be highly insightful to the overall understanding of epilepsy. Solving the genetic complexities of RE, CAE and JME would be greatly aided if any aspect of these conditions, *e.g.* their specific EEG traits, were endophenotypes inherited in simpler, perhaps a Mendelian, fashion. Given the opaqueness of, and contradictions in the literature regarding, the frequencies of EEG abnormalities in unaffected relatives of patients with RE, CAE and JME, we conducted a systematic review and meta-analysis of this literature to clarify the current state of knowledge. It is hoped that this work will serve as a basis and springboard for additional studies that will resolve the genetics of the epileptiform abnormalities underlying RE, CAE and JME.

Methods

Protocol

A protocol was developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols (PRISMA-P) (Moher *et al.,* 2015) and registered with the PROSPERO database (CRD42013005615).

Eligibility criteria

We included studies using cohort, case-control or cross-sectional methodology examining EEG in asymptomatic relatives (parents, siblings or offspring) of epileptic patients of all ages. Both English and non-English language, published and unpublished, reports were included.

Search

Medline, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials were searched on July 5, 2013. Searches were performed with no year or language restrictions, using the Medical Subject Headings and text words and phrases: Juvenile myoclonic epilepsy, Janz syndrome, idiopathic epilepsy, genetic epilepsy, electroencephalograph, humans, childhood absence epilepsy, pyknolepsy, idiopathic generalized epilepsy, centrencephalic epilepsy, Rolandic epilepsy, benign childhood epilepsy with centrotemporal spikes, epilepsy syndrome, and Sylvian seizures. Appropriate wildcards were used to account for plurals and spelling variations. This search was conducted by an experienced librarian and peer-reviewed by another librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist (McGowan *et al.,* 2010). The electronic search was supplemented by scanning the reference lists of included studies and relevant reviews. The full search strategy for MEDLINE can be found in the *supplementary material* and the others are available upon reasonable request from the corresponding author.

Study selection

A pilot test was conducted on a random sample of 25 titles and abstract citations. After 94% agreement was achieved, two reviewers (MT and DB) independently screened the search results for inclusion. We obtained the full-text of potentially relevant articles and assessed them in a similar manner. Discrepancies were resolved by discussion with a third reviewer (BAM).

Data collection process

After a pilot test of 25 articles, two independent reviewers (MT and DB) performed data extraction on all the selected articles using the standardized data extraction form. To ensure accuracy, the reviewers extracted all data in duplicate and conflicts were resolved through discussion amongst the team. When multiple publications reported data from the same population (companion reports), we considered the study with the largest sample size as the major publication, and used the other report(s) for *supplementary material* only.

Methodological quality

We assessed methodological quality of individual studies using the Newcastle-Ottawa Scale (NOS) (Wells *et al.,* 2014), which consists of eight items pertaining to selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study), comparability (comparability of cohorts on the basis of the design or analysis), and outcome (assessment of outcome, sufficient duration of follow-up, adequacy of follow-up). We modified the NOS for cross-sectional studies to include the following five items: representativeness of the exposed cohort, ascertainment of exposure, comparability of cohorts on the basis of the design or analysis, assessment of outcome, adequacy of response rate (Higgins and Thompson, 2002; Fnais *et al.,* 2014; Wells *et al.,* 2014).

Synthesis of results

We described the results narratively and conducted a meta-analysis using a random effects model, as statistical heterogeneity was expected across the studies. For the meta-analysis, we combined the extracted data from the studies to calculate a pooled estimate of the proportion of abnormal EEG in each population along with the corresponding 95% confidence interval (CI) based on a normal distribution (Higgins and Thompson, 2002). We assessed statistical heterogeneity using the I^2 statistic and depicted the studies in a forest plot to examine heterogeneity visually. All analyses were conducted using the R statistical program (R Development Core Team 2010) with the metafor package (Viechtbauer, 2010).

Results

Study selection and study characteristics

The literature search yielded 10,223 citations. After excluding 255 duplicates, 9,968 studies were screened for eligibility. A total of 211 potentially relevant full-text articles met a preliminary screen for epilepsy, EEG examinations, and mention of relatives. From these, 191 were excluded because they clearly did not include asymptomatic relatives (86), did not study the epilepsies in question or their EEGs (77), did not provide primary data (10), or were only abstracts or could not be located (18). A total of 15 studies remained. These had been conducted in Germany (Tsuboi and Christian, 1973; Doose *et al.,* 1973; Degen and Degen, 1992; Wandschneider *et al.,* 2010), the United States (Alonso *et al.,* 2005a, 2005b; Bali *et al.,* 2007), Turkey (Atakli *et al.,* 1999; Akgun *et al.,* 2009), Italy (Serra *et al.,* 2001;

Verrotti *et al.,* 2013), India (Jayalakshmi *et al.,* 2006), Sweden (Heijbel *et al.,* 1975), and Canada (Metrakos and Metrakos, 1961a) and published between 1961 and 2013. EEG recording times ranged from 20 to 60 minutes with varying capture of sleep.

Of the 15 studies, 11 were included in the meta-analysis. The design of two studies by Alonso and colleagues (cohort) differed from all the others (cross-sectional) and thus could not be combined with the others in the meta-analysis. Their results are nevertheless shown (*table 1)*, as they represent valuable relevant data. The two other studies not included in the meta-analysis are those of Metrakos and Metrakos (1961a) and Tsuboi and Christian (1973) (*table 1*), both of which did not formally specify that the relatives studied were asymptomatic. However, this information was gleaned from details in their papers, including their selection of any-comer (and not multiplex) patients, and the sheer number of families and relatives studied. The vast majority of these families and relatives, given what we know of these epilepsies, would be expected to be asymptomatic. As such, we conducted a sensitivity analysis including these two studies in the meta-analysis, in addition to the 11 studies that were previously combined.

Juvenile Myoclonic Epilepsy

Six studies specified that their epileptic patients had JME and reported on EEG abnormalities in the patients and their relatives (Tsuboi and Christian, 1973; Atakli *et al.,* 1999; Alonso *et al.,* 2005a; Jayalakshmi *et al.,* 2006; Akgun *et al.,* 2009; Wandschneider *et al.,* 2010). Two of these studies were not included in the meta-analysis. One (Alonso *et al.,* 2005a) was not included because it differed in design (cohort) from the other studies (cross-sectional). This study also did not specify the degree of relatedness between relatives and patients. Notwithstanding, the results of this study are tabulated: there were 186 JME patients and 1,756 relatives, of whom 24 (1%) had EEG findings that were considered abnormal. These abnormalities were: generalized >3-Hz spike or polyspikes and waves (SPSW) in 15 subjects, 3-Hz spike waves (SW) in three, bursts of focal or diffuse slowing in four, and bursts of focal or diffuse sharp waves in two (*table 1*). The study by Tsuboi *et al*. was the other JME study not included in the meta-analysis, because it did not specify whether the relatives studied were clinically affected or not. There were 136 JME patients and 370 first-degree relatives of whom 262 (*i.e*. 71%) had EEG findings that were considered potentially abnormal. These were SPSW in 57 relatives and paroxysmal sharp waves in the remaining 205 (*table 1*).

The remaining four JME studies were all cross-sectional and specified the relatives as first-degree and unaffected (Atakli *et al.,* 1999; Jayalakshmi *et al.,* 2006; Akgun *et al.,* 2009; Wandschneier *et al.,* 2010). There was a total of 108 JME patients in these studies and 206 first-degree relatives, of whom 39 (19%) had EEG abnormalities. These were SPSW in 18, 'theta waves' or intermittent generalized or paroxysmal slowing in 13, photoparoxysmal response (PPR) in three, centrotemporal spikes in three, bifrontal sharp waves in one, and single spikes in one (*table 1*).

Childhood Absence Epilepsy

Four studies looked at CAE (Metrakos and Metrakos, 1961b; Doose *et al.,* 1973; Degen and Degen, 1990a; Alonso *et al.,* 2005b). Two (Metrakos and Metrakos, 1961b; Alonso *et al.,* 2005b) were not included in the meta-analysis. The Metrakos and Metrakos (1961b) study did not specify the affected status of the relatives. The patients had 'centrencephalic' epilepsy, and were likely to be predominantly a mix of CAE and JME cases. There were 211 patients and 418 relatives. Of the latter, 145 had EEG abnormalities (35%), seven 3-Hz SW, and 138 with an unspecified mix of what were considered abnormalities (*table 1*). The study by Alonso *et al*. (2005b) was not included in the meta-analysis because of its different (cohort) design from the other studies (cross-sectional). In addition, their CAE cases were ones that evolved into JME and thus diverge from the common remitting CAE phenotype. There were 45 patients and 541 relatives of whom 38 (7%) had EEG abnormalities, which included three SPSW, 15 3-Hz SW, and the remainder, a mix of slow waves and isolated generalized or focal spikes (*table 1*).

The remaining two studies (Doose *et al.,* 1973; Degen and Degen, 1990a) were included in the meta-analysis and together encompassed 274 patients and 292 siblings of whom 104 (36%) were considered to have EEG abnormalities. Of these abnormalities, only 12 were 3-Hz SW and the remainder were a mix of runs of focal or generalized slow waves or sharp waves or spikes (*table 1*).

Rolandic Epilepsy

Five RE studies (Heijbel *et al.,* 1975; Degen and Degen, 1990b; Serra *et al.,* 2001; Bali *et al.,* 2007; Verrotti *et al.,* 2013) reported on EEG in unaffected relatives. All could be included in the meta-analysis. Overall, 275 relatives were studied of whom 82 (30%) had EEG abnormalities (*table 1*).

Meta-analysis

Eleven studies (Doose *et al.,* 1973; Heijbel *et al.,* 1975; Degen and Degen, 1990a; Degen and Degen, 1990b; Atakli *et al.,* 1999; Serra *et al.,* 2001; Jayalakshmi *et al.,* 2006; Bali *et al.,* 2007; Akgun *et al.,* 2009; Wandschneider

Table 1. Numbers and characteristics of abnormal EEGs in relatives of patients with JME, CAE and RE.

Author	Epilepsy	Number of patients	Average age of patients	Number of relatives studied*	Average age of relatives	Number and percent of relatives with abnormal EEGs	Number of relatives with SPSW	Number of relatives with 3-Hz SW	Number of relatives with CTS	Number of relatives with runs of focal or generalized slow waves 'theta waves'	Number of relatives with focal or generalized sharp waves or spikes
Alonso *et al.*, 2005a	JME	186	25.9	1756 (relatedness NS)	NS	24 (1%)	15 (1%)	3 (0.17%)	-	4 (0.22%)	2 (0.11%)
Atakli *et al.*, 1999	JME	37	20.33	48 (siblings)	24.17	13 (27%)	10 (20%) (5 PSW and 5 single-spike-wave)	-	3 (6%)	-	-
Akgun *et al.*, 2009	JME	21	23.9	21 (siblings)	22.8	7 (33%)	1 (5%)	-	-	6 (29%)	-
Jayalakshmi *et al.*, 2006	JME	31	22	116 (1st degree NOS)	31.1	15 (13%)	9 (8%) (2 of which were photoparoxysmal)	-	-	6 (5%)	-
Tsuboi and Christian, 1973	JME	136	NS	370 128 (siblings) 128 (parents) 114 (offspring) Relatives' affected status NS	NS	262 (71%) Siblings (*n*=87) (68%) Parents (*n*=73) (57%) Offspring (*n*=102) (89%)	57 (15%) Siblings (*n*=17) (13%) Parents (*n*=12) (9%) Offspring (*n*=28) (25%)	-	-	-	205 (55%) Siblings (*n*=70) (54%) Parents (*n*=61) (48%) Offspring (*n*=74) (65%)
Wandschneider *et al.*, 2010	JME	19	25.5	21 (siblings)	25.1	4 (19%)	1 (5%) photoparoxysmal 1 (5%) bifrontal sharp waves rather than strictly SPSW	-	-	1 (5%)	1 (5%)

Table 1. Numbers and characteristics of abnormal EEGs in relatives of patients with JME, CAE and RE (*Continued*).

Author	Epilepsy	Number of patients	Average age of patients	Number of relatives studied*	Average age of relatives	Number and percent of relatives with abnormal EEGs	Number of relatives with SPSW	Number of relatives with 3-Hz SW	Number of relatives with CTS	Number of relatives with runs of focal or generalized slow waves 'theta waves'	Number of relatives with focal or generalized sharp waves or spikes
Metrakos and Metrakos, 1961a	Centrence-phalic epilepsy (likely a combination of CAE and JME)	211	NS	418 223 (siblings) 195 (parents) Relatives' affected status NS	NS	145 (35%) Siblings (*n*=119) (53%) Parents (*n*=26) (13%)	-	7 (2%) Siblings (*n*=5) (2%) Parents (*n*=2) (1%)	-	138 (33%) (NS mix of focal or generalized slow waves or sharps or spikes) Siblings (*n*=114) (51%) Parents (*n*= 24) (12%)	
Alonso *et al.*, 2005b	CAE evolving to JME	45	6.9	541 (relatedness NS)	NS	38 (7%)	3 (0.55%)	15 (3%)	-	9 (2%)	11 (2%)
Degen and Degen, 1990a	CAE	22	NS	50 (siblings)	NS	36 (72%)	-	-	-	36 (72%) (NS mix of focal or generalized slow waves or sharps or spikes)	
Doose *et al.*, 1973	CAE	252	NS	242 (siblings)	NS	68 (28%)	-	12 (5%)	-	56 (23%) (specified [see reference] mix of EEGs considered abnormal due to runs of slow 'theta' waves with or without additional presence of spikes)	
Bali *et al.*, 2007	RE	23	NS	30 (siblings)	10.3	13 (43%)	-	2 (7%) (these two also had CTS)	13 (43%)	-	-
Degen and Degen, 1990b	RE	43	NS	64 (siblings)	NS	24 (38%)	-	-	2 (3%)	21 (33%) (the abnormality in these 21 is described as mainly hypnagogic or hypnapompic 2.5-4-Hz generalized spikes One child had both typical CTS and this abnormality)	

Table 1. Numbers and characteristics of abnormal EEGs in relatives of patients with JME, CAE and RE (*Continued*).

Author	Epilepsy	Number of patients	Average age of patients	Number of relatives studied*	Average age of relatives	Number and percent of relatives with abnormal EEGs	Number of relatives with SPSW	Number of relatives with 3-Hz SW	Number of relatives with CTS	Number of relatives with runs of focal or generalized slow waves 'theta waves'	Number of relatives with focal or generalized sharp waves or spikes
Verrotti *et al.*, 2013	RE	9	7.8	8 (siblings)	7.7	2 (25%)	-	-	2 (25%)	-	-
Serra *et al.*, 2001	RE	0	NS	114 41 (siblings) 73 (parents)	Siblings 2-16 Parents NS	31 (27%) Siblings (*n*=14) (34%) Parents (*n*=17) (23%)	-	-	14 (34%) (all siblings)	17 (23%) (all parents; specific description: sharp 'theta' waves, uni- or bilateral)	-
Heijbel *et al.*, 1975	RE	19	9.1	59 27 (siblings) 32 (parents)	Siblings 10.3 Parents NS	12 (20%) Siblings (*n*=6) (22%) Parents (*n*=6) (18%)	-	-	7 (12%) Siblings (*n*=6) (22%) Parents (*n*=1) (3%)	5 (15%) (all parents)	-

*Relatives are unaffected siblings except where indicated; JME: juvenile myoclonic epilepsy, CAE: childhood absence epilepsy, NS: not specified, NOS: not otherwise specified; SPSW: generalized >3-Hz spike or polyspike-and-slow waves, 3-Hz SW: 3-Hz spike-and-slow waves, CTS: centrotemporal sharp or spike waves.

et al., 2010; Verrotti *et al.,* 2013) were included in the meta-analysis. The pooled prevalence of abnormal EEG in asymptomatic relatives of patients with JME, CAE and RE was 30.51% (95% CI: 20.70, 40.33; I^2=87.9%). Separating according to epilepsy syndromes showed the highest prevalence in CAE (41.82%), followed by RE (30.42%) and JME (21.10%). Grouping based on asymptomatic siblings only (*i.e.* excluding other relatives), the overall prevalence was 34.76% (95% CI: 24.79, 44.73; I^2=79.61%), and by syndromes: CAE 41.8%, RE 33.76%, and JME 26.57% (*tabulated and detailed in supplementary table 1 and figure 1*).

Grouping according to characteristic EEG abnormalities (SPSW, 3-Hz SW or CTS) or 'other', the pooled prevalences in asymptomatic relatives were: SPSW 7.14%, 3-Hz SW 5.40%, CTS 14.39%, 'other' waves 23.56%, and PPR 9.04%. Restricting to siblings alone: SPSW 7.74%, 3-Hz SW 5.40%, CTS 25.55%, and PPR 14.13% (*supplementary table 2 and figures 2-5*).

Sensitivity analysis

The sensitivity analysis included the 11 studies as well as the results reported in the large Metrakos and Metrakos (1961a) and Tsuboi and Christian (1973) studies. The pooled prevalence of abnormal EEG in asymptomatic relatives was 37.15% (95% CI: 25.53, 48.76; I^2=95.03%). In this case, the highest prevalence was in relatives of patients with JME (42.41%) followed by CAE (38.43%), and RE (28.55%). When only siblings were considered, the pooled prevalence was 41.80% (95% CI: 31.24, 52.35; I^2=88.78%), divided between siblings of JME (43.66%), RE (33.76%), and CAE (46.41%) (*supplementary figure 6*).

The pooled prevalence for SPSW was 10.97%, for 3-Hz SW 3.57%, and CTS 14.39%. The pooled prevalence for 'other' abnormalities was 31% and for PPR 9.04%. Considering only siblings, the pooled prevalences were SPSW 10.97%, 3-Hz SW 4.09%, CTS 25.55%, and PPR 14.13% (*supplementary figures 7-10*). Finally, the pooled prevalence of abnormal EEG in parents was 28.79%.

Quality of included studies

The quality of the included studies is provided in the *supplementary material*. More than 50% of the included studies failed to ascertain exposure adequately.

Discussion

The 15 studies reviewed in this work comprised a total of 4,912 subjects including 1,054 epileptic patients and 3,858 relatives; large numbers that would be difficult to obtain in any one independent study. The highest percentages of 'abnormal' EEG in asymptomatic relatives are obtained by combining all 15 studies (sensitivity analysis) and focusing on siblings alone, which is important given the age dependency of the syndromes studied. The pooled number in that case is 42% distributed as 44% for JME, 34% for RE, and 47% for CAE. Accounting for missed abnormalities due to the short length of routine EEGs, the numbers are sufficiently close to 50% to suggest that EEG abnormalities in these common syndromes are autosomal dominant traits, as proposed by the authors of the earliest and largest studies (Metrakos and Metrakos, 1961a; Doose *et al.,* 1973; Tsuboi and Christian, 1973; Heijbel *et al.,* 1975). If these syndromes indeed include dominant Mendelian contributions to their EEG endophenotypes, the locus could possibly be shared across two (*e.g.* JME and CAE) or more of the syndromes, or be different in each. But even in the latter case, if each of JME, CAE and RE has an underlying dominant locus, it would be surprising that the mutations in these loci have not come to light in the current genomic era, in which many hundreds of these patients have had whole-exome or genome sequencing. It is possible that these loci are in yet to be clarified non-coding genomic regions, or that in each case, there is wide genetic heterogeneity with numerous loci separately acting as a dominant predisposition for the EEG trait in separate families.

However, when certain studies are excluded, the numbers change. For JME, if one excludes the large Tsuboi and Christian (1973) study (506 subjects) on the grounds that the authors never quite specified whether the relatives were clinically affected or not, the prevalence of EEG 'abnormality' drops to close to 27%. Such a number, close to 25%, might suggest that the EEG endophenotype of JME is an autosomal recessive trait (or a series of separate recessive traits in different families). But if one looks closely at what is meant by EEG abnormalities in the different studies, the picture becomes even blurrier. For JME, in the Atakli *et al.* (1999) study, 20% of siblings (10 of 48 siblings studied) had SPSW, a number that approaches the overall ~25% figure. However, in the Akgun *et al.* (2009) study, the percentage for SPSW was only 5% (one of 21 siblings studied), while another 29% of siblings had 'theta' waves (*table 1*). What are the latter? They are bursts of slowing that are not quite epileptiform (*i.e.* lack spikes), but are unexpected enough to have been labelled as an abnormality, or potential abnormality. This raises a major question. To what extent are such irregularities, which in the present age, for clinical purposes, would not be considered epileptiform actual subtle endophenotypes of potential relevance towards understanding the genetic underpinnings of JME?

The above issues are even more pronounced in CAE. Here, the meta-analysis provides a figure of 42% and the sensitivity analysis 46%. However, if one looks at the numbers of siblings of CAE patients who have 3-Hz SW, it is no more than 5%, the remainder of the percentage being made up of 'theta' waves and other non-specific abnormalities/irregularities (*table 1*). Again, to what extent the latter constitute incomplete parts of the syndrome remains unknown.

The situation is slightly clearer in RE. The percentages of EEG abnormalities in unaffected siblings in the five RE studies range from 22 to 43% (*table 1*). In some studies, the entire percentage is composed of the syndrome-specific CTS trait, while in the others, substantial portions of the percentages are derived from non-specific abnormalities such as 'theta' waves and generalized sharp waves (*table 1*). In the large Degen and Degen (1990b) study (64 siblings studied), the vast majority of abnormalities are hypnagogic or hypnapompic 2.5-4-Hz generalized spikes. This abnormality is not commonly discussed in RE, especially in clinical practice, where the CTS is considered the defining feature. However, it has been reported as a particularity of RE by other authors. Not all the RE studies reviewed in the present paper included sleep EEG recording, and none performed overnight EEGs. As such, it is likely that the percentages of CTS or abnormalities related to progression into or out of sleep are underestimated, suggesting a high EEG endophenotype(s) heritability in RE.

The reported incidence of EEG abnormalities in the general non-epileptic population varies drastically from les than 0·1% to 10% (Gibbs *et al.,* 1943; Cavazzuti *et al.,* 1980). This 100-fold range is emblematic of the same issue as in the above studies of epileptic relatives, namely of the question as to what is meant by 'abnormal'. Is uncommon 'abnormal', and by what fold should the frequency of a finding be higher in epileptic versus non-epileptic families to be considered 'abnormal'? Clearly, the EEG in epileptic families is substantially 'different' to that in the general population, with rates of 'abnormality' ranging from ~25 to 50% in the former versus a maximum of 10% in the latter, and therefore there is important information on the genetics of epilepsy within the EEG. A trait occurring at a frequency of 25% in siblings would likely be considered to be inherited in an autosomal recessive manner, and at 50% in an autosomal dominant, Mendelian manner. It is possible that 'defects' in a single gene inherited in a recessive or dominant fashion underlie the constellation of EEG 'abnormalities' in each of the above epilepsies (*i.e.* one gene for RE-associated EEG 'abnormalities' and one each for JME and CAE related-'abnormalities'). It is also possible that defects in any number of single genes underlie the set of 'abnormalities' associated with each syndrome (in other words, that the EEG trait is inherited in a Mendelian fashion but with genetic heterogeneity, *i.e.* different JME families with, for example, segregating 'defects' in different single genes). Another possibility is that variants in different genes underlie different EEG 'abnormalities'. Yet another is that variants in multiple genes summate to result in a range of 'abnormality' from simply 'uncommon' features (*e.g.* 'theta waves') to frank epileptiform spike waves. However, it is important to note that a multiplicity of genes involved cannot be very large, because otherwise rates in the 'Mendelian' range of ~25 to 50% would not be observed.

Clearly, much work lies ahead, but the genetic tools that were not available in the previous century of EEG, now are. Future studies should carefully describe and correlate EEG irregularities of age-appropriate relatives of epileptic patients with their genome sequences. JME, CAE and RE families are highly likely to yield a relatively small number of genes that are important for understanding why and how otherwise, by and large, normally developed brains seize.

Key points

- EEG 'abnormalities'/variants in JME, CAE and RE extend beyond their signature EEG traits and are shared with the general population.
- EEG 'abnormalities'/variants in JME, CAE and RE are genetically less complex than the clinical syndromes and are useful endophenotypes.
- Prevalences of EEG 'abnormalities'/variants in JME, CAE and RE (21%, 42% and 33%, respectively) are within the Mendelian inheritance range.
- EEG endophenotypes of JME, CAE and RE should facilitate identification of genes contributing to hypersynchrony in these common epilepsies.

Supplementary data.

Summary didactic slides and supplementary material are available on the www.epilepticdisorders.com website.

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References

Akgun Y, Soysal A, Atakli D, *et al*. Cortical excitability in juvenile myoclonic epileptic patients and their asymptomatic siblings: a transcranial magnetic stimulation study. *Seizure* 2009; 18: 387-91.

Alonso ME, Medina MT, Martínez-Juárez IE, *et al*. Familial juvenile myoclonic epilepsy. *Adv Neurol* 2005a; 95: 227-43.

Alonso ME, Medina MT, Martínez-Juárez IE, *et al*. Familial juvenile myoclonic epilepsy. *Adv Neurol* 2005b; 95: 227-43.

Anderman E, Metrakos JD. EEG studies of relatives of probands with focal epilepsy who have been treated surgically. *Epilepsia* 1969; 10: 415.

Atakli D, Soysal A, Atay T, *et al*. Somatosensory evoked potentials and EEG findings in siblings of juvenile myoclonic epilepsy patients. *Epileptic Disord* 1999; 1: 173-7.

Avanzini G, Noebels JL. *Genetics of epilepsy and genetic epilepsies*. Montrouge: John Libbey Eurotext, 2009.

Bali B, Kull LL, Strug LJ, *et al*. Autosomal dominant inheritance of centrotemporal sharp waves in rolandic epilepsy families. *Epilepsia* 2007; 48: 2266-72.

Berg AT, Millichap JJ. The 2010 revised classification of seizures and epilepsy. *Continuum* 2013; 19: 571-97.

Bray PF, Wiser WC. Evidence for a genetic etiology of temporal-central abnormalities in focal epilepsy. *N Engl J Med* 1964; 271: 926-33.

Cavazzuti GB, Capella L, Nalin A. Longitudinal study of epileptiform EEG patterns in normal children. *Epilepsia* 1980; 21: 43-55.

Camfield CS, Striano P, Camfield PR. Epidemiology of juvenile myoclonic epilepsy. *Epilepsy Behav* 2013; 28: S2-7.

Degen R, Degen HE, Roth C. Some genetic aspects of idiopathic and symptomatic absence seizures: waking and sleep EEGS in siblings. *Epilepsia* 1990a; 31: 784-94.

Degen R, Degen HE. Some genetic aspects of rolandic epilepsy: waking and sleep EEG in siblings. *Epilepsy* 1990b; 31: 795-801.

Degen R, Degen HE. Contribution to the genetics of rolandic epilepsy: waking and sleep EEGs in siblings. *Epilepsy* 1992; 6: 49-52.

Delgado-Escueta AV. Advances in genetics of juvenile myoclonic epilepsies. *Epilepsy Curr* 2007; 7: 61-7.

Doose H, Gerken H, Horstmann T, *et al*. Genetic factors in spike-wave absences. *Epilepsia* 1973; 14: 57-75.

Fnais N, Soobiah C, Chen MH, *et al*. Harassment and discrimination in medical training: a systematic review and meta-analysis. *Acad Med* 2014; 89: 817-21.

Gibbs FA, Gibbs EL, Lennox WG. Electroencephalographic classification of epileptic patients and control subjects. *Arch Neurol Psychiatry* 1943; 50: 111-28.

Heijbel J, Blom S, Rasmuson M. Benign epilepsy of childhood with centrotemporal EEG foci: a genetic study. *Epilepsia* 1975; 16: 285-93.

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539-58.

Jayalakshmi SS, Mohandas S, Sailaja S, *et al*. Clinical and electroencephalographic study of first-degree relatives and probands with juvenile myoclonic epilepsy. *Seizure* 2006; 15: 177-83.

McGowan J, Sampson M, Lefebvre C. An evidence based checklist for the peer review of electronic search strategies (PRESS EBC). *Evid Based Libr Inf Pract* 2010; 5: 149-54.

Metrakos K, Metrakos JD. Genetics of convulsive disorders. II. Genetic and electroencephalographic studies in centrencephalic epilepsy. *Neurology* 1961a; 11: 474-83.

Metrakos K, Metrakos JD. Is the centrencephalic EEG inherited as a dominant? *Electroencephalogr Clin Neurophysiol* 1961b; 13: 289.

Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1.

Pal DK, Ferrie C, Addis L, *et al*. Idiopathic focal epilepsies: "the lost tribe". *Epileptic Disord* 2016; 18: 1-37.

Panayiotopoulos CP. *A clinical guide to epileptic syndromes and their treatment*. New York: Springer Publishing, 2010.

Panayiotopoulos CP, Bureau M, Caraballo RH, *et al*. Idiopathic focal epilepsies in childhood. In*: Epileptic syndromes in infancy, childhood and adolescence*. 5th Ed. Bureau M, Genton P, Dravet C, *et al*. Montrouge, France: John Libbey Eurotext, 2012.

Penfield W. Epileptic automatism and centrencephalic integrating system. *Res Publ Assoc Res Nerv Ment Dis* 1952; 30: 513-28.

Serra D, Congiu R, Minafra L, *et al*. EEG trait analysis in siblings of patients with benign rolandic epilepsy. *Bollettino-Lega Italiana Contro L'Epilessia* 2001; 113-4: 267-8.

Tsuboi T, Christian W. On the genetics of the primary generalized epilepsy with sporadic myoclonias of impulsive petit mal type. *Humangenetik* 1973; 19: 155-82.

Valdamudi L, Kjeldsen MJ, Corey LA, *et al*. Analyzing the etiology of benign rolandic epilepsy: a multicenter twin collaboration. *Epilepsia* 2006; 47: 550-5.

Verrotti A, Matricardi S, Di Giacomo DL, *et al*. Neuropsychological impairment in children with rolandic epilepsy and in their siblings. *Epilepsy Behav* 2013; 28: 108-12.

Verrotti A, Casciato S, Spalice A, *et al*. Coexistence of childhood absence epilepsy and benign epilepsy with centrotemporal spikes: a case series. *Eur J Paediatr Neurol* 2017; 21: 570-5.

Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; 36: 1-48.

Wandschneider B, Kopp UA, Kliegel M, *et al*. Prospective memory in patients with juvenile myoclonic epilepsy and their healthy siblings. *Neurology* 2010; 75: 2161-7.

Wells GA, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2014.

TEST YOURSELF

(1) What is the approximate reported prevalence of EEG abnormalities in first-degree relatives of patients with juvenile myoclonic, childhood absence and Rolandic epilepsies?
A. 0-1%
B. 10-20%
C. 20-50%

(2) Are the reported EEG abnormalities in first-degree relatives of patients with juvenile myoclonic, childhood absence and Rolandic epilepsies true abnormalities?

(3) Are EEG changes found in relatives of patients with juvenile myoclonic, childhood absence and Rolandic epilepsies developmental stage specific?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Appendix 1. Quality of included studies.

First author	Year	Representativeness of the exposed cohort	Ascertainment of exposure	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Adequacy of response rate
Alonso	2005	B	A	C	A	A
Atakli	1999	B	A	A	D	A
Akgun	2009	B	A	A	D	A
Jayalakshmi	2006	B	D	C	A	A
Tsuboi	1973	A	C	A	B	A
Wandschneider	2010	C	D	A	D	A
Metrakos	1961	A	A	B	A	
Degen	1990	B	D	C	D	A
Doose	1973	C	D	B	A	A
Bali	2007	B	A	A	A	A
Degen	1990	B	D	C	D	A
Verrotti	2013	B	D	A	A	B
Serra	2001	D	D	C	D	D
Heijbel	1975	A	A	C	B	A

Newcastle Ottawa Scale

Selection

1) Representativeness of the exposed cohort
   a) Truly representative of the average individual
   b) Somewhat representative of the average individual
   c) Selected group of users
   d) No description of the derivation of the cohort

2) Ascertainment of exposure
   a) Secure record (*e.g.* surgical records)
   b) Structured interview
   c) Written self report
   d) No description

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) Study controls for age or gender
   b) Study controls for any additional factor (*e.g.* body mass index, comorbidity)
   c) No control

Outcome

1) Assessment of outcome
   a) Independent blind assessment
   b) Record linkage
   c) Self report
   d) No description

2) Adequacy of response rate
   a) All subjects accounted for
   b) Subjects lost unlikely to introduce bias - small number lost (<10%)
   c) Subject loss >10%
   d) No statement

Original article

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DEPDC5 mutation and familial focal epilepsy with variable foci: genotype and phenotype of a family*

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ABSTRACT – *Aims.* Familial focal epilepsy with variable foci is a relatively rare autosomal disease with an unclear incidence, which is characterized by focal seizures arising from different cortical regions in different family members.
Methods. We describe three members of a two-generation Argentine family with familial focal epilepsy with variable foci syndrome and a *DEPDC5* gene mutation.
Results. The mean onset age was nine years old. The father experienced episodes with occipital semiology and both siblings exhibited frontal lobe seizures. Their neurological examination and neuroimaging studies were normal. All three patients are currently seizure-free, in spite of initially experiencing frequent seizures. Complete exome sequencing revealed a new *DEPDC5* gene mutation (NM_001242896: c.4718T>C; p.L1573P).
Conclusions. This study of a family with clinical characteristics that met all the criteria for familial focal epilepsy with variable foci demonstrates the usefulness of exome sequencing as a diagnostic tool. [*Published with video sequence on www.epilepticdisorders.com*]

Key words: familial focal epilepsy with variable foci, *DEPDC5*, semiology, occipital seizure semiology, frontal seizures

VIDEO ONLINE

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Familial focal epilepsy with variable foci (FFEVF) is included among epilepsy syndromes of genetic origin (Dibbens *et al*., 2013). It was first reported in an Australian family in 1998 by Ingrid Scheffer (Scheffer *et al*., 1998), who initially associated it with chromosome 2. Later, in 1999, it was reported in two Canadian families, suggesting linkage to chromosome 22 and showing probable genetic heterogeneity (Xiong *et al*., 1999; Klein *et al*., 2012).

FFEVF is characterized by a wide range of onset age, with an average of 13 years. Epileptic seizures may take place during daytime, night-time, or both, and they frequently originate in the frontal or temporal lobes, although they may occasionally be of occipital or parietal origin (Morales-Corraliza *et al*., 2010; Ishida *et al*., 2013).

Most patients with this syndrome have a normal neurological examination, although there have been isolated reports in which autistic spectrum disorder, psychiatric disorders, and intellectual disability were present as comorbidities (Klein *et al*., 2012).

Neuroimaging studies are also often normal and most patients show an excellent response to antiepileptic drugs (AEDs) (Morales-Corraliza *et al*., 2010).

DEPDC5 is an important gene in focal epilepsy, especially in patients with a positive family history (Tsai *et al*., 2017). Mutations in this gene have been identified in more than 8% of families with FFEVF, causing activation of the downstream mTOR pathway (Weckhuysen *et al*., 2016). Reports suggest that *DEPDC5* is not only the most common gene associated with familial focal epilepsy but also could be a significant gene involved in sporadic focal epilepsy (Tsai *et al*., 2017). *DEPDC5* mutation has also been linked to an increased risk of sudden unexpected death in epilepsy (SUDEP), as it is described in one family with *DEPDC5*-related epilepsy which included two family members with SUDEP (Nascimento *et al*., 2015). The significance of *DEPDC5* mutations in patients with sporadic focal epilepsy has yet to be characterized. Here, we describe an Argentine family meeting all the criteria for FFEVF with *DEPDC5* gene mutation.

Patients and methods

Clinical studies

We studied two generations of a non-consanguineous family. All three affected members had focal epilepsy: two had frontal epilepsy and one had occipital epilepsy.

A 32-channel video-EEG recording was carried out for the proband and an EEG for the other two affected members of the family.

Informed consent was obtained from each participant family member or, in the case of the two children, their legal guardian.

Exome sequencing and Sanger sequencing

Whole-exome sequencing (WES) was performed on purified DNA samples from the patient using the Agilent SureSelect Human All Exon V5 Kit (Agilent Technologies, Santa Clara, CA) with an Illumina sequencing system. Bioinformatic analysis was performed following procedures described by our group (Koile *et al*., 2018). The identified variant in *DEPDC5* was validated by Sanger sequencing following standard procedures. The presence of this variant was investigated in affected members of the family.

Clinical description

The proband was a 10-year-old male who experienced his first seizure at the age of eight. At first, episodes occurred more than 20 times per day, during both sleep and awake states. The episodes were characterized by eye opening, followed by ocular and cephalic deviation to the left, associated with monosyllabic vocalization. He then presented right hand automatisms associated with left upper limb flexion. During some episodes, he extended the lower limbs and flexed the upper limbs, as if he was stretching out. These events were occasionally associated with smiling (mainly while awake).

The patient was initially treated with valproic acid, then clobazam and topiramate. While receiving the latter, he experienced visual hallucinations and hyperexcitability. An increase in seizure frequency was observed when levetiracetam was added to this treatment regimen. He was then started on carbamazepine and became seizure-free.

A 24-hour video telemetry recording revealed seven events. The ictal EEG showed sharp rhythmic spikes in the right fronto-central region, followed by fast low-voltage activity and, four or five seconds later, a sharp-and-slow-wave bilateral fronto-central temporal activity (*figure 1, video sequence*). The interictal EEG showed frequent spike-and-sharp-wave discharges from the right fronto-central temporal region (*figure 2*). These observations led to the hypothesis that the episodes originated in the right fronto-temporal area. A 3-tesla MRI brain scan was performed showing no abnormalities.

The neuropsychological assessment showed normal intellectual performance with language difficulties and attention deficit.

The proband's father presented with episodes with a semiology suggesting occipital lobe involvement;

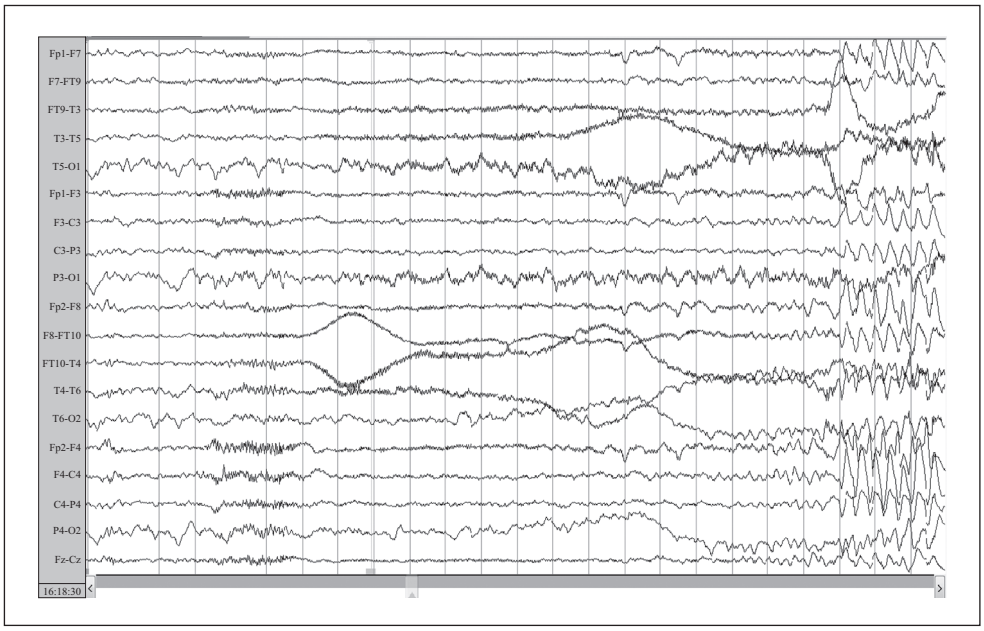

Figure 1. Ictal EEG: bilateral montage showing fronto-central fast activity (27-29-Hz) followed by a diffuse low-voltage fast activity starting three seconds before the clinical onset. Twelve seconds later, a slow fronto-temporal (4-5-Hz) rhythmic activity evolves.

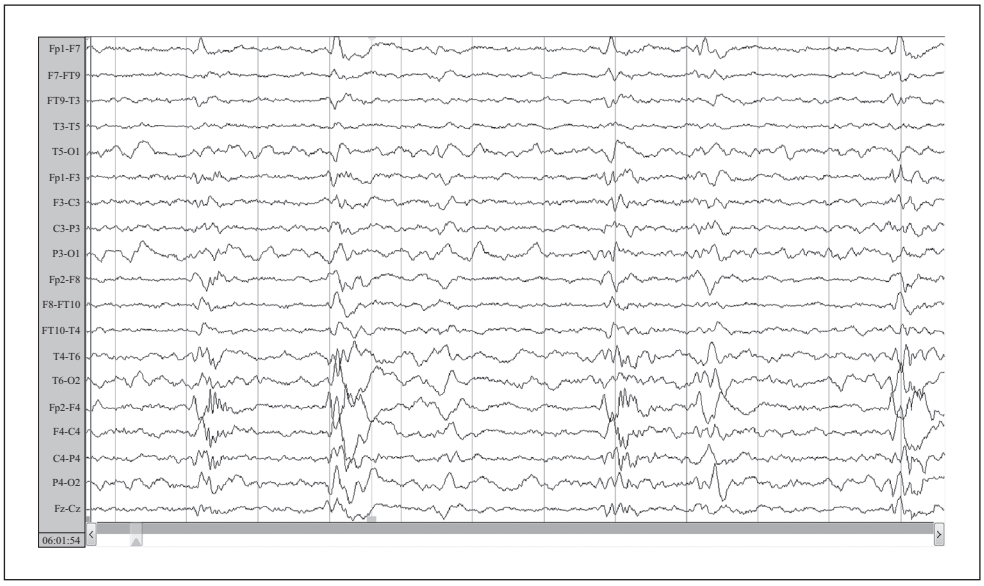

Figure 2. Interictal EEG showing frequent right fronto-temporal polyspikes and sharp waves.

he described elementary hallucinations characterized by flashes of lights. He has been seizure-free for five years, receiving valproic acid. His EEG and MRI showed no abnormalities.

The proband's sister had seizures that exhibited a frontal lobe semiology, characterized by daytime asymmetric tonic posturing of her extremities, evolving into a generalized tonic-clonic seizure. She had a good response to carbamazepine and has been seizure-free for the last three years. Her MRI was normal and EEG showed bilateral anterior sharp waves.

The diagnostic hypothesis was FFEVF due to the epileptic family history.

Genetic investigation: exome sequencing

WES, performed on purified DNA samples from the patient using the Agilent SureSelect Human All Exon

V5 Kit (Agilent Technologies, Santa Clara, CA) with an Illumina sequencing system, led to identification of a likely pathogenic novel mutation in the *DEPDC5* gene (NM_001242896: c.4718T>C; p.L1573P). Segregation analysis by Sanger sequencing confirmed the presence of this variant in the proband and in the other affected relatives.

Discussion

The main familial focal epilepsies of known genetic origin with specific age-related and electroclinical characteristics include: autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), familial mesial temporal lobe epilepsy (FMTLE), familial lateral temporal lobe epilepsy TLE (FLTLE) or autosomal dominant partial epilepsy with auditory features (ADPEAF), and FFEVF. These familial syndromes show phenotypic overlap and small families may be initially labelled with ADNFLE or FLTLE/ADPEAF, and later recognized to have FFEVF when new affected members are identified (Dibbens *et al*., 2013).

FFEVF is a relatively rare autosomal dominant disease with an unclear incidence, characterized by focal seizures arising from different cortical regions in different family members (Klein *et al*., 2012). Reports of FFEVF describe a mean age at onset of 13 years with a large range extending from one month to 52 years. In our study, the proband had his first seizure at the age of eight, the father at ten, and the sibling at age nine.

Patients with FFEVF usually have normal neurological examination and normal neuroimaging (Klein *et al*., 2012). However, based on studies published in 2015, patients with FFEVF and focal neurological deficit (hemiparesis) were reported, together with neuroimaging findings of focal cortical dysplasia. The response to AEDs is variable. While some individuals respond well to first-line AEDs, others are more refractory to treatment. All members of the study family had a normal neurological examination and became seizure-free on AEDs.

ADNFLE (involving *CHRNA4*, *CHRNA2*, *CHRNB2*, and *KCNT1* gene mutations) is characterized by short nocturnal episodes, usually presenting as a cluster with hypermotor seizures, which are also commonly observed in FFEVF (Callenbach *et al*., 2003; Dibbens *et al*., 2013; Ishida *et al*., 2013). As a consequence, the latter is often misdiagnosed as the former, although episodes during daytime are rare in this epilepsy type. The patient we studied presented with focal episodes with and without loss of conscience, which took place during the day and the night, initially with multiple daily seizures. Therefore, video telemetry monitoring was performed, allowing us to hypothesize a frontotemporal epileptogenic origin.

In contrast to other FFEVF families which include individuals with nocturnal frontal lobe epilepsy (NFLE), our family could easily be distinguished from NFLE due to the predominant diurnal seizures and a posterior epilepsy in the other member of the family.

There have been reports of EEG studies with interictal focal discharges, such as in our patients and one report from a French-Canadian family who presented with normal interictal EEG (Xiong *et al*., 1999), as in the father.

The penetrance of *DEPDC5* mutation associated with FFEVF was estimated at 66%, and obligate gene carriers without a history of seizures can often be identified within a family (Dibbens *et al*., 2013). In this study, genetic testing (PCR followed by LOD scores) was only performed in the three symptomatic members of the family. In all of them, FFEVF was associated with chromosome 22q12. We could not perform genetic testing in other family members. In 2012, 16 families with autosomal dominant focal epilepsy were reassessed and exome sequencing was carried out in all cases. Two patients with FFEVF presented with the same *DEPDC5* gene mutation (deletion), which was also detected in asymptomatic relatives. This strengthens the theory of incomplete penetrance and expression variability within a family, suggesting that the phenotype is modulated by other genes or environmental and epigenetic factors (Ishida *et al*., 2013).

The mutation described here would introduce a premature stop, causing loss of *DEPDC5* gene function and the subsequent epilepsy phenotype. Neither the *DEPDC5* nor the *LGI1* gene (associated with autosomal dominant lateral temporal lobe epilepsy) encode a transmembrane receptor subunit or ion channel (Ishida *et al*., 2013). In another study, the exomes of an Australian family and a Dutch family were sequenced, leading to the detection of a nonsense mutation of the *DEPDC5* gene. Thus, different *DEPDC5* gene mutations are associated with FFEVF (Dibbens *et al*., 2013).

Recently, in 2014, Ingrid Scheffer confirmed the variability of phenotypes associated with *DEPDC5* gene mutations. She identified a nonsense variant of the *DEPDC5* gene in two siblings with focal cortical dysplasia type IIA by exome sequencing, which had previously been associated only with normal neuroimaging studies. The father and paternal uncle in her study had the same mutation, but had normal neuroimaging studies and good response to carbamazepine (Scerri *et al*., 2015). A missense variant of the *NF1* and *DEPTOR* genes was also found, but only in both siblings with focal cortical dysplasia. In our study, we did not find other gene mutations in any of the three patients. The three genes, *DEPDC5*, *DEPTOR*, and *NF1*, encode components of the mTOR pathway, which could contribute to the phenotype variability associated with the *DEPDC5* gene (which inhibits mTORC1),

causing both lesional and non-lesional epilepsy. The association between *DEPDC5* and the mTOR pathway genes and the presence of cortical malformations in these patients is still unclear.

Recently, with regards to FFEVF, advances in exome sequencing have revealed an association between DEPDC5 gene mutation and other genes such as *DEPTOR* and *NF1*, which could be linked to severe epilepsy with focal cortical malformations (cortical dysplasia type IIA and focal heterotopia) (Scerri *et al*., 2015; Baulac *et al*., 2015; Tsai *et al*., 2017). No clear genotype-phenotype correlations have been described, although, to date, missense variants have been reported mostly in small families including individuals with apparently non-lesional epilepsies. The family presented here had a missense mutation with normal MRI. Moreover, all individuals with reported brain malformations (focal cortical dysplasia or hemimegalencephaly) had nonsense or frameshift variants leading to a premature stop codon (Scheffer *et al*., 2014; Scerri *et al*., 2015; Ricos *et al*., 2016; Weckhuysen *et al*., 2016).

Conclusion

FFEVF is a genetic epilepsy syndrome with autosomal dominant inheritance, incomplete penetrance, and large phenotypic variability. We emphasize the importance of the patient's family medical history as a basis for selecting relevant diagnostic testing which leads to accurate diagnosis and subsequent management. □

Legend for video sequence

A typical seizure of the patient. The seizure semiology starts three seconds from the first change in EEG with eye opening, followed by ocular and left versive cephalic deviation, associated with vocalization. The patient then presents with right hand automatisms associated with left lower limb flexion, followed by bilateral manual automatisms.

Key words for video research on www.epilepticdisorders.com

Phenomenology: focal seizure
Localisation: variable foci
Syndrome: familial focal epilepsy with variable foci
Aetiology: DEPDC5 mutation

Disclosures.
None of the authors have any conflict of interest to declare.

References

Baulac S, Shida S, Marsan E, *et al*. Familial focal epilepsy with focal cortical displasia due to *DEPDC5* mutations. *Ann Neurol* 2015; 77: 675-83.

Callenbach P, Van den Maagdenberg A, Hottenga J, *et al*. Familial partial epilepsy with variable foci in a Dutch family: clinical characteristics and confirmation of linkage to chromosome 22q. *Epilepsia* 2003; 44: 1298-305.

Dibbens L, De Vries B, Donatello S, *et al*. Mutations in *DEPDC5* cause familial focal epilepsy with variable foci. *Nat Genet* 2013; 45: 546-51.

Ishida S, Picard F, Rudolf G, *et al*. Mutations of *DEPDC5* cause autosomal dominant focal epilepsies. *Nat Genet* 2013; 45: 552-5.

Klein KM, O'Brien TJ, Praveen K, *et al*. Familial focal epilepsy with variable foci mapped to chromosome 22q12: expansion of the phenotypic spectrum. *Epilepsia* 2012; 53: e151-5.

Koile D, Cordoba M, De Sousa Serro M, Kauffman MA, Yankilevich P. GenIO: a phenotype-genotype analysis web server for clinical genomics of rare diseases. *BMC Bioinformatics* 2018; 19: 25.

Morales-Corraliza J, Gomez-Garre P, Sanz R, Diaz Otero G, Gutierrez Delicado E, Serratosa JM. Familial focal epilepsy with variable foci: a new family with suggestion of linkage to chromosome 22q12. *Epilepsia* 2010; 51: 1910-4.

Nascimento FA, Borlot F, Cossette P, Minassian BA, Andrade DM. Two definite cases of sudden unexpected death in epilepsy in a family with a *DEPDC5* mutation. *Neurol Genet* 2015; 1: e28.

Ricos MG, Hodgson BL, Pippucci T, *et al*. Mutations in the mTOR pathway regulators NPRL2 and NPRL3 cause focal epilepsy. *Ann Neurol* 2016; 79: 120-31.

Scerri T, Riseley J, Gillies G, *et al*. Familial cortical displasia type IIA caused by a germline mutation in *DEPDC5*. *Ann Clin Transl Neurol* 2015; 2: 575-80.

Scheffer IE, Phillips HA, O'Brien CE, *et al*. Familial partial epilepsy with variable foci: a new partial epilepsy syndrome with suggestion of linkage to chromosome 2. *Ann Neurol* 1998; 44: 890-9.

Scheffer IE, Heron SE, Regan BM, *et al*. Mutations in mammalian target of rapamycin regulator DEPDC5 cause focal epilepsy with brain malformations. *Ann Neurol* 2014; 75: 782-7.

Tsai MH, Chan CK, Chang YC, *et al*. *DEPDC5* mutations in familial and sporadic focal epilepsy. *Clin Genet* 2017; 92: 397-404.

Weckhuysen S, Marsan E, Lambrecq V, *et al*. Involvement of GATOR complex genes in familial focal epilepsies and focal cortical dysplasia. *Epilepsia* 2016; 57: 994-1003.

Xiong L, Labuda M, Li D, *et al*. Mapping of a gene determining familial focal epilepsy with variable foci to chromosome 22q11-q12. *Am J Hum Genet* 1999; 65: 1698-710.

TEST YOURSELF

(1) In what other epileptic syndromes can *DEPDC5* mutations be found?

(2) Can patients with *DEPDC5* mutations have brain malformations?

(3) What genetic counselling would you give to a patient with *DEPDC5*-related epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Original article

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Quinidine therapy and therapeutic drug monitoring in four patients with *KCNT1* mutations

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ABSTRACT – *Aims*. Several recent studies have reported potassium sodium-activated channel subfamily T member 1 (*KCNT1*) mutations in epilepsy patients on quinidine therapy. The efficacy and safety of quinidine for epilepsy treatment, however, remains controversial.
Methods. We herein report the cases of four patients with *KCNT1* mutations treated with quinidine.
Results. A reduction in seizures of more than 50% after quinidine treatment was observed in one patient with epilepsy of infancy with migrating focal seizures (EIMFS), whereas two patients with EIMFS and one with focal epilepsy did not achieve apparent seizure reduction. The relationship between quinidine dose and serum quinidine concentration was inconsistent, particularly at high quinidine doses. One patient with EIMFS developed ventricular tachycardia the day after an increase in quinidine dose from 114 to 126 mg/kg/day. The serum trough quinidine concentration and the corrected QT interval (QTc) before arrhythmia onset were 2.4 μg/ml and 420 ms, respectively, and peak serum quinidine concentration after arrhythmia onset was 9.4 μg/ml. Another patient with EIMFS showed aberrant intraventricular conduction with a quinidine dose of 74.5 mg/kg/day and a serum trough concentration of 3.2 μg/ml.
Conclusions. Given that serum quinidine levels may elevate sharply after a dose increase, careful monitoring of electrocardiographs and serum concentrations is required. Based on a review of previous reports and our experience with this case, quinidine should be considered as a promising

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drug for patients with EIMFS harbouring *KCNT1* mutations, however, its efficacy remains controversial due to the limited number of cases, and more information on optimal serum concentrations and appropriate titration methods is required.

Key words: *KCNT1*, EIMFS, quinidine, serum concentration, arrhythmia, migrating focal seizures

Potassium sodium-activated channel subfamily T member 1 (*KCNT1*) encodes a sodium-activated potassium channel that is highly expressed in the central nervous system (Bhattacharjee *et al*., 2002; Bhattacharjee and Kaczmarek, 2005). KCNT1 contributes to neuronal excitability and subsequent firing as well as modulation of the resting membrane potential (Bhattacharjee *et al*., 2005). The precise functions of KCNT1, however, remain unclear. *KCNT1* mutations have been described in 39-50% of patients with epilepsy of infancy with migrating focal seizures (EIMFS) (Ohba *et al*., 2015; Lim *et al*., 2016) and in less than 5% of patients with autosomal dominant nocturnal frontal lobe epilepsy (Heron *et al*., 2012).

Recently, several studies have reported patients harbouring *KCNT1* mutations with intractable epileptic seizures who received quinidine treatment (Bearden *et al*., 2014; Mikati *et al*., 2015; Chong *et al*., 2016; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018; Madaan *et al*., 2018; Mullen *et al*., 2018). Although accumulating data from multiple cases have enabled the elucidation of prognostic factors in patients with EIMFS, such as the type of epilepsy and the age at which quinidine is administered, few studies have investigated serum quinidine levels and association between serum quinidine concentration and other antiepileptic drugs that might hinder quinidine, such as phenobarbital in these patients.

Given that quinidine is one of the few drugs with potential as a treatment for patients with *KCNT1* mutations and EIMFS, determining optimal serum quinidine concentration is essential for its safe and effective use. In this report, we present the cases of four patients harbouring *KCNT1* mutations who developed seizures and were treated with quinidine, with the aim of elucidating its efficacy and utility.

Case reports

Patient 1

Patient 1 was a 20-month-old male born at 39 weeks of gestation without distress after *in vitro* fertilisation and embryo transfer. He developed focal seizures comprising asymmetric tonic posturing with eye deviation at one month of age and was diagnosed with EIMFS based on seizure symptoms and migrating foci on ictal EEG. His seizures were unresponsive to phenobarbital, clonazepam, clobazam, levetiracetam or potassium bromide. Whole-exome sequencing revealed a *de novo* heterozygous mutation in *KCNT1* (c.1283G>A: p.Arg428Gln).

The patient was administered quinidine at a starting dose of 2 mg/kg/day at the age of nine months. Cardiological evaluation prior to quinidine administration, including Holter electrocardiography (ECG), echocardiography, and chest X-ray by a paediatric cardiologist, revealed no abnormalities. The antiepileptic drugs used in combination with quinidine were levetiracetam (48 mg/kg/day) and potassium bromide (44 mg/kg/day). Although the dose of quinidine was increased gradually, the frequency of seizures did not change significantly for approximately five months. Six months after the initiation of quinidine therapy, the patient developed ventricular tachycardia and a cluster of focal tonic seizures the day after the increase in quinidine dose from 114 mg/kg/day to 126 mg/kg/day. The peak serum quinidine concentration at the time of the arrhythmic event was 9.4 μg/ml. The corrected QT interval (QTc), which was 362 ms before the initiation of quinidine therapy, was longer at 420 ms during a quinidine dose of 114 mg/kg/day. Arrhythmia disappeared following a reduction in quinidine dose to 73 mg/kg/day. Thereafter, a mild decrease in seizure frequency was observed despite no changes in medication. The average seizure frequency during the three months before the initiation of quinidine therapy was 43.3 times/day, and was 62.4% lower at 16.3 times/day during the last three months (*figure 1A*).

The relationship between serum quinidine concentration and quinidine dose, based on peak and trough levels, is shown in *figure 2A*. Briefly, there was a limited association between the trough level and dose, however, the peak quinidine level was not associated with quinidine dose between 40 and 50 mg/kg/day.

Patient 2

Patient 2 was a three-year-old female born at term without distress. Her first seizure occurred at two months of age, and her seizures comprised asymmetrical tonic convulsions with cyanosis, eye deviation, and oral automatism. She was diagnosed with EIMFS based on seizure symptoms and migrating foci on ictal EEG. The seizures were refractory to conventional antiepileptic drugs. Whole-exome sequencing revealed a *de*

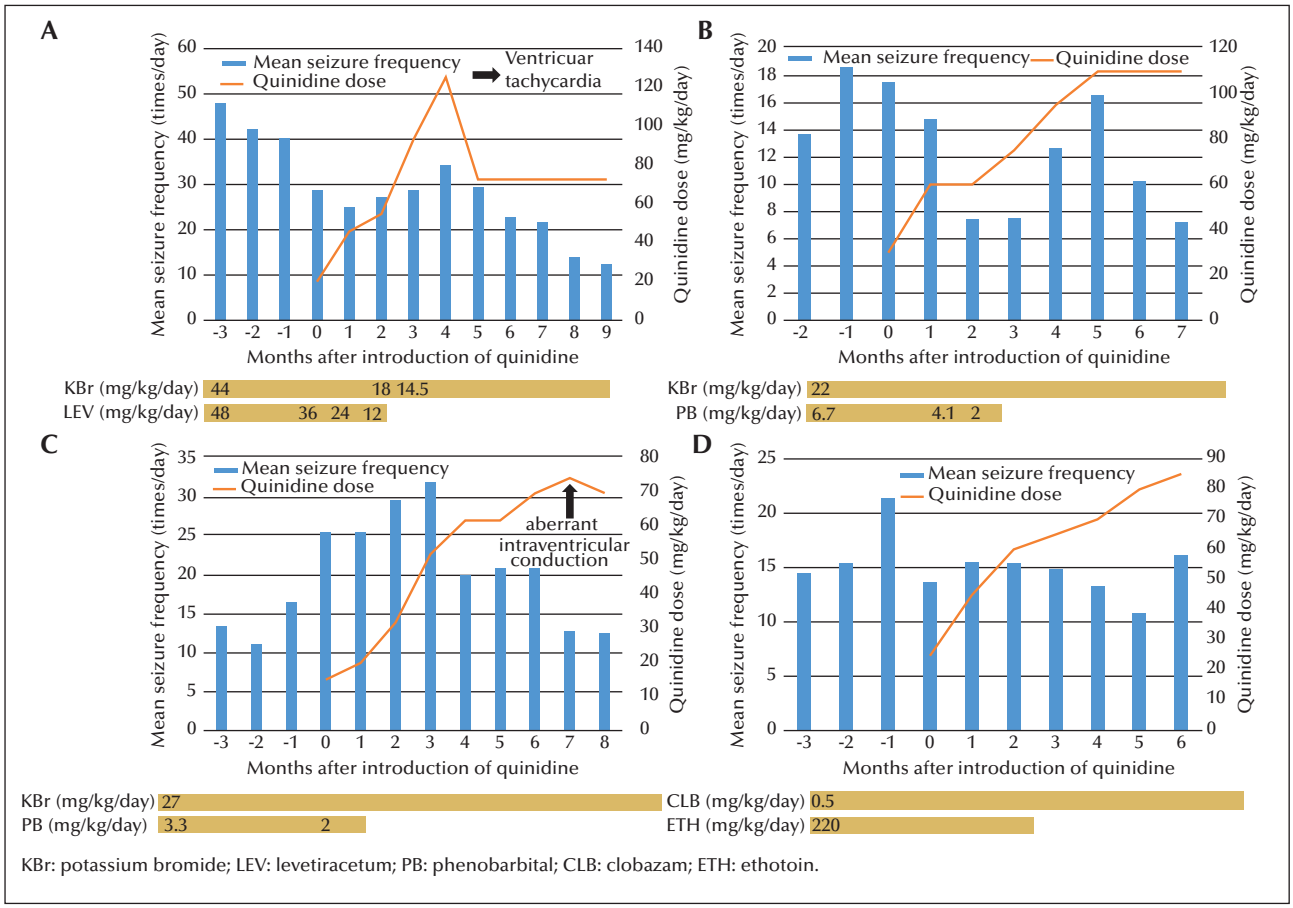

Figure 1. Evolution of seizure frequency: (A) Patient 1; (B) Patient 2; (C) Patient 3; (D) Patient 4.

novo heterozygous mutation in *KCNT1* (c.2800G>A; p.Ala934Thr).

She was administered quinidine at a starting dose of 2 mg/kg/day. The antiepileptic drugs used in combination with quinidine were phenobarbital (6.7 mg/kg/day) and potassium bromide (22 mg/kg/day). Her seizure frequency decreased by approximately 50% after two to three months of quinidine therapy. Subsequently, her seizure frequency increased despite an increase in the quinidine dose at five months after quinidine initiation. The average seizure frequency during the three months before quinidine initiation was 10.8 times/day, and decreased by 48.1% to 5.6 times/day during the last three months (*figure 1B*). The QTc before quinidine initiation was 343 ms, whereas the longest QTc after the initiation of quinidine therapy was 435 ms. The relationship between serum quinidine concentration and quinidine dose is presented in *figure 2B*. The trough levels of quinidine with phenobarbital were lower than those for quinidine without phenobarbital at a quinidine dose of approximately 60 mg/kg/day. The trough and peak levels of quinidine were inconsistent when administered at a dose of around 100 mg/kg/day in the absence of phenobarbital.

Patient 3

Patient 3 was a 21-month-old male born after 36 weeks of gestation. He developed focal seizures comprising eye deviation, oral automatism, asymmetrical tonic posturing, cyanosis, and eye blinking at two months of age. Ictal EEG showed migrating epileptic focus, which resulted in the diagnosis of EIMFS.

Conventional antiepileptic drugs were ineffective, and the frequency of epileptic seizures gradually increased to 30-40 times a day. Phenobarbital was the only anticonvulsant that demonstrated slight efficacy against the seizures, however, the patient suffered from drowsiness as a side effect. Whole-exome sequencing revealed a *de novo* heterozygous mutation in *KCNT1* (c.862G>A; p.Gly288Ser).

At the age of 14 months, the patient was initiated on treatment with quinidine at a dose of 17 mg/kg/day in combination with potassium bromide (27 mg/kg/day) and phenobarbital (3.3 mg/kg/day).

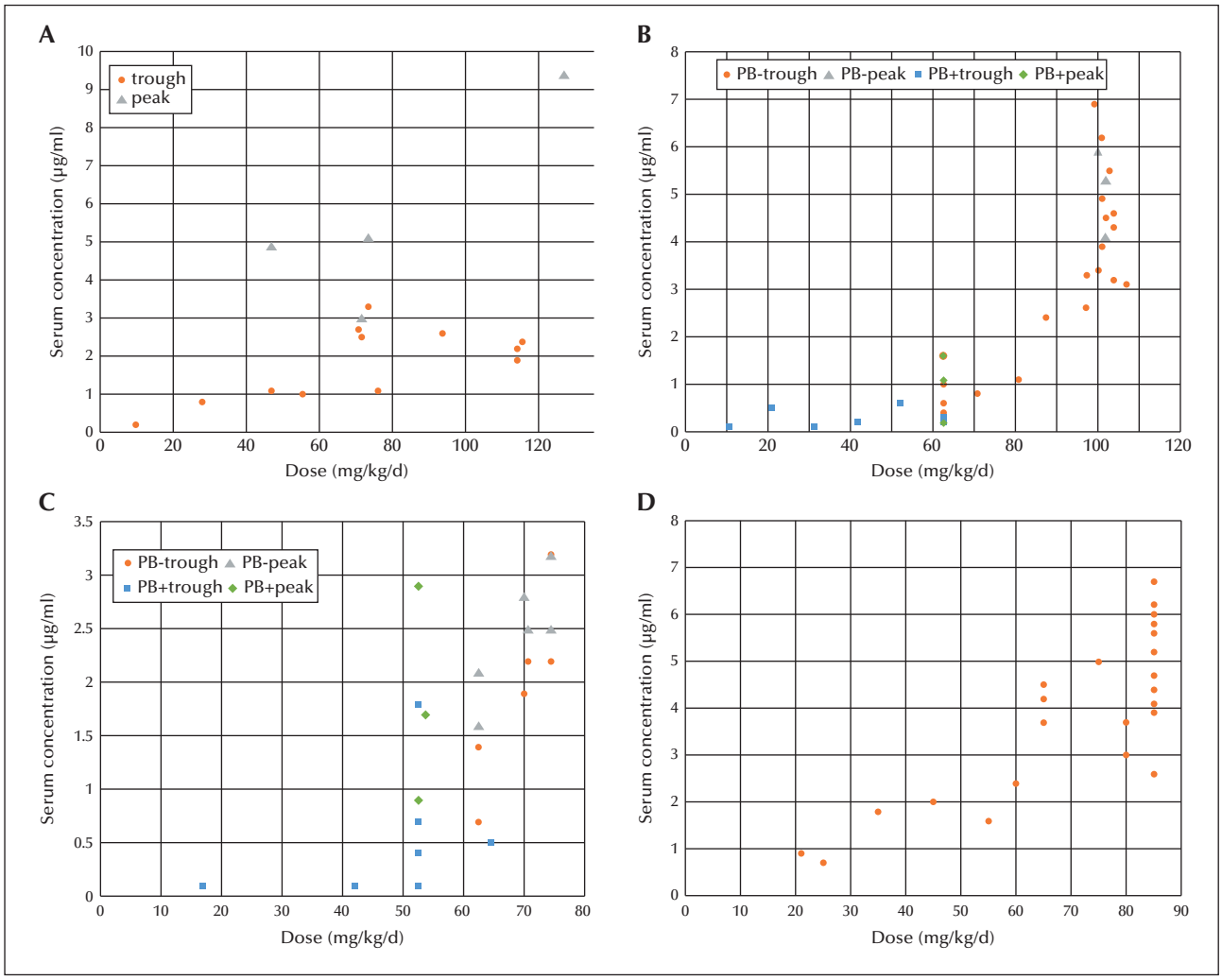

Figure 2. The relationship between serum quinidine concentration and quinidine dose, based on peak and trough levels: (A) Patient 1; (B) Patient 2; (C) Patient 3; (D) Patient 4. PB: phenobarbital.

During the first three months, his seizures worsened despite an increase in the quinidine dose. The average seizure frequency in the three months before quinidine initiation was 14 times/day, and was 12.1% higher at 15.7 times/day during the last three months (*figure 1C*).

The asymptomatic change observed on ECG was noted to comprise a wide QRS, suggesting aberrant intraventricular conduction when the serum trough quinidine concentration was 3.2 μg/ml. Immediately following a reduction in the quinidine dose from 74.5 to 70.7 mg/kg/day, the abnormal ECG findings resolved. The relationship between serum quinidine concentration and quinidine dose is presented in *figure 2C*. Briefly, the trough levels of quinidine at doses less than 50 mg/kg/day remained relatively constant at 0.2 μg/ml despite the increase in dose, which could have been due to a potential effect of phenobarbital. Conversely, the serum quinidine concentrations gradually rose with increases in the quinidine dose to >50 mg/kg/day, in parallel with a reduction in the phenobarbital dose. Serum quinidine concentration was unstable at the quinidine dose of 53 mg/kg/day.

Patient 4

Patient 4 was a nine-year-old male born after 39 weeks of gestation. His focal seizures comprised asymmetrical tonic posturing and eye blinking, which started at the age of one month. The patient's EEG showed a suppression-burst pattern until the age of 20 months, and he was diagnosed with focal epilepsy. Conventional antiepileptic drugs, methyl prednisolone pulse therapy, and the ketogenic diet were ineffective. Whole-exome sequencing revealed a *de novo* heterozygous missense mutation in *KCNT1* (c.1420C>T; p.Arg474Cys).

Quinidine therapy was initiated at a dose of 21 mg/kg/day at seven years of age and was combined with clobazam (0.5 mg/kg/day) and ethotoin (220 mg/kg/day). Although the quinidine dose was increased to 85 mg/kg/day, the average seizure frequency in the three months before quinidine introduction was 17.3 times/day, and was 23.1% lower at 13.3 times/day during the last three months (*figure 1D*). No quinidine-related side effects, such as ECG changes, were observed. The serum quinidine concentrations of the patient are shown in *figure 2D*. Although the trough levels of quinidine were generally associated with quinidine doses <80 mg/kg/day, the serum quinidine concentration was inconsistent at quinidine doses >80 mg/kg/day.

Discussion

Quinidine was effective in only one of the four patients presented herein, based on >50% seizure reduction as the definition of quinidine efficacy. The most effective trough and peak serum quinidine concentrations for Patient 1 were 2.2-3.3 μg/ml and 5.1 μg/ml, respectively. The quinidine levels of Patient 1 were close to the previously reported effective serum quinidine levels for epilepsy that ranged between 0.4 and 5 μg/ml (Bearden *et al*., 2014; Mikati *et al*., 2015; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018). The timing of initiation of treatment in Patient 1, however, was far later than that reported in previous reports (Bearden *et al*., 2014; Mikati *et al*., 2015; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018; Mullen *et al*., 2018). Additionally, seizure frequency often fluctuates during the natural course of EIMFS. Therefore, it is unclear whether the seizure reduction in Patient 1 was indeed due to quinidine.

Seven studies published to date include a total of 15 epilepsy patients treated with quinidine: four patients with EIMFS, 10 with other focal epilepsy, and one with West syndrome (Bearden *et al*., 2014; Mikati *et al*., 2015; Chong *et al*., 2016; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018; Madaan *et al*., 2018; Mullen *et al*., 2018). Among these patients, three of the four patients with EIMFS responded well to quinidine (3/4; 75%). With the inclusion of our three patients with EIMFS, whose statuses improved, quinidine was overall effective in four out of seven patients (4/7; 57.1%). In contrast, no patients with other focal epilepsies, including Patient 4 in the current study, responded to quinidine (0/11; 0%). Quinidine was effective in the only reported patient with West syndrome who was treated with quinidine (1/1; 100%) (Fukuoka *et al*., 2017). Overall, these results suggest quinidine as a promising treatment option for some patients with EIMFS and West syndrome, however, quinidine may not be beneficial for patients with other focal epilepsies.

All *KCNT1* mutations in the current four patients were reported previously (Bearden *et al*., 2014; Mikati *et al*., 2015; Chong *et al*., 2016; Fukuoka *et al*., 2017). The *KCNT1* mutation c.1283G>A (p.Arg428Gly) has been detected in a total of three patients, including Patient 1 in the current study (Bearden *et al*., 2014; Chong *et al*., 2016). Although quinidine was partially effective for Patient 1 in the current study and the patient reported by Bearden *et al*., both of whom had EIMFS, it was not beneficial in patients suffering from focal epilepsy (Chong *et al*., 2016). Although not conclusive, these results based on the available reports and our cases suggest that quinidine therapy should be considered in patients with EIMFS who harbour the *KCNT1* mutation, c.1283G>A (p.Arg428Gly).

A previous study suggested that age of the patients might be an important factor for the efficacy of quinidine therapy (Abdelnour *et al*., 2018). The authors found that all patients who showed good response to quinidine therapy were under the age of four and that no patient over four years of age responded to quinidine. Although the response of Patient 1 in the current report is consistent with their finding, the outcomes of the remaining three patients do not lend support. In another report, a patient with EIMFS who was started on quinidine at six months of age also failed to respond (Madaan *et al*., 2018). Importantly, factors other than age should be considered which could account for the observation of Abelnour *et al*. and the disgreement between their study and ours. In the study by Abdelnour *et al*., the seizure types of the four patients under four years of age corresponded to EIMFS or West syndrome, whereas the seizure types of the four patients over four years of age corresponded to other focal epilepsies (Abdelnour *et al*., 2018). Given that the patients with EIMFS and West syndrome showed a better response to quinidine than those with other focal epilepsies in the study of Abdelnour *et al*. (2018) as well as in the current study, age at the time of quinidine treatment initiation may not be a good prognostic factor. Future studies are warranted to clarify important prognostic factors for good response to quinidine therapy.

Based on previous studies comparing psychomotor development before and after quinidine administration, psychomotor development was reported to improve perceptibly in two patients with EIMFS who achieved complete or partial seizure suppression. A three-year-old male with 80% seizure reduction became more alert and more interactive (Bearden *et al*., 2014), whereas a three-year-old female with complete seizure suppression began to utter words after initiating quinidine therapy (Mikati *et al*., 2015). However, none of the patients in the current study, including those with seizure reduction, showed improvement in their development after initiating

quinidine therapy, and their psychomotor development remains severely delayed.

All patients in the current study were administered quinidine three or four times a day. In this study, trough was defined as the timepoint immediately before the second administration of the day, and peak was defined as the timepoint 2.5 hours after the first administration. The relationship between serum quinidine concentration and quinidine dose was inconsistent among the patients, and increased concentrations were reported even though the dose remained the same.

In the current study, two out of the four patients were administered phenobarbital in combination with quinidine. During the clinical course for these two patients, the elevation in quinidine concentration was significantly hindered due to the induction of cytochrome P450 3A4 by phenobarbital, which metabolises quinidine (*figures 2B, C*). It took several weeks for quinidine concentrations to increase after the discontinuation of phenobarbital, suggesting that the aftereffect of phenobarbital on quinidine concentration lingers. Therefore, careful quinidine titration should be planned when drugs that induce cytochrome P450 3A4 are used in combination with quinidine.

At the time of ventricular tachycardia in Patient 1, the peak serum quinidine concentration with a quinidine dose of 126 mg/kg was 9.4 μg/ml, both of which were higher than previously reported for this patient and the other patients in the current study. Moreover, arrhythmia appeared within one day after the increase in quinidine dose. Several studies have also reported that cardiac arrhythmias generally occur within days of quinidine administration (Cohen *et al*., 1977; Roden *et al*., 1986; Hohnloser *et al*., 1995). These results suggest that careful patient monitoring, particularly after the administration of, and an increase in, the quinidine dose, is critical. Additionally, a previous report described a small number of patients who developed *torsade de pointes* during long-term quinidine therapy, usually in association with hypokalaemia (Roden *et al*., 1986). The serum potassium level of Patient 1 at the onset of arrhythmia was 4.4 mEq/l, which was within normal limits.

QT elongation with quinidine was observed in seven out of the 15 patients reported in the literature (Mikati *et al*., 2015; Fukuoka *et al*., 2017; Abdelnour *et al*., 2018; Mullen *et al*., 2018). Notably, one patient treated with quinidine developed QT elongation despite a low serum quinidine concentration of 0.4 μg/ml (Abdelnour *et al*., 2018) or a low dose of 34.4 mg/kg/day (Mikati *et al*., 2015). Clearly, instances of QT elongation do not translate to an increased risk of arrhythmia or require urgent discontinuation of quinidine, because QT elongation itself only reflects the primary action of quinidine on ion channels. To achieve a truly safe range of serum quinidine level and dose is considerably difficult because its toxic levels depend on genetic factors, electrolytes, and other complications such as serum concentration and dose. However, it remains certain that a quinidine dose over 74.5 mg/kg/day or a serum quinidine concentration above 9.4 μg/ml during treatment can lead to issues that are more serious than QT elongation.

Because quinidine remains one of the few promising therapeutic drugs for patients with EIMFS harbouring *KCNT1* mutations, elucidating optimal serum quinidine concentrations and appropriate methods of titration is essential for its safe and effective use. There is a possibility that serum quinidine levels may not be directly related to efficacy or side effects, which requires additional case reports and case series for clarification.

The current report has several limitations. First, this was a small, open-label study. Additionally, the possibility remains that the seizure reduction observed in our patients after the introduction of quinidine was due to the natural history of the disease, and the true efficacy of quinidine in patients with *KCNT1* mutations remains to be elucidated. Finally, it should be noted that quinidine therapy has not yet been approved in patients with EIMFS and *KCNT1* mutations and should be prescribed with caution due to serious side effects. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.

This study was approved by the Institutional Review Board of the National Epilepsy Center, NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan. None of the authors have any conflict of interest to declare.

Reference

Abdelnour E, Gallentine W, McDonald M, *et al*. Does age affect response to quinidine in patients with *KCNT1* mutations? Report of three new cases and review of the literature. *Seizure* 2018; 55: 1-3.

Bearden D, Strong A, Ehnot J, DiGiovine M, Dlugos D, Goldberg EM. Targeted treatment of migrating partial seizures of infancy with quinidine. *Ann Neurol* 2014; 76: 457-61.

Bhattacharjee A, Kaczmarek LK. For K+ channels, Na+ is the new Ca2+. *Trends Neurosci* 2005; 28: 422-8.

Bhattacharjee A, Gan L, Kaczmarek LK. Localization of the Slack potassium channel in the rat central nervous system. *J Comp Neurol* 2002; 454: 241-54.

Bhattacharjee A, von Hehn CA, Mei X, Kaczmarek LK. Localization of the Na+-activated K+ channel Slick in the rat central nervous system. *J Comp Neurol* 2005; 484: 80-92.

Chong PF, Nakamura R, Saitsu H, Matsumoto N, Kira R. Ineffective quinidine therapy in early onset epileptic encephalopathy with *KCNT1* mutation. *Ann Neurol* 2016; 79: 502-3.

Cohen IS, Jick H, Cohen SI. Adverse reactions to quinidine in hospitalized patients: findings based on data from the Boston Collaborative Drug Surveillance Program. *Prog Cardiovasc Dis* 1977; 20: 151-63.

Fukuoka M, Kuki I, Kawawaki H, *et al*. Quinidine therapy for West syndrome with *KCNT1* mutation: a case report. *Brain Dev* 2017; 39: 80-3.

Heron SE, Smith KR, Bahlo M, *et al*. Missense mutations in the sodium-gated potassium channel gene *KCNT1* cause severe autosomal dominant nocturnal frontal lobe epilepsy. *Nat Genet* 2012; 44: 1188-90.

Hohnloser SH, van de Loo A, Baedeker F. Efficacy and proarrhythmic hazards of pharmacologic cardioversion of atrial fibrillation: prospective comparison of sotalol versus quinidine. *J Am Coll Cardiol* 1995; 26: 852-8.

Lim CX, Ricos MG, Dibbens LM, Heron SE. *KCNT1* mutations in seizure disorders: the phenotypic spectrum and functional effects. *J Med Genet* 2016; 53: 217-25.

Madaan P, Jauhari P, Gupta A, Chakrabarty B, Gulati S. A quinidine non-responsive novel *KCNT1* mutation in an Indian infant with epilepsy of infancy with migrating focal seizures. *Brain Dev* 2018; 40: 229-32.

Mikati MA, Jiang YH, Carboni M, *et al*. Quinidine in the treatment of KCNT1-positive epilepsies. *Ann Neurol* 2015; 78: 995-9.

Mullen SA, Carney PW, Roten A, *et al*. Precision therapy for epilepsy due to *KCNT1* mutations: a randomized trial of oral quinidine. *Neurology* 2018; 90: e67-72.

Ohba C, Kato M, Takahashi N, *et al*. De novo *KCNT1* mutations in early-onset epileptic encephalopathy. *Epilepsia* 2015; 56: 121-8.

Roden DM, Woosley RL, Primm RK. Incidence and clinical features of the quinidine-associated long QT syndrome: implications for patient care. *Am Heart J* 1986; 111: 1088-93.

TEST YOURSELF

(1) Which epilepsy syndromes are believed to show a response to quinidine therapy?

(2) Which antiepileptic drugs suppress serum quinidine concentration?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Original article

Epileptic Disord 2019; 21 (1): 55-64

Functional brain connectivity in electrical status epilepticus in sleep

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ABSTRACT – *Aims*. Electrical status epilepticus in sleep (ESES) is an age-related, self-limited epileptic encephalopathy. The syndrome is characterized by cognitive and behavioral abnormalities and a specific EEG pattern of continuous spikes and waves during slow-wave sleep. While spikes and sharp waves are known to result in transient cognitive impairment during learning and memory tasks performed during the waking state, the effect of epileptiform discharges during sleep on cognition and behavior is unclear. There is increasing evidence that abnormalities of coherence, a measure of the consistency of the phase difference between two EEG signals when compared over time, is an important feature of brain oscillations and plays a role in cognition and behavior. The objective of this study was to determine whether coherence of EEG activity is altered during slow-wave sleep in children with ESES when compared to typically developing children.
Methods. We examined coherence during epochs of ESES versus epochs when ESES was not present. In addition, we compared coherence during slow-wave sleep between typically developing children and children with ESES.
Results. ESES was associated with remarkably high coherences at all bandwidths and most electrode pairs. While the high coherence was largely attributed to the spikes and spike-and-wave discharge, activity between spikes and spike-and-wave discharge also demonstrated high coherence.
Conclusions. This study indicates that EEG coherence during ESES is relatively high. Whether these increases in coherence correlate with the cognitive and behavioral abnormalities seen in children with this EEG pattern remains to be determined.

Key words: electrical status epilepticus in sleep (ESES), EEG, coherence, oscillations, phase lag, continuous spike and waves during slow wave sleep (CSWS)

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Electrical status epilepticus in sleep (ESES) is defined as an age-related, self-limited epileptic encephalopathy. The condition is characterized by cognitive and behavioral abnormalities and a specific electroencephalographic (EEG) pattern of continuous spike and waves during slow-wave sleep (CSWS) (Patry *et al*., 1971; Galanopoulou *et al*., 2000; Scheltens-de Boer, 2009; Sanchez Fernandez *et al*., 2012, 2014; Singhal and Sullivan, 2014; Gencpinar *et al*., 2016). While the clinical presentation of children with ESES is variable, the most severe clinical syndrome presents with global cognitive regression in addition to clinical seizures. The age at onset ranges from one to 14 years, with a peak between four and eight years (van den Munckhof *et al*., 2015). Although seizures may be absent in up to 20% of cases, they are most often the presenting symptom, after which developmental delay, developmental arrest, or regression in cognitive performance or behavior becomes evident (Tassinari *et al*., 2000).

While CSWS and ESES are used interchangeably, ESES typically is used to describe the EEG pattern while CSWS is used to describe the clinical syndrome of cognitive and behavioral abnormalities associated with the ESES pattern (Gencpinar *et al*., 2016). The hallmark EEG features of ESES are:

– a spike and wave occurring "during a significant proportion" of non-REM sleep with a threshold ranging from 25% to 85%;

– continuous or nearly-continuous, bilateral, or occasionally lateralized slow spikes and waves;

– and marked potentiation of epileptiform discharges during non-REM sleep (Sanchez Fernandez *et al*., 2013).

Near-continuous epileptiform discharges have been causally related to neurocognitive regression in CSWS (Tassinari *et al*., 2000; Holmes and Lenck-Santini, 2006). The pathophysiologic mechanisms underlying this condition are still incompletely understood. Recent data suggest that the abnormal epileptic EEG activity occurring during sleep might cause the typical clinical symptoms by interfering with sleep-related physiologic functions, and possible neuroplasticity processes mediating higher cortical functions such as learning and memory consolidation (Tassinari *et al*., 2000; Holmes and Lenck-Santini, 2006). It is known that spikes and spike-and-wave discharges can lead to cognitive impairment in both animals (Kleen *et al*., 2010) and humans (Aarts *et al*., 1984; Binnie *et al*., 1987, 1990, 1991; Shewmon and Erwin, 1989; Krauss *et al*., 1997; Ung *et al*., 2017). However, the cognitive impairment seen with interictal spikes is transient in nature in both humans (Aarts *et al*., 1984; Nair *et al*., 2014; Horak *et al*., 2017) and rodents (Holmes and Lenck-Santini, 2006; Zhou *et al*., 2007; Kleen *et al*., 2010) and it has been difficult to link the neurocognitive regression in CSWS solely to nocturnal spikes (Ebus *et al*., 2011).

There is increasing evidence that abnormalities in underlying oscillatory activity may play an important role in cognitive impairment in children with seizures (Holmes and Lenck-Santini, 2006; Holmes, 2014; Barry and Holmes, 2016). For example, in children with epilepsy, neither spikes nor spike-and-wave discharges correlate with the neuropsychological profile, whereas slow-wave activity on the EEG is related to memory impairment (Koop *et al*., 2005). In a study of children with Dravet syndrome, it was found that cognitive outcome was related more to preserved alpha rhythm of the EEG than seizures or generalized spike-wave discharges on the EEG. Likewise, in an animal model of Dravet syndrome, cognitive impairment was related to altered theta rather than seizures or interictal spikes (Bender *et al*., 2013, 2016). These studies raise the question of whether EEG background abnormalities are related more to cognitive impairment than interictal spikes.

Recent work in humans has demonstrated that coherence is a valuable marker of functional brain organization and connectivity. On a frequency by frequency basis, EEG spectral coherence represents the consistency of the phase difference between two EEG signals when compared over time. EEG coherence is interpreted as a measure of "coupling" and as a measure of the functional association between two brain regions (Thatcher *et al*., 1987, 2012). High coherence values are taken as a measure of strong connectivity between the brain regions that produce the compared EEG signals (Srinivasan *et al*., 2007). In both autistic spectrum disorder (Buckley *et al*., 2015) and West syndrome (Burroughs *et al*., 2014), EEG coherences are abnormally high. Remarkably, there have been no papers to date assessing coherence as a functional measure of brain connectivity in ESES.

We hypothesized that ESES during SWS has high coherence values. To address this hypothesis, we compared coherences across bandwidths and electrode pairs during SWS in children with ESES and normal children. In children with ESES, we also compared coherences during SWS during non-ESES and ESES epochs. Finally, to determine the "driver" of coherence during ESES, we examined epochs containing only spikes with epochs not containing spikes.

Methods

Study design and participants

Twenty-four-hour inpatient EEGs were documented from 29 neurotypically developing (TYP) children (mean±SD: 4.18±1.70 years) and 18 children (5.37±1.85 years) with ESES, as defined as an EEG with generalized spikes, sharp waves, spike and wave or polyspikes and

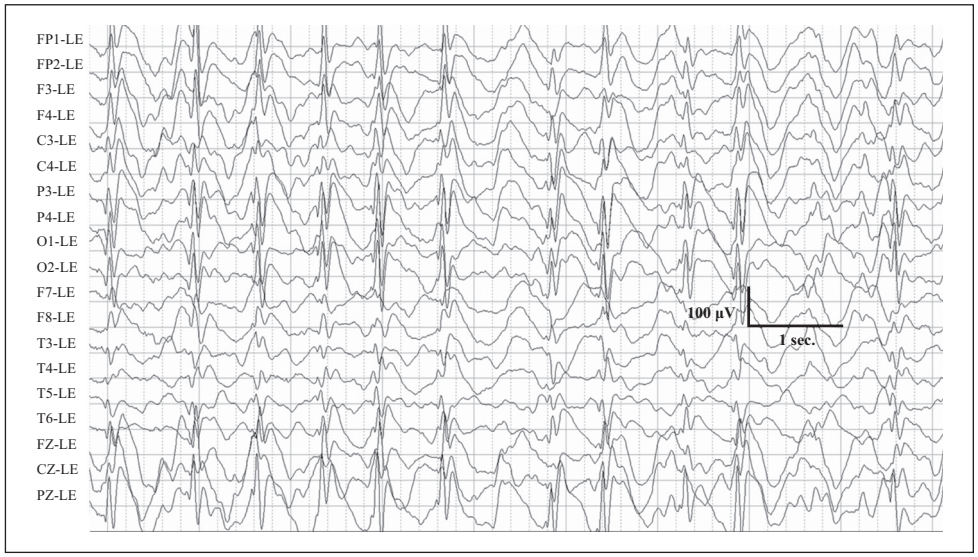

Figure 1. Example of ESES recording during slow-wave sleep. Note the high-amplitude (>150 microvolts) spike-and-wave discharges.

waves, occupying 85% of slow-wave sleep (*figure 1*). For every 10 seconds of SWS, the mean duration of epileptiform discharges had to be equal to 8.5 seconds or more. The TYP group comprised participants in an NIH natural history study of autism approved by the National Institutes of Health Institutional Review Board (NCT00298246). None of the children in the TYP group had autism or relatives with autism. Data from the TYP group have previously been published as part of a study on functional connectivity in children with autism (Buckley *et al*., 2015). The EEGs from the children with ESES were from Dartmouth-Hitchcock Medical Center and the University of Vermont Medical Center with approval of both institutions' Institutional Review Board for analysis of de-identified EEG data. The 10-20 system of electrode placement was used and the Pz electrode served as the reference. The linked-ear montage was used for all EEG analyses. The EEGs were analyzed by SAB, ALK and GLH without any identifying information other than gender and age.

Epochs of artifact-free SWS were identified in each patient. For the ESES group, 60 seconds of non-continuous EEG demonstrating ESES (*figure 2A*) and 60 total seconds of SWS without ESES (*figure 2B*) were obtained. This 60-second epoch exceeds the 20-second time frame which is considered sufficient to assess quantitative EEG measures (Mocks and Gasser, 1984). Split-half reliability and the ratio of variance between the even and odd seconds of the time series of selected digital EEG (variance = sum of the square of the deviation of each time point from the mean of the time points) were calculated for each channel and a reliability of >0.95 was required before analysis. We also performed "test re-test" measures on all EEG data. Test re-test reliability uses the same equations as those used for split-half reliability but refers to the ratio of the variance of the first half of the EEG selections vs the variance of the second half of the EEG selections. A test re-test reliability of >0.90 was required before EEG data was statistically analyzed. In the TYP group, 10 minutes of continuous SWS EEG was analyzed. Since 85% of SWS consist of spikes and spike-and-wave discharges, shorter epochs were used in the children with ESES than the TYP group since it was often difficult to find 10 minutes of SWS without spike-and-wave complexes. In three patients with ESES, we compared 60-second epochs with 10-minute epochs of SWS with ESES and SWS without ESES using the paired-t test. No significant differences were noted in absolute power, relative power, power ratio, coherence or phase lag between 60-second and 10-minute epochs (data not shown). Thus, we concluded that it was appropriate to compare 60-second epochs between ESES patients and the TYP group.

To determine the electrical activity underlying coherence in ESES, epochs containing generalized spikes, sharp waves, spike and wave, or polyspikes and waves (*figure 3A*) were compared with epochs without spikes (*figure 3B*). The slow wave following the spike was considered as part of the epileptic discharge and was included in epochs of epileptiform activity.

EEGs were analyzed using NeuroGuide (Applied Neuroscience, Inc., Largo, FL). Frequencies from 0-30 Hz were analyzed using a Fast Fourier Transform (FTT) with the following parameters: epoch = 2 seconds at a sample rate of 128 samples/second = 256 digital time points and a frequency range from 0.5 to 30 Hz at a resolution of 0.5 Hz using a cosign taper window. FFT absolute and relative power was used for each of the 19 electrodes for delta (δ) (0-4 Hz), theta (θ) (4-8 Hz),

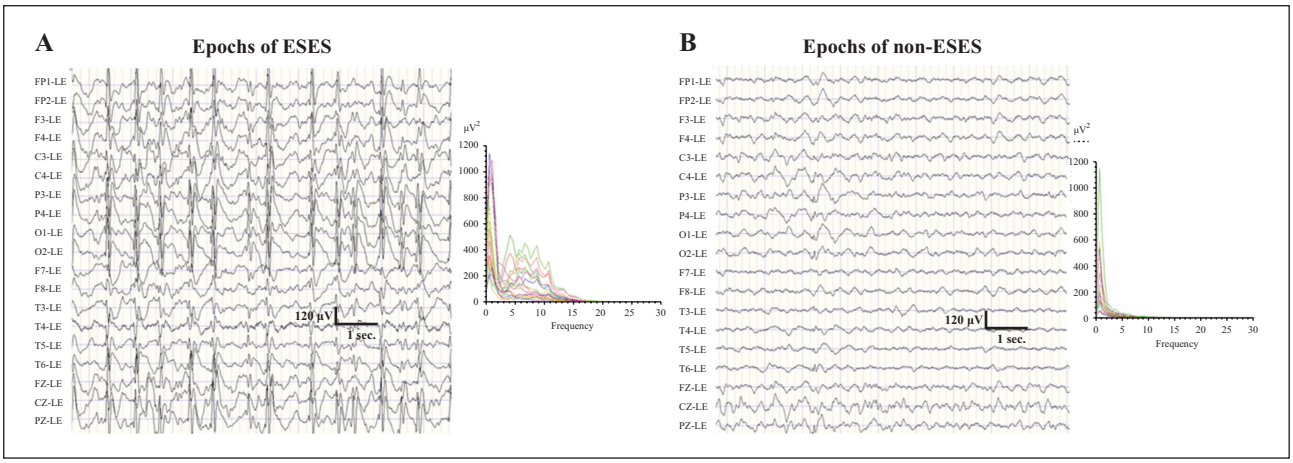

Figure 2. ESES during SWS. (A) Example of ESES during SWS. EEG absolute power is represented on the right. Colored lines represent different electrodes. Note the increased power in frequencies up to the β bandwidth. (B) Example of period during SWS without ESES. EEG absolute power is represented on the right. Compared to (A), the absolute power is primarily in the Δ bandwidth.

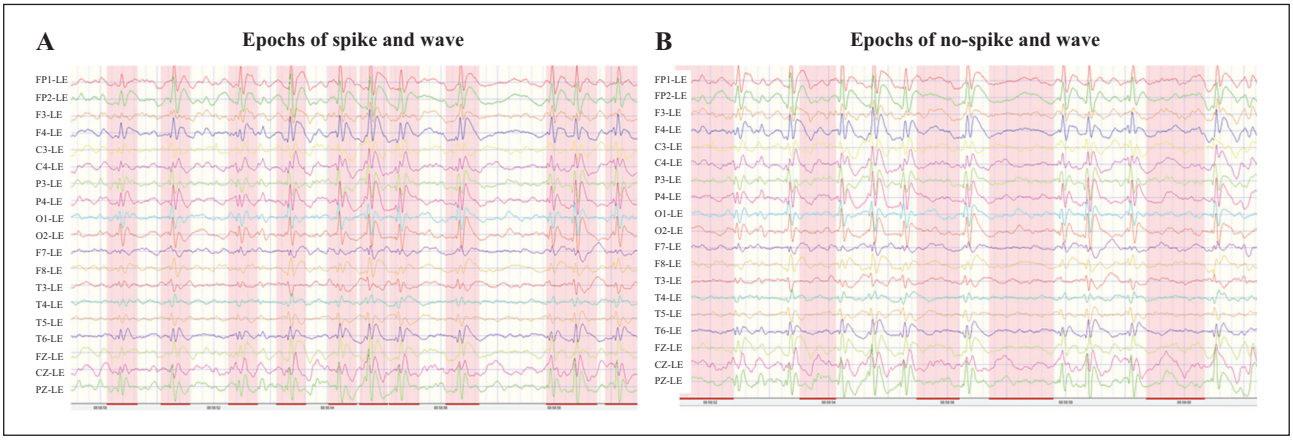

Figure 3. Epochs of EEG used for coherence measurement. (A) Calculation of coherence measure during spike and waves and polyspikes and waves. (B) Epochs of EEG without spikes measured for coherence. Shaded areas in pink are incorporated into the coherence measures.

alpha (α) (8-12 Hz), α1 (8-10 Hz), α2 (10-12 Hz), beta (β) (12-25 Hz), β1 (12-15 Hz), β2 (15-18 Hz), β3 (18-25 Hz), and high β (25-30 Hz). FFT absolute power per Hz (1-30 Hz) and power ratios for each electrode (δ/θ, δ/α, δ/β, θ/α, θ/β, α/β) were measured. FFT coherence for each electrode pair and FFT phase lag (degrees) between electrode pairs were obtained. Intra-hemispheric and inter-hemispheric pair wise combinations of electrodes were evaluated (171 pairs of electrodes).

Coherence represents the consistency of the phase difference between two EEG signals when compared over time and serves as a measure of synchronization between two EEG signals based mainly on phase consistency. Two signals may have different phases but high coherence occurs when this phase difference tends to remain constant. Coherences vary from 0, with no consistency between phases of two EEG signals, to 1, with perfect alignment of phase.

Coherence was defined as:

$$Coherence\,(f)) = \left(G_{xy}(f)^2\right)$$
$$\left(G_{xx}\,(f)\,G_{yy}\,(f)\right)$$

Where $G_{xy}(f)$ is the cross-power spectral density and $G_{xx}(f)$ and $G_{yy}(f)$ are the respective autopower spectral densities. FFT coherence for each electrode pair and FFT phase lag (degrees) between electrode pairs were obtained. Intra-hemispheric and inter-hemispheric pair wise combinations of electrodes were evaluated (171 pairs of electrodes).

Statistical analysis

Hypotheses were proven or discarded based on unpaired t tests for comparisons between the TYP children and ESES children and paired t tests for comparisons within the same patient for SWS with ESES and SWS without ESES using Neurostat EEG statistical software. The t test was used since the data demonstrated a normal distribution. The *p* values are shown in two ways:

– electrode maps with color and thickness of the lines connecting electrodes, reflecting direction of the differences between groups and the degree of significance;

– *p* value heat maps with degree of significance in selected color-coded electrode pairs. Although data were reviewed from 171 electrode pairs, selected electrodes were chosen for illustration.

Results

During ESES, there was a marked increase in coherence compared to the SWS segments without ESES (*figures 4, 5*). This increase in coherence occurred across all bandwidths and many electrode pairs. Of the 62 electrode pairs demonstrated in the heat map in *figure 5*, 12 (19.3%) in the Δ range, 36 (58%) in the Θ range, 49 (79%) in the α range, and 49 (79%) in the β range showed statistically increased coherences. In no electrode pairs did the ESES epochs show lower coherences than the non-ESES epochs. Likewise, there were significant increases in coherence in the EEGs with ESES compared to the TYP group (*figures 6, 7*). Coherences were significantly increased in the ESES group across all bandwidths. Of the 62 electrode pairs demonstrated in the heat map in *figure 8*, 16 (25.8) in the Δ range, 31 (50%) in the Θ range, 54 (87%) in the α range, and 52 (83.8%) in the β range showed statistically increased coherences, other than a few electrode pairs in the high β (25-30-Hz) bandwidth where coherences were lower in the TYP group than the ESES group. While all bandwidths demonstrated increases in coherence, the Δ frequencies were less likely to be significantly increased than the other major bandwidths (Θ, α and β). In the Δ bandwidth, some asymmetries in coherence were seen, with higher coherences noted over the left hemisphere, when compared with the TYP group. The composite coherence score showed that during ESES, coherence was substantially increased compared to non-ESES periods and with slow wave sleep (SWS) in the TYP group (*table 1*). In addition to the mean differences between groups shown in *table 1*, for each individual child, the mean coherences were higher in the ESES patient than the mean score for the TYP group.

To determine the component of the ESES that was contributing to the increased coherences, periods of ESES with and without spikes were compared. As demonstrated in *figure 8*, coherences were significantly higher during the spike component of the ESES than the non-spike component. Likewise, the composite coherence score during spikes was higher during spikes versus no-spike epochs (*table 1*). This was also true for each individual patient. Also, coherence

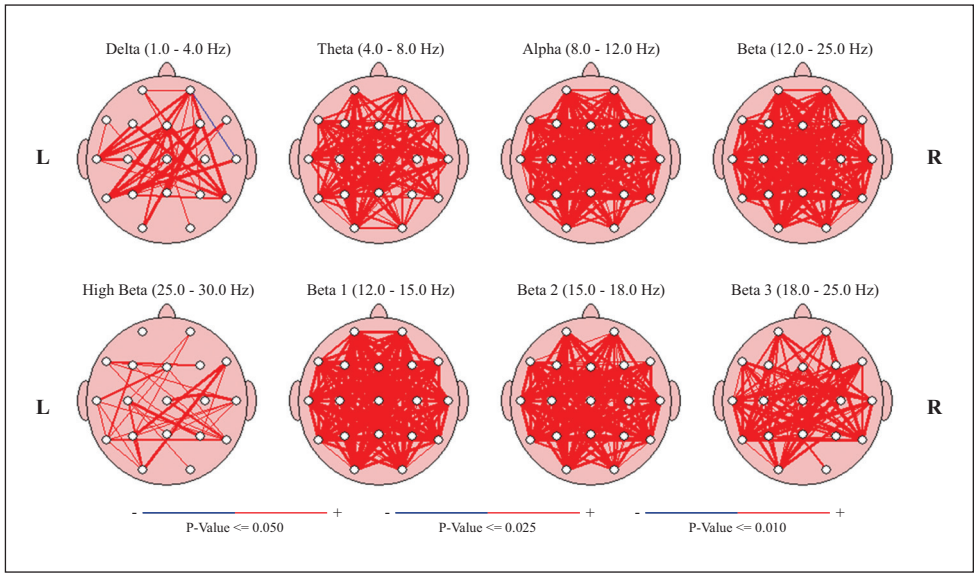

Figure 4. Coherence during ESES. Marked increases in coherence were seen at most electrode pairs during ESES compared to non-ESES periods. Red lines indicate that the ESES segments had higher coherences than during the non-ESES segments during SWS. The significance values are illustrated by weight of the lines. L/R refer to the left and right side of the head.

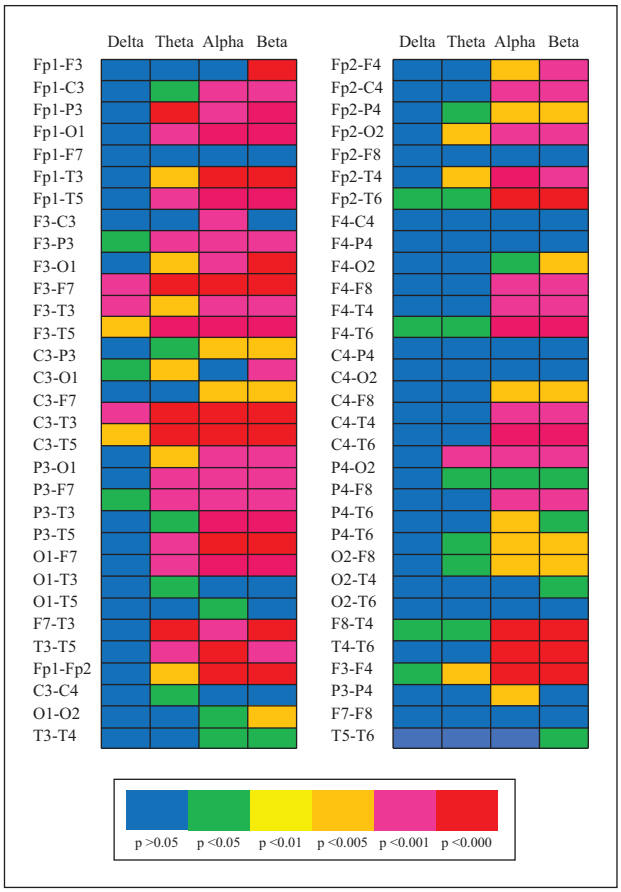

Figure 5. Heat map of *p* values for coherence between selected electrode pairs. Marked increases in coherence were seen during ESES compared to non-ESES periods.

values during no-spike epochs of ESES were significantly higher than those during non-ESES periods in the same patient ($t[15]=4.038$, $p = 0.0011$).

During ESES, there were also large increases in absolute power across the four major bandwidths (Δ, Θ, α and β) and relative power in the δ/θ, δ/α, δ/β, δ/γ, θ/α and θ/β compared to epochs without ESES (data not shown).

Discussion

The major finding in this analysis is that EEGs from children with ESES have marked abnormalities in coherence compared to periods of SWS without ESES and SWS in TYP children. While high coherence seems implicit in a recording with generalized spikes, it should be noted that the coherence values are increased at all bandwidths during spike-free epochs. It also should be noted that coherence cannot be assessed solely by examining the raw EEG signal. For example, in hypsarrhythmia, an abnormal interictal pattern consisting of high-amplitude and irregular waves and spikes in a background of chaotic and disorganized activity, coherence values are high (Burroughs *et al.*, 2014).

The children with ESES were older than those in the TYP group and it is known that coherence increases with age (Gmehlin *et al.*, 2011). In our previous study examining coherence in autism in children, using a series of general linear models controlling for age, we found little difference in coherence between four and

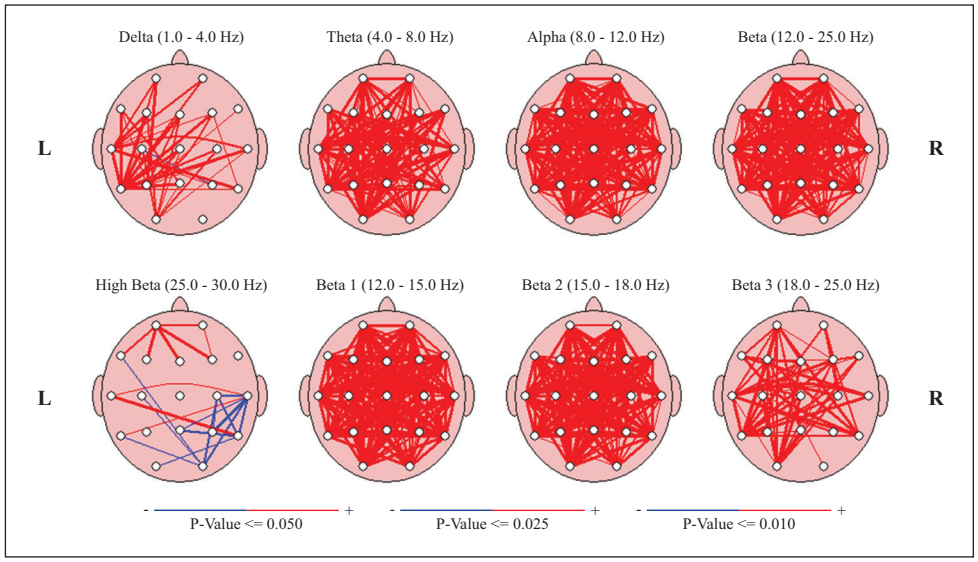

Figure 6. Coherence during SWS in children with ESES and TYP. Marked increases in coherence was seen at most electrode pairs during ESES segments in SWS compared to TYP controls. Red lines indicate that the ESES segments had higher coherences than during the SWS in the TYP controls while blue lines indicate lower coherences in the ESES segments in SWS compared to TYP controls. The significance values are illustrated by weight of the lines. L/R refer to the left and right side of the head.

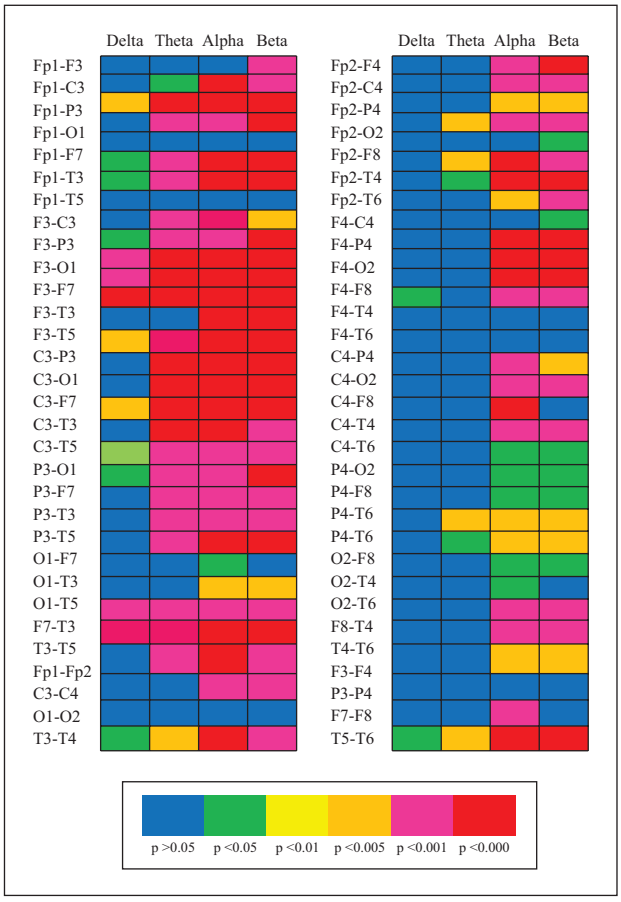

Figure 7. Heat map of *p* values for coherence between selected electrode pairs. Marked increases in coherence were seen during ESES compared to SWS in TYP controls.

five years (Buckley *et al*., 2015), thus making it highly unlikely the differences seen here were due to different ages. In addition, with such a large effect size, it is highly unlikely the increased coherence in the children with ESES was simply due to the ESES population being older. In addition, using paired comparisons, coherences were much higher during ESES periods than during non-ESES periods in SWS within the same patient.

Of interest, in the Δ bandwidths, the ESES group had higher coherences than the TYP group over the left hemisphere relative to the right. Asymmetries of coherence have been reported in other studies (French and Beaumont, 1984; Tucker *et al*., 1986; Nielsen *et al*., 1990; Whedon *et al*., 2016). It is known that many children with ESES have language abnormalities (Nickels and Wirrell, 2008). Whether these aberrant coherences in the dominant hemisphere are correlated with language impairment in our cohort of patients is not known.

As a measure of "coupling" oscillations, coherence provides a dynamic link between brain areas required for the integration of distributed information (Varela *et al*., 2001; Thatcher, 2012). Since high coherence values are an indication of strong connectivity between the brain regions that produce the EEG signals (Srinivasan *et al*., 2007), it is difficult to understand why high coherences would be detrimental. Decreased coherences have been associated with cognitive and behavioral abnormalities. Indeed, in rodent models of stress (Jacinto *et al*., 2013; Oliveira *et al*., 2013) and schizophrenia (Sigurdsson *et al*., 2010),

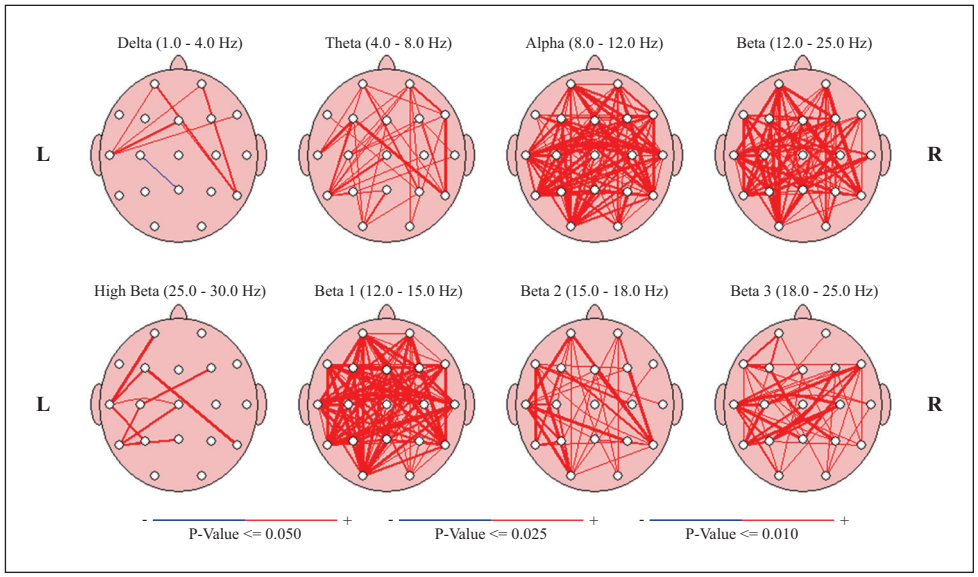

Figure 8. Coherence during spikes and inter-spike intervals in children with ESES. Increases in coherence were seen at most electrode pairs during ESES segments with spikes compared to the inter-spike interval. Red lines indicate that the spike segments had higher coherences than during the inter-spike interval. The significance values are illustrated by weight of the lines. L/R refer to the left and right side of the head.

Table 1. Composite coherence scores (mean of all electrode pairs at all bandwidths) during SWS in the TYP group, periods of ESES and non-ESES and ESES with spikes and ESES without spikes. (*p value of comparison with periods of ESES, **p value comparing ESES-spikes and ESES-no spikes).

	TYP	ESES	Non-ESES	ESES-Spikes	ESES-No Spikes
Minimum	13.29	17.06	9.948	31.42	16.54
Medium	19.93	33.85	18.10	41.42	26.07
Maximum	29.04	45.05	29.27	41.73	27.56
Mean	20.95	33.72	17.81	35.08	24.65
S.D.	4.266	1.758	1.033	4.894	3.805
P	<0.0001*		<0.0001*		0.0054**

coherences in the hippocampus and prefrontal cortex are decreased. Likewise, decreases in coherence occur in conditions such as Alzheimer's disease (Besthorn *et al*., 1994), intellectual impairment (Thatcher *et al*., 2005), attention-deficit disorder and reading difficulties (Barry *et al*., 2009), and autism (Coben *et al*., 2008; Mathewson *et al*., 2012; Khan *et al*., 2013). However, neuronal synchrony in the brain is finely tuned and it is likely that functional "over connectivity" may be as detrimental as "under-connectivity" as a network that is over-connected may not be able to adapt to increased cognitive demand (Supekar *et al*., 2013). High phase locking of neurons in multiple brain regions likely results in neurons in both structures firing with excessive synchrony with a diminished ability to develop localized functional ensembles (Voytek and Knight, 2015). We suggest that, as with other electrophysiological processes, there is an ideal "sweet spot" for coherence and that deviations in either a positive or negative direction can alter behavior and cognition. The findings must be interpreted cautiously. This is an EEG study that examined the relationship of coherence with ESES and we provide no data indicating that increased coherence during ESES in SWS is responsible for the behavioral and cognitive issues in children with CSWS. Rather, we wish to raise the possibility that an overly coherent brain during SWS during childhood may play a role in the behavioral and cognitive problems seen in these children. In one of the other epileptic encephalopathies, West syndrome, it has been shown that children have marked abnormalities in coherence and that improvement in seizures and development are seen only in children in whom the coherences improved (Burroughs *et al*., 2014). In future studies, it will be valuable to examine the relationship of coherences during SWS with clinical symptoms in children with CSWS and whether changes in coherence are a predictor of treatment success. □

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References

Aarts JH, Binnie CD, Smit AM, Wilkins AJ. Selective cognitive impairment during focal and generalized epileptiform EEG activity. *Brain* 1984; 107: 293-308.

Barry JM, Holmes GL. Why are children with epileptic encephalopathies encephalopathic? *J Child Neurol* 2016; 31: 1495-504.

Barry RJ, Clarke AR, Mccarthy R, Selikowitz M. EEG coherence in children with attention-deficit/hyperactivity disorder and comorbid reading disabilities. *Int J Psychophysiol* 2009; 71: 205-10.

Bender AC, Natola H, Ndong C, Holmes GL, Scott RC, Lenck-Santini PP. Focal Scn1a knockdown induces cognitive impairment without seizures. *Neurobiol Dis* 2013; 54: 297-307.

Bender AC, Luikart BW, Lenck-Santini PP. Cognitive deficits associated with Nav1.1 alterations: involvement of neuronal firing dynamics and oscillations. *PLoS ONE* 2016; 11: e0151538.

Besthorn C, Forstl H, Geiger-Kabisch C, Sattel H, Gasser T, Schreiter-Gasser U. EEG coherence in Alzheimer disease. *Electroencephalogr Clin Neurophysiol* 1994; 90: 242-5.

Binnie CD, Kasteleijn-Nolst Trenite DG, Smit AM, Wilkins AJ. Interactions of epileptiform EEG discharges and cognition. *Epilepsy Res* 1987; 1: 239-45.

Binnie CD, Channon S, Marston D. Learning disabilities in epilepsy: neurophysiological aspects. *Epilepsia* 1990; 31: S2-8.

Binnie CD, Channon S, Marston DL. Behavioral correlates of interictal spikes. *Adv Neurol* 1991; 55: 113-26.

Buckley AW, Scott R, Tyler A, *et al*. State-dependent differences in functional connectivity in young children with autism spectrum disorder. *EBioMedicine* 2015; 2: 1905-15.

Burroughs SA, Morse RP, Mott SH, Holmes GL. Brain connectivity in West syndrome. *Seizure* 2014; 23: 576-9.

Coben R, Clarke AR, Hudspeth W, Barry RJ. EEG power and coherence in autistic spectrum disorder. *Clin Neurophysiol* 2008; 119: 1002-9.

Ebus SC, Overvliet GM, Arends JB, Aldenkamp AP. Reading performance in children with rolandic epilepsy correlates with nocturnal epileptiform activity, but not with epileptiform activity while awake. *Epilepsy Behav* 2011; 22: 518-22.

French CC, Beaumont JG. A critical review of EEG coherence studies of hemisphere function. *Int J Psychophysiol* 1984; 1: 241-54.

Galanopoulou AS, Bojko A, Lado F, Moshe SL. The spectrum of neuropsychiatric abnormalities associated with electrical status epilepticus in sleep. *Brain Dev* 2000; 22: 279-95.

Gencpinar P, Dundar NO, Tekgul H. Electrical status epilepticus in sleep (ESES)/continuous spikes and waves during slow sleep (CSWS) syndrome in children: an electroclinical evaluation according to the EEG patterns. *Epilepsy Behav* 2016; 61: 107-11.

Gmehlin D, Thomas C, Weisbrod M, Walther S, Resch F, Oelkers-Ax R. Development of brain synchronisation within school-age: individual analysis of resting (alpha) coherence in a longitudinal data set. *Clin Neurophysiol* 2011; 122: 1973-83.

Holmes GL. What is more harmful, seizures or epileptic EEG abnormalities? Is there any clinical data? *Epileptic Disord* 2014; 16: 12-22.

Holmes GL, Lenck-Santini PP. Role of interictal epileptiform abnormalities in cognitive impairment. *Epilepsy Behav* 2006; 8: 504-15.

Horak PC, Meisenhelter S, Song Y, *et al*. Interictal epileptiform discharges impair word recall in multiple brain areas. *Epilepsia* 2017; 58: 373-80.

Jacinto LR, Reis JS, Dias NS, Cerqueira JJ, Correia JH, Sousa N. Stress affects theta activity in limbic networks and impairs novelty-induced exploration and familiarization. *Front Behav Neurosci* 2013; 7: 127.

Khan S, Gramfort A, Shetty NR, *et al*. Local and long-range functional connectivity is reduced in concert in autism spectrum disorders. *Proc Natl Acad Sci USA* 2013; 110: 3107-12.

Kleen JK, Scott RC, Holmes GL, Lenck-Santini PP. Hippocampal interictal spikes disrupt cognition in rats. *Ann Neurol* 2010; 67: 250-7.

Koop JI, Fastenau PS, Dunn DW, Austin JK. Neuropsychological correlates of electroencephalograms in children with epilepsy. *Epilepsy Res* 2005; 64: 49-62.

Krauss GL, Summerfield M, Brandt J, Breiter S, Ruchkin D. Mesial temporal spikes interfere with working memory. *Neurology* 1997; 49: 975-80.

Mathewson KJ, Jetha MK, Drmic IE, Bryson SE, Goldberg JO, Schmidt LA. Regional EEG alpha power, coherence, and behavioral symptomatology in autism spectrum disorder. *Clin Neurophysiol* 2012; 123: 1798-809.

Mocks J, Gasser T. How to select epochs of the EEG at rest for quantitative analysis. *Electroencephalogr Clin Neurophysiol* 1984; 58: 89-92.

Nair A, Keown CL, Datko M, Shih P, Keehn B, Muller RA. Impact of methodological variables on functional connectivity findings in autism spectrum disorders. *Hum Brain Mapp* 2014; 35: 4035-48.

Nickels K, Wirrell E. Electrical status epilepticus in sleep. *Semin Pediatr Neurol* 2008; 15: 50-60.

Nielsen T, Abel A, Lorrain D, Montplaisir J. Interhemispheric EEG coherence during sleep and wakefulness in left- and right-handed subjects. *Brain Cogn* 1990; 14: 113-25.

Oliveira JF, Dias NS, Correia M, *et al*. Chronic stress disrupts neural coherence between cortico-limbic structures. *Front Neural Circuits* 2013; 7: 10.

Patry G, Lyagoubi S, Tassinari CA. Subclinical "electrical status epilepticus" induced by sleep in children. *Arch Neurol* 1971; 24: 242-52.

Sanchez Fernandez I, Loddenkemper T, Peters JM, Kothare SV. Electrical status epilepticus in sleep: clinical presentation and pathophysiology. *Pediatr Neurol* 2012; 47: 390-410.

Sanchez Fernandez I, Chapman KE, Peters JM, Harini C, Rotenberg A, Loddenkemper T. Continuous spikes and waves during sleep: electroclinical presentation and suggestions for management. *Epilepsy Res Treat* 2013; 2013: 583531.

Sanchez Fernandez I, Chapman K, Peters JM, *et al*. Treatment for continuous spikes and waves during sleep (CSWS): survey on treatment choices in North America. *Epilepsia* 2014; 55: 1099-108.

Scheltens-de Boer M. Guidelines for EEG in encephalopathy related to ESES/CSWS in children. *Epilepsia* 2009; 50: 13-7.

Shewmon DA, Erwin RJ. Transient impairment of visual perception induced by single interictal occipital spikes. *J Clin Exp Neuropsychol* 1989; 1: 675-91.

Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. *Nature* 2010; 464: 763-7.

Singhal NS, Sullivan JE. Continuous spike-wave during slow wave sleep and related conditions. *ISRN Neurol* 2014; 2014: 619079.

Srinivasan R, Winter WR, Ding J, Nunez PL. EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. *J Neurosci Methods* 2007; 166: 41-52.

Supekar K, Uddin LQ, Khouzam A, *et al*. Brain hyperconnectivity in children with autism and its links to social deficits. *Cell Rep* 2013; 5: 738-47.

Tassinari CA, Rubboli G, Volpi L, *et al*. Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clin Neurophysiol* 2000; 111: S94-102.

Thatcher RW. Coherence, phase differences, phase shift, and phase lock in EEG/ERP analyses. *Dev Neuropsychol* 2012; 37: 476-96.

Thatcher RW, Walker RA, Giudice S. Human cerebral hemispheres develop at different rates and ages. *Science* 1987; 236: 1110-3.

Thatcher RW, North D, Biver C. EEG and intelligence: relations between EEG coherence, EEG phase delay and power. *Clin Neurophysiol* 2005; 116: 2129-41.

Thatcher RW, Krause PJ, Hrybyk M. Cortico-cortical associations and EEG coherence: a two-compartmental model. *Electroencephalogr Clin Neurophysiol* 2012; 64: 123-43.

Tucker DM, Roth DL, Bair TB. Functional connections among cortical regions: topography of EEG coherence. *Electroencephalogr Clin Neurophysiol* 1986; 63: 242-50.

Ung H, Cazares C, Nanivadekar A, *et al*. Interictal epileptiform activity outside the seizure onset zone impacts cognition. *Brain* 2017; 140: 2157-68.

Van den Munckhof B, Van D, Sagi L, *et al*. Treatment of electrical status epilepticus in sleep: a pooled analysis of 575 cases. *Epilepsia* 2015; 56: 1738-46.

Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci* 2001; 2: 229-39.

Voytek B, Knight RT. Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. *Biol Psychiatry* 2015; 77: 1089-97.

Whedon M, Perry NB, Calkins SD, Bell MA. Changes in frontal EEG coherence across infancy predict cognitive abilities at age 3: the mediating role of attentional control. *Dev Psychol* 2016; 52: 1341-52.

Zhou JL, Lenck-Santini PP, Zhao Q, Holmes GL. Effect of interictal spikes on single-cell firing patterns in the hippocampus. *Epilepsia* 2007; 48: 720-31.

Original article

Epileptic Disord 2019; 21 (1): 65-77

A comprehensive clinico-pathological and genetic evaluation of bottom-of-sulcus focal cortical dysplasia in patients with difficult-to-localize focal epilepsy

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ABSTRACT – *Aims*. We comprehensively studied the clinical presentation, stereo-EEG and MRI findings, histopathological diagnosis, and brain somatic mutations in a retrospective series of drug-resistant patients with difficult-to-localize epilepsy due to focal cortical dysplasia at the bottom of a sulcus (BOS-FCD).

Methods. We identified 10 patients with BOS-FCD from the Cleveland Clinic epilepsy surgery database submitted for intracranial video-EEG monitoring. Brain MRI, including voxel-based morphometric analysis and surgical tissue submitted for histopathology, was reviewed. Paraffin tissue samples from five patients were made available for targeted next-generation sequencing. Postsurgical follow-up was available in nine patients.

Results. BOS-FCD was identified in the superior frontal sulcus in six patients, inferior frontal sulcus in one patient, central sulcus in one patient, and intraparietal sulcus in two patients. All patients had stereotyped seizures. Intracranial EEG recordings identified ictal onset at the BOS-FCD in all 10 patients, whereas ictal scalp EEG had a localizing value in only six patients. Complete resection was achieved by lesionectomy or focal corticectomy in nine patients. Histopathologically, six patients had FCD type IIb and three had FCD type IIa. Next-generation sequencing analysis of DNA

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extracted from lesion-enriched (micro-dissected) tissue from five patients with FCD type II led to the identification of a germline frameshift insertion in *DEPDC5,* introducing a premature stop in one patient. Eight out of nine patients with available follow-up were completely seizure-free (Engel Class IA) after a mean follow-up period of six years.
Conclusion. Our results confirm previous studies classifying difficult-to-localize BOS-FCD into the emerging spectrum of FCD ILAE type II mTORopathies. Further studies with large patient numbers and ultra-deep genetic testing may help to bridge the current knowledge gap in genetic aetiologies of FCD.

Key words: brain, seizure, mTOR, epilepsy surgery, outcome

Focal cortical dysplasia (FCD) are common histopathological lesions in children and adults with drug-resistant focal epilepsy (Blümcke *et al*., 2017), and hitherto classified into separate clinico-pathological subtypes (Blümcke *et al*., 2011). However, the aetiology and pathogenesis of most of these subtypes remain to be clarified (Najm *et al*., 2018). Such knowledge will be mandatory to also understand their variable occurrence in size, cellular phenotypes, brain localization and clinical presentation (Krsek *et al*., 2008; Lerner *et al*., 2009; Blümcke *et al*., 2010; Chassoux *et al*., 2012; Harvey *et al*., 2015). Continuous improvement in magnetic field strength for MRI diagnosis and the application of advanced post-processing analyses has significantly enhanced clinical identification of FCD subtypes *in vivo*, in particular, of FCD ILAE type II (Urbach *et al*., 2002; Besson *et al*., 2008; Bernasconi *et al*., 2011; Wagner *et al*., 2011; Mellerio *et al*., 2014; Wang *et al*., 2014). As a pertinent example, hyperintense MRI signalling from the lateral ventricle towards the crown of the gyrus was described as a "transmantle sign" (Barkovich *et al*., 1997), and mostly confirmed in FCD IIb and in the frontal lobe (Colombo *et al*., 2009; Colombo *et al*., 2012). Not all FCD II present, however, with a transmantle sign suggesting a larger clinico-pathological spectrum disorder or even separate disease entities. Two previous reports focused on FCD II located at the bottom of sulcus and highlighted these challenges in neuroimaging, clinical, and electroclinical presentation (Chassoux *et al*., 2012; Harvey *et al*., 2015). Tailored surgical resection was particular favourable, with 87-94% of reported patients (n=57) being completely seizure-free. Intriguingly, about 25% of patients did not reveal abnormal signals at initial MRI examination, and the combination of PET with MRI increased the detection rate (Chassoux *et al*., 2010).
With few exceptions, current research has failed to establish pathology-specific molecular biomarkers that clearly distinguish FCD subtypes (Guerrini *et al*., 2015). In the absence of adequate animal models, surgical brain tissue samples open the unique opportunity to further study tissue-specific signatures. A milestone in FCD research represented the identification of brain somatic mutations, germline mutations, or second-hit mosaic mutations activating the mTOR pathway in surgical brain specimens with histopathology-proven FCD type II (Jamuar *et al*., 2014; Scheffer *et al*., 2014; Baulac *et al*., 2015; D'Gama *et al*., 2015; Lim *et al*., 2015; Mirzaa *et al*., 2016; Moller *et al*., 2016; D'Gama *et al*., 2017; Ribierre *et al*., 2018). With only a third of published cases showing a genetic lesion (Marsan and Baulac, 2018), however, continuous efforts are required to improve our understanding of clinically-meaningful FCD subtypes and successful treatment strategies in the near future. The integration of clinical phenotypes with histopathology and genetic analysis is a powerful option, as recently proposed and already implemented by the WHO for the diagnosis of malignant gliomas and embryonal brain tumours (Louis *et al*., 2016).

Methods

Selection of patients

To investigate patients with difficult-to-localize epilepsy due to cortical dysplasia at the bottom of sulcus, we retrospectively reviewed the Cleveland Clinic Epilepsy Center's surgery database with patients who underwent invasive intracranial studies from 2004 to 2014 (as approved by the Cleveland Clinic Institutional Review Board). Inclusion of patients was based on the following criteria:
– drug-resistant focal epilepsy;
– a single MRI lesion restricted to the bottom of a sulcus;
– no previous epilepsy surgery;
– intracranial video-EEG monitoring prior to surgery;
– no concomitant other diagnosis, such as tuberous sclerosis or brain tumour;
– post-operative MRI available to assess the extent of the resection;
– and histopathology slides available for post hoc microscopic review.

Magnetic resonance imaging (MRI)

Four patients were imaged with a 3 T Siemens Trio/Skyra scanner (Erlangen, Germany) and six

patients with a 1.5 T Siemens Avanto scanner (Erlangen, Germany). Sequence parameters at 3 T were: repetition time = 1,860 milliseconds, echo time = 3.4 milliseconds, inversion time = 1,100 milliseconds, flip angle = 10 degrees, band width = 130 kHz, slice thickness = 0.94 mm, no gap, and a 256 × 256 matrix providing isotropic voxels of 0.94 mm. Sequence parameters at 1.5 T were: repetition time = 11 milliseconds, echo time = 4.6 milliseconds, no inversion, flip angle = 20 degrees, band width = 130 kHz, slice thickness = 1.25 mm, no gap, and a 256 × 256 matrix providing 0.9 mm in-plane resolution. All MR images were reviewed by experienced board-certified neuroradiologists specialized in epileptology. Morphometric MRI analysis was available in one patient at the time of surgical evaluation and was retrospectively processed in the remaining nine patients. A voxel-based morphometric analysis program (MAP) was carried out in SPM (Wellcome Department of Cognitive Neurology, London, UK) and Matlab (MathWorks, Natick, Massachusetts) following established protocols (Huppertz *et al*., 2005). MAP was performed on T1-weighted MPRAGE sequence, and the grey-white junction output was examined in each patient with a z-score threshold of 4; the choice of threshold was consistent with previous reports (Wang *et al*., 2014, 2015) (*figure 1*). All 10 patients had FDG-PET. Ictal SPECT was successfully accomplished in six patients and subtraction ictal SPECT coregistered with MRI (SISCOM) was performed.

Neurophysiology

All patients had continuous scalp video-EEG monitoring to confirm the focal epilepsy and characterize the seizure semiology (*table 1*). Following the initial non-invasive evaluation, a recommendation for an invasive intracranial video-EEG evaluation was made during the Cleveland Clinic Epilepsy Center multidisciplinary patient management conference in all 10 patients for three reasons:

– ictal EEG findings and FDG-PET or ictal SPECT was discordant in five patients (*table 1*);

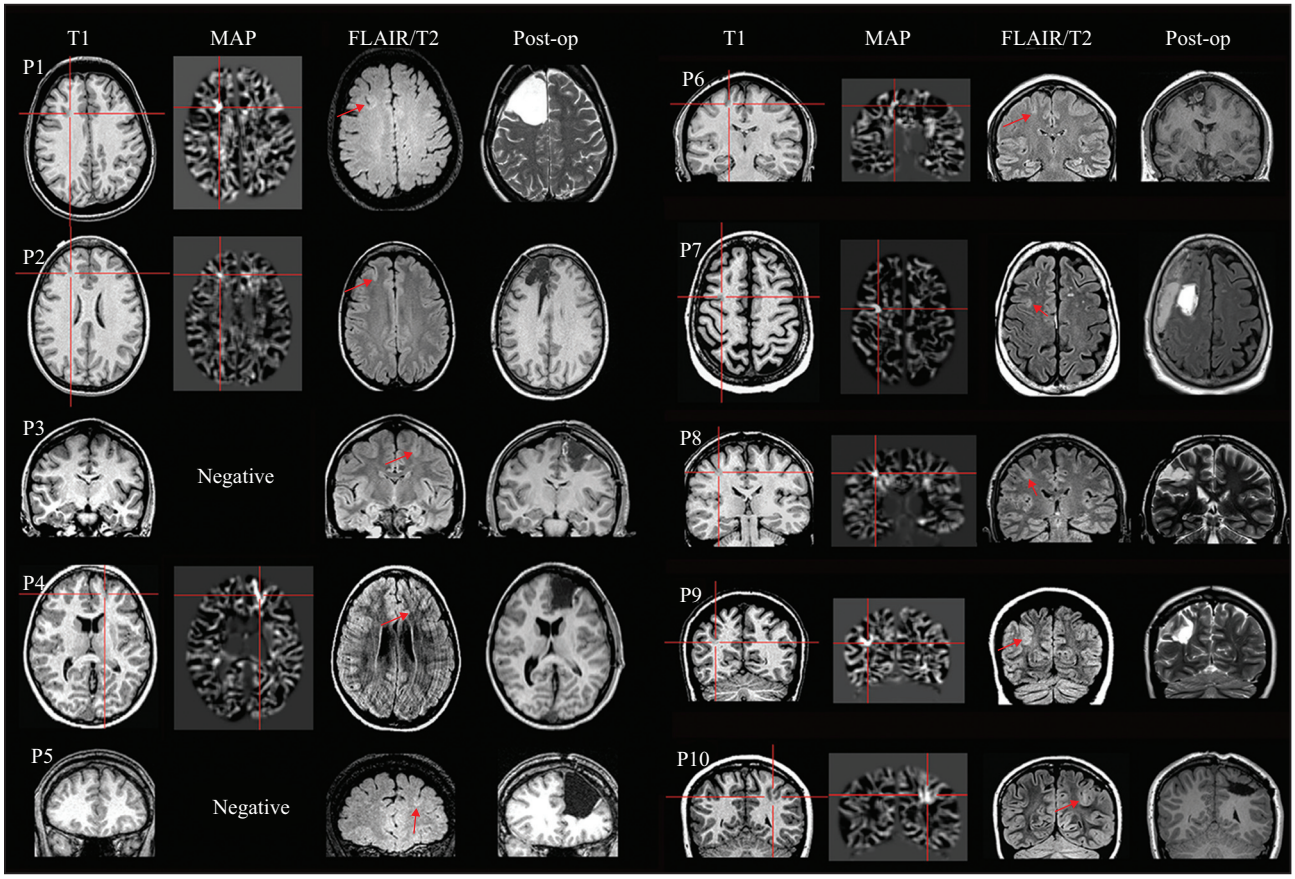

Figure 1. MRI findings and post-processing results for all patients included in the study. The first two columns are the preoperative T1w MPRAGE images and the coregistered MAP grey-white junction output. The crosshair pinpoints the location of the lesion. Absence of the MAP junction image indicates that the MAP processing was negative. The third column is the preoperative FLAIR/T2 images, whichever best depict the lesion (shown by arrow) in that particular patient. The rightmost column shows the postoperative MRI, indicating the extent of resection of the lesions.

Table 1. Detailed demographics and clinical data.

Pt	Age onset (yr)	Age surgery (yr)	MRI	MAP	Other presurgical studies	Seizure semiology	Scalp EEG SZ, interictal SW	Why intra-cranial VEEG?	Intracranial video-EEG	Surgery	Pathology/ Genetics	Outcome	Follow-up (yrs)
1	0.75	46	Right SFS	+	PET: non-contributory Ictal SPECT: concordant	Complex motor ->2nd GTC	SZ: non-localizable SW: none	Scalp EEG seizure non-localizable	SDG+depth	Focal CTX	FCD IIa	Engel IA	5
2	12	35	Right SFS	+	Ictal SPECT and PET: concordant	Non-specific aura -> axial tonic ->complex motor	SZ: non-localizable SW: none	Scalp EEG seizure non-localizable	SDG+depth	LTX	FCD IIb FFPE (10.07%)	Engel IA	5
3	4	20	Left SFS	-	PET: concordant. Ictal SPECT: non-contributory	Non-specific aura -> asymmetric tonic -> right arm clonic	SZ: vertex region SW: vertex, and left centro-parietal	Scalp EEG seizure non-lateralizing	SDG	LTX	FCD IIb FFPE (10.47%)	Engel IA	11
4	1.5	13	Left SFS	+	PET: discordant Ictal SPECT: unsuccess-ful	Right versive -> asymmetric tonic -> 2nd GTC	SZ: left frontal SW: left frontal, left frontal polar	Discordant PET findings	SDG+depth	Focal CTX	FCD IIa FFPE (7.01%) *DEPDC5*	Engel IA	9
5	9	37	Left SFS	-	Ictal SEPCT and PET: concordant with subtle abnormal findings on MRI	Complex motor	SZ (1) left frontal and central; (2) non-localizable SW: none	MRI lesion not clear	SDG+depth	Focal CTX	FCD IIb FFPE (7.79%)	Engel IA	6.5
6	8	29	Right SFS	+	Ictal SPECT and PET : discordant MEG: normal	Head turning to right then left arm elevation	SZ: vertex region and maximum right central; SW: none	Discordant semiology and MRI lesion	SDG+depth	LTX	FCD IIa	Engel IA	2.5

Table 1. Detailed demographics and clinical data (*Continued*).

Pt	Age onset (yr)	Age surgery (yr)	MRI	MAP	Other presurgical studies	Seizure semiology	Scalp EEG SZ, interictal SW	Why intra-cranial VEEG?	Intracranial video-EEG	Surgery	Pathology/ Genetics	Outcome	Follow-up (yrs)
7	13	59	Right IFS	+	PET: non-contributory Ictal SPECT: concordant	Non-specific aura -> left eye/head tonic -> left versive -> 2nd GTC	SZ: (1) right temporo-parietal; (2) right frontocentral; SW: right frontocentral	Functional mapping	SDG+depth	LTX	FCD IIb	NA	NA
8	5	33	Right CS	+	PET: non-contributory Ictal SPECT: unsuccessful	Non-specific aura in left eye -> left face/arm tonic -> 2nd GTC	SZ: right central SW: none	Functional mapping	SEEG	LTX	Small fragment	Engel IA	5.25
9	14	23	Right IPS	+	PET: concordant	Complex visual aura -> dialeptic	SZ: right parieto occipital; SW: right parieto-occipital, posterior temporal	Determine margins of resection	SDG+depth	LTX	FCD IIb FFPE (7.78%)	Engel IA	4.25
10	12	13	Left IPs	+	PET: concordant	Non-specific aura with visual component -> right arm tonic, tonic-clonic -> 2nd GTC	SZ: left centro-parietal SW: left centro-parietal	Functional mapping	SDG+depth	Incomplete LTX	FCD IIb	Engel III	2 months

Pt: patient; yr: year; SFS: superior frontal sulcus; IFS: inferior frontal sulcus; CS: central sulcus; IPS: intra-parietal sulcus; MAP: morphometric analysis program (retrospectively processed in nine patients [Patients 1-9] and not available at the time of surgical evaluation); SDG+depth: subdural grids plus depth electrodes; CTX: corticoectomy; LTX: lesionectomy; SZ: ictal EEG seizure; SW: interictal sharp wave; FFPE: formalin-fixed, paraffin-embedded. Genetic studies were performed in Patients 2, 3, 4, 5 and 9 (numbers within parentheses indicate percentages of dysplastic cells).

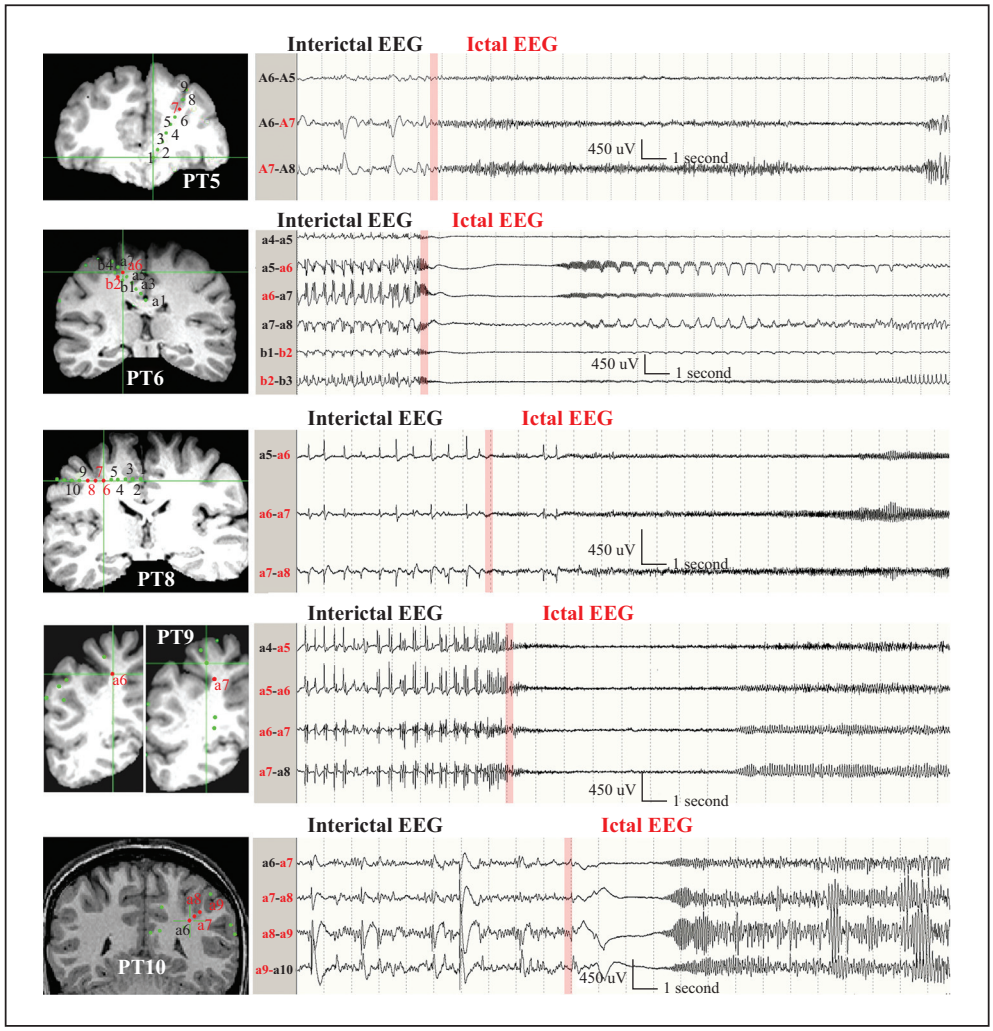

Figure 2. Location of the depth electrode contacts and their anatomic relation to BOS lesions as co-registered on T1-weighted MRI coronal cuts in five patients are shown on the left. The electrode contacts recording ictal EEG onset are labelled in red. The samples of EEG channels recording ictal EEG onset from the depth electrodes (bipolar montage) are shown on the right. The red bars point to the ictal EEG onsets that were preceded by the preictal repetitive spikes/polyspikes in each of the patients. Patients (PT) 6 and 9 showed interictal rhythmic polyspikes and wave discharges that became more frequent immediately prior to the ictal onset. Patients 5 and 10 showed interictal repetitive spikes that were intermixed with low-voltage fast activities. In all patients, ictal EEGs showed tonic fast-frequency discharges. Seizures in Patients 6 and 10 were characterized by a brief initial attenuation of the EEG prior to the emergence of the low-amplitude fast activities.

– eloquent cortical areas had to be mapped for the definition of surgical resection borders in four patients;
– and BOS-FCD was not unambiguously accepted by the group in one patient (Patient 5) (*table 1*).

Eight patients had an implantation of subdural grid electrodes (SDG) together with intracerebral depth electrodes targeting the BOS-FCD of interest. The placement of depth electrodes and their 3D spatial correlation with the MRI-identified lesion was verified through co-registration of post-implantation volume acquisition CT scans and preimplantation high-resolution MRI volume acquisition sequences (*figure 2*). One patient had SDGs without depth electrode implantation (Patient 3) (*table 1*). Patient 8 had stereotactic implantation of depth electrodes according to the SEEG methodology, as previously described (Gonzalez-Martinez *et al.*, 2014).

Neurosurgery

Surgical resection strategies were discussed following the invasive evaluation at our patient management conference, integrating all available data from MRI analysis and neurophysiological recordings. *Post hoc* analysis of the extent of surgical resection was obtained from post-surgical MRI. Post-operative

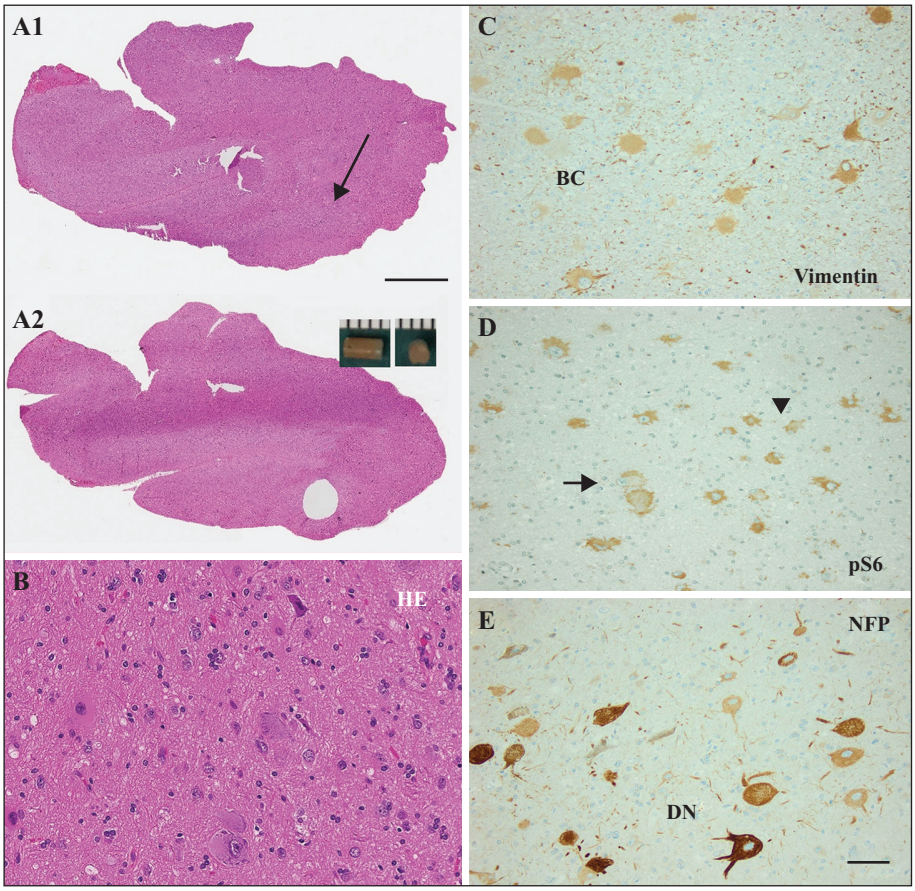

Figure 3. (A-C) H&E staining: whole-slide imaging of Patient 9 (*table 1*) before (A1) and after (A2) microdissection with a 2-mm diameter punching device (scale bar = 4 mm); (B) higher magnification of area indicated by arrow in (A) and used for DNA extraction following micro-dissection (shown in [A']). (C) Vimentin immunohistochemistry highlighting balloon cells (BC); serial section from (B). (D) phosphorylated S6 (pS6) immunohistochemistry highlighting both FCD II cell types, dysmorphic neurons (arrow), and balloon cells (arrowheads); serial section from (B). (E) Immunohistochemistry for neurofilament protein highlighting dysmorphic neurons (DN); serial section from (B). Microscopic measurements reveal 8% of cells with a FCDII phenotype. Scale bar in (B-E) = 50 μm.

seizure outcome was assessed during regular outpatient visits using Engel's classification scale (Engel *et al*., 1993).

Immunohistochemistry

For histopathological diagnosis, surgical specimens were formalin-fixed and paraffin-embedded. Post hoc review of all surgical tissue was based on immunohistochemical stainings to visualize architectural dysplasia (Blümcke *et al*., 2016) using antibodies directed against NeuN (clone A60, Chemicon, USA) and MAP2 (clone HM2, DAKO, Denmark), to visualize dysmorphic neurons with antibodies directed against non-phosphorylated neurofilaments (clone SMI32, Covance, USA) or balloon cells with antibodies directed against vimentin (polyclonal antibody V9, DAKO, Denmark) (*see also* Blümcke *et al*. [2016]). Immunohistochemical detection of the phospho-S6 epitope (clone ser235/236, Cell Signaling Technology, USA) was used to demonstrate an activated mTOR pathway. Areas with highest content of abnormal cells were identified on the H&E section, and the same area labelled in the FFPE bloc. In nine patients, FFPE tissue was micro-dissected using a 2-mm diameter large punching needle (*figure 3*). DNA extraction from the FFPE tissue punch was performed using customized protocols for small FFPE tissue (Qiagen, Germany) with sufficient DNA available for deep sequencing in five patients. Semi-quantitative cell measurements were performed as following: a HE stained section was prepared before and after the tissue punch and fully digitized using whole slide digital imaging (3DHistech, Hungary). All cells within 1 mm^2 of the punched area were counted from the computer screen (range: 171-673 cells). FCD-specific cells referred to dysmorphic neurons in FCD IIa and IIb and balloon cells in FCD IIb and were counted from the same region of interest (range: 18-80 cells). Results were expressed as percentage of FCD-specific from total cells.

Genetic analysis

To perform the targeted sequencing, we used the Agilent SureSelect Custom Enrichment Kit for library preparation of 166 self-selected genes. Library preparation was conducted according to the manufacturer's protocols and subsequent paired-end library sequencing was performed using the Illumina HiSeq4000. The targeted genes included those encoding proteins of the mTOR and PI3K-AKT signalling pathway, genes associated with low-grade brain tumours, and genes associated with epilepsy. The list of mTOR pathway genes was derived from the Kegg Pathway (ID: hsa04150). The PI3K-AKT pathway genes were derived from RT2 Profiler PCR Array (Qiagen, Product no.: 330231). Genes associated with low-grade brain tumours were derived from the recent literature and epilepsy genes were derived from the EpiPM Consortium review in 2015 (Vogelstein *et al.*, 2013; EpiPMConsortium, 2015). The full list of included genes is disclosed in *supplementary table 1*.

For bioinformatic analysis, we generated analysis-ready bam files using BWA to map reads to the human genome reference build GRCh37 (Li and Durbin, 2009). GATK was used to mark duplicated reads (McKenna *et al.*, 2010), perform local realignment, recalibrate the base quality scores, and call SNPs and short indels together with SAM tools and Dindel (Li *et al.*, 2009; Albers *et al.*, 2011). In addition, we used Platypus to call low allele frequency variants (Rimmer *et al.*, 2014). We used the human reference genome build GRCh37 and annotated variant functional consequences and population allele frequencies using wANNOVAR (excessed: 12/2016; http://wannovar.wglab.org). We removed non-protein-coding variants and variants present in individuals from the general population with allele frequency >0.1% to enrich for rare variants of large effect. Variants passing our applied filters, were manually inspected for sequencing and variant calling quality using the Integrative Genomics Viewer (Robinson *et al.*, 2011). The manual evaluation was conducted by three independent scientists. Variant pathogenicity was assessed in accordance with 28 criteria defined by guidelines of the American College of Medical Genetics and Genomics (ACMG) (Richards *et al.*, 2015). We used the online tool, InterVar, to facilitate the variant interpretation process (Li and Wang, 2017).

Results

Patient data

Ten patients fulfilled our inclusion criteria; four males and six females. None of the patients had any neurological deficit at clinical examination. One patient had mild developmental delay (Patient 4) (*table 1*). All patients presented with stereotyped seizures (*see table 1*), without a history of *status epilepticus*, infantile spasms or febrile seizures. Age at epilepsy onset ranged from 0.75 to 14 years (mean: 7.2 years). Age at time of surgery ranged from 13 to 59 years (mean: 33.2 years). Epilepsy duration was between one and 46 years (mean: 23.4 years). None of the patients had a history of pre- or perinatal injuries except for one patient who was born two months premature (Patient 7) (*table 1*). Clinical histories and seizure description of all patients included in the study are summarized in *table 1*.

Imaging data

BOS-FCD was identified in all patients by epilepsy expert neuroradiology review (*figure 1*). Six lesions were located in the superior frontal sulcus, one lesion in the inferior frontal sulcus, one lesion in the central sulcus, and two lesions in the intraparietal sulcus. Focal cortical thickening and blurring of the grey-white matter junction at the bottom of a sulcus was a common MRI finding in all patients, as illustrated in *figure 1*. These abnormalities were best visible on FLAIR sequences. Eight out of 10 patients had concordant signal changes on T1w images (*figure 1*). Blurring of the grey-white matter junction was evident on T1w images in four patients by visual inspection (Patients 1, 4, 9, and 10) (*table 1*), and eight patients showed positive MAP foci. Blurring of the grey-white matter junction on T1w images became evident in four patients only after MAP analysis with a z-score set >4 (Patients 2, 6, 7, and 8). No T1w signal changes were observed visually or by MAP analysis in the remaining two patients (Patients 3 and 5). A funnel-shaped, subcortical hyper-intensity tapering abnormality towards the ventricular surface (transmantle sign) was seen in three patients (Patients 1, 8 and 9) (*see figure 1*).

Scalp video-EEG monitoring

Habitual seizures were documented in all patients by scalp video-EEG-monitoring. Semiology could not be, however, correlated simply with lobar location of the BOS-FCD (*table 1*). As an example, most of the auras were non-specific. Secondly, presence of auras with eye involvement could be anatomically misleading in both patients (Patients 9 and 10) with intraparietal BOS-FCD. Ictal EEG patterns were non-localizable in two patients (Patients 1 and 2) (*table 1*), regional lobar for two patients in one brain region (Patients 4 and 8) and for two patients with two adjacent brain regions

(Patients 9 and 10), and at the midline vertex region in two patients (Patients 3 and 6). Interictal sharp waves were absent in five patients and did not add localizing value in non-localizing ictal EEGs.

FDG-PET and ictal SPECT

Interictal FDG-PET studies were performed in all patients (*table 1*); only five out of 10 patients exhibited focal hypometabolism concordant with the lesion detected by MRI, whereas the remaining five patients had non-contributory results, including two patients with discordant PET localization. In four out of six patients with successful ictal SPECT and SISCOM, the area of hyperperfusion was concordant with the MRI-visible BOS-FCD (*table 1*).

Invasive video-EEG monitoring

At the time of surgical evaluation, all 10 patients proceeded to invasive EEG evaluation based on the decision of the patient management conference at that time (*table 1*): non-localizing ictal EEG in three patients, atypical semiology associated with the lesion in one patient, MRI lesion was not unanimously convinced by the committee in one patient, discordant PET hypometabolism in one patient, and functional mapping was recommended in four patients.

Habitual seizures were documented in all patients also by invasive video-EEG monitoring. Ictal EEG onset was mapped to depth electrode contacts localized in the BOS-FCD or in areas sampled adjacent to the lesion in eight patients (*figure 2*). In the remaining two patients (Patient 2 with no depth electrode contacts in the proximity of the lesion or depth of sulcus, and Patient 3 with SDG electrodes only), ictal EEG onset was recorded from electrodes placed in the gyral crown of the sulci harbouring the lesion.

The depth electrodes were located within or in close vicinity to the BOS-FCD in seven patients (*table 1*). Only in Patient 2, co-registration revealed the depth electrode not inside or close to the lesion. Histopathology analysis confirmed the iEEG trajectory in close vicinity to the FCD in one patient (data not shown). Intracranial EEG recordings with depth electrode contacts in bottom-of-sulcus lesions showed continuous interictal discharge patterns consisting of rhythmic (1-3-Hz) spikes/polyspikes and waves. The rhythmic spiking pattern was intermixed with low-amplitude fast discharges (*figure 2*). Extraoperative video and EEG recordings captured the patients' typical clinical seizures with stereotyped ictal EEG onset patterns that were localized at the depth electrode contacts in or near the BOS-FCD (*figure 2, also in reference to figure 1*). All EEG seizures transitioned from continuous pre-ictal rhythmic epileptiform discharges to tonic fast frequency discharges of variable voltage for durations ranging from 15 to 25 seconds (*figure 2*).

Surgical resection and seizure outcome

Neurosurgical resection of the lesion was limited to overlying and surrounding cortex (*i.e.* lesionectomy) in seven patients and corticoectomy with resection of the lesion plus adjacent gyri was performed in three patients (*table 1*). *Figure 1* illustrates the anatomy of the resection in all patients (post-operative MRI). Eight patients became free of seizures and auras (Engel Class 1A) (*table 1*) with a mean follow-up time of six years (2.5 years to 11 years). One patient (Patient 7) did not return for follow-up. One patient (Patient 10) had incomplete resection due to the epileptic zone overlapping with eloquent cortex, as determined by extraoperative brain stimulation via subdural grids and depth electrodes, and this patient continued to have seizures (Engel Class III).

Histopathological findings

All surgical specimens were histopathologically and immunohistochemically reviewed and classified as FCD ILAE type II, with a combination of dysmorphic neurons and balloon cells (FCD IIb) in six patients and dysmorphic neurons only (FCD IIa) in three patients (*table 1*). Only small tissue fragments were submitted for pathological examination in one patient and microscopic review remained inconclusive (Patient 8). The gross neuroanatomical presentation of FCD IIb can be demonstrated best using immunohistochemical labelling of surgically well-preserved specimens with the characteristic presentation of vimentin-immunoreactive balloon cells and neurofilament-accumulating dysmorphic neurons (*figures 3, 4*). In addition, immunohistochemical labelling of the phospho-S6 epitope revealed specific staining in all specimens.

Genetic findings

Targeted next-generation sequencing (NGS) achieved a mean coverage of 245 × (SD = 60) across the target genes, with 96.3% (SD = 0.95) of bases covered at 50 × (*supplementary table 1*). The microdissected patient samples harboured a mean fraction of dysplastic cells of 8.6% (SD=1.4). Given our sequencing coverage and the assumption that all dysplastic cells should carry the variant, we would have been able to detect 99% of all brain somatic variants with Platypus in these cells (Richards *et al.*, 2015). We screened for coding variants in 166

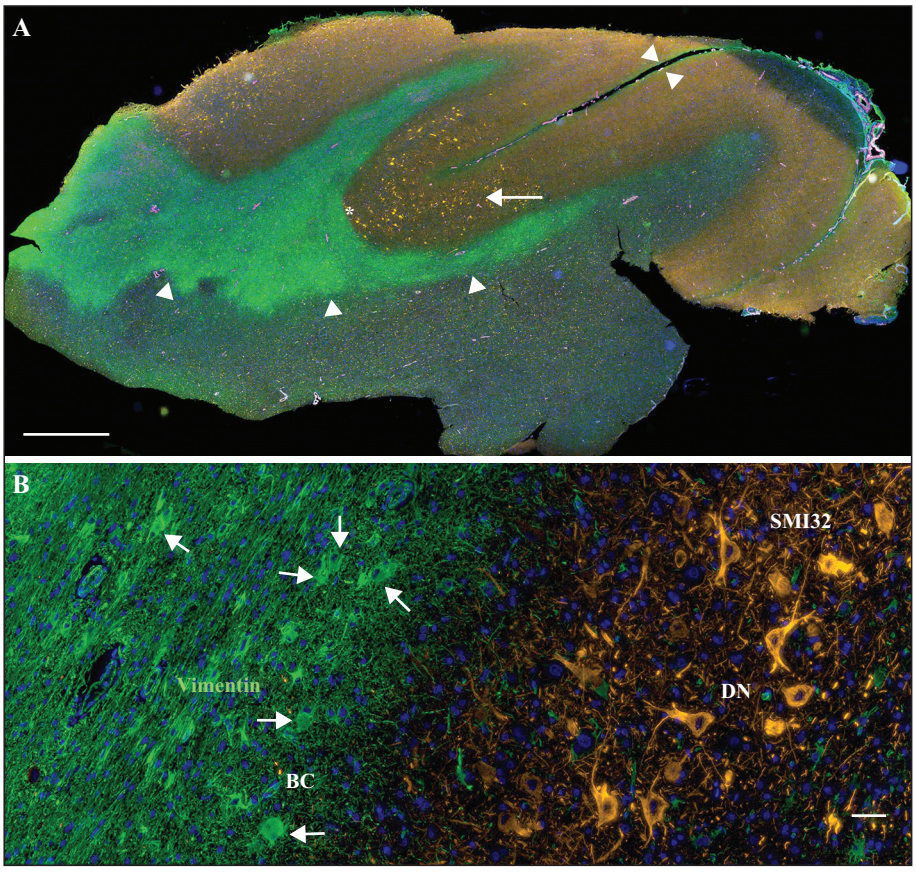

Figure 4. Surgical histopathology of Patient 9 (*table 1*). (A) Concentration of dysmorphic neurons (arrow) decorated with anti-non-phosphorylated neurofilament H-specific antibodies (clone SMI32, Alexa555-labeled anti-mouse IgG1 secondary antibody, orange pseudocolour) at the bottom of a sulcus (sulcal surface indicated by small arrowheads), with concomitant accumulation of vimentin-positive balloon cells (clone SP20, Alexa488-labeled anti-rabbit IgG secondary antibody, green pseudocolour; arrowheads) in the underlying white matter. In addition, vascular myocytes expressing smooth muscle actin (clone 1A4, Alexa647-labelled anti-murine IgG2a secondary antibody, magenta pseudocolour) and nuclei (Hoechst 33342, blue pseudocolour) are visualized (multichannel-immunofluorescence whole slide imaging, 3DHistech MIDI). (B) High-power magnification of area indicated by asterisk in (A) showing predominant localization of vimentin-immunopositive balloon cells (BC) in white matter (as indicated by arrows) and SMI32-immunopositive dysmorphic neurons (DN) in grey matter. Scale bar in (A) = 2 mm, in (B) = 50 μm.

candidate genes (*supplementary table 1*) and did not identify brain somatic variants. DNA obtained from blood leucocytes was, however, not available in this retrospective analysis to confirm germline origin. The variants were identified in eight genes and comprised nine exonic heterozygous missense variants (mean allele frequency = 47%; SD = 3.6) and one frameshift insertion introducing a stop codon. All nine missense variants were classified as 'variants of uncertain significance' (VUS) using state-of-the-art guidelines in the field (Richards *et al.*, 2015). The frameshift insertion (NM_001136029, p.Asp1075Glufs*3) introduces a premature stop codon in *DEPDC5*, likely leading to haploinsufficiency and was classified as 'likely pathogenic' for the epilepsy according to recommended ACMG guidelines and current epilepsy literature (Ishida *et al.*, 2013; Lal *et al.*, 2014; Epi4Kconsortium, 2017).

Discussion

Our comprehensive analysis of 10 patients with difficult-to-localize BOS-FCD confirms previous studies with a "syndromic description" of FCD ILAE type II:

– seizure onset at preschool or school age;
– mostly of frontal localization;
– stereotyped seizures;
– distinct MRI features;
– intrinsic epileptogenicity;
– favourable postsurgical seizure outcome following complete resection of the epileptic region;
– and exclusivity of FCD type II with immunohistochemical or genetic evidence for activation of the mTOR pathway.

The fact that FCD-BOS lesions are small and localized to the bottom of sulcus suggested, however, a later

occurrence of a (presumably) genetically acquired pathogen during the estimated 32 mitotic cycles of cortical brain development, compared to FCD II lesions involving a larger cortical area or extending even to hemimegalencephaly (D'Gama *et al*., 2017; Blümcke and Sarnat, 2016).

NGS analysis of a panel of 166 mTor, PIK3/Akt, and other epilepsy-related genes detected a likely pathogenic, epilepsy-associated variant in *DEPDC5* (terminology used according to ACMG guidelines) in only one out of five patients studied. This is consistent with previous studies, which reported 'likely pathogenic' variants in mTOR pathway-associated genes in only 25% (SD=40) of patients with histopathologically confirmed FCD II (Marsan and Baulac, 2018). The majority of variants have been reported as brain somatic with allele frequencies of 1-12.6%, and predominantly affecting the *MTOR* gene (Baulac *et al*., 2015; D'Gama *et al*., 2015; Lim *et al*., 2015; Mirzaa *et al*., 2016; Moller *et al*., 2016; D'Gama *et al*., 2017). One study reported germline *DEPDC5* mutations in cases of BOS-FCD, which further stressed the association with mTORopathies (Scheffer *et al*., 2014). Recently described second-hit mosaic mutations may be another etiologic pathomechanism to be taken into consideration (Ribierre *et al*., 2018). In our present study, we detected a new pathogenic *DEPDC5* heterozygous variant in one patient with FCD IIa. Stop codon-inducing germline variants in *DEPDC5* have recently been shown to be present in 3% of patients (cohort: n=1187) with familial non-acquired focal epilepsy without cortical structural abnormalities and only in 0.05% of controls (cohort: n=3877; $p=9.6 \times 10^{-12}$) (Epi4Kconsortium, 2017). In addition, one study identified a somatic mutation in *DEPDC5* in addition to an existing germline mutation (Baulac *et al*., 2015). The *DEPDC*5 variant identified in this study had an allele frequency of 41%. However, only 8.6% (SD=1.4) of cells shared a dysplastic phenotype by microscopic review, indicating that the identified p.Asp1075Glufs*3 *DEPDC5* variant is unlikely to be only present in dysplastic cells. Unfortunately, we were not able to validate this prediction because blood samples were not available retrospectively. Further studies should clarify whether this *DEPDC5* variant is causal for the epilepsy or if the epilepsy is secondary to FCDII. In all other BOS-FCD patients, no likely pathogenic or pathogenic variant was identified. However, our NGS coverage was, for the majority of samples, higher compared to previous reports (median: 243.72x *vs*. 180x), which should enable us to detect 99% of all somatic variants with variant allele frequencies of $> 8\%$. Our results call for extended molecular/genetic investigations integrating ultra-deep exome-wide DNA and single-cell RNA sequencing, as well as methylome and proteomic analysis to identify a possible pathogenic cause(s). Future progress in precision medicine will build on such analysis to develop a targeted drug treatment for specific mTOR signalling molecules, in particular, when epilepsy surgery is not an option for a given patient.

Despite the fact that our study addressed only a small number of patients and any conclusion would need confirmation by larger and prospectively collected patient series, the comprehensive approach integrating genotype with phenotype analysis will help to consolidate the recognition of FCD-BOS in focal and difficult-to-localize epilepsies. Re-review of MRI and application of post-processing methodologies led to the identification of cortical dysplasia at BOS localization in all our patients, most often in the frontal or parietal lobes. Favourable outcome after neurosurgical resection, histopathological diagnosis of FCD II, and genetic testing helped to validate the clinical hypothesis. No other diagnostic modality added significant value in clinical management, as seen from a retrospective angle. In the future, MRI fingerprinting is the resolution for this population of patients (Ma *et al*., 2013). □

Supplementary data.

Supplementary table is available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

References

Albers CA, Lunter G, MacArthur DG, McVean G, Ouwehand WH, Durbin R. Dindel: accurate indel calls from short-read data. *Genome Res* 2011; 21: 961-73.

Barkovich AJ, Kuzniecky RI, Bollen AW, Grant PE. Focal transmantle dysplasia: a specific malformation of cortical development. *Neurology* 1997; 49: 1148-52.

Baulac S, Ishida S, Marsan E, *et al*. Familial focal epilepsy with focal cortical dysplasia due to *DEPDC5* mutations. *Ann Neurol* 2015; 77: 675-83.

Bernasconi A, Bernasconi N, Bernhardt BC, Schrader D. Advances in MRI for 'cryptogenic' epilepsies. *Nat Rev Neurol* 2011; 7: 99-108.

Besson P, Andermann F, Dubeau F, Bernasconi A. Small focal cortical dysplasia lesions are located at the bottom of a deep sulcus. *Brain* 2008; 131: 3246-55.

Blümcke I, Sarnat HB. Somatic mutations rather than viral infection classify focal cortical dysplasia type II as mTORopathy. *Curr Opin Neurol* 2016; 29: 388-95.

Blümcke I, Pieper T, Pauli E, *et al*. A distinct variant of focal cortical dysplasia type I characterised by magnetic resonance imaging and neuropathological examination in children with severe epilepsies. *Epileptic Disord* 2010; 12: 172-80.

Blümcke I, Thom M, Aronica E, *et al*. The clinico-pathological spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 2011; 52: 158-74.

Blümcke I, Aronica E, Miyata H, *et al*. International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: a consensus Task Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia* 2016; 57: 348-58.

Blümcke I, Spreafico R, Haaker G, *et al*. Histopathological findings in brain tissue obtained during epilepsy surgery. *New Engl J Med* 2017; 377: 1648-56.

Chassoux F, Rodrigo S, Semah F, *et al*. FDG-PET improves surgical outcome in negative MRI Taylor-type focal cortical dysplasias. *Neurology* 2010; 75: 2168-75.

Chassoux F, Landre E, Mellerio C, *et al*. Type II focal cortical dysplasia: electroclinical phenotype and surgical outcome related to imaging. *Epilepsia* 2012; 53: 349-58.

Colombo N, Salamon N, Raybaud C, Ozkara C, Barkovich AJ. Imaging of malformations of cortical development. *Epileptic Disord* 2009; 11: 194-205.

Colombo N, Tassi L, Deleo F, *et al*. Focal cortical dysplasia type IIa and IIb: MRI aspects in 118 cases proven by histopathology. *Neuroradiology* 2012; 54: 1065-77.

D'Gama AM, Geng Y, Couto JA, *et al*. Mammalian target of rapamycin pathway mutations cause hemimegalencephaly and focal cortical dysplasia. *Ann Neurol* 2015; 77: 720-5.

D'Gama AM, Woodworth MB, Hossain AA, *et al*. Somatic mutations activating the mtor pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias. *Cell Rep* 2017; 21: 3754-66.

Engel J Jr, Van Ness PC, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: *Surgical treatment of the epilepsies*. Engel J Jr. New York: Raven Press, 1993.

EpiPMConsortium. A roadmap for precision medicine in the epilepsies. *Lancet Neurol* 2015; 14: 1219-28.

Epi4Kconsortium. Ultra-rare genetic variation in common epilepsies: a case-control sequencing study. *Lancet Neurol* 2017; 16: 135-43.

Gonzalez-Martinez J, Mullin J, Bulacio J, *et al*. Stereoelectroencephalography in children and adolescents with difficult-to-localize refractory focal epilepsy. *Neurosurgery* 2014; 75: 258-68, discussion: 67-8.

Guerrini R, Duchowny M, Jayakar P, *et al*. Diagnostic methods and treatment options for focal cortical dysplasia. *Epilepsia* 2015; 56: 1669-86.

Harvey AS, Mandelstam SA, Maixner WJ, *et al*. The surgically remediable syndrome of epilepsy associated with bottom-of-sulcus dysplasia. *Neurology* 2015; 84: 2021-8.

Huppertz HJ, Grimm C, Fauser S, *et al*. Enhanced visualization of blurred gray-white matter junctions in focal cortical dysplasia by voxel-based 3D MRI analysis. *Epilepsy Res* 2005; 67: 35-50.

Ishida S, Picard F, Rudolf G, *et al*. Mutations of *DEPDC5* cause autosomal dominant focal epilepsies. *Nat Genet* 2013; 45: 552-5.

Jamuar SS, Lam AT, Kircher M, *et al*. Somatic mutations in cerebral cortical malformations. *New Engl J Med* 2014; 371: 733-43.

Krsek P, Maton B, Korman B, *et al*. Different features of histopathological subtypes of pediatric focal cortical dysplasia. *Ann Neurol* 2008; 63: 758-69.

Lal D, Reinthaler EM, Schubert J, *et al*. *DEPDC5* mutations in genetic focal epilepsies of childhood. *Ann Neurol* 2014; 75: 788-92.

Lerner JT, Salamon N, Hauptman JS, *et al*. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: a critical review and the UCLA experience. *Epilepsia* 2009; 50: 1310-35.

Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* 2009; 25: 1754-60.

Li Q, Wang K. InterVar: clinical interpretation of genetic variants by the 2015 ACMG-AMP Guidelines. *Am J Hum Genet* 2017; 100: 267-80.

Li H, Handsaker B, Wysoker A, *et al*. The sequence alignment/map format and SAMtools. *Bioinformatics* 2009; 25: 2078-9.

Lim JS, Kim WI, Kang HC, *et al*. Brain somatic mutations in MTOR cause focal cortical dysplasia type II leading to intractable epilepsy. *Nature Med* 2015; 21: 395-400.

Louis DN, Perry A, Reifenberger G, *et al*. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 2016; 131: 803-20.

Ma D, Gulani V, Seiberlich N, *et al*. Magnetic resonance fingerprinting. *Nature* 2013; 495: 187-92.

Marsan E, Baulac S. Review: Mechanistic target of rapamycin (mTOR) pathway, focal cortical dysplasia and epilepsy. *Neuropathol Appl Neurobiol* 2018; 44: 6-17.

McKenna A, Hanna M, Banks E, *et al*. The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. *Genome Res* 2010; 20: 1297-303.

Mellerio C, Labeyrie MA, Chassoux F, *et al*. 3T MRI improves the detection of transmantle sign in type 2 focal cortical dysplasia. *Epilepsia* 2014; 55: 117-22.

Mirzaa GM, Campbell CD, Solovieff N, *et al*. Association of MTOR mutations with developmental brain disorders, including megalencephaly, focal cortical dysplasia, and pigmentary mosaicism. *JAMA Neurol* 2016; 73: 836-45.

Moller RS, Weckhuysen S, Chipaux M, *et al*. Germline and somatic mutations in the MTOR gene in focal cortical dysplasia and epilepsy. *Neurol Genet* 2016; 2: e118.

Najm IM, Sarnat HB, Blümcke I. Review: the international consensus classification of focal cortical dysplasia - a critical update 2018. *Neuropathol Appl Neurobiol* 2018; 44: 18-31.

Ribierre T, Deleuze C, Bacq A, *et al*. Second-hit mosaic mutation in mTORC1 repressor DEPDC5 causes focal cortical dysplasia-associated epilepsy. *J Clin Invest* 2018; 128: 2452-8.

Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; 17: 405-24.

Rimmer A, Phan H, Mathieson I, *et al*. Integrating mapping-, assembly- and haplotype-based approaches for calling variants in clinical sequencing applications. *Nat Genet* 2014; 46: 912-8.

Robinson JT, Thorvaldsdottir H, Winckler W, *et al*. Integrative genomics viewer. *Nature Biotech* 2011; 29: 24-6.

Scheffer IE, Heron SE, Regan BM, *et al*. Mutations in mammalian target of rapamycin regulator DEPDC5 cause focal epilepsy with brain malformations. *Ann Neurol* 2014; 75: 782-7.

Urbach H, Scheffler B, Heinrichsmeier T, *et al*. Focal cortical dysplasia of Taylor's balloon cell type: a clinicopathological entity with characteristic neuroimaging and histopathological features, and favorable postsurgical outcome. *Epilepsia* 2002; 43: 33-40.

Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz Jr. LA, Kinzler KW. Cancer genome landscapes. *Science* 2013; 339: 1546-58.

Wagner J, Weber B, Urbach H, Elger CE, Huppertz HJ. Morphometric MRI analysis improves detection of focal cortical dysplasia type II. *Brain* 2011; 134: 2844-54.

Wang ZI, Alexopoulos AV, Jones SE, *et al*. Linking MRI postprocessing with magnetic source imaging in MRI-negative epilepsy. *Ann Neurol* 2014; 75: 759-70.

Wang ZI, Jones SE, Jaisani Z, *et al*. Voxel-based morphometric magnetic resonance imaging (MRI) postprocessing in MRI-negative epilepsies. *Ann Neurol* 2015; 77: 1060-75.

Original article

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Neuropsychological correlates of obstructive sleep apnea severity in patients with epilepsy

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ABSTRACT – *Aims*. Obstructive sleep apnea affects up to 30% of patients with epilepsy. As obstructive sleep apnea represents a clinical risk factor for cognitive deficits, its occurrence in epilepsy patients may exacerbate cognitive deficits associated with this condition. However, the cognitive burden of obstructive sleep apnea in epilepsy remains poorly understood. We conducted a retrospective record review of adults with epilepsy who underwent a polysomnography and a neuropsychological assessment at Brigham and Women's Hospital.

Methods. We examined the relationship between obstructive sleep apnea severity and cognitive functioning, particularly attention/executive functions, memory, and processing speed in untreated obstructive sleep apnea patients with epilepsy. Twenty patients with epilepsy and mild-to-severe obstructive sleep apnea were included in the analyses.

Results. We found significant positive correlations between the oxygen saturation levels during rapid-eye-movement sleep and attention/executive tests ($p<0.05$), as well as time spent with saturation levels $\leq$90% and executive functioning ($p=0.008$). Similarly, worse verbal memory performances were associated with lower oxygen levels ($p=0.003$). In addition, more severe respiratory events during rapid-eye-movement sleep were associated with worse performances on attention tests ($p=0.03$).

Conclusions. Our findings indicate that more severe obstructive sleep apnea-related hypoxemia during sleep is associated with poorer cognitive performances on tests that assess attention/executive functions and verbal memory in patients with epilepsy. Overall, these results are consistent with the sleep apnea literature, and suggest that patients with epilepsy are also vulnerable to the effects of obstructive sleep apnea. Future prospective studies will help in determining whether treatment of obstructive sleep apnea may help improve cognitive functioning in patients with epilepsy.

Key words: epilepsy, polysomnography, obstructive sleep apnea, neuropsychology, cognition

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Sleep-related breathing disorders, such as obstructive sleep apnea (OSA), are common in adults with epilepsy, affecting up to one third of patients (Lin *et al*., 2017). OSA is one of the most common reported factors associated with reduced quality of life in individuals with epilepsy (Piperidou *et al*., 2008). These patients also frequently report excessive daytime sleepiness (Manni *et al*., 2003; Gammino *et al*., 2016) and are more likely to have seizures during sleep (Malow *et al*., 2000; Manni *et al*., 2003). OSA may exacerbate seizure occurrence by causing nocturnal episodes of intermittent hypoxemia and electroencephalographic (EEG) arousals (Devinsky *et al*., 1994).

When left untreated, OSA can have major negative health consequences; it increases the risk of hypertension, type 2 diabetes, and cardiovascular diseases (Shahar *et al*., 2001); for a review see Maeder *et al*. (2016). OSA is also a well-known risk factor for cognitive deficits (Yaffe *et al*., 2011; Rosenzweig *et al*., 2015). Indeed, accumulating evidence demonstrates the negative impacts of OSA on nearly all domains of cognition, though larger effect sizes are more commonly found for attention, executive functions, and psychomotor speed (Rosenzweig *et al*., 2015; Stranks and Crowe, 2016). Several facets of executive functioning are impaired in adults with OSA as compared to healthy controls, including set-shifting, working memory, inhibition, and problem-solving (Olaithe and Bucks, 2013; Bucks *et al*., 2017). The mechanisms by which OSA may impair cognition are not yet fully clear, but it is postulated that the combination of sleep fragmentation, cyclical intermittent hypoxemia, and hypercapnia, as well as ensuing metabolic consequences, may all play a role (Rosenzweig *et al*., 2015).

Cognitive problems are also often reported in patients with various epilepsy syndromes. On neuropsychological testing, many studies have demonstrated significant impairments in cognitive flexibility, attention, psychomotor speed, and memory functions in patients with epilepsy (Elger *et al*., 2004; Hermann *et al*., 2007; Loughman *et al*., 2014). As OSA is frequent in epilepsy and represents a clinical risk factor for cognitive deficits, its occurrence in epilepsy patients might worsen initial cognitive impairments. However, the cognitive burden of OSA in epilepsy is poorly understood, and only one study to date investigated subjective cognitive functioning in epilepsy patients at risk of OSA (Piperidou *et al*., 2008).

We conducted a retrospective study to examine the effects of sleep apnea severity on cognitive functioning in untreated OSA patients with epilepsy. We hypothesized that more severe OSA would be associated with poorer cognitive performances, particularly on tests assessing attention/executive functions and processing speed.

Material and methods

Participants

We retrospectively reviewed clinical data of all adult individuals with epilepsy seen in the neurology clinic at Brigham and Women's Hospital who underwent a polysomnography (PSG) for evaluation of OSA and complete neuropsychological testing (with an interval of less than 18 months), from May 2012 to November 2017. The study was approved by the institutional review board.

Diagnosis of epilepsy was confirmed by expert epileptologists using history, seizure semiology, EEG, and neuroimaging data. Patients with non-epileptic seizures were not included in the study. Subjects were also excluded from the analysis if they received treatment for OSA at the time of the neuropsychological assessment, and if they were diagnosed with dementia. For each subject, we examined demographic and clinical data, including education level, body mass index (BMI), neck circumference, cardiovascular risk factors (such as hypertension, diabetes, and hypercholesterolemia), smoking status, epilepsy refractoriness (defined as the persistence of seizures despite adequate trials of two antiepileptic drugs [AEDs]), epilepsy duration, seizure characteristics, and the number of AEDs. We also collected data on subjective daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS), when available.

Polysomnographic recordings

All subjects underwent in-laboratory overnight sleep recordings. The PSG montage included EEG, electrooculography, electromyography, and electrocardiography recordings. Respiration was monitored continuously using nasal thermistor flow, nasal pressure, pharyngeal snoring, and thoracic and abdominal belts. Oxygen saturation was monitored using finger pulse oximetry sensors. Leg movements were recorded using surface electrodes on anterior tibialis muscles. Sleep stages were visually scored per standard criteria (Iber *et al*., 2007). Apneas were documented if they occurred for 10 seconds or longer and hypopneas were scored when there was at least 30% decrement in nasal pressure signal for at least 10 seconds in combination with either a 3% oxygen desaturation or EEG arousal (Berry *et al*., 2012). The apnea-hypopnea index (AHI) was defined as the sum of all apnea and hypopnea events divided by total sleep time.

Baseline PSG variables included total sleep time, sleep latency and efficiency, rapid-eye-movement (REM) sleep latency, wakefulness after sleep onset, apnea-hypopnea arousal index (number of apnea and

hypopnea events associated with an EEG arousal per hour), periodic limb movement during sleep index, and duration of sleep stages. In addition to the well-studied AHI in OSA research, we also included for analysis variables that reflected the severity of OSA associated hypoxemia, such as the nadir oxygen saturation (SaO_2) levels and percent of time spent with SaO_2 levels lower or equal to 90%. Such variables have been suggested to be more sensitive measures of the effects of OSA on cognition, as compared to solely the number of apnea events (Quan *et al*., 2011). Thus, in the present analysis, OSA-related variables of interest included total and REM AHI, apnea-hypopnea arousal index, total and REM nadir SaO_2, and percent of total sleep time with $SaO_2 \leq 90\%$.

Neuropsychological assessment

Complete neuropsychological testing was performed at Brigham and Women's Hospital either as part of the pre-surgical assessment or upon referral from the treating physician (as part of the epilepsy evaluation). The neuropsychological battery assessed several cognitive domains, including attention, executive functions, episodic memory, language, visuospatial skills, and speed processing. To focus the number of comparisons, and given that previous studies have shown more consistently that OSA has a negative impact on attention, executive, and speed functions (Rosenzweig *et al*., 2015; Stranks and Crowe, 2016), we included tests that assess attention/executive functions, episodic memory, and processing speed.

Moreover, because the testing was performed as part of a clinical investigation, and therefore individualized for each patient, we selected for analysis only the tests for which sufficient data (>50% of patients) were available (with the exception of episodic memory tests; see details below). Converted z-scores of the following neuropsychological variables were included in the analyses: (1) *Attention/Executive functions*: Trail Making Test Part A and B (time), Digit Span subtest from the Wechsler Adult Intelligence Scale (WAIS-III or IV editions), and Phonemic (F, A, and S) Verbal Fluency; and (2) *Speed processing*: the Coding subtest from the WAIS-III or IV editions. For episodic memory tests, composite scores were computed for the verbal and non-verbal domains using averaged z-scores to account for the large heterogeneity of tests used to assess memory processes. The following tests were included in the composite scores for (3) *Verbal episodic memory*: the Rey Auditory Verbal Learning Test (learning trials, immediate and delayed recalls), Logical Memory (immediate and delayed recalls) subtest from the Wechsler Memory Scale-Third Edition, and California Verbal Learning Test-Second edition (learning trials, short and long delay free recalls); and (4) *Non-verbal episodic memory*: the Brief Visuospatial Memory Test-Revised (learning trials and delayed recall), 7/24 Spatial Recall Test (immediate and delayed recalls), Visual Reproduction (immediate and delayed recalls) from the Wechsler Memory Scale-IV Edition, and Rey-Osterrieth Complex Figure (immediate and delayed recalls).

All the neuropsychological test scores were converted to age-corrected z-scores using standard normative data. The Trail Making Test, Verbal Fluency, and episodic memory scores were also corrected for education.

Statistical analyses

All neuropsychological z-scores, except the Trail Making Test Part B, followed a normal distribution (Shapiro-Wilk test; $p>0.05$). However, none of the OSA-related variables were normally distributed, and therefore non-parametric tests were used for these variables.

First, to identify potential clinical confounding variables, we performed correlations between clinical data (age, BMI, number of AEDs, and duration of epilepsy) and our variables of interest, including both OSA (total AHI, REM sleep AHI, apnea-hypopnea arousal index, nadir SaO_2, REM sleep nadir SaO_2, and time spent in $SaO_2 \leq 90\%$) and neuropsychological variables in all patients. Partial correlation was then used to control for potential confounding factors when a significant relationship was found, and this was done separately for each analysis. If no confounding factors were identified, Pearson or Spearman correlation was used to assess the relationship between OSA-related variables and neuropsychological scores. Statistical analyses were performed using SPSS, version 24. Significance was set at $p<0.05$.

Results

A total of 34 adults diagnosed with epilepsy underwent a PSG and a neuropsychological assessment within an 18-month interval at Brigham and Women's Hospital between May 2012 and November 2017. All patients reported complaints of sleep apnea, including hypersomnolence and snoring, and one patient also reported insomnia symptoms. Twenty-eight patients met OSA criteria (AHI ≥ 5). Of that sample, eight patients were excluded because of dementia (n=1), initiation of OSA therapy at the time of testing (n=6), and invalid test results (n=1). Thus, 20 patients with epilepsy and comorbid OSA were included in the analysis. Demographic, clinical, and sleep data of our study sample of epilepsy patients are presented in *table 1*.

Table 1. Demographic, clinical, and sleep data of all epilepsy patients.

Clinical characteristics	Patients, *n* = 20	Polysomnographic data	Patients, *n* = 20
Age (years)	50.3 ± 15.1	Total AHI	22.4 ± 20.3
Gender (M/F)	13/7	REM sleep AHI	26.5 ± 28.5
Education (years)	15.1 ± 2.9	Total nadir SaO_2	85.8 ± 5.4
Body mass index	30.8 ± 8.9	REM sleep nadir SaO_2	88.6 ± 5.4
Neck circumference (inches)	15.4 ± 1.7	% total sleep time with SaO_2 ≤90%	4.1 ± 5.2
ESS score	10.4 ± 6.9	PLMS index	8.7 ± 23.3
Cardiovascular risk factors (n [%])		Total sleep time (minutes)	293.5 ± 95.4
0	13 (65%)	Sleep latency (minutes)	41.9 ± 69.4
1-2	6 (30%)		
>3	1 (5%)	Sleep efficiency (%)	73.6 ± 19.2
Active smoking status (n [%])	2 (10%)	Wakefulness after sleep onset (minutes)	76.0 ± 55.5
Duration of epilepsy (years)	22.9 ± 20.0	Apnea-hypopnea arousal index	14.6 ± 14.7
Drug-resistant epilepsy (n [%])	6 (30%)	Stage N1 (%)	15.6 ± 12.0
Seizure frequency per month (range)	3.8 ± 9.1 (0-30)	Stage N2 (%)	54.9 ± 13.9
Nocturnal seizures (n [%])	7 (35%)	Stage N3 (%)	9.0 ± 8.8
Number of antiepileptic drugs	1.7 ± 0.8	Stage REM (%)	18.6 ± 8.5
Epilepsy type (n [%])			
Focal	16 (80%)		
Generalized	4 (20%)		

ESS: Epworth Sleepiness Score; ED: epileptiform discharges (ictal and interictal); AHI: apnea/hypopnea index; SaO_2: oxygen saturation; REM: rapid eye movement; OSA: obstructive sleep apnea; PLMS: periodic limb movement during sleep.

Most patients had left temporal lobe epilepsy (60%) and seizures were medically well-controlled in 70% of patients. Nine (45%) patients had mild OSA (AHI ≥5 and <15), five (25%) patients had moderate OSA (AHI ≥15 and <30), and six (30%) patients had severe OSA (AHI ≥30). Of note, none of the patients had a seizure during the PSG recordings.

Table 2 shows the averaged neuropsychological z-scores of all epilepsy patients. Overall, worse group performances were observed for the Trail Making Test Part B and the non-verbal memory composite score (mean <1 standard deviation).

Table 2. Neuropsychological z-scores of all epilepsy patients.

Neuropsychological variables	Z-score
Trail Making Test Part A	-0.86 ± 1.66
Trail Making Test Part B	-3.81 ± 4.76
Digit Span	-0.32 ± 1.11
Phonemic Verbal Fluency	-0.72 ± 1.51
Coding	-0.60 ± 1.03
Verbal memory composite score	-0.48 ± 1.16
Non-verbal memory composite score	-1.22 ± 1.37

Association of OSA severity with neuropsychological variables

Significant negative correlations were found between the BMI and REM sleep nadir SaO_2 (r=-0.52, p=0.02), as well as between the number of AEDs and scores on

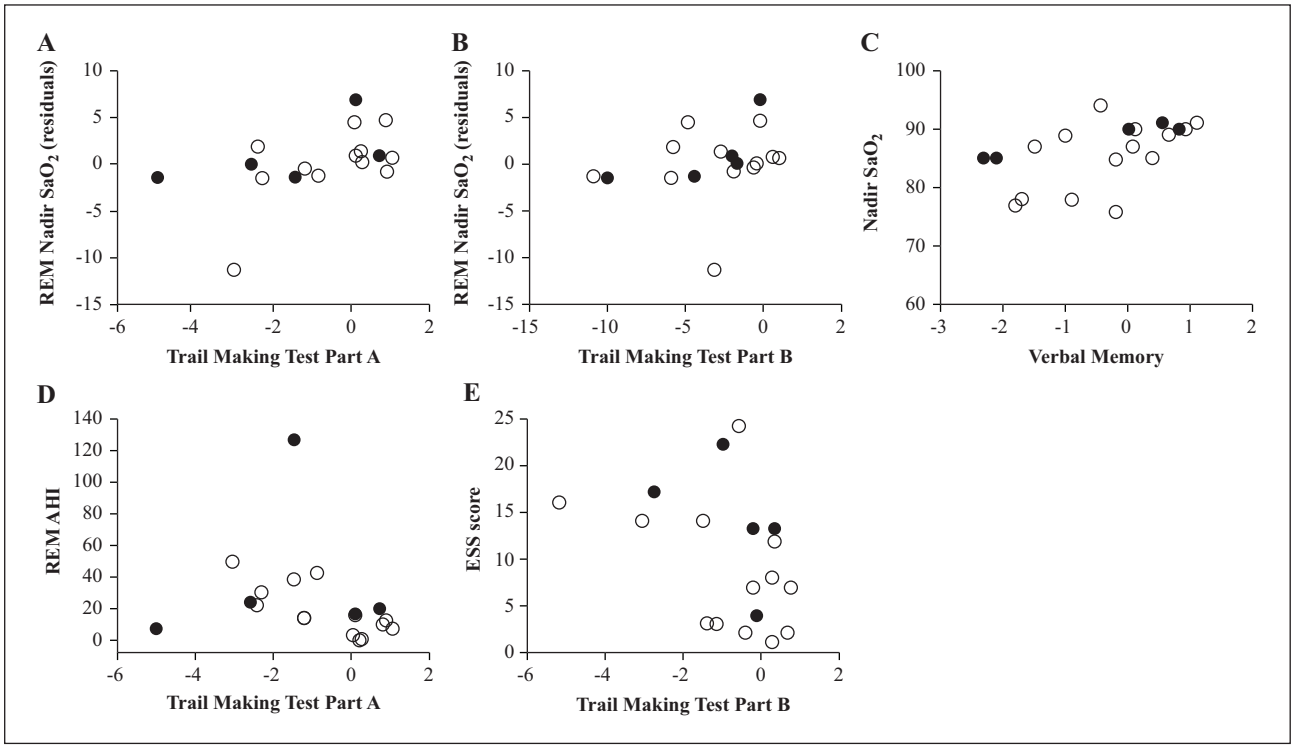

Figure 1. Scatter plots of relationships between OSA-related variables and neuropsychological and sleepiness outcomes in epilepsy patients. BMI-adjusted REM nadir SaO_2 data are represented using unstandardized residuals. Filled dots represent drug-resistant epilepsy patients; empty dots represent medically controlled epilepsy patients.
REM: rapid eye movement; SaO_2: oxygen saturation; AHI: apnea-hypopnea index; ESS: Epworth Sleepiness Scale.

the Digit Span (r=-0.49, p=0.04). No significant correlation was found for any other potential confounding factors (age and duration of epilepsy). The BMI and number of AEDs were therefore used as covariates for these specific analyses.

Significant correlations were observed between OSA-related variables and neuropsychological z-scores in epilepsy patients (a subset of these correlations is illustrated in *figure 1*). More specifically, we found a significant positive correlation between REM sleep nadir SaO_2 and scores on the Trail Making Test Part A (r=0.50, p=0.047) (*figure 1A*) and B (r=0.52, p=0.038) (*figure 1B*), indicating that lower oxygen level during REM sleep is related to lower attentional and executive functioning. Moreover, increased time spent with SaO_2 levels $\leq$90% is associated with worse performances on the Trail Making Test Part B (r=-0.62, p=0.008). We also found significant correlations between the verbal memory composite scores and total nadir SaO_2 levels (r=0.63, p=0.003) (*figure 1C*) and time spent with SaO_2 levels $\leq$90% (r=-0.55, p=0.015), suggesting that higher oxygen levels during sleep were associated with better verbal memory performances in patients.

In addition, we found significant negative correlations between the REM sleep AHI and scores on the Trail Making Test Part A (r=-0.55, p=0.019) (*figure 1D*) and Coding (r=-0.50; p=0.031), indicating that higher OSA severity during REM sleep is associated with poorer cognitive performances on tests assessing attention and processing speed in epilepsy patients. One patient with drug-resistant epilepsy showed a remarkably high REM sleep AHI (126 events/hour; 3 standard deviations above the mean of the sample). The scatter plot shows that this patient strongly affects the correlation analysis (*figure 1D*). Upon exclusion of this subject, the correlation between the REM AHI and Trail Making Test Part A remained (r=-0.53, p=0.03), however REM AHI was no longer associated with scores on the Coding subtest (p>0.05).

Given the limited sample size, supplementary analysis of the relationship between OSA severity and neuropsychological scores according to epilepsy refractoriness was not performed (drug-resistant epilepsy; n=6). However, as illustrated in *figure 1*, these patients were identified using a different symbol, with drug-resistant epilepsy patients represented by filled dots. Overall, there does not seem to be a clear pattern emerging from the data.

We also performed correlations between the ESS and neuropsychological scores and found a significant

negative correlation with the Trail Making Test Part B (r=-0.49, p=0.041), indicating that higher daytime sleepiness is associated with worse executive functioning in epilepsy patients (*figure 1E*).

Finally, although we initially included the number of AEDs as a potential confounding factor in our analyses, our sample size limited specific analysis of AED types and dosages, particularly the AEDs with known cognitive side effects (such as phenobarbital, phenytoin, topiramate, valproic acid, and benzodiazepines) (Eddy *et al*., 2011; Witt and Helmstaedter, 2017). Nevertheless, we examined the number of patients taking these AEDs, and found that only a small number were taking valproic acid (n=6) and benzodiazepines (for anxiety, n=2). None of the subjects were taking phenobarbital, phenytoin, or topiramate at the time of testing, which are the ones associated with the most negative cognitive profile (Eddy *et al*., 2011; Witt and Helmstaedter, 2017). Again, given the limited sample size, supplementary analysis according to polytherapy (n=13) status was not performed, but data are presented visually in *supplementary figure 1*. Patients on polytherapy are represented by the filled stars. Overall, there does not seem to be a clear pattern, with patients on polytherapy being spread at both ends of the data spectrum.

Discussion

Our findings indicate that higher OSA severity and associated intermittent nocturnal hypoxemia is linked to worse cognitive performances in adults with epilepsy. More specifically, we found that lower oxygen levels across all sleep stages are associated with lower scores on tests assessing executive functioning and verbal memory. Impaired breathing during REM sleep appears to have a strong relationship with cognition, affecting predominantly attention and executive functions. Epilepsy patients who reported more daytime sleepiness were also more likely to have lower executive functioning.

To our knowledge, this is the first study that has examined the effects of OSA severity on cognitive functioning as assessed by comprehensive neuropsychological testing in adults with epilepsy. Our results are consistent with the literature findings in the OSA population, showing that OSA is linked with poorer cognitive performances, especially based on tests assessing attention, and executive and psychomotor speed functions (Rosenzweig *et al*., 2015; Stranks and Crowe, 2016). Although larger effect sizes are usually found for the above-mentioned cognitive domains, episodic verbal memory (mainly retrieval processes, which are closely related to executive capacity) has also been reported to be impacted by OSA (Bucks *et al*., 2017).

Our results also extend previous reports that OSA-related hypoxemia variables may be more sensitive measures of the effects of OSA on cognition, by contrast to the frequency of apnea events per hour (Quan *et al*., 2011). Similarly, in older adults with OSA, nocturnal hypoxemia was found to be a significant risk factor of future cognitive decline, while the number of respiratory events was not (Yaffe *et al*., 2011). Besides, we found no significant relationship between OSA-associated arousals (apnea-hypopnea arousal index) and any cognitive measure in our patients. Although we did not have a group of healthy controls as comparison, sleep architecture variables such as sleep latency, duration of sleep stages, and number of awakenings were overall within the normal range. Therefore, our results suggest that nocturnal hypoxemia may be more debilitating for cognition than the number of apnea events and global sleep architecture in adults with epilepsy.

The mechanisms by which OSA may impair cognition are not fully understood. Yet, it has been proposed that both sleep fragmentation and intermittent hypoxemia may play a role (Rosenzweig *et al*., 2015). Several studies have demonstrated that OSA is associated with structural and functional cerebral abnormalities, which are thought to underlie the cognitive deficits observed in these patients. Indeed, adults with OSA have reduced grey matter volume (Shi *et al*., 2017), white matter fiber integrity (Castronovo *et al*., 2014), and cerebral glucose metabolism (Yaouhi *et al*., 2009; Ju *et al*., 2012) in multiple areas, including the frontal and temporal lobes. These areas are known to be involved in executive functions and memory processes, and thus may explain why these are particularly impaired in OSA individuals. Although no study to date has investigated the effects of OSA on specific areas of the brain in patients with epilepsy, it may be postulated that these patients may be more vulnerable and show more pronounced brain abnormalities relative to individuals with OSA but without epilepsy. Future large case-control prospective studies will be needed to examine whether epilepsy patients are indeed more vulnerable to the effects of OSA from a cognitive and neuronal standpoint. Moreover, whether a specific seizure onset zone has a differential vulnerability to the effects of OSA will require further investigation. Importantly, these brain abnormalities and associated cognitive consequences can be, at least partially, reversed by consistent and accurate treatment. Indeed, meta-analytic studies in patients with OSA have shown that treatment with continuous positive airway pressure (CPAP) therapy may improve vigilance, attention, and executive functions (Olaithe and Bucks, 2013; Pan *et al*., 2015). These improvements in cognitive functioning in OSA patients, compliantly treated with CPAP, were paralleled by positive

changes in grey and white matter integrity and cerebral glucose metabolism (Canessa *et al.*, 2011; Ju *et al.*, 2012; Castronovo *et al.*, 2014). Other treatments such as mandibular advancement has also been found to improve executive functioning, psychomotor skills, daytime sleepiness, and quality of life in OSA patients (Galic *et al.*, 2016). In epilepsy patients, studies have also shown that patients treated with CPAP were more than five times more likely to have a significant reduction in seizure frequency and daytime sleepiness compared to untreated patients (Lin *et al.*, 2017). These results suggest that CPAP may help reduce sleep apnea-related hypoxemia and arousals, further improving sleep stability, and thereby reducing seizure susceptibility. CPAP might also help in reducing OSA consequences in epilepsy patients such as cognitive impairment, but also apnea-related cardiovascular, metabolic, and neuronal dysfunctions.

Limitations

Some limitations of our study should be noted. It is a retrospective chart review and uses a patient population that is seen in the regular epilepsy clinic, and as such, our inclusion criteria were more limited. Thus, we cannot exclude that some potential confounding factors such as other OSA-related comorbidities or the effects of AEDs could have had an impact on our sleep and cognitive measurements. However, we have included the number of AEDs as a potential confounding factor in our analysis so that it was controlled for when significantly associated with our variables of interest. Moreover, a minority of subjects were taking AEDs with known cognitive side effects. While this does not preclude any potential contribution of drug-related cognitive side effects on our main results, it is unlikely to explain all of our findings. Visual analysis of the relationships between our OSA and neuropsychological variables according to drug polytherapy status also revealed no clear pattern, with patients on polytherapy being spread at both ends of the OSA or cognitive spectrum. Additionally, the retrospective nature of the study (medical chart review) limited extensive evaluation of OSA-related clinical outcomes, such as duration of OSA symptoms. One could hypothesize that longer duration of OSA symptoms would lead to more severe cognitive impairment in the long-term. However, based on the clinical notes, patients usually reported unclear onset of symptoms ('for several years'), long-standing daytime sleepiness ('always been sleepy'), and/or no bed partner to confirm snoring or witness apneas. We also had a small number of patients, which precluded a more detailed analysis of the effects of OSA on cognition in relation to epilepsy types (*e.g.* temporal versus extra-temporal) or seizure characteristics, in particular, seizure frequency. Since only six patients had drug-resistant epilepsy (with large heterogeneity in seizure frequency), we lacked statistical power to perform correlations between seizure frequency and cognitive functioning/OSA-related variables. Yet, it was shown previously in a cohort of older adults with epilepsy that OSA was associated with a higher seizure frequency (Chihorek *et al.*, 2007). In this study, it was not just the hypoxemia, but also probably the arousals from apnea/hypopnea that lead to the worsening of seizure frequency (Chihorek *et al.*, 2007). Moreover, nocturnal seizures were reported in some patients (7/20). It is likely that nocturnal seizures contribute to worsen sleep quality (sleep fragmentation, lighter sleep), and vice-versa. Yet it is still undetermined whether cognitive dysfunction in epilepsy patients is driven by the impact of nocturnal seizures on sleep quality. It is not possible with our current sample to examine this question, but future work using a mediation model with a large sample of patients could help better understand these mechanisms.

Finally, we acknowledge that the use of a delay interval of up to 18 months between the PSG and neuropsychological testing constitutes a limitation. Ideally, in a prospective study, the PSG would have been performed at the same time as the neuropsychological testing (and review of epilepsy-related data). For patients with the longest intervals, it is possible that the clinical profile (OSA severity, cognition, and seizure frequency) changed, thereby modifying the relationships we observed. Yet, only a minority of patients (n=3) had more than 12 months delay between the PSG and neuropsychological examination.

As far as we know, this is the first study that has examined the relationship between OSA severity and cognitive dysfunctions in patients with epilepsy using objective measures. These results remain to be tested for replication in larger cohorts of epilepsy patients. Although no comparison group was included, this is a first step towards a better understanding of the potential consequences of OSA in epilepsy. In fact, we were quite surprised that from our chart review, only a small number of patients who were referred for a neuropsychological assessment also underwent PSG. Yet sleep disorders are very common in epilepsy, with OSA affecting up to one third of patients (Lin *et al.*, 2017). This highlights the need for clinicians to screen, on a regular basis, their patients at high risk of OSA so that they can be referred and treated accordingly.

Conclusions

OSA is frequent in adults with epilepsy and is one of the most common reported factors associated with

reduced quality of life. Our study shows that OSA is also associated with worse cognitive functioning in epilepsy, affecting primarily attention, executive functions, and verbal memory processes. These results are consistent with the OSA literature and suggest that patients with epilepsy are also vulnerable to the effects of OSA. Future prospective studies will help in determining whether treatment of OSA may help improve cognitive functioning in patients with epilepsy. □

Supplementary data.
Supplementary figure is available on the www.epilepticdisorders.com website.

Disclosures.
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References

Berry RB, Budhiraja R, Gottlieb DJ, *et al*. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. *J Clin Sleep Med* 2012; 8: 597-619.

Bucks RS, Olaithe M, Rosenzweig I, Morrell MJ. Reviewing the relationship between OSA and cognition: where do we go from here? *Respirology* 2017; 22: 1253-61.

Canessa N, Castronovo V, Cappa SF, *et al*. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med* 2011; 183: 1419-26.

Castronovo V, Scifo P, Castellano A, *et al*. White matter integrity in obstructive sleep apnea before and after treatment. *Sleep* 2014; 37: 1465-75.

Chihorek AM, Abou-Khalil B, Malow BA. Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy. *Neurology* 2007; 69: 1823-7.

Devinsky O, Ehrenberg B, Barthlen GM, Abramson HS, Luciano D. Epilepsy and sleep apnea syndrome. *Neurology* 1994; 44: 2060-4.

Eddy CM, Rickards HE, Cavanna AE. The cognitive impact of antiepileptic drugs. *Ther Adv Neurol Disord* 2011; 4: 385-407.

Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. *Lancet Neurol* 2004; 3: 663-72.

Galic T, Bozic J, Ivkovic N, Gunjaca G, Ticinovic TK, Dogas Z. Effects of mandibular advancement device treatment on arterial stiffness and glucose metabolism in patients with mild to moderate obstructive sleep apnea: a prospective 1-year study. *Sleep Breath* 2016; 20: 69-77.

Gammino M, Zummo L, Bue AL, *et al*. Excessive daytime sleepiness and sleep disorders in a population of patients with epilepsy: a case-control study. *J Epilepsy Res* 2016; 6: 79-86.

Hermann B, Seidenberg M, Lee EJ, Chan F, Rutecki P. Cognitive phenotypes in temporal lobe epilepsy. *J Int Neuropsychol Soc* 2007; 13: 12-20.

Iber C, Ancoli-Israel S, Chesson A, Quan S. The AASM Manual for the Scoring of Sleep and Associates Events: Rules. *Terminology and technical specifications. Sleep (Rochester)* 2007: 59.

Ju G, Yoon IY, Lee SD, Kim YK, Yoon E, Kim JW. Modest changes in cerebral glucose metabolism in patients with sleep apnea syndrome after continuous positive airway pressure treatment. *Respiration* 2012; 84: 212-8.

Lin Z, Si Q, Xiaoyi Z. Obstructive sleep apnoea in patients with epilepsy: a meta-analysis. *Sleep Breath* 2017; 21: 263-70.

Loughman A, Bowden SC, D'Souza W. Cognitive functioning in idiopathic generalised epilepsies: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2014; 43: 20-34.

Maeder MT, Schoch OD, Rickli H. A clinical approach to obstructive sleep apnea as a risk factor for cardiovascular disease. *Vasc Health Risk Manag* 2016; 12: 85-103.

Malow BA, Levy K, Maturen K, Bowes R. Obstructive sleep apnea is common in medically refractory epilepsy patients. *Neurology* 2000; 55: 1002-7.

Manni R, Terzaghi M, Arbasino C, Sartori I, Galimberti CA, Tartara A. Obstructive sleep apnea in a clinical series of adult epilepsy patients: frequency and features of the comorbidity. *Epilepsia* 2003; 44: 836-40.

Olaithe M, Bucks RS. Executive dysfunction in OSA before and after treatment: a meta-analysis. *Sleep* 2013; 36: 1297-305.

Pan YY, Deng Y, Xu X, Liu YP, Liu HG. Effects of continuous positive airway pressure on cognitive deficits in middle-aged patients with obstructive sleep apnea syndrome: a meta-analysis of randomized controlled trials. *Chin Med J* 2015; 128: 2365-73.

Piperidou C, Karlovasitou A, Triantafyllou N, *et al*. Influence of sleep disturbance on quality of life of patients with epilepsy. *Seizure* 2008; 17: 588-94.

Quan SF, Chan CS, Dement WC, *et al*. The association between obstructive sleep apnea and neurocognitive performance-the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* 2011; 34: 303-14.

Rosenzweig I, Glasser M, Polsek D, Leschziner GD, Williams SC, Morrell MJ. Sleep apnoea and the brain: a complex relationship. *Lancet Respir Med* 2015; 3: 404-14.

Shahar E, Whitney CW, Redline S, *et al*. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001; 163: 19-25.

Shi Y, Chen L, Chen T, *et al*. A meta-analysis of voxel-based brain morphometry studies in obstructive sleep apnea. *Sci Rep* 2017; 7: 10095.

Stranks EK, Crowe SF. The cognitive effects of obstructive sleep apnea: an updated meta-analysis. *Arch Clin Neuropsychol* 2016; 31: 186-93.

Witt JA, Helmstaedter C. How can we overcome neuropsychological adverse effects of antiepileptic drugs? *Expert Opin Pharmacother* 2017; 18: 551-4.

Yaffe K, Laffan AM, Harrison SL, *et al*. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 2011; 306: 613-9.

Yaouhi K, Bertran F, Clochon P, *et al*. A combined neuropsychological and brain imaging study of obstructive sleep apnea. *J Sleep Res* 2009; 18: 36-48.

TEST YOURSELF

(1) When left untreated, obstructive sleep apnea can have major impact on cognition. Which cognitive domains are particularly affected by obstructive sleep apnea in the general population?

(2) According to this study, which cognitive domains seem particularly affected by more severe obstructive sleep apnea in epilepsy?

(3) When designing a prospective study to examine the effects of obstructive sleep apnea on cognitive functioning in patients with epilepsy and whether treatment of obstructive sleep apnea may help improve cognition, what would be the most sensitive OSA-related measure?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

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A novel mutation in *KCNQ3*-related benign familial neonatal epilepsy: electroclinical features and neurodevelopmental outcome

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ABSTRACT – Benign familial neonatal epilepsy (BFNE) is caused, in about 5% of families, by mutations in the *KCNQ3* gene encoding voltage-gated potassium channel subunits. Usually, newborns with BFNE show a normal neurological outcome, but recently, refractory seizures and/or developmental disability have been reported suggesting phenotype variability associated with *KCNQ3*-related BFNE. Here, we describe a proband from a BFNE family carrying a novel variant in the *KCNQ3* gene. Regarding the paucity of data in the literature, we describe the presented case with a view to further establishing: (1) a genotype/phenotype correlation in order to define a BFNE phenotype associated with favourable outcome; (2) an electroclinical pattern associated with BFNE based on video-EEG recording; (3) appropriate first-line AEDs; and (4) the duration of AED treatment. The presented case from Day 3 exhibited a cluster of ictal events, identified as epileptic seizures on Day 10 based on continuous video-EEG polygraphy. The seizures were characterized by asymmetric tonic posturing, associated with a generalized decrease in EEG amplitude, and followed by bilateral asynchronous clonic movements associated with bicentral sharp-wave discharges. The seizures were refractory to intravenous pyridoxine, whereas levetiracetam resulted in rapid total seizure control which has remained to date. This study demonstrates that the novel heterozygous *KCNQ3* (c. 914A>T; p.Asp305Val) variant, affecting residues in the pore region, is associated with a specific electroclinical pattern and favourable neurodevelopmental outcome. [*Published with video sequence on www.epilepticdisorders.com*]

Key words: benign familial neonatal epilepsy, *KCNQ*, voltage-gated potassium channels, genotype-phenotype correlations, electroclinical features

VIDEO ONLINE

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Benign familial neonatal epilepsy (BFNE) is an autosomal dominant epilepsy syndrome characterized by frequent unprovoked focal or generalized tonic seizures, followed by apnoea and clonic movements with oculofacial features often associated with autonomic signs, starting around the second/third day of life and occurring during wakefulness and sleep, up to 30 times a day. The seizures often remit spontaneously within weeks or months, but some patients become seizure-free only after trials with different antiepileptic drugs (AEDs) (Ryan *et al*., 1991; Ronen *et al*., 1993). BFNE is caused in >80% of families by mutations in the *KCNQ2* and *KCNQ3* genes encoding for voltage-gated potassium channel subunits, which underlie a slowly activating, non-inactivating potassium current called M-current (Biervert *et al*., 1998; Charlier *et al*., 1998; Singh *et al*., 1998; Wang *et al*., 1998).

A reduction in M-current emerged as the common factor underlying neonatal seizures and haploinsufficiency, as the primary pathogenetic mechanism for BFNE (Soldovieri *et al*., 2007). Usually, newborns with BFNE show normal neurological and physical examination and unremarkable laboratory and neuroradiological investigations. Follow-up studies reveal that about 10-15% of patients develop a form of benign focal or generalized epilepsy later in life within a context of normal neurocognitive development (Ronen *et al*., 1993; Singh *et al*., 2003). Given the recent emergence of phenotype variability concerning the clinical course, the sensitivity to AEDs, and the treatment duration, in the present study, we describe the clinical course, electroclinical pattern revealed by video-EEG monitoring, response to AEDs, and the apparently favourable outcome of a proband from a BFNE family carrying a novel variant in the *KCNQ3* gene.

Case study

The proband was a 13-month-old male; the second born to non-consanguineous and apparently healthy parents at 38 + 6 weeks of gestation by elective Caesarean section following an uncomplicated pregnancy. The study was approved by the Ethics Committee "Palermo 1" of the University Hospital. Written informed consent for publication was obtained from the parents.

Apgar score at birth was 9 and 10 at one minute and five minutes, respectively. His weight was 3,240 g (36^{th} centile), length 50 cm (44^{th} centile), and head circumference 35 cm (63^{th} centile).

From Day 3, he exhibited recurrent postprandial episodes of jerking involving the upper limbs, perioral cyanosis, and crying; symptoms considered to be associated with gastroesophageal reflux disease. As paroxysmal events recurred, on Day 9, the patient was referred to our NICU. On admission, the new-born showed mild axial hypotonia and reduced spontaneous motility. Complete blood count, procalcitonin, CRP, blood cultures, glucose, serum electrolytes, neonatal metabolic screening, and a head ultrasound were normal.

On Day 10, during a conventional EEG polygraphy (*see video*), the new-born showed, in active sleep, a cluster of three similar ictal events characterized by generalized or focal tonic (asymmetric tonic posturing) seizures with shallow breathing, mild desaturation, eye blinking, and tachycardia associated with a generalized decrease in EEG amplitude. The tonic component of the seizure progressed during a vibratory phase, gradually evolving into unilateral or bilateral asynchronous clonic movements, lasting for about a minute and associated with bicentral sharp-wave discharges. The focal seizures involved both sides, varying from one seizure to another one. The seizures ended without focal clinical and EEG signs or postictal EEG depression (*figure 1*).

After careful clinical and EEG evaluation suggesting the epileptic nature of paroxysmal events, we administered pyridoxine (100 mg; intravenous). Another similar seizure occurred three hours later. Therefore, after parental informed consent, we shifted to levetiracetam (LEV) (20 mg/kg; intravenous), repeated 12 hours later. A third brief seizure occurred 13 hours later; treatment with pyridoxine was interrupted and LEV was increased to 60 mg/Kg/day in two doses, resulting, after the first dose, in full seizure control. By Day 14, axial tone and spontaneous motility were normalised.

On Day 18, the infant was discharged, seizure-free, with oral LEV (200 mg/day). At one month of age, brain MRI and EEG were normal. At eight months of age, the baby showed normal global development and social contact. Oral LEV dosage (22 mg/Kg/day, equivalent to 200 mg/day) was then gradually withdrawn.

At clinical evaluation performed at 13 months and seven days of age, the child was alert, perceptive, and sensitive. He demonstrated a healthy interest in the testing materials with an appropriate level of activity, attention, adaptation to changes, and task persistence. He was socially engaged with the examiner, showing good communicative intent and reciprocity. He could stand without support. He vocalized in response to the examiner and to express attitude. His developmental functioning, assessed using the Bayley Scales of Infant and Toddler Development (Bayley III), showed scores in the average/upper average range (cognitive: 125; language: 94; motor: 91; social-emotional: 95; adaptive behaviour: 90). He walked without support at 13 months and 15 days of age.

The neurological signs of the proband observed in the neonatal period, the family history with three previous miscarriages, and the occurrence of uncertain paternal neonatal clinical events suggested that genetic testing

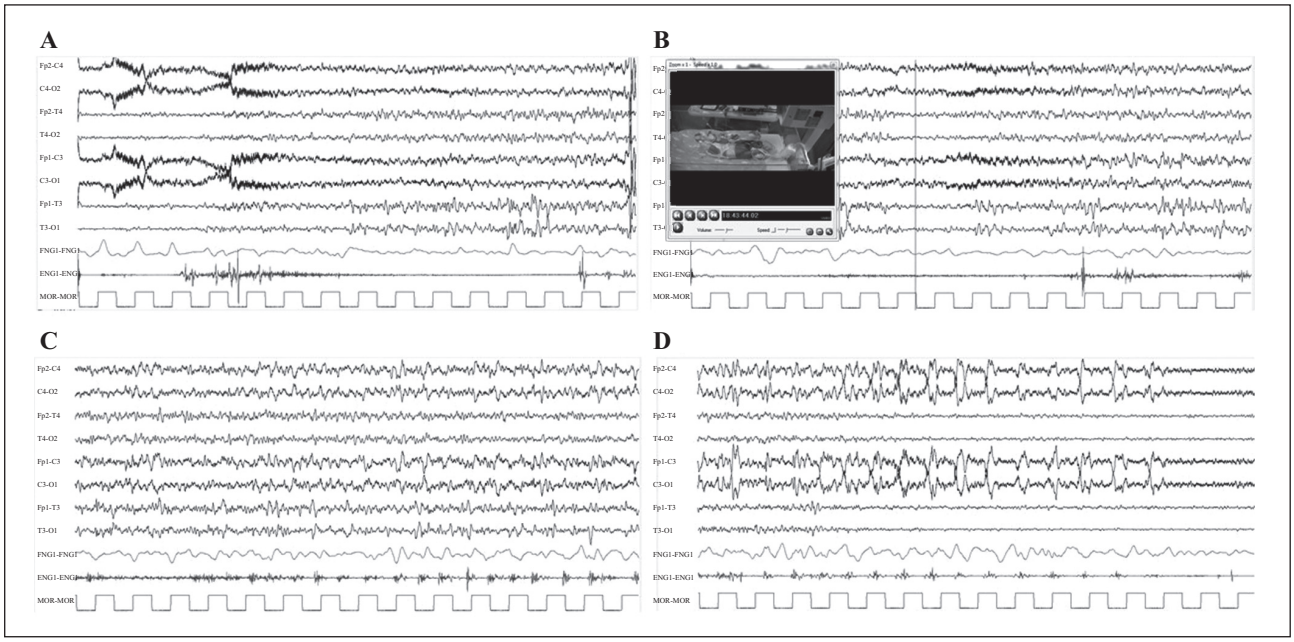

Figure 1. Electroclinical phenotype of the presented patient with BFNE. The seizure, following active sleep and arousal (A), is characterized by tonic extension and adduction of the upper limbs, flexion of the lower limbs, left trunk and head rotation associated with shallow breathing, tachycardia, and generalized decrease in EEG amplitude (B).
The tonic seizure evolves into a vibratory phase (C), and then gradually into bilateral asynchronous clonic movements of the limbs and ocular-facial regions associated with bicentral sharp-wave discharges (D).

should be performed. Based on a next-generation sequencing panel, not including the *KCNQ3* gene, no pathogenetically-relevant gene variants were detected. In close analogy to *KCNQ2* variants, phenotypic heterogeneity during the clinical course has also been reported in families carrying variants in *KCNQ3* (Miceli *et al*., 2017), therefore direct sequencing of the *KCNQ3* gene (NM_004519.3) was also performed, revealing the occurrence of a c.914A>T heterozygous variant. This nucleotide substitution, inherited by the symptomatic father, is responsible for the missense mutation, p.Asp305Val. The variant, affecting a highly conserved residue located in the S5-S6 pore region of the protein, is predicted to be "pathogenic" based on PolyPhen2 and Mutation Taster with a very high confidence score (>0.999). Multiplex ligation-dependent probe amplification of *KCNQ2* and *KCNQ3* did not disclose indels (*for more details, see the supplementary material*). The same variant was found in the father who likely suffered from neonatal epileptic seizures and in an asymptomatic sister. In addition, his paternal uncle, whose genetic data were not available, had neonatal seizures and an isolated seizure at 13 years old (*figure 2*).

Discussion

About 5% of families with BFNE carry *KCNQ3* pathogenetic variants with incomplete (0.8-0.85) penetrance (Miceli *et al*., 2017). *KCNQ3* mutations have been for a long time considered to cause a typical phenotype characterized by neonatal seizures that remit spontaneously after a few months with normal neurocognitive development (Charlier *et al*., 1998; Singh *et al*., 2003). Instead, in close analogy to the wide phenotypic spectrum associated with *KCNQ2* mutations, some *KCNQ3* mutations were recently found to be associated with more severe phenotypes characterized by refractory seizures and variable motor and cognitive impairment (Soldovieri *et al*., 2014; Miceli *et al*., 2015). The rare occurrence of *KCNQ3*-related BFNE and the uncertainty about the electroclinical phenotype, outlined mainly by retrospective studies or, sometimes, by incomplete clinical observations, has hampered the identification of accurate genotype-phenotype correlations. Thus, we believe that video-EEG monitoring is the best method to define a specific BFNE electroclinical pattern. We present the electroclinical, genetic, and developmental data from a family with neonatal seizures and a novel *KCNQ3* mutation identified in three affected individuals over two generations (*figure 2*).

The ictal electroclinical features, documented by video-EEG monitoring, showed initial asymmetric tonic posturing, shallow breathing, inconstant desaturation, and tachycardia, associated with a generalized decrease in EEG amplitude. The tonic phase was followed by unilateral or asynchronous bilateral clonic

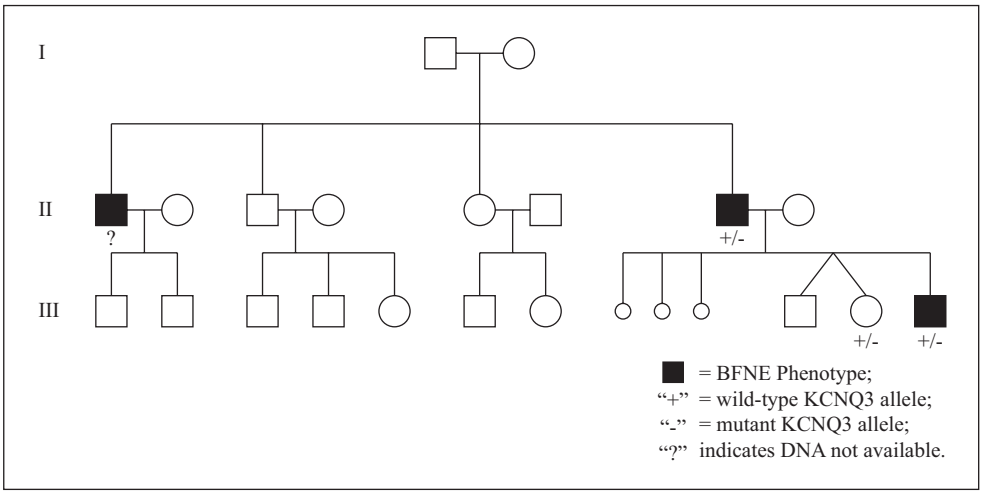

Figure 2. Pedigree of the family with BFNE.

movements associated with generalized sharp-wave discharges without postictal depression. Both clinical and EEG data of our patient seem to be consistent with the electroclinical pattern previously reported (Hirsch *et al*., 1993; Ronen *et al*., 1993; Maljevic *et al*., 2016; Sands *et al*., 2016). The *KCNQ3* variant found in our family is the substitution c.914A>T, which leads to the p.Asp305Val missense mutation. This substitution affects a residue located in the S5-S6 pore region of the protein, likely altering the potassium channel structure at this functionally-critical region. A mutation at the same codon (c.914A>G), but resulting in a different amino acid substitution (p.Asp305Gly), was found in a patient described by Ryan *et al*. (1991) exhibiting a typical BFNE phenotype, characterized by onset of seizures at two days, positive response to phenobarbital, seizure freedom from the third week of life, and normal psychomotor development at 10 months of age. When expressed with *KCNQ2* subunits, incorporation of *KCNQ3* mutant subunits into heteromeric channels decreased the maximal M-current by ~40%. Notably, both Asp305Gly found in the family studied by Ryan *et al*. and the Asp305Val variant described in the present study cause the replacement of a negatively charged amino acid with a smaller, non-polar amino acid. Such structural similarities likely translate into a comparable degree of channel dysfunction and current decrease, although functional studies would be needed to confirm such a hypothesis.

Until now, seizures in BFNE patients have been treated with various conventional AEDs (Miceli *et al*., 2015), and only recently have first-line drugs emerged. In particular, evidence indicates that carbamazepine or oxcarbazepine are safe and more effective, providing a rapid response, seizure control, shorter hospitalisation, and favourable long-term outcome for BFNE patients (Sands *et al*., 2016).

Our patient showed a rapid and effective response to LEV and remained seizure-free from the third dose, similar to the patient of Maljevic *et al*. (2016). The duration of treatment reported in previous studies is unclear, ranging from a few weeks to 18 months. In our case, we are unable to state whether the child recovered from active epilepsy before eight months of age, as a gradual reduction in LEV was initiated with termination of treatment at 10 months following a lack of seizure relapse. The electroclinical outcome of our patient seems to be consistent with the typical course of the disorder. The composite scores of Bayley III were within normal range with cognitive performance being particularly strong.

Similar to a previous report (Ryan *et al*., 1991), the developmental follow-up of our patient was limited to the first 13 months of age, however, the lack of seizure relapse without evidence of significant developmental delay suggests that the novel variant, c.914A>T (p.Asp305Val), is likely to be associated with a favourable outcome.

In conclusion, we demonstrate a novel variant in the *KCNQ3* gene within a family with rather typical BFNE electroclinical features, consistent with the previously described benign outcome associated with heterozygous variants affecting residues in the pore region of this voltage-gated potassium channel subunit (Miceli *et al*., 2017). □

Supplementary data.
Summary didactic slides and supplementary materials are available on the www.epilepticdisorders.com website.

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We thank the children and parents who participated in this study. None of the authors have any conflict of interest to declare.

Legend for video sequence

On Day 10, the newborn showed, in active sleep, a cluster of three similar ictal events characterized by generalized or focal tonic (asymmetric tonic posturing) seizures with shallow breathing, mild desaturation, eye blinking, and tachycardia associated with a generalized decrease in EEG amplitude. The tonic component of the seizure progressed into a vibratory phase, gradually evolving into unilateral or bilateral asynchronous clonic movements, lasting for about a minute, and associated with bicentral sharp-wave discharges. The focal seizures involved both sides, varying from one seizure to another one.

Key words for video research on www.epilepticdisorders.com

Phenomenology: neonatal seizure
Localisation: focal seizure not otherwise specified
Syndrome: benign familial neonatal epilepsy (bfne)
Aetiology: KCNQ3 mutation

References

Biervert C, Schroeder BC, Kubisch C, *et al*. A potassium channel mutation in neonatal human epilepsy. *Science* 1998; 279: 403-6.

Charlier C, Singh NA, Ryan SG, *et al*. A pore mutation in a novel *KQT*-like potassium channel gene in an idiopathic epilepsy family. *Nat Genet* 1998; 18: 53-5.

Hirsch E, Velez A, Sellal F, *et al*. Electroclinical signs of benign neonatal familial convulsions. *Ann Neurol* 1993; 34: 835-41.

Maljevic S, Vejzovic S, Bernhard MK, *et al*. Novel *KCNQ3* mutation in a large family with benign familial neonatal epilepsy: a rare cause of neonatal seizures. *Mol Syndromol* 2016; 7: 189-96.

Miceli F, Striano P, Soldovieri MV, *et al*. A novel *KCNQ3* mutation in familial epilepsy with focal seizures and intellectual disability. *Epilepsia* 2015; 56: e15-20.

Miceli F, Soldovieri MV, Joshi N, Weckhuysen S, Cooper EC, Taglialatela M. KCNQ3-related disorders. In: *GeneReviews®*. Adam MP, Ardinger HH, Pagon RA, *et al*. Seattle (WA): University of Washington, 2017.

Ronen GM, Rosales TO, Connolly M, Anderson VE, Leppert M. Seizure characteristics in chromosome 20 benign familial neonatal convulsions. *Neurology* 1993; 43: 1355-60.

Ryan SG, Wiznitzer M, Hollman C, Torres MC, Szekeresova M, Schneider S. Benign familial neonatal convulsions: evidence for clinical and genetic heterogeneity. *Ann Neurol* 1991; 29: 469-73.

Sands TT, Balestri M, Bellini G, *et al*. Rapid and safe response to low-dose carbamazepine in neonatal epilepsy. *Epilepsia* 2016; 57: 2019-30.

Singh NA, Charlier C, Stauffer D, *et al*. A novel potassium channel gene, *KCNQ2*, is mutated in an inherited epilepsy of newborns. *Nat Genet* 1998; 18: 25-9.

Singh NA, Westenskow P, Charlier C, *et al*. *KCNQ2* and *KCNQ3* potassium channel genes in benign familial neonatal convulsions: expansion of the functional and mutation spectrum. *Brain* 2003; 126: 2726-37.

Soldovieri MV, Miceli F, Bellini G, Coppola G, Pascotto A, Taglialatela M. Correlating the clinical and genetic features of benign familial neonatal seizures (BFNS) with the functional consequences of underlying mutations. *Channels (Austin)* 2007; 1: 228-33.

Soldovieri MV, Boutry-Kryza N, Milh M, *et al*. Novel *KCNQ2* and *KCNQ3* mutations in a large cohort of families with benign neonatal epilepsy: first evidence for an altered channel regulation by Syntaxin-1A. *Human Mutat* 2014; 35: 356-67.

Wang HS, Pan Z, Shi W, *et al*. *KCNQ2* and *KCNQ3* potassium channel subunits: molecular correlates of the M-channel. *Science* 1998; 282: 1890-3.

TEST YOURSELF

(1) Which of the following statements about families with BFNE carrying *KCNQ3* pathogenic variants is correct?
A. About 15% show complete penetrance
B. About 10% show incomplete penetrance
C. About 5% show incomplete penetrance

(2) Which of the following statements about BFNE associated with *KCNQ3* mutations is not correct?
A. BFNE associated with *KCNQ3* mutation is an autosomal dominant epilepsy syndrome
B. *KCNQ3* mutations are always associated with severe phenotypes
C. The phenotypic spectrum associated with *KCNQ3* and *KCNQ2* mutations is similar.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

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Tonic status epilepticus in a centenarian woman

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ABSTRACT – Generalized tonic status epilepticus (TSE) is a rare epileptic condition. It occurs usually in the context of symptomatic generalized epilepsy, in particular, in subjects with a diagnosis of Lennox-Gastaut syndrome, atypical forms of idiopathic (genetic) generalized epilepsy, or as a paradoxical effect during treatment with diverse antiepileptic drugs. Herein, we describe the case of an elderly woman on chronic treatment with psychotropic drugs who developed an episode of generalized TSE. Motor manifestations were subtle and difficult to recognize as seizures, and a detailed video-EEG importantly contributed to accurate and prompt diagnosis. TSE was initially refractory to conventional anti-seizure drug therapy including levetiracetam and valproate but was finally controlled with lacosamide. Our case indicates a potential therapeutic effect of lacosamide on TSE in the elderly after treatment failure with first-line anti-seizure drugs. [*Published with video sequence on www.epilepticdisorders.com*]

Key words: tonic status epilepticus, video-EEG, elderly patient, lacosamide

Tonic status epilepticus (TSE) is a rare epileptic condition. It occurs usually in the context of symptomatic generalized epilepsy, in particular, in subjects with a diagnosis of Lennox-Gastaut syndrome or atypical forms of idiopathic generalized epilepsy (IGE) (Kobayashi *et al*., 2005). Moreover, TSE has been also described as a paradoxical effect during treatment with diverse antiepileptic drugs (Prior *et al*., 1972; Capocchi *et al*., 1998; Grande-Martín *et al*., 2016). Herein, we describe the case of a centenarian woman who developed an episode of generalized TSE, possibly secondary to chronic use of psychotropic drugs.

Case study

A 102-year-old woman, partially dependent in daily-life activities, with antecedents of hypertension and atrial fibrillation, was admitted to our hospital because of general deterioration and dyspnoea. She was on chronic treatment with trazodone, amiloride, hydrochlorothiazide, pantroprazole, and bromazepam. On general

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physical examination, she was haemodynamically stable with a temperature of 36.0° C. Routine laboratory tests were within normal limits except for the presence of severe bacteriuria. With these results in mind, she was diagnosed with urinary tract infection, and oral treatment with amoxicillin-clavulanic acid was started for five days. On Day 5 of admission, after finishing the antibiotic treatment, she complained of "funny" movements as a "tremor" of both lower limbs. These episodes were interpreted as anxiety and nervousness, and treatment with clonazepam and risperidone was initiated. The next day, these "funny" episodes in both legs persisted and the patient was evaluated by our neurologists. On neurological examination, she was awake and alert, but disoriented to time. No focal motor or sensory deficits were seen. She reported self-limited involuntary movements in the lower limbs. These movements were synchronous, fast, and were not accompanied by cognitive disconnection, automatisms or loss of consciousness. On some occasions, she acquired a certain tonic aspect in both feet, but "funny" movements were not clearly tremulous. At that moment, a video-electroencephalogram (v-EEG) study was requested. On v-EEG, recurrent generalized bursts of rhythmic, high-voltage, sharp, well-defined, sinusoidal, beta activity, lasting from 2 to 6 seconds, were observed (*figure 1*). Simultaneously, the patient experienced a subtle increase in tone and stiffness involving the axial musculature and both lower limbs (*see video sequence*). Occasionally, she also experienced subtle jerks in both feet. Autonomic manifestations were not evident. Irregular theta and delta waves were seen between bursts. The episodes recurred continuously in clusters along the recording and, therefore, a diagnosis of generalized TSE was suggested. A computed tomography (CT) scan of the brain disclosed diffuse and symmetric cortico-subcortical atrophy and subcortical hypodense lesions compatible with chronic small vessel ischaemia. Treatment with intravenous levetiracetam (LEV) (1,000 mg/day) was initiated. During the following four days, tonic seizures were less frequent but were not completely controlled and intravenous valproate (VPA) (800 mg/24 hours) was added to her anti-seizure drug (ASD) therapy. On Day 11, tonic seizures worsened involving also upper limbs and the dose of VPA was increased (1,000 mg/24 hours). One day later, the episodes of stiffness persisted and intravenous lacosamide (LCM) (100 mg/24 hours) was included in the ASD therapy. After the onset of treatment with LCM, tonic seizures were completely controlled, and clinical improvement persisted for the next days. On Day 14, the patient was discharged under chronic ASD therapy with LEV (750 mg/24 hours), VPA (1,200 mg/24 hours), and LCM (100 mg/24 hours) with follow-up via neurology consultation.

Discussion

It is well known that tonic seizures and TSE typically occur in patients with intellectual disability and severe symptomatic epilepsy. However, the occurrence of episodes of generalized TSE is fairly rare in adults and elderly subjects without antecedents of epilepsy. Nevertheless, Kobayashi *et al*. (2005) drew attention to the possibility that status epilepticus (SE) with minor tonic seizures may occur in IGE.

The case of our centenarian patient without antecedents of epilepsy shows a different scenario. Previously, Garmel *et al*. (1992) described an episode of unresponsiveness in a 73-year-old woman as secondary to generalized TSE. These authors emphasized the complexity of diagnosis since motor manifestations may be subtle and difficult to recognize. Our findings support this conclusion because in the case report described here, tonic seizures were initially interpreted to result from the patient's anxiety. More recently, Ostrow and Kaplan (2011) reported a young woman with prolonged TSE which evolved into a stimulus-induced diffuse voltage attenuation (SIDVA) pattern in the setting of aseptic meningoencephalitis. This was the first report of a SIDVA pattern in an adult without a history of epilepsy. The ictal EEG pattern observed in our patient consisted of recurrent generalized bursts of rhythmic, sinusoidal, beta-like activity, lasting several seconds without spike-wave complexes. This ictal EEG pattern resembled that typically observed in tonic seizures of Lennox-Gastaut syndrome (Prior *et al*., 1972).

TSE is more difficult to recognize than other forms of SE. This is because, firstly, TSE is rare in adults or elderly subjects, in comparison with generalized tonic-clonic SE or partial motor SE, and secondly, motor symptoms may be subtle and the fact that increased tone or stiffness in isolation may have an epileptic origin is not widely known. Thus, fine tonic seizures may only be evident with careful video analysis or with the use of muscle recording electrodes. The description of our case may help to emphasize that TSE may occur in the elderly population and, in particular, in patients with chronic psychotropic drug therapy.

We cannot rule out that the treatment with amoxicillin-clavulanic acid could have precipitated the episode of TSE. However, we believe that this was unlikely because the clinical manifestations occurred once the treatment was completed. Moreover, in a recent article in which the current evidence for seizures associated with the use of antibiotics was systematically reviewed, the authors did not find reports or studies confirming a seizure threshold-lowering effect of amoxicillin-clavulanic, and an association with seizures or SE was not demonstrated (Sutter *et al*., 2015). The confluence of multiple factors seems more plausible.

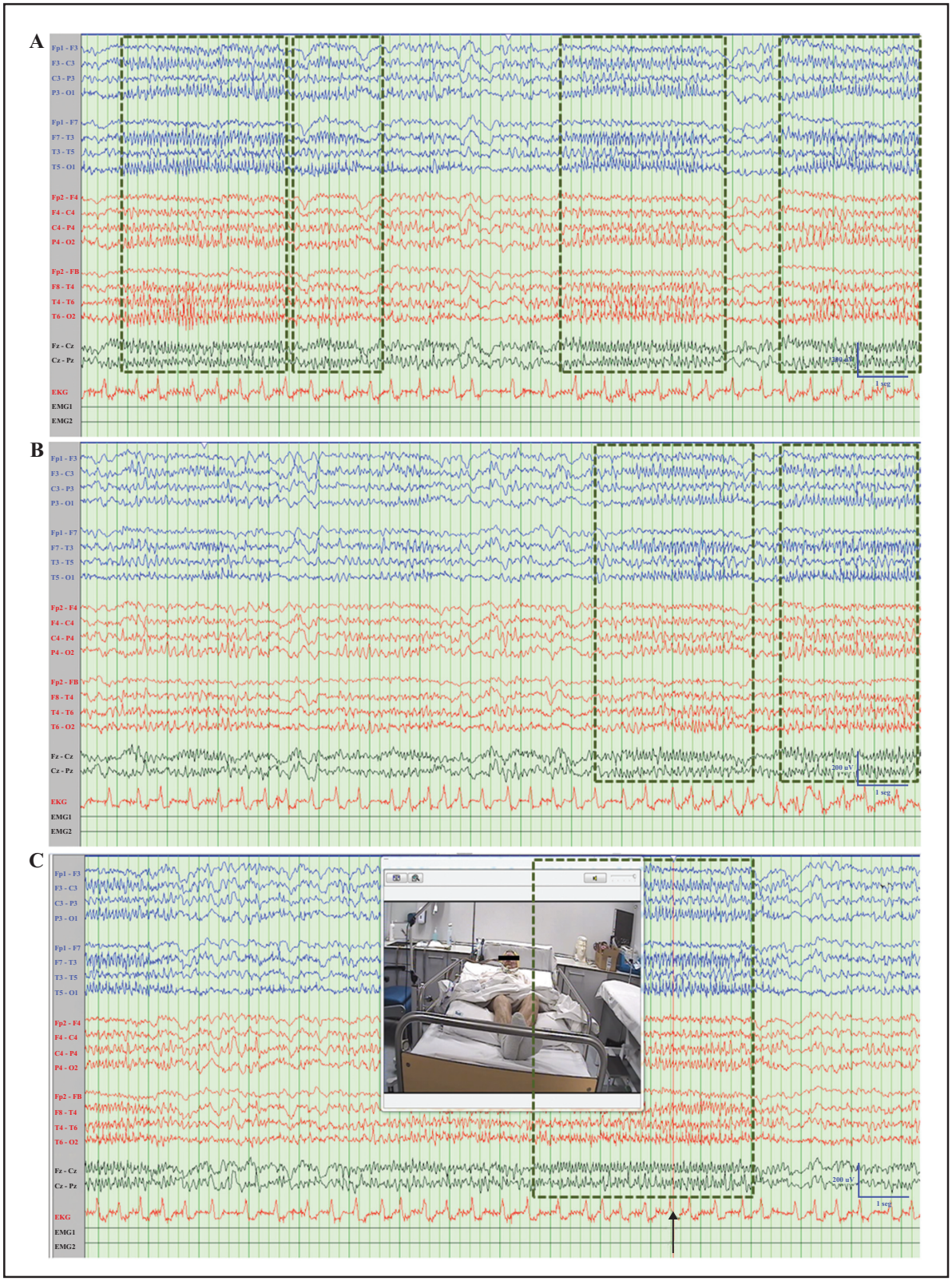

Figure 1. (A, B) The presence of a recurrent burst of sharp, sinusoidal, high-voltage, beta activity lasting from 2 to 5 seconds (green dashed line), compatible with the diagnosis of generalized TSE. (C) Tonic contraction of both legs coinciding with ictal EEG changes (arrow and green dashed line). Low filter: 0.53 Hz; high filter: 70 Hz; notch filter: 50 Hz.

Our patient had a chronic vascular disorder and she was a chronic consumer of psychotropic medication. It is possible that under these circumstances, a homeostatic imbalance secondary to urinary tract infection could account for the occurrence of SE.

In this case, TSE was refractory to conventional ASD treatment. It is well known that tonic seizures and TSE, particularly associated with Lennox-Gastaut syndrome, can be aggravated by benzodiazepines. We used VPA and LEV as first-line treatment in order to prevent this potential complication. Although initially, tonic seizures improved after several days, the seizures remained uncontrolled and we therefore added LCM to her antiepileptic treatment. LCM is a relatively new ASD therapy that has become a well-established anticonvulsive medication for the treatment of focal-onset seizures, with and without secondary generalization. Treatment with LCM has demonstrated efficacy in patients with absence SE in whom VPA and LEV have previously failed (Reif *et al*., 2018). Moreover, LCM was noninferior to fosphenytoin as treatment for nonconvulsive seizures in critically ill patients (Hussain *et al*., 2018). Conversely, the use of high doses of LCM combined with other antiepileptic drugs in a case of super-refractory TSE was ineffective (Thompson and Cock, 2016). The patient was a 24-year-old man with autistic spectrum disorder and learning disability with an electroclinical picture reminiscent of Lennox-Gastaut syndrome, who responded to a rapid increase in rufinamide.

In summary, TSE may occur in elderly patients under chronic psychotropic drug treatment. Motor manifestations can be subtle and, therefore, a detailed v-EEG contributes to accurate and prompt diagnosis. Our case indicates a potential therapeutic effect of LCM on TSE in the elderly after treatment failure with first-line ASDs. □

Legend for video sequence

Recurrent and continuous episodes in which there is flexion of the patient's entire body along with hip, knee and ankle flexion of both lower limbs. Note the flexion of the left arm during the second sequence.

Key words for video research on www.epilepticdisorders.com

Phenomenology: status epilepticus (convulsive)/tonic seizure
Localisation: generalized
Syndrome: not applicable
Aetiology: toxics abuse

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

References

Capocchi G, Balducci A, Cecconi M, *et al*. Valproate-induced epileptic tonic status. *Seizure* 1998; 7: 237-41.

Garmel GM, Jacobs AK, Eilers MA. Tonic status epilepticus: an unusual presentation of unresponsiveness. *Ann Emerg Med* 1992; 21: 223-7.

Grande-Martín A, Pardal-Fernández JM, Carrascosa-Romero MC, De Cabo C. Tonic seizure status epilepticus triggered by valproate in a child with Doose syndrome. *Neuropediatrics* 2016; 47: 187-9.

Hussain AM, Lee JW, Kolls BJ, *et al*. Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. *Ann Neurol* 2018; 83: 1174-85.

Kobayashi E, Thomas P, Andermann F. Tonic status epilepticus in patients with idiopathic generalized epilepsy. *Epileptic Disord* 2005; 7: 327-31.

Ostrow LW, Kaplan PW. Tonic status and electrodecremental paroxysms in an adult without epilepsy. *Epileptic Disord* 2011; 13: 99-101.

Prior PF, Maclaine GN, Scott DF, Laurance BM. Tonic status epilepticus precipitated by intravenous diazepam in a child with petit mal status. *Epilepsia* 1972; 13: 467-72.

Reif PS, Männer A, Willems LM, *et al*. Intravenous lacosamide for treatment of absence status epilepticus in genetic generalized epilepsy: a case report and review of literature. *Acta Neurol Scand* 2018; 138: 259-62.

Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs. A systematic review. *Neurology* 2015; 85: 1332-41.

Thompson AGB, Cock HR. Successful treatment of super-refractory tonic status epilepticus with rufinamide: first clinical report. *Seizure* 2016; 39: 1-4.

TEST YOURSELF

(1) List three epileptic conditions associated with tonic status epilepticus.

(2) What is the most frequent ictal EEG pattern during tonic status epilepticus in patients with Lennox-Gastaut syndrome?

(3) Which antiepileptic drug can trigger tonic status epilepticus in generalized epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Clinical commentary

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Absence status induced by lacosamide adjunctive therapy

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ABSTRACT – Since lacosamide was approved as an adjuvant agent for the treatment of medically refractory focal epilepsy over ten years ago, it is becoming more widely used for the treatment of idiopathic (genetic) generalized epilepsies. Several studies have demonstrated efficacy in reducing primary generalized tonic-clonic seizures (GTCS), but efficacy is less well-characterized for myoclonic and absence seizures. A 29-year-old man with juvenile myoclonic epilepsy and medically refractory GTCS on a combination of levetiracetam and topiramate was started on lacosamide adjunctive therapy with the plan to replace topiramate. While his GTCS became controlled, he was witnessed to have confusional episodes, with waxing and waning responsiveness, lasting a few days, several times a month. After eight months of adjunctive lacosamide therapy, he was admitted to the epilepsy monitoring unit, where paroxysms of generalized spike-and-wave complexes, lasting for 30-90 minutes, were recorded, interrupted only by sleep. During these periods, he demonstrated psychomotor slowing and disorientation on examination. The absence status was successfully broken by lorazepam, and lacosamide was discontinued. The patient had no further confusional episodes at the most recent follow-up visit, four months after discharge.

Key words: lacosamide, absence status, idiopathic generalized epilepsy, antiepileptic medications, seizure aggravation

Lacosamide was initially approved as an adjunctive agent for the treatment of medically refractory focal-onset seizures in adults in 2007 (Ben-Menachem *et al*., 2007; Chung *et al*., 2010). Since it was introduced, its indications have increased to include children and adolescents, and even as monotherapy in adults (Vimpat US Prescribing Information, 2018). Similar to carbamazepine, phenytoin or lamotrigine, lacosamide targets voltage-gated sodium channels, but instead of blocking rapidly depolarizing currents, it enhances slow inactivation of the channels. There are reports regarding the efficacy of lacosamide for the treatment of idiopathic generalized epilepsy syndromes, juvenile myoclonic epilepsy in particular (Afra and Adamolekun, 2012). A recent study demonstrated short-term efficacy for the treatment of GTCS, which was further improved during the course of a 59-week open-label extension of this study (Wechsler *et al*., 2017). Absence and myoclonic seizures were also reduced in the open-label phase, as well as a decrease in the overall burden of generalized spike-and-wave discharges. Nonetheless, five patients

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in the pilot study experienced an increase in absence or myoclonic seizures, two of whom exhibited absence seizures for the first time. In the extended study, only one patient experienced an increase in absence seizures at a dose of 800 mg/day, but these resolved with dose reduction, and another demonstrated a self-limited period of increased myoclonic seizures. There have been no reports of absence status to date. In this report, we present a patient with a history of juvenile myoclonic epilepsy who experienced control of his GTCS with lacosamide adjunctive therapy, but also developed frequently recurring confusional episodes consistent with absence status.

Case study

The patient was a 29-year-old right-handed man presenting for video-EEG evaluation, with a history of epilepsy beginning at age six years old. He initially presented with absence seizures, developing myoclonic seizures, and GTCS in adolescence. The GTCS occurred only a few times per year, but were always followed by a prolonged period of confusion, which could last from hours to days.

He had no family history of epilepsy but was born prematurely in the 28th week of gestation, weighing two pounds and seven ounces. He denied a history of focal neurological abnormalities postnatally but suffered from mild developmental delay and was eventually treated for attention deficit disorder.

Other co-morbidities included hyperlipidaemia which was treated with fenofibrate and obstructive sleep apnoea with CPAP. He had chronic insomnia requiring a combination of 100 mg trazodone and 50 mg hydroxyzine at night.

His most recent brain MRI was normal except for a Chiari I malformation. His EEG was normal just prior to starting lacosamide but generalized 3-5-Hz spike-and-wave as well as generalized polyspike-and-wave discharges resurfaced once started on lacosamide; findings that were mirrored by earlier EEG reports. He had failed topiramate, zonisamide, valproic acid, lamotrigine, phenytoin, carbamazepine, clonazepam, and gabapentin.

Lacosamide was introduced to replace topiramate as the adjunctive agent for levetiracetam and titrated to 500 mg daily. This combination controlled his GTCS for eight months, but he was witnessed as having 2-3-day periods of waxing and waning confusion. As these were occurring several times a month, he was no longer able to be gainfully employed.

At the time of his admission, his random levetiracetam level was 17 mcg/ml (normal range: 15-40 mcg/ml) and lacosamide level was 12.3 mcg/ml (normal range: 5-10 mcg/ml). He did not complain of any side effects on this regimen, and previous trough lacosamide levels were within the normal range. His metabolic profile demonstrated mild elevation of ALT/SGPT and AST/SGOT, but no other abnormalities.

His EEG at admission indicated prolonged paroxysms of 3-5-Hz generalized spike- and polyspike-and-wave discharges, occurring in runs of 20-30 seconds, with a brief 1-2-second interruption with transient return of his posterior background (*figure 1*). This EEG pattern lasted from 9:30 am into early afternoon, resolving briefly whenever he fell asleep. The absence status was finally aborted by two doses of lorazepam at 1 mg, with the EEG pattern responding within 10 minutes of its administration. During his absence status, he underwent bedside testing and was only oriented to place but not to person or the current date. He was not able to solve simple single-digit mathematical additions, suffered from short-term memory impairment, and could not recall what he had eaten for lunch that day. His partner confirmed that these symptoms were consistent with the confusional episodes he witnessed at home. Repeat testing after the absence status was aborted, with subsequent resolution of his disorientation to person and place and improvement in his dyscalculia and short-term memory deficits.

Lacosamide was held, while levetiracetam was increased to 1,000 mg twice daily to prevent GTCS. His EEG reverted to his normal awake and sleep background with brief generalized spike-and-wave discharges, not lasting longer than a second in duration (*figure 2*). Ethosuximide was also added prior to discharge to help control the absence seizures, but was poorly tolerated by the patient due to nausea and hiccoughs, requiring a dose reduction of 500 mg to 250 mg twice daily. His levetiracetam and ethosuximide levels were 11 mcg/ml and 26 mcg/ml (therapeutic range: 40-100 mcg/ml), respectively. According to the patient and his partner, he had no further confusional episodes in the four months since lacosamide was withdrawn.

Discussion

This case report describes a patient with juvenile myoclonic epilepsy presenting with recurrent bouts of absence status on lacosamide, despite improved control of his GTCS. While there is concern that lacosamide can aggravate absence and myoclonic seizures in some patients, absence status has not been reported to date (Wechsler *et al*., 2017). The patient started experiencing 2-3-day periods of confusion, several times each month, soon after lacosamide was introduced, despite complete control of his GTCS. The episodes did not recur afterwards, within four months following his discharge from hospital. Other

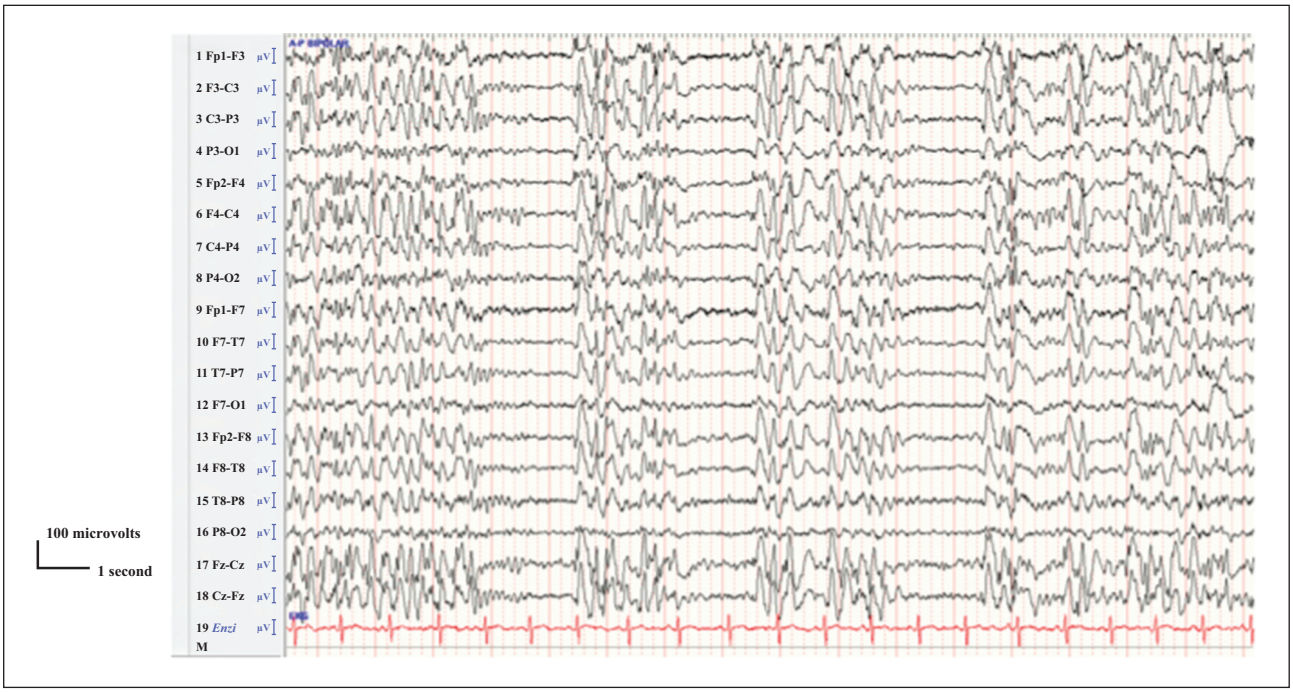

Figure 1. Absence status. Paroxysms of 3-5-Hz generalized spike- and polyspike-and-wave discharges are demonstrated on this 20-second EEG sample recorded using an anterior-posterior bipolar montage (Nihon-Kohden, Japan). Note the brief return of the patient's normal background activity between the paroxysms.

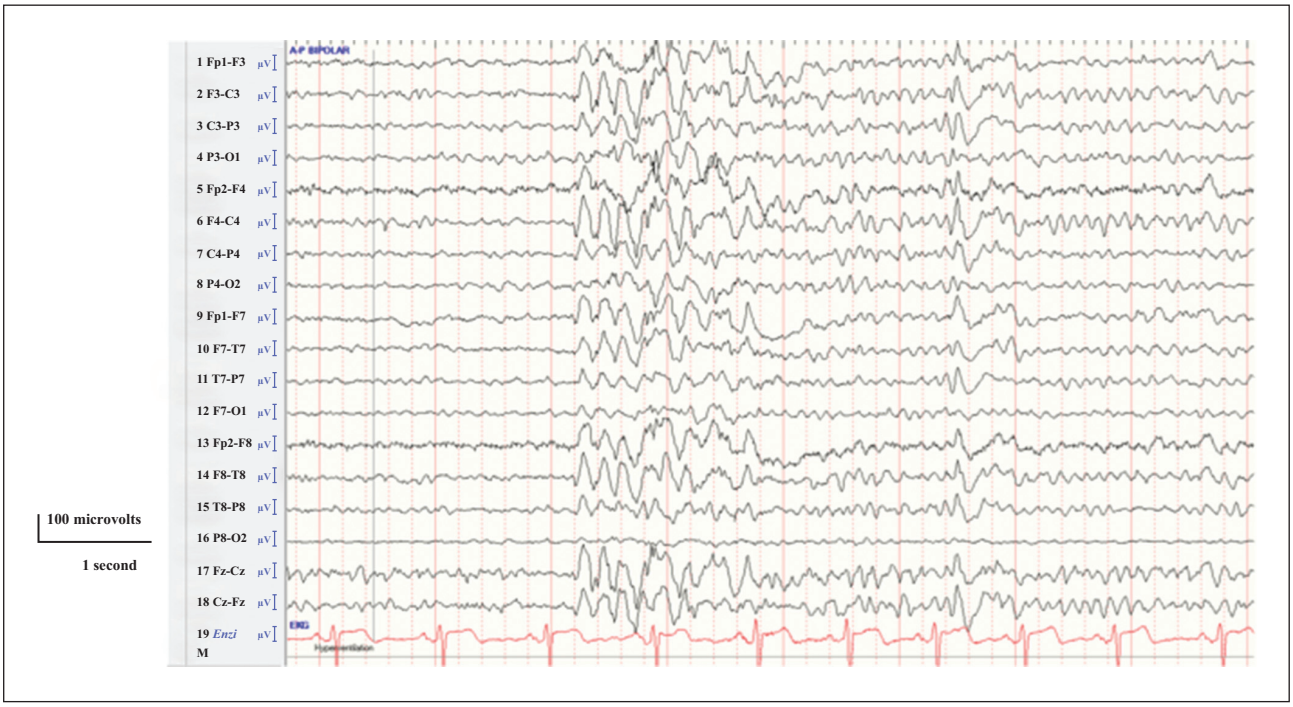

Figure 2. Interictal epileptic discharges triggered by hyperventilation. A 3-5-Hz generalized spike-and-wave discharge is triggered by hyperventilation after resolution of the absence status on this 10-second EEG sample, recorded using an anterior-posterior bipolar montage (Nihon-Kohden, Japan).

than the discontinuation of lacosamide, levetiracetam was increased by 500 mg a day at discharge, and ethosuximide was added. However, at the most recent follow-up visit, the levels of both of these medications were subtherapeutic, therefore less likely to be the cause of the prevention of absence status. Hence, based on the evidence that absence status started when lacosamide was introduced and resolved with its discontinuation, this is the most likely explanation of this adverse effect. Future case reports or series may be helpful to better characterize whether or not this lacosamide effect is dose-dependent.

The mechanism underlying the paroxysmal enhancement of spike-and-wave discharges is unclear. Several medications have been reported to trigger absence status including carbamazepine and oxcarbazepine (Genton *et al*., 2000; Gelisse *et al*., 2004), putatively as sodium-channel blockers, as well as vigabatrin and tiagabine (Panayiotopoulos *et al*., 1997; Knake *et al*., 1999) due to potentiation of $GABA_B$-receptor activation. While lacosamide's action on the sodium channel differs from that of carbamazepine and oxcarbazepine, the overall effect may be similar (Hebeisen *et al*., 2015). As in the case of carbamazepine and oxcarbazepine, it is still unclear why absence seizures would respond to lacosamide adjunctive therapy in most patients with idiopathic generalized epilepsy, yet worsen in a few patients, and, in this case, even evolve to absence epilepsy (Wechsler *et al*., 2017). The answers could include clinical, electrophysiological or even genetic factors. □

Key Points

In addition to focal-onset seizures, lacosamide may be helpful for the treatment of primary GTCS.
The efficacy of lacosamide for the treatment of other generalized seizure types is still being evaluated.
We report exacerbation of absence status epilepticus in a person with lacosamide adjunctive therapy.
Caution is advised when using lacosamide to treat idiopathic generalized epilepsy.

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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References

Afra P, Adamolekun B. Lacosamide treatment of juvenile myoclonic epilepsy. *Seizure* 2012; 21: 2024.

Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P, Rudd GD. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial onset seizures. *Epilepsia* 2007; 48: 1308-17.

Chung S, Sperling MR, Biton V, *et al*. Lacosamide as adjunctive therapy for partial-onset seizures: a randomized and controlled trial. *Epilepsia* 2010; 51: 958-67.

Gelisse P, Genton P, Kuate C, Pesenti A, Baldy-Moulinier M, Crespel A. Worsening of seizures by oxcarbazepine in juvenile idiopathic generalized epilepsies. *Epilepsia* 2004; 45: 1282-6.

Genton P, Gelisse P, Thomas P, Dravet C. Do carbamazepine and phenytoin aggravate juvenile myoclonic epilepsy? *Neurology* 2000; 55: 1106-9.

Hebeisen S, Pires N, Louriero AI, *et al*. Eslicarbazepine and the enhancement of slow inactivation of voltage-gated sodium channels: a comparison with carbamazepine, oxcarbazepine and lacosamide. *Neuropharmacology* 2015; 89: 122-35.

Knake S, Hamer HM, Schomburg U, Oertel WH, Rosenow F. Tiagabine-induced absence status in idiopathic generalized epilepsy. *Seizure* 1999; 8: 314-7.

Panayiotopoulos CP, Agathonikou A, Ahmed-Sharoqi I, Parker APJ. Vigabatrin aggravates absences and absence status. *Neurology* 1997; 49: 1467.

Vimpat US prescribing information: Available at: https://www.vimpat.com/vimpat-prescribing-information.pdf.

Wechsler RT, Yates SL, Messenheimer J, *et al*. Lacosamide for uncontrolled primary generalized tonic-clonic seizures: an open pilot study with 59-week extension. *Epilepsy Res* 2017; 130: 13-20.

TEST YOURSELF

(1) Which of the following medications can cause an aggravation of absence seizures in people with idiopathic generalized epilepsy?
A. Vigabatrin and tiagabine
B. Lacosamide
C. Carbamazepine and phenytoin
D. All of the above

(2) Lacosamide's main mechanism of action is due to enhancement of _____ of sodium channels.
A. Rapid activation
B. Slow inactivation
C. Rapid inactivation
D. Slow activation

(3) Lacosamide is a promising treatment for idiopathic generalized epilepsy, but caution is advised in patients with _____ seizures.
A. Bilateral convulsive seizures
B. Myoclonic seizures
C. Absence seizures
D. All of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Clinical commentary

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Focal visual status epilepticus*

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ABSTRACT – Epileptic visual auras are elementary to complex and sometimes occur as colourful visual phenomena located close to or within the central part of the contralateral hemi-field. They typically last from seconds to a few minutes, which discriminates them from the usually longer-lasting visual auras (5-30 minutes) of patients suffering from migraine. We present an adult patient with occipital lobe epilepsy whose visual aura under epilepsy monitoring lasted for more than 30 minutes with almost no propagation, demonstrating a rare, but remarkable, sustained local epileptic network activity associated with resection of an occipital arterio-venous malformation.

Key words: epilepsy, status epilepticus, visual aura, occipital epilepsy, migraine, arterio-venous malformation

The majority of epileptic seizures last from seconds to a few minutes. A longer duration may point to an alternative cause such as psychogenic non-epileptic seizures or indicate status epilepticus, operationally defined as the persistence of a (tonic-clonic) seizure for more than five minutes or the occurrence of more than one (tonic-clonic) seizure without restoration of consciousness in between (Trinka *et al*., 2015). However, such pathophysiology-based conventions have not been fully established for non-convulsive status epilepticus without alteration of consciousness (Trinka *et al*., 2015). In addition, "epilepsia partialis continua" refers to a subgroup of focal status epilepticus with motor or non-motor phenomena, the latter alternatively termed "aura continua", lasting for at least 60 minutes (Mameniskiene *et al*., 2011).

Case study

A right-handed, 41-year-old woman had suffered an atypical intracerebral haemorrhage from an arterio-venous malformation (AVM) in the right occipital lobe two years previously. She reported a left paracentral visual scotoma but no other sequelae. Half a year after the event and after resection of the AVM, she experienced a visual aura that evolved into a tonic-clonic seizure.

Despite antiepileptic treatment, she reported experiencing visual auras on a weekly basis. She described them as bright, at times rotating, otherwise largely immobile,

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*This case has been presented as a poster and in an oral form at the meeting of the German Society for Clinical Neurophysiology in March 2018.

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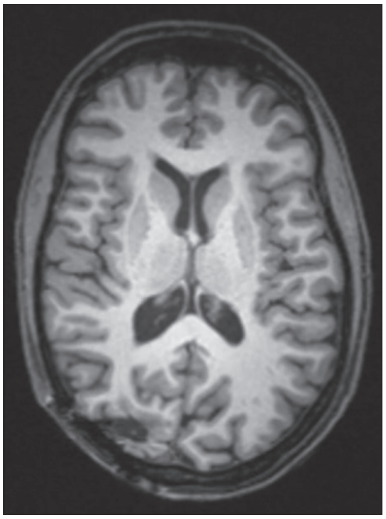

Figure 1. T1-weighed MRI demonstrating a right occipital scar two years after resection of an arterio-venous malformation.

sometimes colourful spots in the lower left visual field. These would often last for minutes, and she had noticed a duration of 15 minutes. She then occasionally developed epigastric and/or unpleasant olfactory sensations that could last for more than a minute. Every two months, on average, she suffered a tonic-clonic seizure. Several days after withdrawing her medication under epilepsy monitoring during pre-surgical workup, such a visual aura, lasting for 40 minutes and arising within her left lower visual field close to the permanent scotoma, occurred. The EEG seizure pattern remained highly localized to electrode O_2 and thus close to the right occipital scar throughout most of the seizure (*figures 1, 2*). After it spread to electrodes T6 and P4, clonazepam (1 mg; IV) was administered which quickly terminated the seizure. Source localization (solely based on a routine electrode montage with 20 electrodes) placed the epileptogenic source right of the pole of the right calcarine cortex, as expected by the highly localized seizure pattern. fMRI-retinotopy as well as tractography demonstrated a close relationship between epileptic scar and visual tract, indicating that a visual field defect may be regarded as an inevitable risk of potential occipital lobe epilepsy surgery in our case.

Discussion

Due to their duration, visual status epilepticus and visual epilepsia partialis continua may be difficult to differentiate from similar phenomena arising with migraine. In the clinical context, however, a definitive diagnosis is usually possible (Panayiotopoulos, 1999a; Eriksen *et al*., 2005; Hartl *et al*., 2017). Indeed, there are only very few reports of focal visual status epilepticus with symptoms lasting for longer than five minutes. These are summarized in *table 1*. Epileptic amaurosis which is poorly distinguished from postictal deficits and status epilepticus originating in the occipital lobe, where visual hallucinations are only the initial and not the predominating symptom, were excluded. In such cases, the criteria reported to be most reliable in differentiating between an epileptic and a migraine aura are the unilaterality of the former and the longer duration of the latter (Panayiotopoulos, 1999a). Eriksen *et al*. (2005) proposed a five-item score that assesses duration, symptom-dynamic, scotoma, fortification, and unilaterality in order to recognize visual auras associated with migraine and aid in clinical decision-making. Panayiotopoulos (1999b) found a prevalence of occipital lobe epilepsy of about 5%; 63 of his 1,360 epilepsy patients had occipital lobe epilepsy. The underlying conditions were early onset, benign childhood epilepsy (40%), idiopathic occipital epilepsy without photosensitivity, symptomatic occipital lobe epilepsy (25% each), and idiopathic photosensitive epilepsy (10%). Importantly, the prevalence of interictal epileptiform activity is particularly low. Based on neurosurgical series, only 20% of patients with symptomatic occipital lobe epilepsy exhibit interictal occipital epileptiform activity (Adcock and Panayiotopoulos, 2012). The same authors stated that "a well-localized unifocal rhythmic ictal discharge during occipital seizures is infrequent", indicating the rather unusual presentation in the current report (Adcock and Panayiotopoulos, 2012).

A search of the literature for similar cases yielded a report nearly identical to ours; a 42-year-old, right-handed woman with a history of epilepsy after embolization of a right parieto-occipital arterio-venous malformation, who had prolonged visual auras, one lasting for 13 minutes, documented during video-EEG monitoring. The lesion was eventually resected, and the patient remained seizure-free, albeit with impaired consciousness and occasional visual seizures (Hartl *et al*., 2015). Another similar case was recently published with an arterio-venous malformation again as the epileptogenic lesion. After embolization and complete resection of the lesion, the patient had been seizure-free for three years without any further neurological deficits (Strzelczyk *et al*., 2017). This may be of relevance to the issue of the long-lasting focality of the ictal discharges. While in our case, withdrawal of the antiepileptic medication certainly did increase the chance of occurrence and a longer duration of seizures, it did not induce rapid propagation as often seen after withdrawal of anticonvulsive therapy. The mechanisms by which epileptic activity is maintained within a focal network are not well defined. Apparently, epileptogenic tissue in these cases is, or becomes,

Table 1. Case reports of EEG-confirmed visual status epilepticus; association with vascular malformation is highlighted in bold.

Maximum duration	Age of onset	Seizure characteristics	Imaging	EEG	Reference
1 minute every 10 minutes	83	Multicoloured spots in the lower right quadrant spreading over the whole right visual field	Left mesio-occipital possible **vascular malformation**	Left occipital seizure pattern	Spatt and Mamoli, 2000
13 minutes (V-EEG)	39	Pulsating spots over the entire visual field with predominance on the left, moving to the left and becoming greenish	Post resection of an **arterio-venous malformation,** right parieto-occipital	Right parieto-occipital seizure pattern (V-EEG)	Hartl *et al.*, 2015
17 minutes (V-EEG)	15	Flickering in the right visual field, followed by a contralateral scotoma and colourful visual sensations	Left occipital gliosis	Left occipital seizure pattern (V-EEG)	Hartl *et al.*, 2015
20-30 minutes	14	Transparent, flickering line in the middle of the right hemi-field, expanding over the whole right hemifield and becoming colourful	**Arterio-venous malformation,** left temporo-occipital	Left occipital seizure pattern (V-EEG)	Strzelczyk *et al.*, 2017
45 minutes	32	Hallucination of "red flashing lights" in the left hemifield	Right mesio-occipital encephalomalacia in cCT	Frequent biposterior spikes + spike-waves, dominant posterior temporal	Aldrich *et al.*, 1989
>1 h	-	Continuous whitish photomes at the outer rim of the visual field, sometimes evolving over the entire visual field	**Operated haemangioma**	Unrevealing EEG	Mameniskiene *et al.*, 2011

Table 1. Case reports of EEG-confirmed visual status epilepticus; association with vascular malformation is highlighted in bold (*Continued*).

Maximum duration	Age of onset	Seizure characteristics	Imaging	EEG	Reference
>1 h	-	Flickering in the left visual field	-	Right occipital epileptiform EEG activity	Mameniskiene *et al.*, 2011
>1 h	-	Flickering in the left visual field, repetitive 1-2-h episodes	Non-specified occipital lesion	Non-specific focal ictal EEG abnormalities	Mameniskiene *et al.*, 2011
>1 h	-	Visual hallucinations of lines and circles	-	Left occipital runs of spikes	Mameniskiene *et al.*, 2011
60-90 minutes	42	Yellow, red and blue spots	Right occipital lesion after mycoplasmic meningoencephalitis	Right occipital interictal sharp waves; right occipital seizure pattern	Jobst *et al.*, 2009
A few hours	60	Palinopsia or abnormally recurring visual imagery, macropsia, unformed hallucinations, hemianopia	Left temporooccipital **cavernous haemangioma**	Left occipital seizure pattern	Kawai *et al.*, 2006
Up to 2 days	3	Flickering lights, obfuscation of vision by red and green lights; or shimmering ellipsoid, silver lights ("like a camera flash")	Hemispheric asymmetry	Right occipital lobe seizure pattern; abnormal photic stimulation response	Walker *et al.*, 1995
>3 years	10	Visual learning disorder; no visual hallucination	MRI normal; but FDG-PET with prominent left occipital hypermetabolism	Right occipital status epilepticus	Sheth and Riggs, 1999

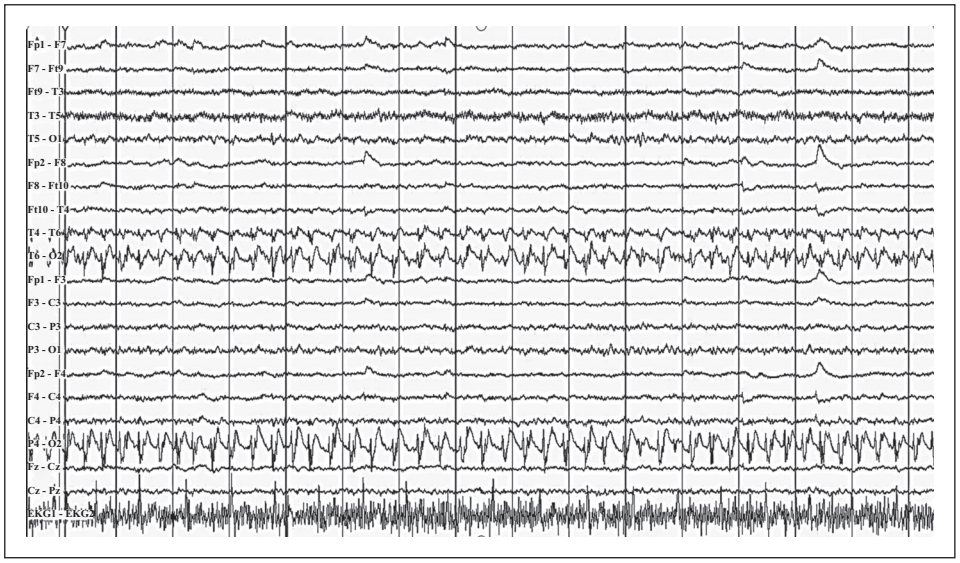

Figure 2. Well-localized EEG seizure pattern at electrode O_2.

electrically isolated. Isolation in such cases may be induced by proliferation of non-neurogenic tissue of inflammatory, glial or vascular origin. The high prevalence of vascular malformations in the cases presented in *table 1*, as well as in cases of amaurotic status epilepticus (Barry *et al*., 1985), indicate that such tissue, or scar tissue after its resection, may provide suitable conditions for focal status epilepticus. On the other hand, and taking into account the long duration of visual auras in migraine, conditions in the striate cortex itself may render spreading of electric activity less likely than in other cortices. Whether this property could be related to the macroscopic "stria" of Gennari -the dense stripe of highly myelinated horizontal fibres in layer IV of the primary visual cortex- remains to be shown.

Long-lasting epileptic visual auras illustrate the wide spectrum of propagation dynamics within epileptogenic networks and can be associated with vascular malformations. □

Disclosures.

None of the authors have any conflict of interest to declare.

References

Adcock JE, Panayiotopoulos P. Occipital lobe seizures and epilepsies. *J Clin Neurophysiol* 2012; 29: 397-407.

Aldrich MS, Vanderzant CW, Alessi AG, Abou-Khalil B, Sackellares JC. Ictal cortical blindness with permanent visual loss. *Epilepsia* 1989; 30: 116-20.

Barry E, Sussman NM, Bosley TM, Harner RN. Ictal blindness and status epilepticus amauroticus. *Epilepsia* 1985; 26: 577-84.

Eriksen MK, Thomsen LL, Olesen J. The Visual Aura Rating Scale (VARS) for migraine aura diagnosis. *Cephalalgia* 2005; 25: 801-10.

Hartl E, Rémi J, Noachtar S. Two patients with visual aura - migraine, epilepsy or migralepsy? *Headache* 2015; 55: 1148-51.

Hartl E, Gonzalez-Victores JA, Rémi J, Schankin CJ, Noachtar S. Visual auras in epilepsy and migraine - an analysis of clinical characteristics. *Headache* 2017; 57: 908-16.

Jobst BC, Roberts DW, Williamson PD. Occipital lobe nonconvulsive status epilepticus. In: *Nonconvulsive status epilepticus*. Kaplan PW, Drislane FW. New York: Demos Medical, 2009.

Kawai M, Cherches IM, Goldsmith IL. Visual illusory and hallucinatory phenomena in a patient with left occipital seizures. *Neurology* 2006; 67: 1457.

Mameniskiene R, Bast T, Bentes C, *et al*. Clinical course and variability of non-Rasmussen, nonstroke motor and sensory epilepsia partialis continua: a European survey and analysis of 65 cases. *Epilepsia* 2011; 52: 1168-76.

Panayiotopoulos CP. Elementary visual hallucinations, blindness, and headache in idiopathic occipital epilepsy: differentiation from migraine. *J Neurol Neurosurg Psychiatry* 1999a; 66: 536-40.

Panayiotopoulos CP. Visual phenomena and headache in occipital epilepsy: a review, a systematic study and differentiation from migraine. *Epileptic Disord* 1999b; 1: 205-16.

Sheth RD, Riggs JE. Persistent occipital electrographic status epilepticus. *J Child Neurol* 1999; 14: 334-6.

Spatt J, Mamoli B. Ictal visual hallucinations and post-ictal hemianopia with anosognosia. *Seizure* 2000; 9: 502-4.

Strzelczyk A, Gaul C, Rosenow F, Kurlemann G. Visuelle Auren im Grenzgebiet zwischen Epilepsie und Migräne. *Z Epileptol* 2017; 20: 21-7.

Trinka E, Cock H, Hesdorffer D, *et al*. A definition and classification of status epilepticus-report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015; 56: 1515-23.

Walker MC, Smith SJ, Sisodiya SM, Shorvon SD. Case of simple partial status epilepticus in occipital lobe epilepsy misdiagnosed as migraine: clinical, electrophysiological, and magnetic resonance imaging characteristics. *Epilepsia* 1995; 36: 1233-6.

TEST YOURSELF

(1) Which clinical criteria differentiate best between a migrainous and an epileptic visual aura?

(2) Which clinical criteria currently define convulsive status epilepticus?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Clinical commentary

Epileptic Disord 2019; 21 (1): 108-11

Rasmussen syndrome: absence seizures may be induced by oxcarbazepine

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ABSTRACT – A female patient with electroclinical and neuroradiological features compatible with Rasmussen syndrome developed a particular clinical and EEG pattern. As the seizures were refractory to valproate at 750 mg/kg/day, oxcarbazepine (OXC) at 30 mg/kg/day was added. Seizures became more frequent and on neurological examination, no hemiparesis was detected. The interictal EEG showed focal spikes and diffuse paroxysms in the right fronto-temporal regions. Brain MRI revealed right hemiatrophy, mainly at the Sylvian fissure. After initiating OXC daily, brief absence seizures, lasting less than 20 seconds and associated with bilateral and synchronous 2.5-3-Hz spike-and-waves compatible with typical absences, were observed. OXC was discontinued and the typical absences disappeared. Treatment with intravenous gammaglobulin was started. At the last control visit, at nine years of age, no absence seizures were observed either by the parents or on the EEG recording. Our patient who met the diagnostic criteria for Rasmussen syndrome presented with absence seizures that may have been induced by OXC. The absence seizures disappeared after OXC was discontinued.

Key words: absences, epilepsia partialis continua, Rasmussen syndrome, oxcarbazepine

Rasmussen syndrome (RS) is a rare and severe immune-mediated brain disorder resulting in unilateral brain atrophy and leading to progressive neurological dysfunction and refractory seizures (Bien *et al.*, 2005). Different mechanisms have been suggested, however, the aetiopathogenesis is not fully understood (Bien *et al.*, 2005; Caraballo *et al*., 2013).

In the literature, patients with atypical features have been published (Granata *et al*., 2012). These patients may manifest with absence or delayed-onset seizures, unusual events such as epileptic spasms and hemidystonic episodes, headache as the initial manifestation, dual pathology, or bilateral brain involvement. A dual pathology is seen in 10% of patients and varies from low-grade tumour, cortical dysplasia, tuberous sclerosis, mesial temporal sclerosis, vascular abnormalities, to old ischaemic lesions (Bien *et al*., 2007; Granata *et al*., 2012).

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The aim of this study was to describe the electroclinical pattern of absence seizures (AS) that may have been induced by oxcarbazepine (OXC) in a child with RS.

Case study

The patient was a seven-year-old girl, born to non-consanguineous parents with an unremarkable personal and family history, who consulted because of focal seizures with impaired consciousness, oroalimentary automatisms, and left-sided clonic movements with onset in the left leg, progressing to the ipsilateral arm. The episodes were preceded by a tingling sensation in the left leg. The interictal EEG recording showed focal theta activity in the right frontal region. Neurological examination as well as brain MRI were normal.

Valproic acid (VPA) was started at 750 mg/kg/day without response. The seizures increased in frequency and, in addition, continuous partial seizures were observed.

As the focal seizures were not controlled, at seven years and six months of age, OXC at 30 mg/kg/day was added. The seizures became more frequent, occurring daily and associated with loss of consciousness. The girl's school performance was good with a mild attention deficit and reading and writing difficulties for which she received educational therapy. On neurological examination, no hemiparesis was detected. The interictal EEG showed focal spikes and diffuse paroxysms in the right fronto-temporal regions. Brain MRI revealed right hemiatrophy, mainly at the Sylvian fissure (*figure 1*). Oligoclonal bands were found in the CSF. The electroclinical features, CSF findings, and MRI abnormalities met the criteria for RS, according to Bien *et al*. (2005).

Other immune-mediated epileptic encephalopathies, *i.e*. cerebral vasculitis including lupus erythematosus, subacute measles encephalitis with or without immunodeficiency, hemiconvulsion-hemiplegia-epilepsy syndrome, focal cortical dysplasia including hemimegalencephaly, tumour, stroke, Sturge-Weber syndrome, and neurometabolic diseases, particularly mitochondriopathies, were ruled out.

At eight years of age, in addition to the focal seizures, the patient developed brief absence seizures (AS) lasting less than 20 seconds and occurring many times daily, associated with bilateral, synchronous and asymmetric 3-Hz spike-and-waves, compatible with typical absences (*figure 2*). The AS were induced by hyperventilation. OXC was discontinued and subsequently clobazam was started. The typical AS disappeared while the focal motor seizures persisted with occasional secondary generalization.

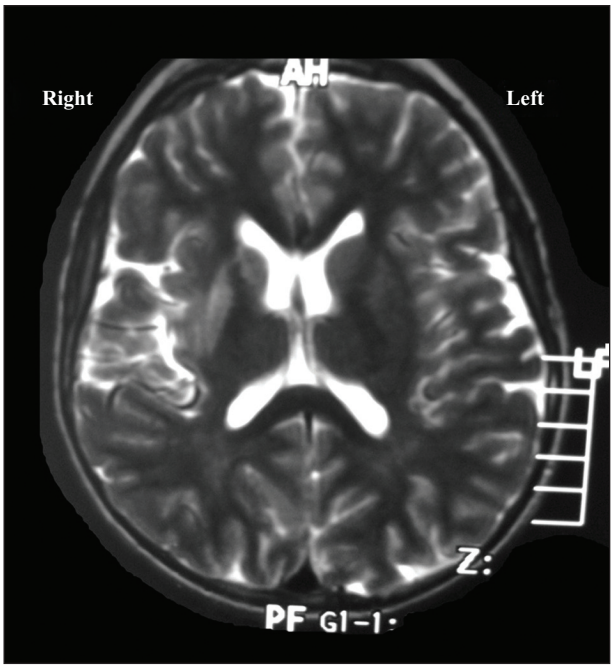

Figure 1. T2-weighted axial section shows right cerebral hemiatrophy predominantly in the perisylvian region; hyperintense lesions are also observed in this region.

Treatment with intravenous gammaglobulin was started every 30 days and gradual improvement of the seizures was observed. The seizures were short, lasting no more than three minutes, and occurred with a frequency of seven to 15 a month. At the last control visit, at nine years of age, no new neurological signs were detected. No further AS were observed either by the parents or on the EEG recording. The focal motor seizures persisted while the patient was receiving VPA at 1,250 mg/day, clobazam at 22.5 mg/day, and monthly intravenous gammaglobulin.

Discussion

Here, we present a patient who met the diagnostic criteria for RS with a particular type of seizure and electroclinical features of typical AS.

Typical AS are characterized by absences that last 5-25 seconds with abrupt and clear impairment or loss of consciousness, occurring several times a day. The ictal EEG shows discharges of generalized high-amplitude spikes and slow-wave complexes with rhythmic spike-waves at around 3 Hz.

Considering that, in our patient, the typical AS disappeared after withdrawing OXC, we may hypothesize that OXC was the culprit drug.

Differentiating between typical AS and complex focal seizures should be easy, although automatisms may be

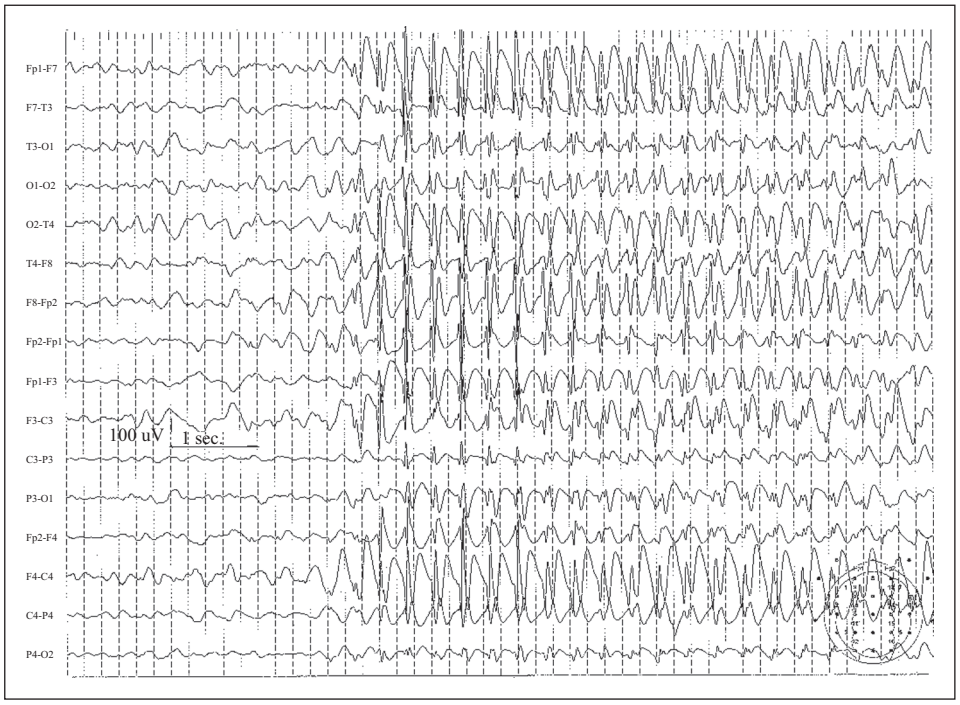

Figure 2. The ictal EEG recording shows bilateral, synchronous and asymmetric spike-waves at 3 Hz, associated with an absence seizure.

common in both. One of the main problems involves typical AS of frontopolar lobe origin that may also exhibit concomitant, more or less, regular bilateral 3-Hz spike-wave discharges (Medina *et al*., 2012). Focal motor components, asymmetric ictal discharges, or stable interictal frontal foci on the EEG may help to distinguish them. MRI may show frontal abnormalities. Ferrie *et al*. (1995) listed diffuse and focal brain disorders in which AS have been reported.

Typical AS should be distinguished from atypical AS that occur in children with epileptic encephalopathies, mainly Lennox-Gastaut syndrome. These are distinct from typical absences in that onset and termination is slow, impairment of consciousness is mild, and they are often associated with loss of muscle tone. On the ictal EEG, the diffuse spikes and waves are slower than those observed in typical AS, usually between 1.5 and 2.5 Hz.

In our case, considering the presence of focal frontal spikes and the focal brain lesion in the insular region on brain MRI, the AS may have arisen from the right frontal lobe, triggering a thalamo-cortical system due to secondary bilateral synchrony (Medina *et al*., 2012). In our patient, the AS may have been induced by OXC, since upon discontinuation of this antiepileptic drug (AED), the AS disappeared. It is widely known that many AEDs, such as carbamazepine (CBZ), OXC, gabapentin, vigabatrine, and tiagabine, may aggravate absence epilepsies (Genton *et al*., 2012). Phenytoin (PHT) seems to be less aggravating for AS (Genton *et al*., 2012). Phenobarbital may have a dual effect by increasing absences at high doses and decreasing them at low doses (Genton *et al*., 2012). In one study, aggravation of AS was reported in eight cases within days of VPA introduction. All improved after VPA discontinuation. In five, VPA was reintroduced, resulting in new seizure aggravation (Lerman-Sagie *et al*., 2001). An aggravation of AS was reported in three adolescents with juvenile absence epilepsy by levetiracetam at a daily dose of more than 1,750 mg/day (Auvin *et al*., 2011).

In rat models of genetic absence epilepsy, certain AEDs, such as CBZ and PHT, have been found to worsen spiking (Depaulis and Van Luijteaar, 2006).

In our case, the AS may have resulted from the relationship between RS and the reaction to OXC or may have occurred as a coincidence. □

Disclosures.

None of the authors have any conflict of interest to declare.

References

Auvin S, Chhun S, Berquin P, Ponchel E, Delanoe C, Chiron C. Aggravation of absence seizure related to levetiracetam. *Eur J Paediatr Neurol* 2011; 15: 506-11.

Bien CG, Granata T, Antozzi C, *et al*. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. *Brain* 2005; 128: 454-71.

Bien CG, Elger CE, Leitner Y, *et al*. Slowly progressive hemiparesis in childhood as a consequence of Rasmussen encephalitis without or with delayed-onset seizures. *Eur J Neurol* 2007; 14: 387-90.

Caraballo RH, Fortini S, Cersósimo R, *et al*. Rasmussen syndrome: an Argentinean experience in 32 patients. *Seizure* 2013; 22: 360-7.

Depaulis A, Van Luijteaar G. Genetic models of absence epilepsy in the rat. In: *Models of seizures and epilepsy*. Pitkanen A, Schwartzkroin P, Moshé S. Burlington: Elsevier Academic Press, 2006.

Ferrie C, Giannakodimo S, Robinson R, Panayiotopoulos C. Symptomatic typical absences seizures. In: *Typical absences and related epileptic syndromes*. Duncan JS, Panayiotopoulos C. Edinburgh: Churchill Livingstone, 1995.

Genton P, Fejerman N, Gelisse P. Syndromes and antiepilepsy drugs. In: *Epileptic syndromes in infancy, childhood and adolescence*. 5th Edition. Bureau M, Genton P, Dravet C, *et al*. Montrouge: John Libbey Eurotext, 2012.

Granata T, Hart Y, Andermann F. Rasmussen's encephalitis. In: *Epileptic syndromes in infancy, childhood and adolescence*. 5th Edition. Bureau M, Genton P, Dravet C, *et al*. Montrouge: John Libbey Eurotext, 2012.

Lerman-Sagie T, Watemberg N, Kramer U, Shahar E, Lerman P. Absence seizures aggravated by valproic acid. *Epilepsia* 2001; 42: 941-3.

Medina M, Bureau M, Hirsch E, Panayiotopoulos C. Childhood absence epilepsy. In: *Epileptic syndromes in infancy, childhood and adolescence*. 5th Edition. Bureau M, Genton P, Dravet C, *et al*. Montrouge: John Libbey Eurotext, 2012.

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A Rasmussen encephalitis, autoimmune encephalitis, and mitochondrial disease mimicker: expanding the *DNM1L*-associated intractable epilepsy and encephalopathy phenotype

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ABSTRACT – Dynamin-1-like protein (*DNM1L*) gene variants have been linked to childhood refractory epilepsy, developmental delay, encephalopathy, microcephaly, and progressive diffuse cerebral atrophy. However, only a few cases have been reported in the literature and there is still a limited amount of information about the symptomatology and pathophysiology associated with pathogenic variants of *DNM1L*. We report a 10-year-old girl with a one-year history of mild learning disorder and absence seizures who presented with new-onset focal status epilepticus which progressed to severe encephalopathy and asymmetric hemispheric cerebral atrophy. Differential diagnosis included mitochondrial disease, Rasmussen's encephalitis, and autoimmune encephalitis. Disease progressed from one hemisphere to the other despite anti-seizure medications, hemispherectomy, vagus nerve stimulator, ketogenic diet, and immunomodulators. Continued cerebral atrophy and refractory seizures evolved until death four years after initial presentation. Post-mortem whole-exome sequencing revealed a pathogenic *DNM1L* variant. This paper presents a novel case of adolescent-onset *DNM1L*-related intractable epilepsy and encephalopathy.

Key words: developmental delay, seizure, refractory epilepsy, cerebral atrophy, encephalopathy congenital, *DNM1L*

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The advent of next-generation sequencing is rapidly expanding the already genetically and phenotypically heterogenous category of mitochondrial disorders. Epilepsy gene panels are now identifying novel nuclear mitochondrial pathologic variants, including those in the *DNM1L* (dynamin-1-like, MIM*603850) gene.

DNM1L is a nuclear mitochondrial gene that encodes dynamic-related protein 1 (DRP1) and plays a critical role in mediating the mitochondrial fission process and in regulating peroxisomal fission (Archer, 2013; Lackner, 2014). *DNM1L*-related disorders present during infancy with early-onset diffuse cerebral abnormalities, microcephaly, optic atrophy, lactic acidosis, hypotonia, and death within early infancy (Waterham *et al*., 2007). Recently, there have been reports of *DNM1L*-related disorders that include: developmental delay, refractory epilepsy, normal brain MRI, and prolonged survival (Vanstone *et al*., 2016); childhood-onset epileptic encephalopathy with diffuse cerebral atrophy (Fahrner *et al*., 2016); postnatal microcephaly, developmental delay, and pain insensitivity (Sheffer *et al*., 2016); or progressive neurological disease, characterized by mild cognitive impairment, cerebellar and pyramidal signs, and ocular involvement (Nasca *et al*., 2016).

Here, we report a patient with disease progression that mimicked Rasmussen encephalitis, autoimmune encephalitis, and mitochondrial disease. Onset of absence seizures at age nine was followed by focal status epilepticus in early adolescence at age 10, with development of severe encephalopathy, progressive hemiparesis, developmental regression, refractory focal epilepsy, and notably asymmetric progressive cerebral atrophy. The asymmetric atrophy was concerning for Rasmussen encephalitis, autoimmune encephalitis, or mitochondrial disease that did not improve with typical therapies. Post-mortem whole-exome sequencing was diagnostic for a pathogenic *DNM1L* variant (c.1207C>T [p.R403C]; a heterozygous *de novo* mutation) (Fahrner *et al*., 2016) associated with *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 (OMIM #614388).

Case study

The proband was a right-handed Caucasian female who had an uneventful birth and appropriate development, aside from a mild learning disorder. She had no prior history of traumatic brain injury, abnormal birth history/development, personal/family history of seizures, nor family history of epilepsy. She was diagnosed with typical absence seizures at age nine that initially responded to ethosuximide. One year after her initial diagnosis, at 10 years of age, the proband experienced new-onset frontal headache for one week before suddenly developing left neck twitching. This progressed to involve her left arm and leg, followed by sudden left hemibody loss of sensation. She presented to the emergency department (ED) and clinically demonstrated non-resolving rhythmic left arm and leg twitching with altered awareness. Continuous EEG revealed electroclinical status epilepticus with right hemispheric 2-Hz spike and wave discharges, alternating with diffuse background slowing. Her seizures continued despite escalating treatment with lorazepam, diazepam, and levetiracetam; she was intubated and placed on a propofol infusion. Her seizures continued and she was further treated with a midazolam infusion, fosphenytoin, phenobarbital, and ethosuximide. Pentobarbital infusion was started and a burst suppression pattern was obtained with resolution of electrographic seizures.

Initial magnetic resonance imaging (MRI) demonstrated extensive areas of restricted diffusion within the right cerebral hemisphere, predominantly at the vertex and involving the right frontal and parietal lobes, right insular cortex, and right thalamus with corresponding increased T2/FLAIR signal and cortical edema. The findings were suggestive of changes seen with status epilepticus (*figure 1*). Magnetic resonance spectroscopy demonstrated decreased n-acetyl aspartate (NAA) and minimally increased choline peaks of the right cerebral hemisphere compared to the contralateral side. Magnetic resonance perfusion images demonstrated overall symmetric perfusion, bilaterally. At this time, hemispheric presentation was most concerning for a mitochondrial disorder versus an autoimmune etiology, such as Rasmussen-type phenomena. Initial CSF studies were unrevealing.

Unfortunately, right hemispheric electroclinical seizures returned following pentobarbital discontinuation despite treatment with IVIG. An outside center evaluated and performed a right hemispherectomy 13 days after her initial presentation, sparing portions of the right thalamus and medial right basal ganglia. Seizures reoccurred almost immediately post-operatively, presenting with right facial twitching, nystagmus, and right hemibody twitching. Continuous EEG now demonstrated left hemispheric and multi-focal left hemispheric epileptiform discharges, in addition to expected post-surgical right hemispheric attenuation. She exhibited epilepsia partialis continua clinically as well as electroclinical left frontotemporal focal seizures. At that time, she was maintained on levetiracetam, lacosamide, clobazam, and topiramate. An autoimmune encephalopathy panel revealed elevated anti-glutamic acid decarboxylase (GAD) antibodies, furthering the concern for autoimmune encephalitis. She was started on monthly IVIG and high-dose steroids as well as

zonisamide and phenobarbital with minimal clinical improvement. Perampanel caused clinical worsening of seizure frequency. A vagus nerve stimulator (VNS) was placed with a decrease in seizure frequency but was complicated by sinus bradycardia and first-degree atrioventricular block requiring device removal.

Repeat MRI, seven months post-hemispherectomy, now demonstrated restricted diffusion along the cortex of the left anterior frontal lobe extending into the anterior insula with sparing of the medial most portion of the frontal lobe. There was similar cortically based restricted diffusion in the left parietal lobe extending into the medial left occipital lobe and minimal portions

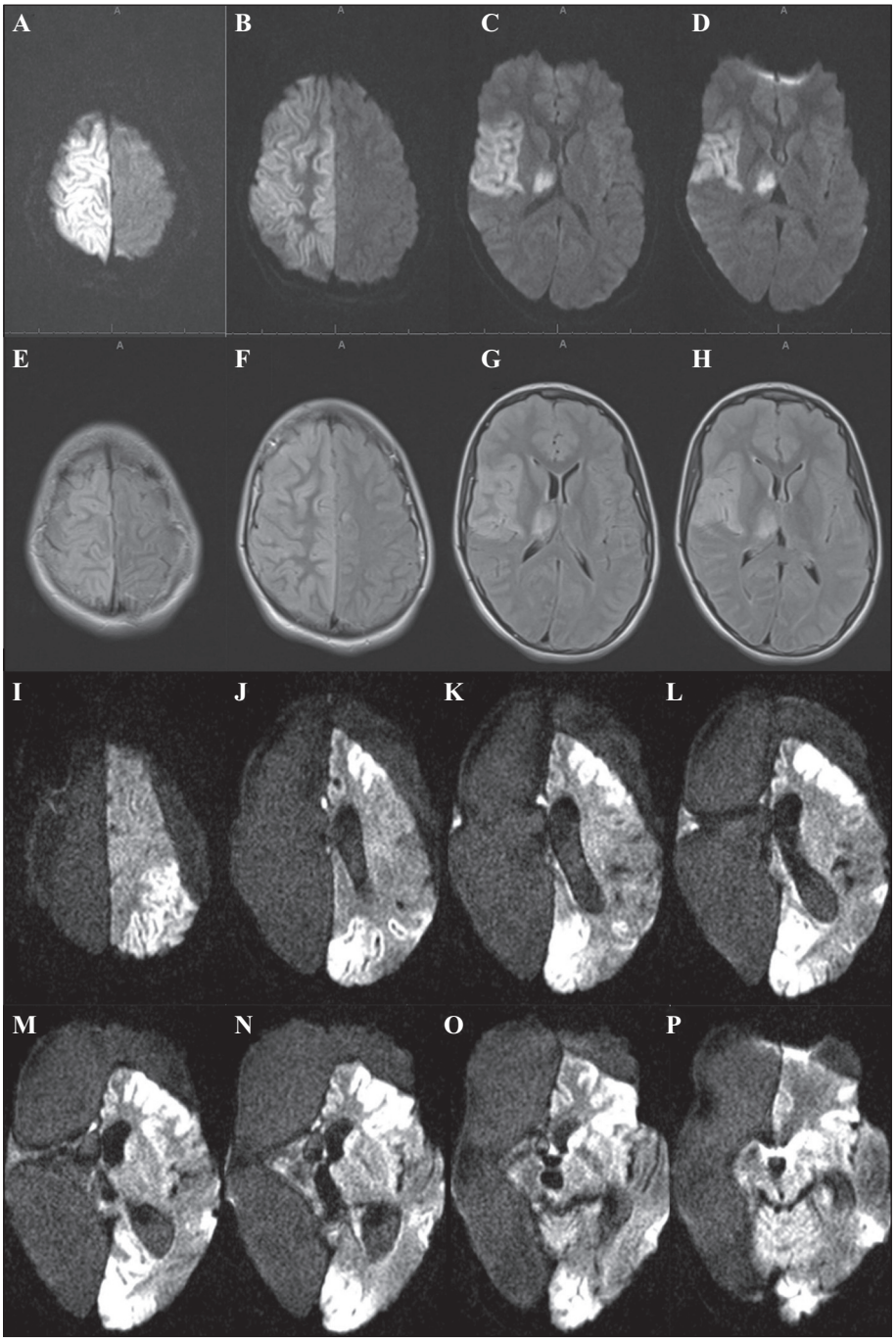

Figure 1. Initial MRI demonstrating extensive areas of restricted diffusion within the right cerebral hemisphere, predominantly at the vertex and involving the right frontal and parietal lobes, right insular cortex, and right thalamus with corresponding increased T2/FLAIR signal and cortical edema.

of the left temporal lobe. The appearance of the diffusion restriction was relatively similar in appearance to the abnormalities seen in the right cerebral hemisphere on the initial MRI prior to the patient's right hemispherectomy (*figure 1*).

The patient's clinical status continued to deteriorate from difficulty performing functional activities (*e.g.* grooming, dressing, bathing, toileting) to requiring maximal assistance for bilateral hemiparesis, aphasia, contractures of the hip and knees, and severe muscle wasting requiring a wheelchair and gastrostomy tube. Twenty months after initial EPC presentation at age 12, the patient became ventilator-dependent due to chronic respiratory failure. Repeat MRI now revealed ventricular enlargement and progressive left hemisphere atrophy. Magnetic resonance spectroscopy (MRS) showed high lactate peaks in her basal ganglia (*figure 2*). Despite multiple anti-seizure drugs, she continued to have daily breakthrough seizures complicated by recurrent pneumonia and urinary tract infections. The patient was eventually admitted to a hospice due to decreasing quality of life and died four years and three months after initial EPC presentation.

Autopsy revealed atrophy of the right cerebellar hemisphere and right pyramidal tracts, and areas of neuronal loss in the left visual and temporal lobe cortex and in the left pons. Muscle biopsy revealed only neuropathic changes. No myopathic features were present and no morphologic evidence of metabolic myopathy was present. Post-mortem whole-exome sequencing in the patient identified a *de novo* heterozygous pathogenic variant in the *DNM1L* gene (c.1207 C>T [p.R403C]). The *DNM1L* variant identified correlated with the proband's clinical presentation and provided a likely genetic diagnosis of *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 (OMIM #614388). Written informed consent for this case report could not be obtained from the patient because the patient deceased before the conception of this manuscript.

Discussion

DNM1L-related biologic function in mitochondrial and peroxisomal fission has been well described in the literature, yet the associated disease spectrum is only beginning to be clarified. The majority of reported cases presented during infancy or within the first few years of life (Waterham *et al*., 2007; Chao *et al*., 2016; Nasca *et al*., 2016; Sheffer *et al*., 2016; Vanstone *et al*., 2016; Yoon *et al*., 2016). There has been one case report of two individuals presenting at four and five years of age, respectively (Fahrner *et al*., 2016). Our case report describes a *de novo* variant in the *DNM1L* gene (c.1207 C>T [p.R403C]) in a patient with initial typical early-adolescent absence epilepsy that quickly progressed to refractory epilepsy with severe encephalopathy, asymmetrically progressive cerebral atrophy, and eventual death. To our knowledge, our

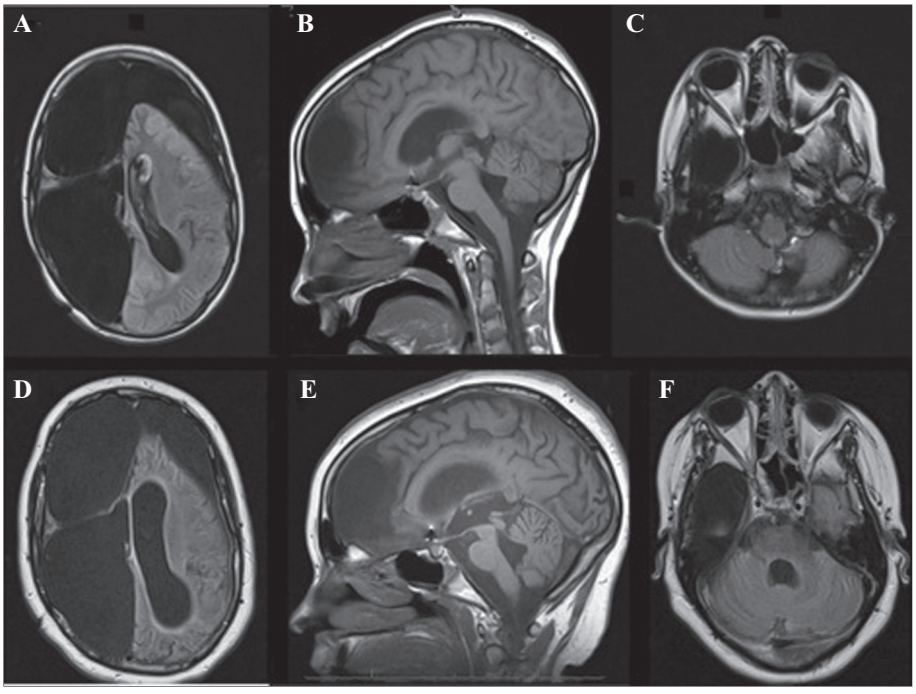

Figure 2. MRS showing high lactate peaks in the basal ganglia.

patient had the latest onset of encephalopathy at age 10, compared to the described infantile onset of *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 (OMIM #614388), expanding the described age of presentation for this disorder. This case report also suggests that *DNM1L*-related disorders may initially present with a more seemingly benign presentation, such as absence epilepsy, which is not atypical in this age range.

In addition to this patient's relatively late onset, this case was notable due to the shifting focal hemispheric predominance of the status epilepticus. This is the first report of *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 that presented with focal hemispheric findings initially, as opposed to global atrophy. This suggests that in patients with rapid progression of hemispheric refractory epilepsy, an underlying genetic etiology should be considered in conjunction with autoimmune etiologies. Typical first-step genetic testing, chromosomal microarray (CMA), and epilepsy panels are not sufficient in such cases. Indeed, in our case, reported negative first-line genetic testing and the etiology was not revealed until post-mortem whole-exome sequencing was performed. If *DNM1L*-related refractory epilepsy had been identified during that initial testing, the expected prognosis may have drastically changed management or provided parental guidance during a challenging time. In refractory epilepsy patients, especially those who demonstrate rapid clinical deterioration, whole-exome sequencing should be considered early in the diagnostic process.

To conclude, this case report presents a patient with a novel DNM1L R403C variant and clinical findings of early-adolescent-onset refractory seizures with severe encephalopathy and progressive asymmetric cerebral atrophy associated with *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1. This patient's presentation not only expands the phenotypic age range of the disorder but also demonstrates how the initial presentation can show focal findings that may mimic an autoimmune disorder such as Rasmussen's encephalopathy. □

Disclosures.
None of the authors have any conflict of interest to declare.

References

Archer SL. Mitochondrial dynamics-mitochondrial fission and fusion in human diseases. *N Engl J Med* 2013; 369: 2236-51.

Chao YH, Robak LA, Xia F, *et al*. Missense variants in the middle domain of DNM1L in cases of infantile encephalopathy alter peroxisomes and mitochondria when assayed in Drosophila. *Hum Mol Genet* 2016; 25: 1846-56.

Fahrner JA, Liu R, Perry MS, Klein J, Chan DC. A novel *de novo* dominant negative mutation in *DNM1L* impairs mitochondrial fission and presents as childhood epileptic encephalopathy. *Am J Med Genet A* 2016; 170: 2002-11.

Lackner LL. Shaping the dynamic mitochondrial network. *BMC Biol* 2014; 12: 35.

Nasca A, Legati A, Baruffini E, *et al*. Biallelic mutations in *DNM1L* are associated with a slowly progressive infantile encephalopathy. *Hum Mutat* 2016; 37: 898-903.

Sheffer R, Douiev L, Edvardson S, *et al*. Postnatal microcephaly and pain insensitivity due to a *de novo* heterozygous *DNM1L* mutation causing impaired mitochondrial fission and function. *Am J Med Genet A* 2016; 170: 1603-7.

Vanstone JR, Smith AM, Mcbride S, *et al*. DNM1L-related mitochondrial fission defect presenting as refractory epilepsy. *Eur J Hum Genet* 2016; 24: 1084-8.

Waterham HR, Koster J, Van Roermund CW, *et al*. A lethal defect of mitochondrial and peroxisomal fission. *N Engl J Med* 2007; 356: 1736-41.

Yoon G, Malam Z, Paton T, *et al*. Lethal disorder of mitochondrial fission caused by mutations in *DNM1L*. *J Pediatr* 2016; 171: 313-6.e1-2.

TEST YOURSELF

(1) Name a disorder that can mimic *DNM1L*-associated lethal encephalopathy.

(2) If chromosomal microarray and a gene panel are negative, what genetic test should be considered next in the investigation?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

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Berardinelli-Seip syndrome and progressive myoclonus epilepsy

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ABSTRACT – Berardinelli-Seip syndrome, or congenital generalized lipodystrophy type 2 (CGL2), is characterized by a lack of subcutaneous adipose tissue and precocious metabolic syndrome with insulin resistance, resulting in diabetes, dyslipidaemia, hepatic steatosis, cardiomyopathy, and acanthosis nigricans. Most reported mutations are associated with mild, non-progressive neurological impairment. We describe the clinical and EEG data of a patient with progressive myoclonus epilepsy (PME), CGL2, and progressive neurological impairment, carrying a homozygous *BSCL2* nonsense mutation. The patient had epilepsy onset at the age of two, characterized by monthly generalized tonic-clonic seizures. By the age of three, he presented with drug-resistant ongoing myoclonic absence seizures, photosensitivity, progressive neurological degeneration, and moderate cognitive delay. Molecular analysis of the *BSCL2* gene yielded a homozygous c.(1076dupC) p.(Glu360*) mutation. Application of a vagus nerve stimulator led to temporary improvement in seizure frequency, general neurological condition, and EEG background activity. Specific *BSCL2* mutations may lead to a peculiar CGL2 phenotype characterized by PME and progressive neurodegeneration. Application of a vagus nerve stimulator, rarely used for PMEs, may prove beneficial, if only temporarily, for both seizure frequency and general neurological condition.

Key words: lipodystrophy type 2, Berardinelli-Seip syndrome, *BSCL2*, progressive myoclonus epilepsy, neurodegenerative encephalopathy, EEG, vagus nerve stimulator

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Berardinelli-Seip syndrome, or congenital generalized lipodystrophy type 2 (CGL2), is characterized by a lack of subcutaneous adipose tissue and precocious metabolic syndrome with insulin resistance, resulting in diabetes, dyslipidaemia, hepatic steatosis, cardiomyopathy, and acanthosis nigricans. Genotype-phenotype correlations and an autosomal recessive inheritance were proposed with regards to a number of mutations in the *BSCL2* gene, that encodes Seipin. Most reported mutations are associated with mild, non-progressive neurological impairment. In 2016, Opri *et al*. published a small case series

of three patients with a rare association between CGL2, progressive myoclonus epilepsy (PME) and severe progressive neurological impairment (Opri *et al*., 2016). In one patient, a novel compound heterozygous *BSCL2* gene mutation was found, resulting in two different frameshift mutations. Here, we describe clinical and EEG data of a further patient with PME, CGL2, and progressive neurological impairment, carrying a homozygous *BSCL2* nonsense mutation.

Methods

After obtaining informed consent from the patient's parents, genetic molecular analysis was performed. Blood genomic DNA was extracted from whole peripheral blood. Exons and exon-intron boundaries of *BSCL2* were analysed by PCR amplification and direct sequencing (the first nucleotide of the ATG initiation codon was considered as the first nucleotide of the gene).

Case study

The patient was a male born in Macedonia in 2013. Pregnancy was reported as uneventful and psychomotor development as normal. At the age of 12 months, he developed monthly tonic seizures and antiepileptic drug (AED) therapy with valproic acid (VPA) was introduced in his home country, resulting in good seizure control. He moved to Italy at the age of two and a new medical evaluation was undertaken. Lack of subcutaneous adipose tissue, moderate psychomotor delay with speech impairment, and severe hyperactivity prompted metabolic testing.

Hypertriglyceridaemia, hypertransaminasaemia, and hepatic steatosis were documented and a low fat diet was implemented. Cerebral MRI was normal.

Molecular analysis of the *BSCL2* gene yielded a homozygous c.(1076dupC)/p.(Glu360*) mutation. Seizure recurrence followed the parents' autonomous suspension of VPA, and was characterized by generalized tonic seizures and episodes of loss of consciousness, perioral cyanosis, and bilateral eye retropulsion. The EEG correlate of such episodes was characterized by brief diffuse discharges of spike-wave (SW) complexes, followed by slow waves (*figure 1*). Seizure control was briefly obtained after gradual introduction of lamotrigine (LTG). During the following three months, the patient developed numerous daily absence seizures with eyelid myoclonias and forward head tilt, and VPA was reintroduced as add-on. After one month, there was a recurrence of absence seizures and an appearance of frequent drop attacks. The patient was eventually hospitalized for non-convulsive status epilepticus. A significant, albeit temporary, reduction in absence seizure and drop attack frequency was obtained with introduction of ethosuximide (ESM) and substitution of LTG with clonazepam (CZP). CPZ, however, severely worsened hyperactivity which led to accidental head trauma with subdural haemorrhage and transitory left facial nerve palsy. At this stage, ataxic gate and severe psychomotor delay were also evident. Serial brain MRI scans did not show signs of cerebral atrophy. Worsening of the general neurological condition paralleled degeneration of EEG background activity, especially during sleep, and an increase in photosensitivity, which was evident even at 1-Hz photic stimulation. A steady increase in seizure frequency gave way to relapsing refractory non-convulsive status, controlled with second-line IV administration of phenobarbital (PB) (*figure 2*). Introduction of PB therapy resulted in temporary improvement in seizure control but worsening of ataxic gait. A vagal nerve stimulator (VNS) was implanted (cyclic stimulation: 30 sec on; 5 min off; 30 Hz; 500 msec). The VNS was gradually calibrated to 1.2 mA with temporary improvement in seizure frequency, general neurological condition, and EEG background activity. After three months, PB was substituted with perampanel because of a relapse in drop attacks and the appearance of prolonged generalized tonic seizures. After two months of follow-up, tonic seizures disappeared and drop attack frequency and absence seizure frequency and duration were reduced with improvement in general neurological condition (gait, speech, and social interaction).

Discussion

Evidence that a form of PME exists in the context of CGL2 has already been suggested (Tseng *et al*., 2009; Guillén-Navarro *et al*., 2013; Opri *et al*., 2016). Guillèn-Navarro *et al*. described six patients affected by a fatal neurodegenerative syndrome who had homozygous or compound heterozygous *BSCL2* gene mutations. Five out of six patients developed myoclonic seizures between two and four years of age. This peculiar clinical presentation was named "Celia's encephalopathy" (CE), characterized by the presence of intranuclear aggregates of mutated, misfolded Seipin which are thought to have a pathogenic role in neurodegeneration by inducing endoplasmic reticulum stress in neurons (Ruiz-Riquelme *et al*., 2015). Even though there were no available data to demonstrate a pathogenic role for Seipin aggregates, PAS-positive inclusions were also found in the patients described by Tseng *et al*. and Opri *et al*. While the *BSCL2* transcripts of the patients described by Guillèn-Navarro *et al*. lacked exon 7, those described by Opri *et al*. presented with a heterozygous mutation

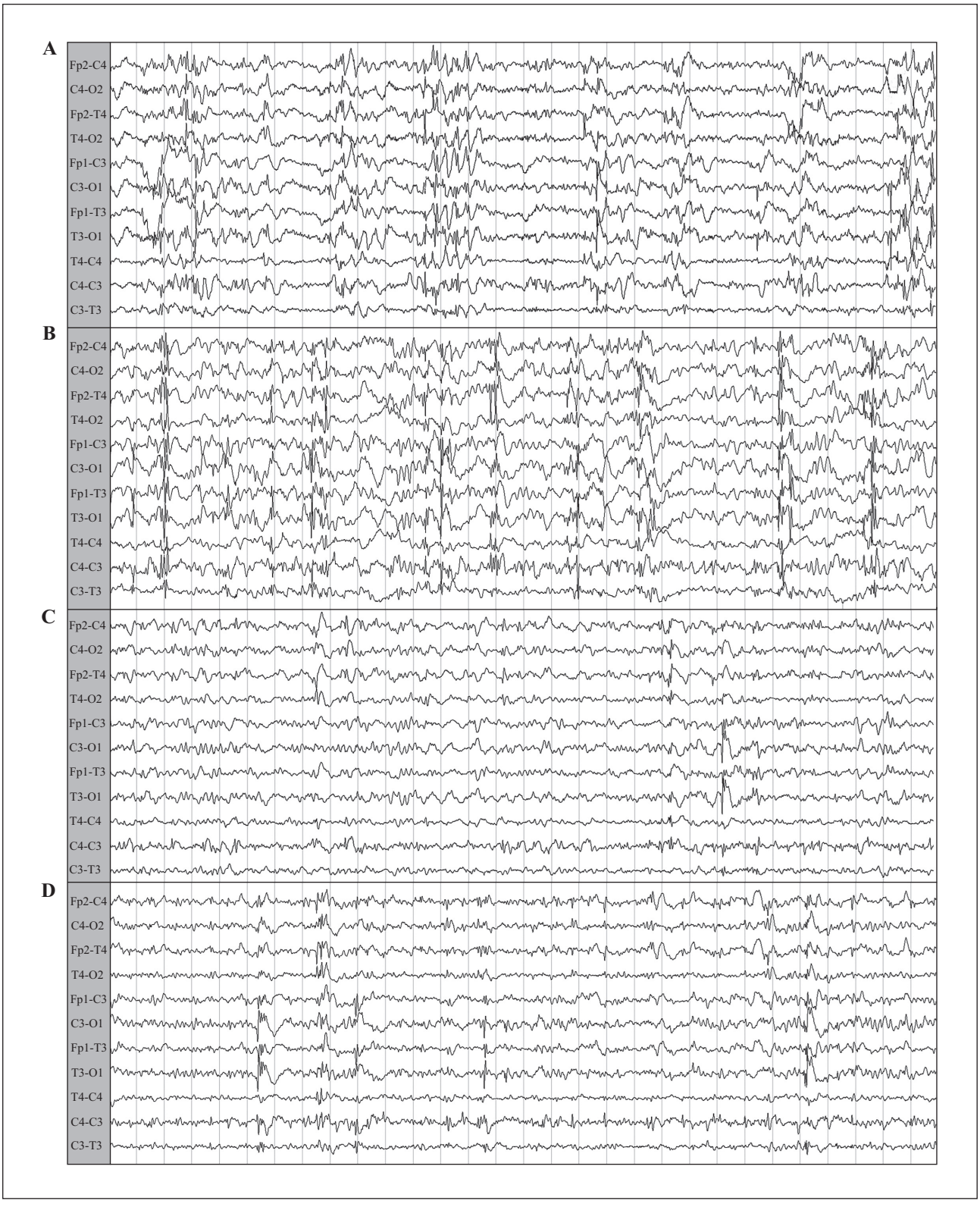

Figure 1. (A-D). Continuous EEG recording showing the EEG correlate of episodes characterized by brief diffuse discharges of spike-wave (SW) complexes, followed by slow waves.

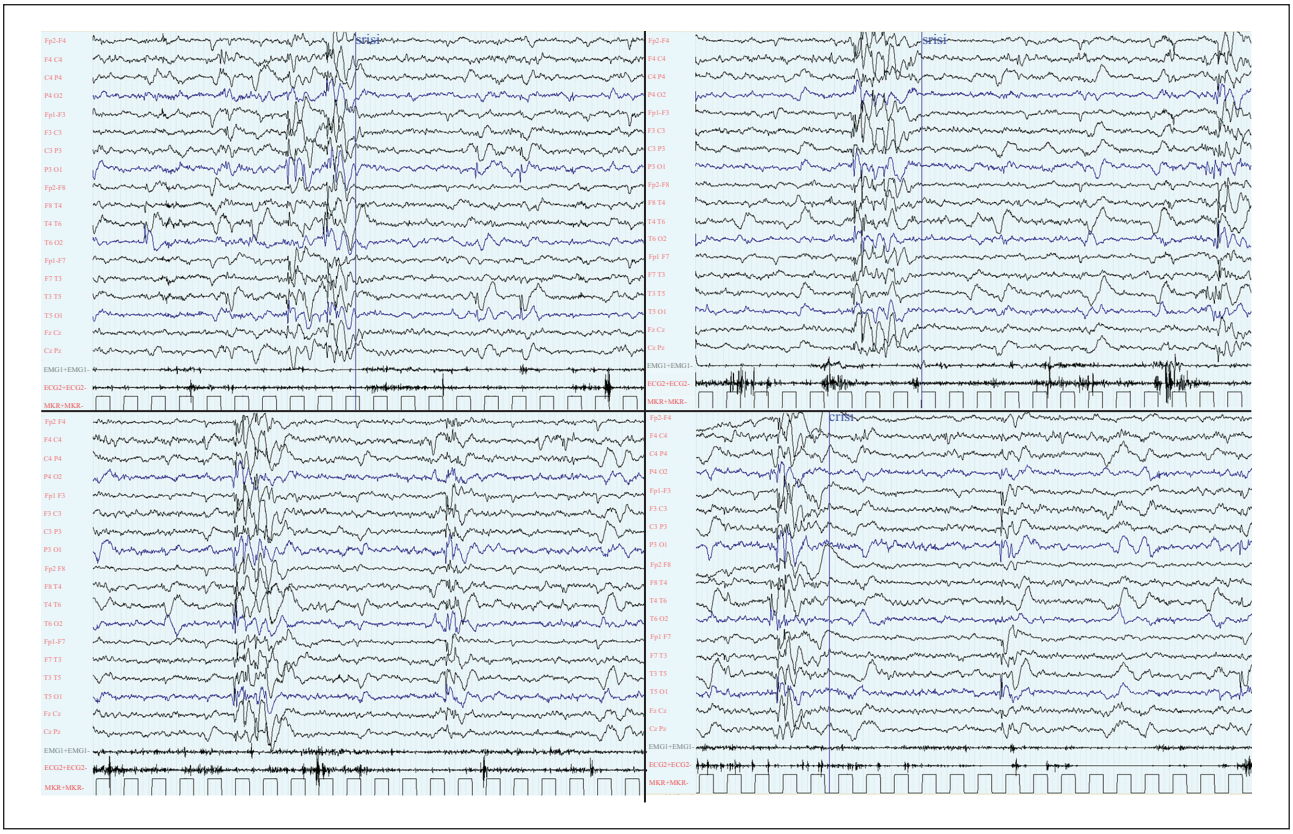

Figure 2. EEG revealing relapsing refractory non-convulsive status, controlled with second-line IV administration of phenobarbital.

involving exons 8 and 9. Thus, the authors argued that the pathogenic mechanism described for CE might not be unique to *BSCL2* exon 7 skipping. Our patient presented with a homozygous c.1076dupC mutation, involving exon 9 and resulting in a premature stop codon. Even though histological evidence of neuronal inclusion was not available, in the light of such a mutation, we believe that the presence of misfolded aggregates was very likely. Interestingly, there was no MRI evidence of brain atrophy in our case, in contrast to other patients, although these patients were described with a longer follow-up period. However, our report seems to validate the hypothesis that this peculiar type of CGL2 is not uniquely linked to exon 7 and provides further evidence towards a link between specific *BSCL2* mutations and a peculiar CGL2 phenotype characterized by PME and progressive neurodegeneration. Our report may also provide some insight into the possible role of VNS implantation. VNS is rarely used in PME but appeared to prove beneficial, although only temporarily, regarding both seizure frequency and the general neurological condition. Changes in amperage and stimulation pattern during follow-up might hopefully yield more data on potential effectiveness. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

References

Opri R, Fabrizi GM, Cantalupo G, *et al*. Progressive myoclonus epilepsy in congenital generalized lipodystrophy type 2: report of 3 cases and literature review. *Seizure* 2016; 42: 1-6.

Guillén-Navarro E, Sánchez-Iglesias S, Domingo-Jiménez R, *et al*. A new seipin-associated neurodegenerative syndrome. *J Med Genet* 2013; 50: 401-9.

Tseng CF, Ho CS, Chiu NC, Lin SP, Tzen CY, Wu YH. Lafora disease and congenital generalized lipodystrophy: a case report. *Kaohsiung J Med Sci* 2009; 25: 663-8.

Ruiz-Riquelme A, Sánchez-Iglesias S, Rábano A, *et al*. Larger aggregates of mutant seipin in Celia's encephalopathy, a new protein misfolding neurodegenerative disease. *Neurobiol Dis* 2015; 83: 44-53.

TEST YOURSELF

(1) Is CGL2 usually associated with progressive neurological impairment?

(2) Is CGL2 usually associated with epilepsy?

(3) What seems to be the pathogenetic mechanism behind the neurodegenerative CGL2 phenotype associated with epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Epileptic Disord 2019; 21 (1): 122-7

Epilepsy surgery in the first months of life: a large type IIb focal cortical dysplasia causing neonatal drug-resistant epilepsy

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ABSTRACT – Focal cortical dysplasia is a common cause of medically refractory epilepsy in infancy and childhood. We report a neonate with seizures occurring within the first day of life. Continuous video-EEG monitoring led to detection of left motor seizures and a right frontal EEG seizure pattern. Brain MRI revealed a lesion within the right frontal lobe without contrast enhancement. The patient was referred for epilepsy surgery due to drug resistance to vitamin B6 and four antiepileptic drugs. Lesionectomy was performed at the age of two and a half months, and histopathological evaluation confirmed the diagnosis of focal cortical dysplasia type IIb (FCD IIb). The patient is free of unprovoked seizures without medication (Engel Class I) and is normally developed at 36 months after surgery. The case study demonstrates that FCD IIb may cause seizures within the first day of life and that epilepsy surgery can be successfully performed in medically intractable patients with a clearly identifiable seizure onset zone within the first three months of life. Although radical surgery such as hemispherectomy and multi-lobar resections are over-represented in early infancy, this case also illustrates a favourable outcome with a more limited resection in this age group.

Key words: neonate, seizure, focal cortical dysplasia, type IIb, surgery

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Focal cortical dysplasia type IIb (FCD IIb) is a major cause of drug-resistant focal epilepsy (Palmini and Holthausen, 2013). The pathogenesis has not yet been completely unravelled, but dysregulation of the mTOR pathway appears to play a role in the formation of dysplastic neurons (Crino, 2015). The histopathological hallmark of FCD IIb is the presence of dysmorphic neurons and balloon cells (Blümcke *et al*., 2009, 2011). Typical magnetic resonance imaging (MRI) findings consist of an increased subcortical signal on T2-weighted (w) and FLAIR sequences, often in a wedge-shape configuration with a blurring of the grey-white matter interface. FCD IIb arises during foetal brain development. However, seizures rarely occur within the neonatal period but typically in infancy and childhood. Here, we report a patient with seizure manifestation as early as within the first 24 hours of life due to right frontal FCD IIb.

Case study

Patient history and clinical findings

The patient was a female newborn with a history of an uneventful pregnancy and vaginal delivery at 39 weeks of gestational age. After normal postnatal adaptation (APGAR: 10/10; umbilical cord: pH 7.35), seizures started 16 hours after birth. Seizure semiology comprised left motor seizures of the arm and leg evolving to generalized tonic-clonic seizures. There was no family history of epilepsy, stillbirths, or neurodegenerative disorders of early infancy. An extensive work-up for neurometabolic diseases revealed no abnormalities. Seizures were refractory to age-appropriate dosages of vitamin B6, phenobarbitone, levetiracetam, topiramate, and oxcarbazepine. None of the criteria for tuberous sclerosis complex were met.

Routine EEG, continuous video-EEG monitoring, and brain MRI

Routine and continuous video-EEG monitoring using Xltek hard- and software equipment (Natus DBA, Excel-Tech Corp., Oakville, Canada) were performed using standard adjustments (0.5-Hz low-frequency filter, 70-Hz high-frequency filter; resistance <10 kΩ). Routine EEG revealed subclinical seizure patterns, intermittent slow activity, and sharp waves over the right frontal region. Continuous video-EEG monitoring detected right frontal seizure patterns, 13 to 30 seconds prior to clinical seizure onset (*figure 1A, B*). Seizure semiology comprised clonic seizures of the left extremities and bilateral clonic seizures. Brain MRI was obtained using a 1.5-Tesla scanner (3D sequences with an isotropic resolution of 1.0 to 1.5 mm: T1w sequences before and after the administration of a gadolinium-based contrast agent and T2w and fluid attenuated inversion recovery [FLAIR] sequences, with axial, sagittal, and coronal reformations; Siemens Magnetom Aera, Munich, Germany). A well delineated lesion of the right frontal lobe was observed, measuring $2.0 \times 2.5 \times 2.6$ cm (*figures 2A, B*). The MRI signal intensity was hyperintense on T1w imaging and hypointense on T2w imaging compared to the surrounding unmyelinated white matter. There was neither contrast enhancement nor perifocal oedema. As a reference, the MRI of an eight-year-old boy with histologically proven FCD IIb is shown (*figures 2C, D*). This reference patient was operated due to medically refractory epilepsy at the age of eight years and is seizure-free after an observation period of five years (Engel Class I). The boundaries of the FCD IIb of the reference patient appear much less sharp and reveal hypointensity on T1w imaging and hyperintensity on T2w imaging.

Epilepsy surgery, genetics, and outcome

The patient was referred for epilepsy surgery based on concordant results from presurgical evaluation ([1] seizure semiology: left motor seizure; [2] EEG seizure onset zone: right frontal; and [3] MRI lesion: right frontal). Lesionectomy was performed at the age of two and a half months and histopathological investigation of the surgical specimen revealed FCD with balloon cells fulfilling criteria for FCD type IIb (Blümcke, Thom *et al*., 2011). The specimen revealed higher cellularity (*figures 3A-D*) compared to the specimen of the reference patient mentioned above who was operated on at the age of eight years (*figures 3E-G*). Trio exome sequencing on a HighSeq2500 (Illumina Inc., San Diego, USA) after SureSelect v6 enrichment (Agilent Technologies Inc., Santa Clara, USA) for the index patient and both parents revealed no pathogenic mutations of proteins involved in mTOR pathway regulation. The antiepileptic medication was tapered six months after surgery. During a post-surgical observational period of 36 months, the patient suffered from a fever-associated seizure at the age of two years. She reached age-appropriate milestones for infant development (*i.e.* motor skills and speech) and revealed no functional deficits.

Discussion

We report a patient with type IIb FCD and seizure onset on Day 1 of life who successfully underwent resective epilepsy surgery at two and a half months of life.

The epileptogenic zone may significantly extend beyond the visible lesion on brain imaging (Bouet *et*

al., 2017). Invasive studies are therefore often necessary for epilepsy surgery candidates to further map the epileptogenic zone and to delineate eloquent cortex (Noachtar and Borggraefe, 2009). We did not perform invasive studies in our patient due to the following:
– an appropriate distance of the lesion to eloquent areas such as the primary motor cortex;
– concordant results for EEG seizure onset, seizure semiology, and location of the lesion;
– and a clearly delineated lesion.
Given these three findings, we weighted the risks and benefits and decided against an invasive study which, in general, can be performed even in this age group (Duchowny *et al.*, 1998). Although reports on epilepsy surgery within the first years of life are less common than in older patients, the results of surgery with respect to seizure freedom or seizure reduction are at least comparable. In a recent Canadian survey, 66% and 100% of patients reached seizure freedom (Engel Class 1) after lesionectomy within the first three years of life due to FCD and low-grade tumours, respectively (Steinbok *et al.*, 2009). The need for contemporary epilepsy surgery for appropriate candidates is further supported as patients with

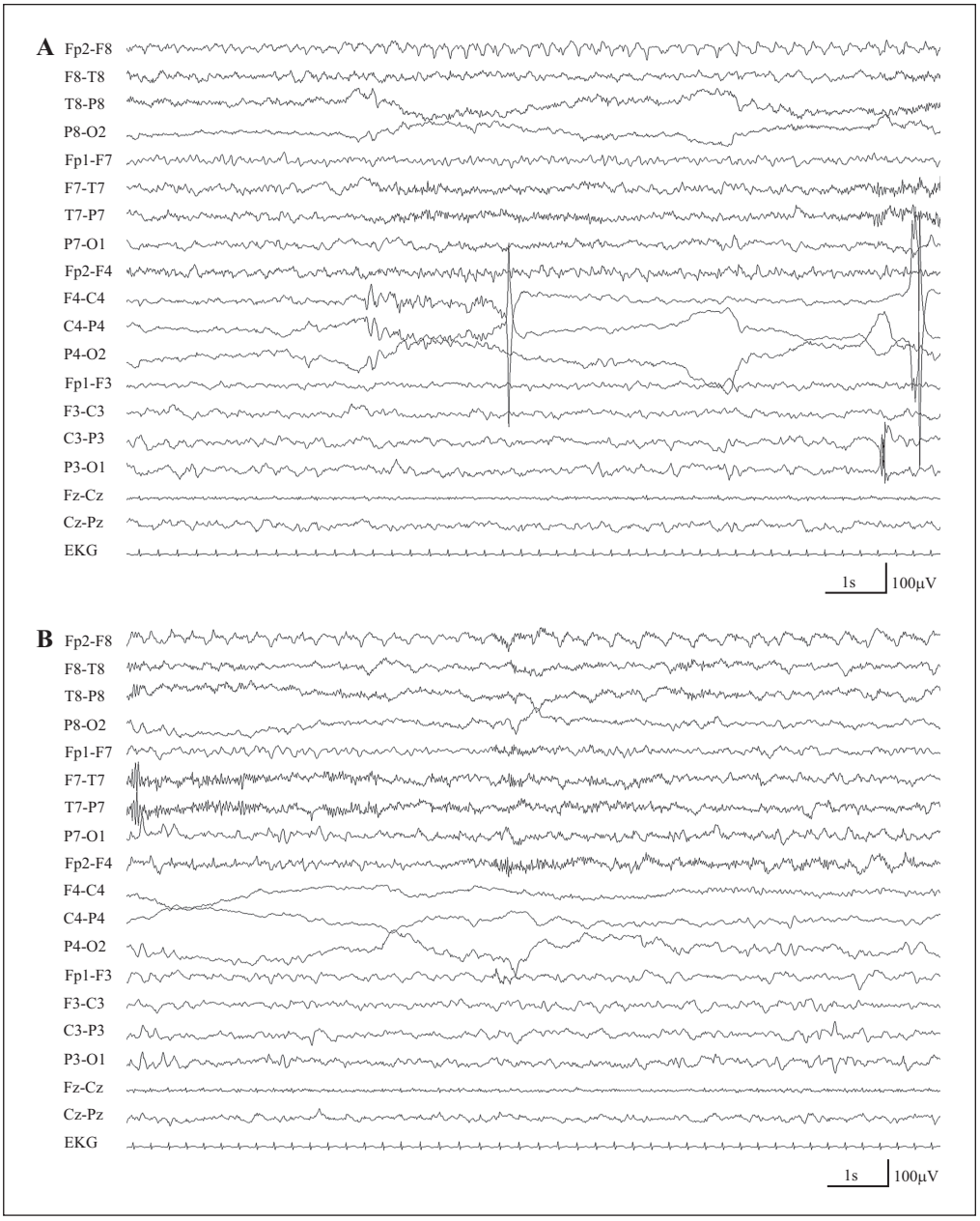

Figure 1. (A, B) Right frontal EEG seizure pattern (maximum lead: F8) recorded at six weeks of age.

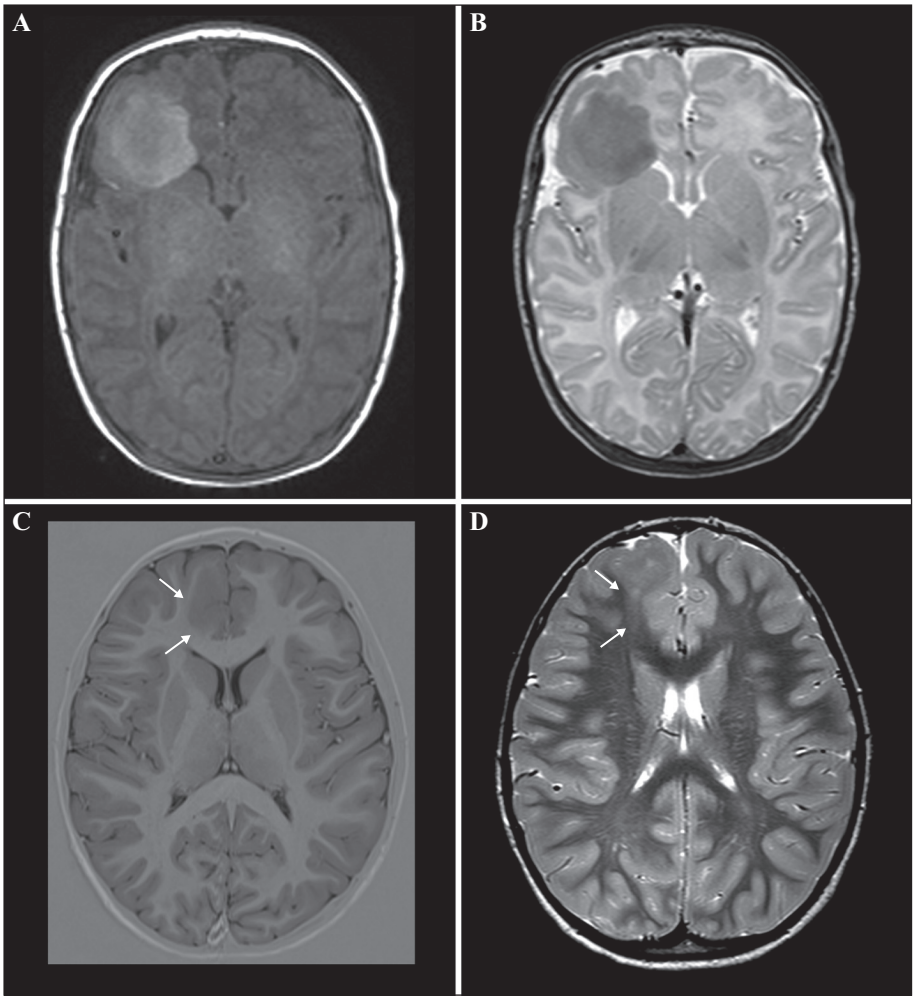

Figure 2. MRI at the age of six weeks shows a 2.0 × 2.5 × 2.6-cm lesion with hyperintense signal on T1-weighted (w) imaging (A) and hypointense signal on T2w imaging (B) with moderate non-homogeneity primarily seen within the centre of the lesion on T1w images. The opposite pattern could be detected in a reference patient with proven FCD IIb in a similar location to that of the index patient, whose MRI at the age of eight years is depicted in panels (C) and (D), showing a less well delineated hypointense signal on T1w imaging (C) and hyperintense signal on T2w imaging (D).

early-onset epilepsy (<one year of age) show a better developmental outcome when surgery is performed within the first year of life, compared to patients in whom surgery was scheduled later (Loddenkemper *et al*., 2007). Epilepsy surgery within the first year of life tends to comprise disconnection procedures, such as functional hemispherotomy for large dysplastic unilateral malformations (such as hemimegalencephaly), structural brain damage due to neonatal stroke, and vascular malformations such as cerebral angiomatosis (Sturge Weber Syndrome), rather than tailored resections of well delineated lesions, as reported in this case (Steinbok *et al*., 2009). This is most likely due to the fact that patients with large unilateral lesions manifest earlier with medically refractory seizures and cognitive deterioration than patients with smaller lesions (Fauser *et al*., 2006; Honda *et al*., 2013; Wu *et al*., 2014).

Gross cerebral lesions are rarely encountered within the neonatal period. The most frequent entities with supratentorial location are teratomas, low-grade astrocytomas, and primitive neuroectodermal tumours (PNETs) (Buetow *et al*., 1990). These lesions should be distinguished from FCDs based on distinct neuroimaging findings such as non-homogeneous signals (*i.e*. teratoma), cystic components (*i.e*. astrocytoma), and contrast enhancement (*i.e*. PNETs) (Borja *et al*., 2013). However, histological evaluation of the surgical specimen is warranted to ascertain the diagnosis which is essential for further prognosis and management.

The imaging findings in our patient contrast the common MRI findings of FCD IIb. Commonly, FCD IIb appears on brain MRI as a blurry, wedged-shaped lesion. In addition, lesions typically exhibit a hyperrather than hypointense signal on T2w imaging.

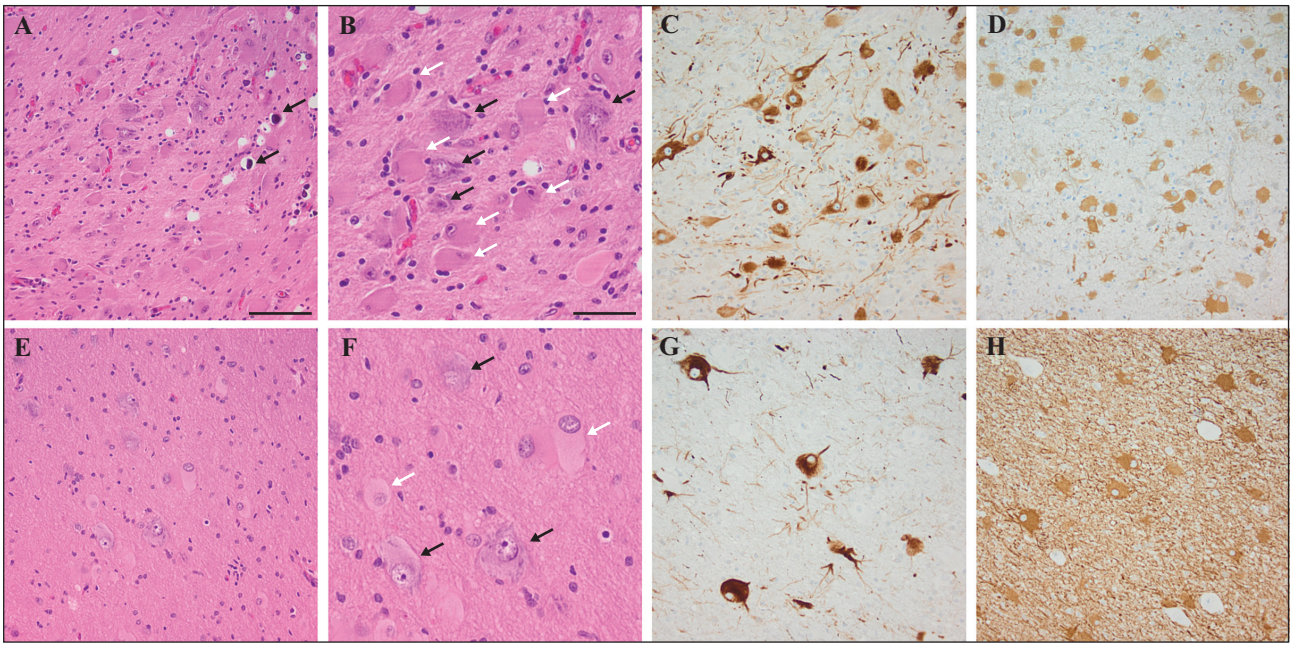

Figure 3. (A-D) Index patient; (E-H) reference patient. (A) H&E-staining of the index patient with neonatal FCD IIb showing increased cellularity with numerous balloon cells and dysmorphic neurons, as well as focal calcifications (black arrows). (B) Higher magnification of (A) showing balloon cells with homogeneous eosinophilic cytoplasm (white arrows) and dysmorphic neurons with prominent nissl substance (black arrows). In contrast, H&E staining of specimens from the reference patient (who received MRI and surgery due to medically refractory epilepsy, performed at the age of eight years) (E, F) shows similar cytological abnormalities with balloon cells (white arrows in [F]) and dysmorphic neurons (black arrows in [F]), although with a lower cellularity/density compared to the index patient with neonatal FCD IIb (A, B). These differences are highlighted by the accumulation of neurofilament protein (NF SMI32) in dysmorphic neurons (C, G) and vimentin expression in balloon cells (D, H) based on immunohistochemical staining. Scale bar: (A, C, D, E, G, H) 100 μm; (B, F) 50 μm.

We hypothesize that the signal appearance of FCD IIb in our case was most likely due to increased cellularity and myelination in the affected area, as demonstrated in the histopathological specimen of the index patient at two months of life compared to a reference patient aged eight years. These observations are supported by recent findings that myelin loss in combination with a reduced number of oligodendroglia cells occurs over time in FCD IIb specimens compared to normal neuronal tissue, and this is probably due to activation of the mTOR pathway (Scholl *et al.*, 2016). The authors also identified a correlation between the duration of epilepsy and loss of myelin. These findings might support that FCD IIb is not a stable disease on a molecular level but rather undergoes changes over time with mTOR activation and subsequent myelin loss. In addition, the contrast with the surrounding physiologically unmyelinated white matter may have also contributed to the well delineated borders of the neonatal FCD IIb on MRI in the presented case.

In summary, FCD IIb may manifest as early as the first day of life and may show a different pattern on neuroimaging in the neonatal period compared to older age groups. Epilepsy surgery should be performed as early as possible in order to reduce seizure burden and secondary complications such as cognitive impairment, behavioural problems, and social sequelae (Elliott *et al.*, 2008; Berg *et al.*, 2016). □

Key points

- Seizures due to focal cortical dysplasia type IIb (FCD IIb) may manifest within the first days of life.
- Imaging features of FCD IIb may be atypical in neonates.
- Epilepsy surgery can be successfully performed within the first three months of life.

Disclosures.
None of the authors have any conflict of interest to declare.

References

Berg AT, Baca CB, Rychlik K, *et al.* Determinants of social outcomes in adults with childhood-onset epilepsy. *Pediatrics* 2016; 137: e20153944.

Blümcke I, Vinters HV, Armstrong D, *et al*. Malformations of cortical development and epilepsies: neuropathological findings with emphasis on focal cortical dysplasia. *Epileptic Disord* 2009; 11: 181-93.

Blümcke I, Thom M, Aronica E, *et al*. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 2011; 52: 158-74.

Borja MJ, Plaza MJ, Altman N, *et al*. Conventional and advanced MRI features of pediatric intracranial tumors: supratentorial tumors. *AJR Am J Roentgenol* 2013; 200: 483-503.

Bouet R, Mauguiere F, Daligault S, *et al*. The relationship between morphological lesion, magnetic source imaging, and intracranial stereo-electroencephalography in focal cortical dysplasia. *Neuroimage Clin* 2017; 15: 71-9.

Buetow PC, Smirniotopoulos JG, Done S. Congenital brain tumors: a review of 45 cases. *AJR Am J Roentgenol* 1990; 155: 587-93.

Crino PB. mTOR signaling in epilepsy: insights from malformations of cortical development. *Cold Spring Harb Perspect Med* 2015; 5: a022442.

Duchowny M, Jayakar P, Resnick T, *et al*. Epilepsy surgery in the first three years of life. *Epilepsia* 1998; 39: 737-43.

Elliott IM, Lach L, Kadis DS, *et al*. Psychosocial outcomes in children two years after epilepsy surgery: has anything changed? *Epilepsia* 2008; 49: 634-41.

Fauser S, Huppertz HJ, Bast T, *et al*. Clinical characteristics in focal cortical dysplasia: a retrospective evaluation in a series of 120 patients. *Brain* 2006; 129: 1907-16.

Honda R, Kaido T, Sugai K, *et al*. Long-term developmental outcome after early hemispherotomy for hemimegalencephaly in infants with epileptic encephalopathy. *Epilepsy Behav* 2013; 29: 30-5.

Loddenkemper T, Holland KD, Stanford LD, *et al*. Developmental outcome after epilepsy surgery in infancy. *Pediatrics* 2007; 119: 930-5.

Noachtar S, Borggraefe I. Epilepsy surgery: a critical review. *Epilepsy Behav* 2009; 15: 66-72.

Palmini A, Holthausen H. Focal malformations of cortical development: a most relevant etiology of epilepsy in children. *Handb Clin Neurol* 2013; 111: 549-65.

Scholl T, Muhlebner A, Ricken G, *et al*. Impaired oligodendroglial turnover is associated with myelin pathology in focal cortical dysplasia and tuberous sclerosis complex. *Brain Pathol* 2016; 27: 770-80.

Steinbok P, Gan PY, Connolly MB, *et al*. Epilepsy surgery in the first 3 years of life: a Canadian survey. *Epilepsia* 2009; 50: 1442-9.

Wu N, Borlot F, Ali A, *et al*. Hemimegalencephaly: what happens when children get older? *Dev Med Child Neurol* 2014; 56: 905-9.

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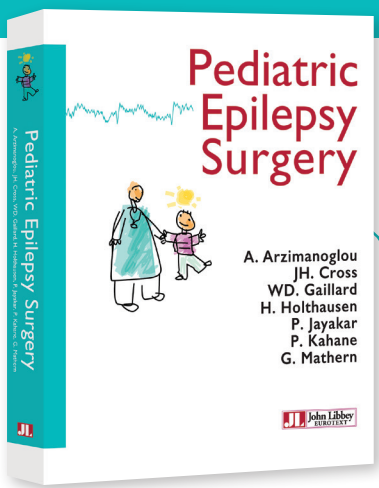

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