Original article

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Encephalopathy related to status epilepticus during slow sleep (ESES) as atypical evolution of Panayiotopoulos syndrome: an EEG and neuropsychological study

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ABSTRACT – *Aim.* We report two patients with Panayiotopoulos syndrome (PS) who developed encephalopathy related to status epilepticus during slow sleep (ESES) at the peak of their clinical course.
Methods. Clinical charts and EEG data were reviewed.
Results. The patients exhibited nocturnal autonomic seizures and occipital EEG foci, the latter of which later evolved into multifocal EEG foci with synchronous frontopolar and occipital spikes (Fp-O EEG foci), and finally into continuous spikes-waves during sleep (CSWS; spike-wave index >85% based on whole-night sleep recording) at eight years and seven years of age, respectively. The occipital spikes always preceded frontopolar spikes by 30∼50 mseconds based on the analysis of CSWS. Neuropsychological ability, including IQ, deteriorated during the CSWS period in both patients. The autonomic seizures and focal to bilateral tonic-clonic seizures were initially resistant to antiepileptic drugs (AEDs), and occurred more than 10 times in both patients. However, the seizures and EEG findings gradually resolved, and AEDs were successfully terminated in both patients.
Conclusion. PS can progress to ESES if the clinical course exhibits atypical evolution. The initial autonomic symptom of the seizures and interictal Fp-O EEG foci should be carefully monitored in patients with CSWS or ESES.

Key words: Panayiotopoulos syndrome, Atypical evolution, CSWS, ESES, Fp-O EEG pattern, epileptic encephalopathy

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Encephalopathy related to status epilepticus during slow sleep (ESES) is a specific type of epileptic and neurodevelopmental encephalopathy, characterized by continuous diffuse spike-wave discharges (CSWS), initially described as comprising more than 85% of the non-REM sleep period, with slowly progressive decline of cognitive function due to the persistence of these abnormal EEG discharges (Patry *et al*., 1971; Tassinari *et al*., 2012; Tassinari and Rubboli, 2019). On the other hand, Panayiotopoulos syndrome (PS) is an age-dependent self-limiting focal epilepsy occurring during early childhood in otherwise normal young children with an ultimately favourable outcome (Panayiotopoulos *et al*., 2012). However, we previously reported that approximately 10 to 20% of PS patients exhibit an atypical electro-clinical course, characterized by prolonged autonomic seizures (occurring 10 to 50 times) associated with active diffuse and multifocal epileptic abnormalities despite ultimate remission before adolescence (Oguni *et al*., 1999; Hirano *et al*., 2009). In addition, there have already been a few other case reports describing atypical electroclinical features in PS patients who developed CSWS or ESES (Caraballo *et al*., 2001, 2013, 2015). Here, we report two PS patients with recurrent pharmaco-resistant autonomic seizures and ESES at the peak of their clinical course. These patients may help clarify the nosological relationship between PS and ESES, which is similar to the well-known relationship between benign Rolandic epilepsy (BRE) and ESES or atypical benign partial epilepsy of childhood (ABPE) (Doose and Baier, 1989; Dalla Bernardina *et al*., 1991; Fujii *et al*., 2010; Pal *et al*., 2016).

Subjects and methods

The subjects were two patients with PS, who had been followed at our epilepsy clinic and satisfied the strict EEG diagnosis of CSWS based on whole-night EEG recording. At the time of this study, there were 106 patients with PS in our epilepsy database. Among them, these two patients exhibited a CSWS pattern based on routine EEG examinations and underwent long-term EEG monitoring.

A spike-wave index (SWI) was calculated according to the total duration of the spike-wave/non-REM EEG background (%). In addition, we measured the small time difference between frontopolar spikes and (parieto-) occipital spikes in CSWS using our previously reported method (Ueno *et al*., 2001). The EEG was sampled at 512 Hz, and analysed using Nihon-Koden-based back-averaging software.

Results

Clinical details of the two patients

Patient 1

Patient 1 was a 14-year, six-month-old girl. She was born at 38 weeks of gestation weighing 2,640 g after Caesarean section. According to her family history, her elder brother had one seizure during infancy. She had perinatal asphyxia with prolonged pulmonary hypertension requiring artificial respiratory assistance and nitro-oxide treatment for three weeks. Her subsequent psychomotor development was normal. At five years and 11 months of age, she developed an autonomic seizure characterized by initial vomiting followed by loss of consciousness and flaccid paralysis (known as ictal syncope) lasting for a few minutes, which repeated six months and eight months later. At six years and 10 months of age, she was referred to our clinic and diagnosed with PS based on the combination of autonomic seizures and occipital spike-waves during sleep (*figure 1A*). Despite the administration of carbamazepine (CBZ) and valproic

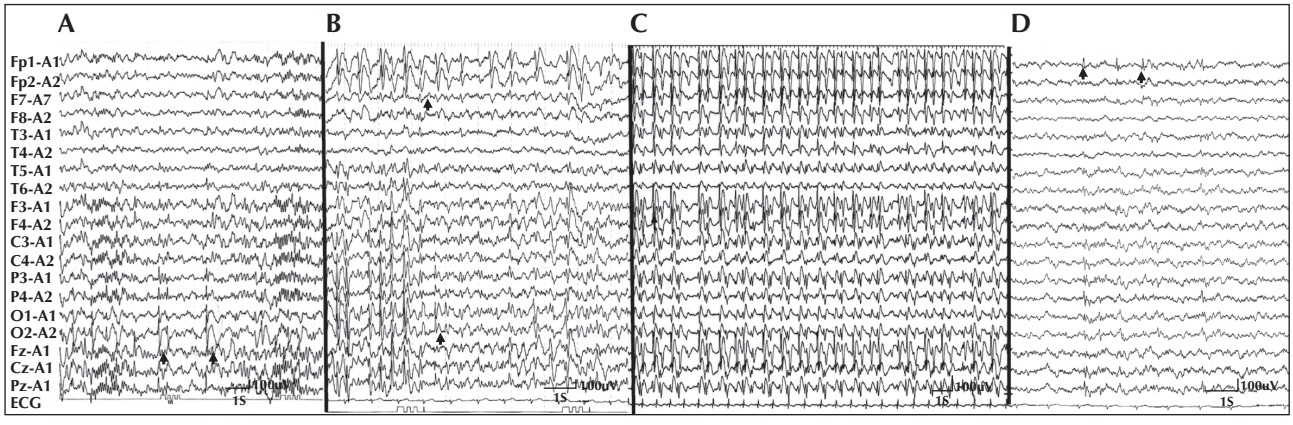

Figure 1. Sleep EEG changes in Patient 1. (A) At six years and 10 months of age, the most predominant spike focus was in the right occipital region. (B) At seven years and seven months of age, frequent spike-waves appeared diffusely with frontopolar and parieto-occipital predominance. (C) At eight years and two months of age, CSWS was confirmed based on whole-night EEG recording (SWI= 95%). (D) At 10 years and nine months of age, CSWS was resolved and only low-amplitude spikes were shown in the left frontopolar region.

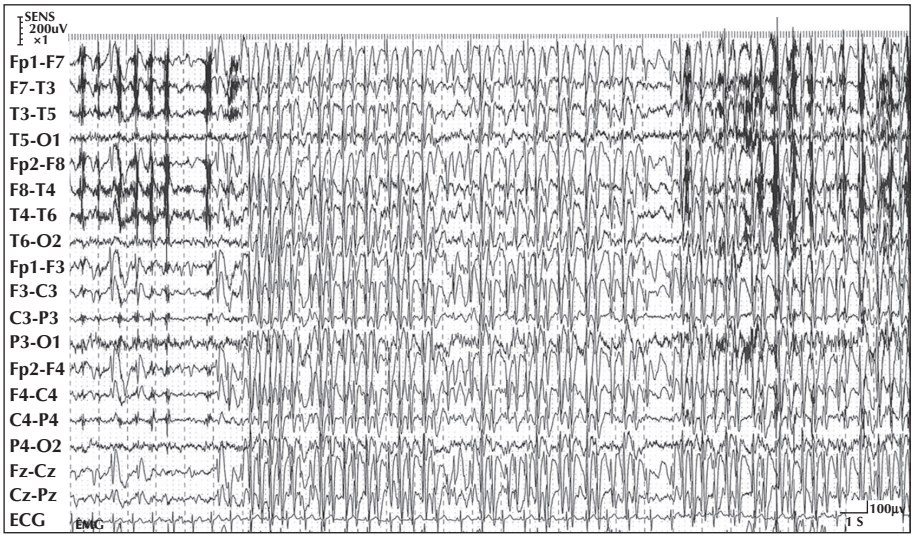

Figure 2. Ictal video-EEG of atypical absence seizures in Patient 1. The video shows the patient eating a meal and then suddenly stopping, remaining in the same posture until the spike-wave discharges disappear.

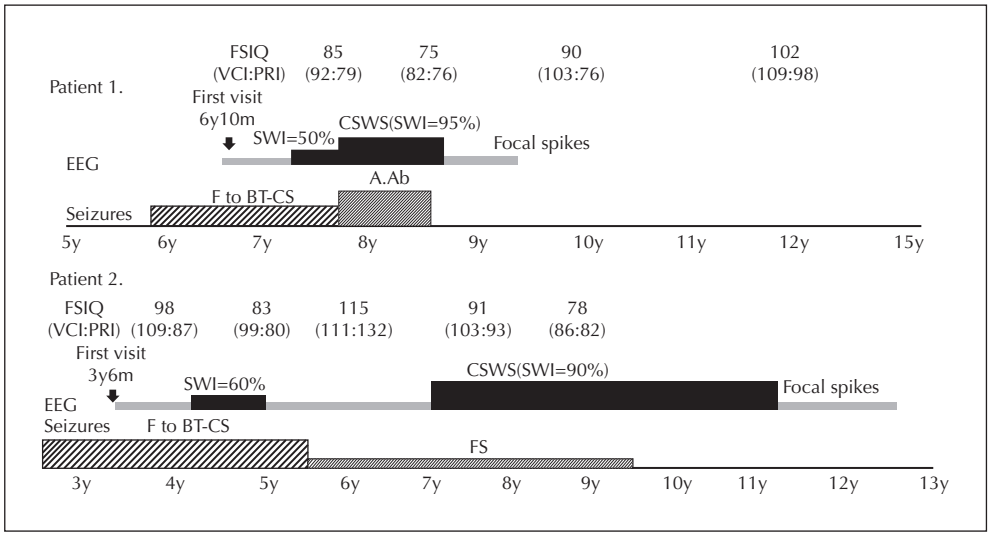

Figure 3. The relationship between EEG findings and IQ values. The IQ values dropped significantly during the period of CSWS in both patients and increased after the disappearance of CSWS in Patient 1. Although Patient 2 did not undergo an IQ test after the disappearance of CSWS, behaviour and school achievement improved significantly. FSIQ: full scale IQ; VCI: Verbal Comprehension Index; PRI: Perceptual Reasoning Index; F to BT-CS: focal to bilateral tonic-clonic seizures; FS: focal seizures, SWI: spike-wave index.

acid (VPA), she experienced recurrent brief and prolonged focal to bilateral tonic-clonic seizures (F to BT-CS) until seven years and seven month of age, when sleep EEG demonstrated diffuse spike-waves with frontopolar and parieto-occipital predominance (*figure 1B*). Two months later, she developed recurrent daily "absence" attacks and underwent a 24-hour long-term video-EEG study. Frequent atypical absence seizures corresponding to diffuse 2-Hz spike-wave bursts, lasting for 10 to 20 seconds, were observed during wakefulness and CSWS (SWI= 95%) (*figure 1C*, *figure 2*). Brain MRI was normal. We added ethosuximide (ESM) to clobazam (CLB) and levetiracetam (LEV), which immediately controlled the atypical absence seizures, whereas CSWS resolved at eight years and nine months of age (*figure 1D*). All epileptic EEG abnormalities disappeared at nine years and five months of age. She has been free of antiepileptic drugs (AEDs) since 12 years and two months of age. The relationship between IQ values and EEG findings during the clinical course is shown in *figure 3*. She is now attending regular high school.

Patient 2

Patient 2 was a 13-year, three-month-old boy. Birth was uneventful after 41 weeks of gestation, with a weight

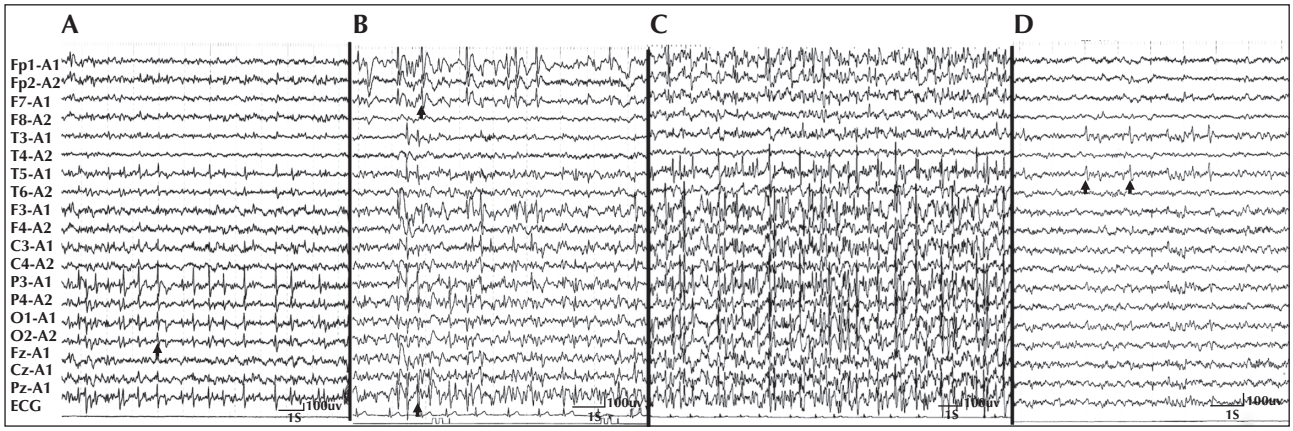

Figure 4. Sleep EEG changes in Patient 2. (A) At four years and two months of age, the most predominant spike EEG foci were recorded in both parieto-occipital regions. (B) At six years and 0 months of age, frequent multifocal spike-waves appeared predominantly over both frontopolar and parieto-occipital regions, both synchronously and asynchronously. (C) At seven years and 0 months of age, CSWS with left hemispheric predominance was confirmed based on whole-night EEG recording (SWI= 90%). (D) At 12 years and 11 months of age, CSWS resolved and only infrequent low-amplitude sharp-wave discharges remained in the left temporal region.

of 3,136 g. The patient met normal developmental milestones. According to his family history, a maternal cousin had febrile seizures. At two years and eight months of age, he had an autonomic seizure characterized by sudden-onset nausea and vomiting, followed by BT-CS lasting for 30 minutes. He then experienced recurrent autonomic F to BT-CS lasting longer than 15 minutes, once a month. He was given a diagnosis of cryptogenic focal epilepsy at the local hospital, and was treated with CBZ without effect. He was referred to our clinic at three years and six months of age, when we made a diagnosis of PS based on the combination of autonomic seizures, frequent parieto-occipital spike-waves during sleep EEG, normal brain MRI, and normal development (*figure 4A*). Despite the administration of VPA and CLB, the autonomic seizures continued to occur once every three to six months, and the epileptic EEG foci became multifocal with frontopolar involvement (*figure 4B*). Subsequently, sleep EEG gradually evolved to CSWS (SWI= 90%) from seven years of age (*figure 4C*). Although his sleep EEG continued to demonstrate the CSWS pattern, the seizures themselves had been completely controlled from nine years and six months of age. CSWS finally resolved at 11 years and six months of age. Rare low-amplitude focal spikes in the left temporal region were observed on EEG at 12 years and 11 months of age, when AEDs were successfully stopped (*figure 4D*). IQ values dropped significantly during the period of CSWS (*figure 3*), however, his behaviour as well as school achievement improved significantly after the disappearance of CSWS.

Fp-O spike-peak latency study

The EEG data were averaged at the trigger points, which were placed on the peak of the spikes at Fp1 and O1 independently in Patient 1, and at Fp1 and P3 independently in Patient 2. At each trigger point, the parieto-occipital spikes always preceded frontopolar spikes by 30∼50 mseconds for the synchronous frontopolar and occipital spikes (Fp-O EEG foci) in both patients (*figure 5*).

Discussion

In PS, the EEG findings in most patients demonstrate age-dependent change with shifting location, multiplication and diffuse propagation rather than persistent localization in the occipital region (Oguni *et al*., 1999; Ohtsu *et al*., 2003). Previously, we classified the EEG evolutional changes into five patterns, among which we introduced the "generalized EEG pattern" characterized by initial occipital (O) EEG foci, evolving to synchronous and asynchronous Fp and O spikes (Fp-O EEG foci), and subsequently to generalized rhythmic spike-waves with age, similar to CSWS (Ueno *et al*., 2001; Ohtsu *et al*., 2003; Wyllie and Moosa, 2017). The generalized EEG pattern group, demonstrating the most active and florid epileptic EEG abnormalities, had the highest frequency of seizures and longest active seizure period among the five groups. Here, we present two PS patients who exhibited atypical electroclinical evolution with frequent pharmaco-resistant seizures, CSWS and cognitive decline (satisfying the definition of ESES) at the peak of their clinical course, which resolved before adolescence. The patients were followed prospectively under the diagnosis of PS because they had characteristic prolonged autonomic seizures lasting longer than 15 minutes and parieto-occipital EEG foci during early childhood even though the seizures themselves reoccurred more than 10 times before remission.

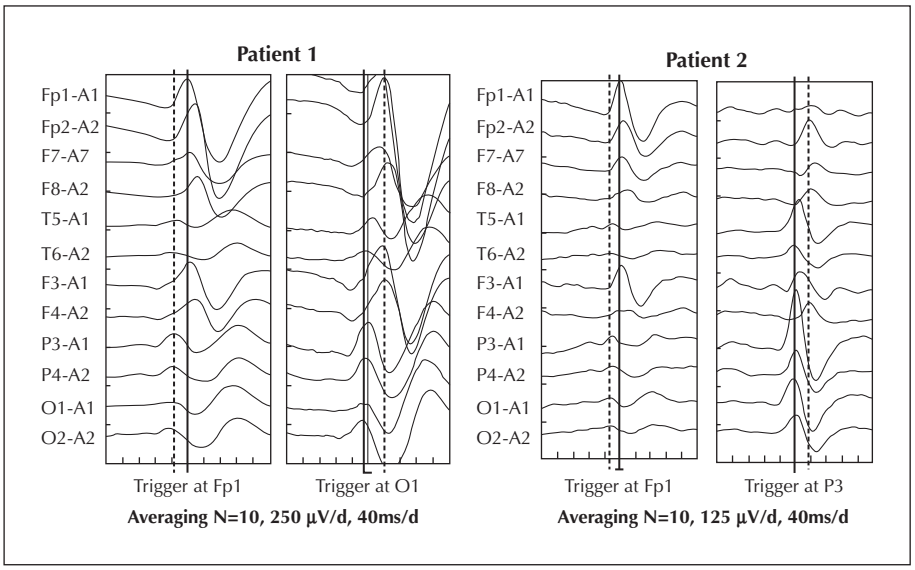

Figure 5. Fp-O spike-peak latency study. In Patient 1, the EEG data averaged (*n*=10) at the Fp1 and O1 trigger points demonstrated O1 spikes preceding Fp1 spikes by 30 and 50 mseconds, respectively. In Patient 2, P3 spikes always preceded Fp1 spikes by 30 mseconds and 35 mseconds, respectively. The EEG data were sampled from CSWS in both patients.

ESES has been classified either based on aetiology (idiopathic, cryptogenic or symptomatic), seizure patterns (combination of absence or atonic seizures), severity of the SWI (50% or >85%) or clinical evolution (Tassinari *et al*., 2012; Tassinari and Rubboli, 2019). Caraballo *et al*. (2013) described 8/117 CSWS patients, diagnosed with PS before developing CSWS, although they did not refer to the detailed clinical or EEG findings, including SWI. SWI > 85% during whole-night sleep has been regarded as important and an undisputed criterion for diagnosing CSWS despite the opinion that corresponding cognitive deterioration is more important than SWI >85% (Tassinari *et al*., 2012). These two PS patients satisfied both criteria. In this regard, PS can evolve into ESES if the clinical course exhibits atypical evolution. Moreover, the number of patients with PS that progressed to CSWS or ESES might be underestimated because the initial vomiting immediately before F to BT-CS and the typical change in EEG may be easily missed, leading to a non-specific epilepsy diagnosis, such as idiopathic focal epilepsy progressing to ESES (Saltik *et al*., 2005). In both patients, we confirmed the presence of typical secondary synchronous occipito-frontopolar spikes, in which parieto-occipital spikes constantly lead frontopolar spikes by approximately 30 mseconds. We previously described the details of this EEG phenomenon in patients with PS as well as those with CSWS (Ohtsu *et al*., 2003; Ueno *et al*., 2001). Leal *et al*. studied frontal EEG spikes in PS using the spline-laplacian montage and also confirmed postero-anterior spike propagation (Leal *et al*., 2008). Thus, it is reasonable to speculate that for some patients, CSWS and ESES is a consequence of atypical evolution of PS.

Doose and Baier (1989) previously proposed the concept of hereditary impairment of brain maturation, which underlies childhood epilepsies with multifocal sharp waves, including benign childhood epilepsy with occipital paroxysms, BRE, electrical status epilepticus during sleep, Landau-Kleffner syndrome and ABPE, suggesting that these syndromes are not independent, but represent one clinical EEG spectrum of genetically-determined childhood epilepsy. This concept helps clarify the nosological relationship between PS and ESES; as shown in the present two PS patients.

We previously hypothesized that the association with pre-existing neurobehavioral disorders or mild cerebral disturbances causes atypical PS evolution in which these acquired factors may further reduce the seizure threshold (Hirano *et al*., 2009). In this context, Patient 1 may have had a mild cerebral insult due to perinatal asphyxia despite normal brain MRI.

In conclusion, PS can progress to ESES if the clinical course exhibits atypical evolution, however, this is a rare occurrence. The initial autonomic symptom of the seizures and interictal Fp-O EEG foci should be carefully monitored in patients with CSWS or ESES. □

Supplementary data.

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

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

References

Caraballo RH, Astorino F, Cersosimo R, Soprano AM, Fejerman N. Atypical evolution in childhood epilepsy with occipital paroxysms (Panayiotopoulos type). *Epileptic Disord* 2001; 3: 157-62.

Caraballo RH, Veggiotti P, Kaltenmeier MC, *et al*. Encephalopathy with status epilepticus during sleep or continuous spikes and waves during slow sleep syndrome: a multicenter, long-term follow-up study of 117 patients. *Epilepsy Res* 2013; 105: 164-73.

Caraballo RH, Pasteris MC, Portuondo E, Fortini PS. Panayiotopoulos syndrome and diffuse paroxysms as the first EEG manifestation at clinical onset: a study of nine patients. *Epileptic Disord* 2015; 17: 143-9.

Dalla Bernardina B, Sgro V, Caraballo R, *et al*. Sleep and benign partial epilepsies of childhood: EEG and evoked potentials study. *Epilepsy Res* 1991; 2: 83-96.

Doose H, Baier WK. Benign partial epilepsy and related conditions: multifactorial pathogenesis with hereditary impairment of brain maturation. *Eur J Pediatr* 1989; 149: 152-8.

Fujii A, Oguni H, Hirano Y, Osawa M. Atypical benign partial epilepsy: recognition can prevent pseudocatastrophe. *Pediatr Neurol* 2010; 43: 411-9.

Hirano Y, Oguni H, Funatsuka M, Imai K, Osawa M. Neurobehavioral abnormalities may correlate with increased seizure burden in children with Panayiotopoulos syndrome. *Pediatr Neurol* 2009; 40: 443-8.

Leal AJ, Ferreira JC, Dias AI, Calado E. Origin of frontal lobe spikes in the early onset benign occipital lobe epilepsy (Panayiotopoulos syndrome). *Clin Neurophysiol* 2008; 119: 1985-91.

Oguni H, Hayashi K, Imai K, *et al*. Study on the early-onset variant of benign childhood epilepsy with occipital paroxysms otherwise described as early-onset benign occipital seizure susceptibility syndrome. *Epilepsia* 1999; 40: 1020-30.

Ohtsu M, Oguni H, Hayashi K, *et al*. EEG in children with early-onset benign occipital seizure susceptibility syndrome: Panayiotopoulos syndrome. *Epilepsia* 2003; 44: 435-42.

Pal DK, Ferrie C, Addis L, Akiyama T, Capovilla G, Caraballo R, *et al*. Idiopathic focal epilepsies: the "lost tribe". *Epileptic Disord* 2016; 18(3): 252-88.

Panayiotopoulos C, Bureau M, Caraballo R, Dalla Bernardina B, Valeta T. Idiopathic focal epilepsies in childhood. In: Bureau M, Genton P, Dravet C, *et al*. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. Montrouge: John Libbey Eurotext, 2012.

Patry G, Lyagoubi S, Tassinari CA. Subclinical "electrical status epilepticus" induced by sleep in children. A clinical and electroencephalographic study of six cases. *Arch Neurol* 1971; 24: 242-52.

Saltik S, Uluduz D, Cokar O, Demirbilek V, Dervent A. A clinical and EEG study on idiopathic partial epilepsies with evolution into ESES spectrum disorders. *Epilepsia* 2005; 46: 524-33.

Tassinari CA, Rubboli G. Encephalopathy related to status epilepticus during slow sleep: current concepts and future directions. *Epileptic Disord* 2019; 21: 82-7.

Tassinari CA, Cantalupo G, Dalla Bernardina B, *et al*. Encephalopathy related to status epilepticus during slow sleep (ESES) including Landau-Kleffner syndrome. In: Bureau M, Genton P, Dravet C, *et al*. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. Montrouge: John Libbey Eurotext, 2012: 255-75.

Ueno M, Oguni H, Yasuda K, Osawa M. Neurophysiological study of secondary synchronous occipito-frontopolar spikes in childhood. *Clin Neurophysiol* 2001; 112: 2106-12.

Wyllie E, Moosa ANV. Occipito-frontal sharp waves-an underrecognized electroencephalogram pattern in self-limited idiopathic childhood focal epilepsy. *J Clin Neurophysiol* 2017; 34: e9-14.

TEST YOURSELF

(1) What is the typical interictal EEG pattern in Panayiotopoulos syndrome?

(2) Describe the atypical evolution of childhood self-limiting focal epilepsy?

(3) What is inter-hemispheric synchrony and intra-hemispheric synchrony (Fp-O pattern)?

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".