Clinical commentary

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Frequent epileptic apnoea in a patient with Pitt-Hopkins syndrome

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ABSTRACT – Pitt-Hopkins syndrome is a rare genetic disease, characterised by severe intellectual disability, distinctive dysmorphic features, epilepsy and distinctive breathing abnormalities during wakefulness. Here, we describe the case of a 22-year-old woman with Pitt-Hopkins syndrome who presented with intractable generalised tonic seizures from the age of 11 years, which increased in frequency with age and onset of menstruation despite usage of some anticonvulsant drugs. From the age of 16 years, polysomnography and video-EEG led to the detection of frequent epileptic apnoea during sleep. Although the frequency of generalised tonic seizure clusters was reduced by treatment with phenobarbital and potassium bromide, epileptic apnoea persisted. Furthermore, frequent epileptic apnoea observed in our patient was regarded as a factor for aspiration and deterioration of respiratory function. This study indicates that patients with Pitt-Hopkins syndrome require close monitoring for epileptic apnoea. Moreover, long-term EEG and respiratory monitoring are necessary to distinguish epileptic apnoea from other respiratory disorders in patients with Pitt-Hopkins syndrome.

Key words: Pitt-Hopkins syndrome, epileptic apnoea, breathing abnormality, EEG, polysomnography

Patients with Pitt-Hopkins syndrome (PTHS) present with characteristic non-epileptic breathing abnormalities during wakefulness. The most common breathing abnormality is paroxysm associated with hyperventilation, followed by cyanotic breath-holding spells while awake. Apnoea and hyperventilation may occur independently of each other. In a previous study, nearly half of the patients with PTHS presented with these respiratory disturbances (Peippo *et al.*, 2006; Whalen *et al.*, 2012). However, there have been few reports regarding breathing abnormalities during sleep (Giurgea *et al.*, 2008; de Winter *et al.*, 2016; Motojima *et al.*, 2018). Moreover,

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almost half of the patients with PTHS develop epilepsy, although this can be controlled relatively well with antiepileptic drugs (Zollino *et al.*, 2019). Here, we describe the case of a patient with PTHS who developed frequent epileptic apnoea during sleep and intractable generalised tonic seizures. Our experience in this case indicates that EEG monitoring and polysomnography (PSG) might be useful for the detection and management of epileptic apnoea during sleep and intractable seizures in patients with PTHS.

Case study

A 22-year-old Japanese woman presented to our hospital for assessment of epilepsy potentially related to PTHS. She had been born following full-term pregnancy and had no history of problems during the perinatal or neonatal period. She exhibited developmental delay and muscular hypotonia throughout her infancy and childhood. She developed slowly; she required guidance while learning to walk and was able to speak a few words by the age of six years. At the age of 11 years, she began to demonstrate frequent generalised tonic seizures. The frequency of seizures increased with age and was aggravated at the onset of menstruation. Motor and mental abilities deteriorated with increasing frequency of seizures. At approximately 16 years of age, she exhibited frequent apnoea during sleep, as detected by PSG, when deterioration of generalised tonic seizure clusters was observed over a period of at least two and a half weeks (*figure 1*). She was referred to our hospital at the age of 18 years for seizure control and examination of underlying disease. Cerebral MRI at this age revealed mild atrophy of the bilateral anterior, parietal and left temporal lobes, indicating decreased white matter volume. At the age of approximately 20 years, she required frequent hospitalisation owing to the occurrence of clusters of seizures and the onset of aspiration pneumonia. Interictal EEG at the age of 20 years revealed periodic diffuse slow spikes and waves of 1-2 Hz, which lasted for a few seconds (*figure 2A*). These characteristic abnormal waves were observed in both awake and sleep states. Furthermore, ictal EEG at the same time revealed diffuse 13-15-Hz fast waves predominantly in the bilateral central-parietal-occipital region, followed by rhythmic α and β waves, which corresponded to the arrest of the thoracic movement (*figure 2B*). Ictal EEG of another episode of apnoea showed a sudden onset of diffuse rhythmic 12-14-Hz α and β waves, which lasted for 5-40 seconds, accompanied by an arrest of thoracic movements (*figure 2C*). The patient also exhibited breath-holding followed by deep expiration while awake, although this was not accompanied by epileptic discharges, as observed on EEG. After experiencing involuntary arm movements for a few seconds, the patient also presented with generalised tonic seizures with neck flexion. Ictal EEG of this seizure revealed generalised α and β waves with a gradual increase in amplitude, preceded by generalised spike, shifting to slow spike-and-wave activities (*supplementary figure*). The frequency of clusters of generalised tonic seizures decreased following administration of phenobarbital (PB) and potassium bromide (KBr). However, epileptic apnoea during sleep, followed by video-EEG monitoring, was resistant to any antiepileptic drugs. When the patient was 21 years of age, PTHS was suspected owing to her dysmorphic features, up slanting palpebral fissures, deep-set eyes, wide mouth with thick lips, long and slender fingers and toes, microcephaly, severe intellectual disability, lack of speech, breath-holding followed by deep expiration while awake, and sudden-onset smiling. The patient became wheelchair-bound and could not sit without support; at the age of 21 years, gastrostomy tube feeding was initiated because of dysphagia and repeated aspiration pneumoniae. The clusters of generalised tonic seizures have been controlled relatively well, however, regular EEG monitoring demonstrates persistence of epileptic apnoea.

After receiving relevant written informed consent, genomic DNA extracted from peripheral blood samples from the proband was analysed using multiplex targeted sequencing. Amplicon libraries of target exons from seven genes with phenotypes overlapping with Angelman syndrome (*UBE3A*, *SLC9A6*, *TCF4*, *MBD5*, *CDKL5*, *MECP2*, and *FOXG1*) were prepared using the Ion AmpliSeq Custom Panel (Thermo Fisher Scientific, Waltham, MA, USA). Data processing was performed as described previously (Negishi *et al.*, 2017). In the *TCF4* gene (NM_001083962.1), we identified a heterozygous single nucleotide substitution (c.1732C>T; p.Arg578Cys), which was previously reported as the cause of PTHS (Marangi *et al.*, 2012). The presence of this variant was validated using Sanger sequencing. The institutional review board of Graduate School of Medical Sciences of Nagoya City University approved the genetic analyses performed in this study.

Discussion

The disease course in this patient highlighted two important clinical issues. First, overnight EEG monitoring and PSG revealed frequent epileptic apnoea during sleep. Second, the patient developed intractable generalised tonic seizures, which were well controlled with PB and KBr.

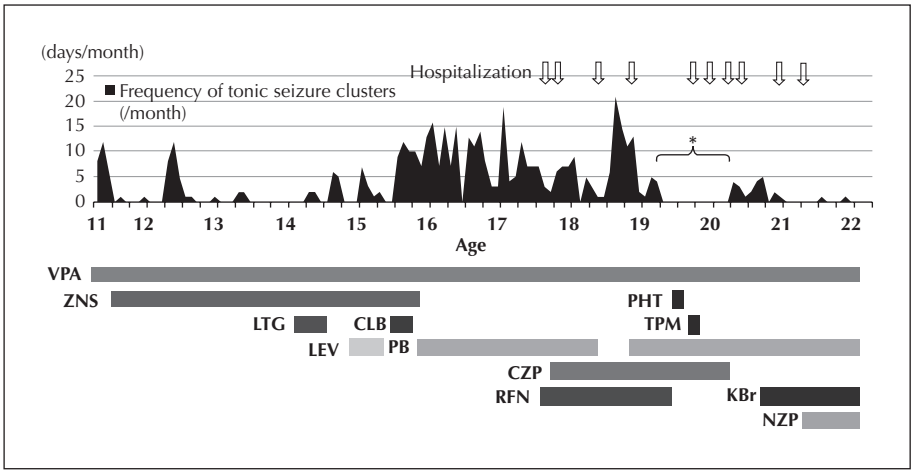

Figure 1. Clinical course of epilepsy. The line graph shows the number of days per month when the patient experienced tonic seizure clusters. The periods of treatment using different antiepileptic drugs are indicated by their respective abbreviations (VPA: valproic acid, ZNS: zonisamide, LTG: lamotrigine, CLB: clobazam, PHT: phenytoin, NZP: nitrazepam, TPM: topiramate, LEV: levetiracetam, PB: phenobarbital, CZP: clonazepam, RFN: rufinamide, KBr: potassium bromide). *No specific records were collected during this period.

There have been few reports describing breathing abnormalities during sleep in patients with PTHS; only obstructive sleep apnoea, catathrenia, and nocturnal irregular breathing have been documented (Giurgea *et al*., 2008; de Winter *et al*., 2016; Motojima *et al*., 2018). Furthermore, to the best of our knowledge, there have been no descriptions of using overnight EEG monitoring or PSG to evaluate sleep disorders for patients with PTHS. Presumably, typical characteristic breathing abnormalities of PTHS during wakefulness (*i.e*. hyperventilation followed by breath-holding) do not accompany paroxysmal EEG abnormalities (Amiel *et al*., 2007; Takano *et al*., 2010; de Winter *et al*., 2016). PTHS is caused by haploinsufficiency of *TCF4* that encodes for a basic helix-loop-helix (bHLH) transcription factor (Amiel *et al*., 2007; Zweier *et al*., 2007). TCF4 forms a heterodimer with Achaete-scute homolog 1 (ASCL1), which is another bHLH transcription factor, and activates the ASCL1-PHOX-RET pathway, responsible for the development of noradrenergic neurons in the brainstem (de Pontual *et al*., 2003; Zweier *et al*., 2007). Mutation in the *TCF4* gene therefore causes impaired neuronal development in the brainstem and breathing abnormalities while awake. Moreover, these breathing abnormalities during wakefulness are likely to be caused by congenital brainstem dysfunction, and are not an epileptic characteristic. Breath-holding followed by deep expiration while awake, as observed in this patient, was presumed to be a characteristic breathing abnormality in patients with PTHS. Meanwhile, regarding nocturnal breathing abnormalities, Maini *et al*. reported a single case with PTHS presenting with a physiologically normal sleep structure confirmed via PSG (Maini *et al*, 2012). Whalen *et al*. described nocturnal apnoea without preceding hyperventilation in three patients with PTHS as a characteristic breathing abnormality. In those patients, the possibility of epileptic apnoea could not be denied because EEG and PSG were not performed (Whalen *et al*., 2012). Whether apnoea is accompanied by deep expiration or hyperventilation might be important to distinguish between epileptic and non-epileptic breathing abnormalities. Notably, breathing abnormalities, particularly apnoea without accompanying hyperventilation, during sleep might represent an epileptic condition and involve different mechanisms from those associated with characteristic breathing abnormalities during wakefulness. Furthermore, epileptic apnoea observed in the present patient should be differentiated from arrest of thoracic movement secondarily caused by generalised tonic seizures because ictal EEG corresponding to the arrest of thoracic movement (*figure 2C*) and onset of generalised tonic seizure (*supplementary figure*) were similar. Although no clinical seizure was observed upon video monitoring, it was unclear whether apnoea was associated with generalised tonic seizures due to the absence of simultaneous recording of electromyography with ictal EEG. In summary, in patients with nocturnal breathing disturbances, epileptic apnoea should be more closely examined, and overnight EEG monitoring with electromyography and recording of thoracic movement should be performed for the detection and management of epileptic seizures, in addition to PSG, as recommended in the most recent international consensus statement for PTHS (Zollino *et al*., 2019).

Our patient developed intractable generalised tonic seizures at the age of 11 years. Clusters of generalised tonic seizures were aggravated with the onset

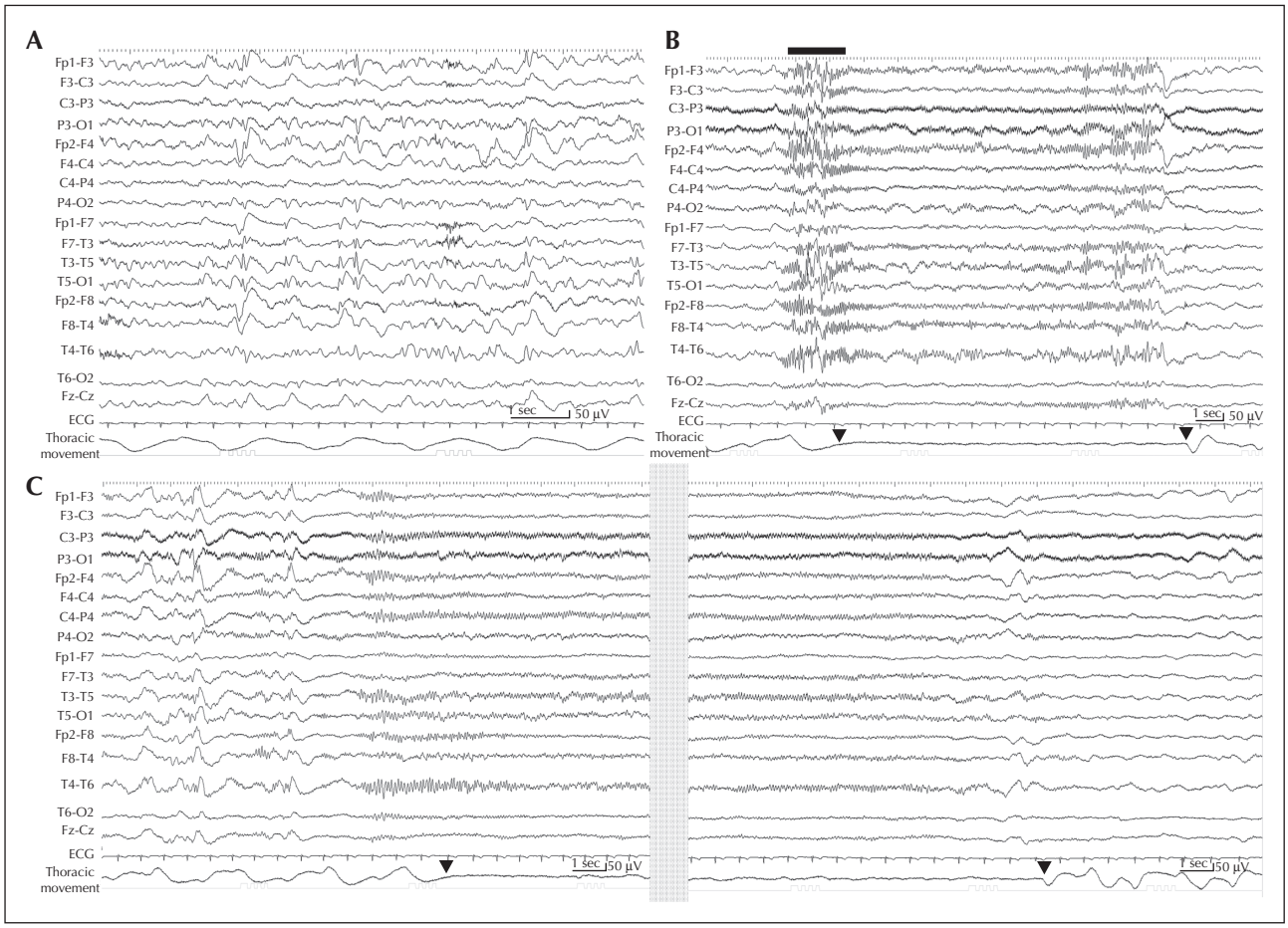

Figure 2. Interictal and ictal EEG findings. (A) Interictal EEG findings during sleep at 20 years of age reveal diffuse periodic 1-2-Hz diffuse slow spikes and waves lasting for a few seconds. (B) Ictal EEG findings during apnoea at 20 years of age showing diffuse 200-300-μV high-amplitude and diffuse 13-15-Hz fast waves (Black bar) followed by rhythmic α and β activities corresponding to the arrest of thoracic movements. **C)** Ictal EEG findings of consecutive epileptic apnoea showing diffuse rhythmic 12-14-Hz α and β waves preceded by arrest of the thoracic movement lasting for 30 seconds. Arrowheads indicate the onset and cessation of apnoea. EEG corresponding to the middle of the apnoea event (approximately 10 seconds) has been omitted.

of menstruation; these seizures were refractory to various antiepileptic drugs during early treatment. The patient was frequently admitted to the hospital due to recurring aspiration pneumonia associated with clusters of generalised tonic seizures. We assumed that this patient had recurrent aspiration pneumonia related to dysphagia caused by brainstem dysfunction associated with PTHS, which led to deteriorating respiratory function. However, there have been few reports describing the detailed clinical courses of epilepsy in patients with PTHS. According to previous reports, epilepsy in patients with PTHS can be controlled relatively well with one or two standard antiepileptic drugs (Whalen *et al.*, 2012; Marangi and Zollino, 2015; de Winter *et al.*, 2016), although a few patients may develop intractable epilepsy, such as infantile spasms and Lennox-Gastaut syndrome (Peippo *et al.*, 2006; de Pontual *et al.*, 2009). However, the most effective AED is unclear because the number of reports is extremely limited (de Winter *et al.*, 2016). Because phenobarbital and KBr were effective in reducing the frequency of generalised tonic seizure clusters in our patient, they might be useful for suppressing seizure clusters in patients with PTHS. In conclusion, patients with PTHS can present with frequent epileptic apnoea during sleep as well as intractable generalised tonic seizures. EEG monitoring and PSG should therefore be performed for patients with PTHS. Further investigations of epilepsy, EEG as well as PSG findings and detailed examinations of sleep disturbances are needed to determine whether epileptic apnoea and intractable seizures occur more frequently in patients with PTHS and to determine which AEDs are the most effective in these patients. □

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

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

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TEST YOURSELF

(1) What types of sleep disturbances have been reported in patients with PTHS?

(2) What percentage of patients with PTHS experience epilepsy and what is the optimal treatment for epilepsy?

(3) What examinations were useful in distinguishing nocturnal breathing abnormalities in this patient?

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".