Clinical commentary

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Sleep-related hypermotor epilepsy and peri-ictal hypotension in a patient with syntaxin-1B mutation

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ABSTRACT – *STX1B* is a gene that encodes syntaxin-1B. *STX1B* mutations have recently been implicated in fever-associated epilepsy syndromes. However, these have not previously been reported in sleep-related hypermotor epilepsy. A 20-year-old man with a strong family history of epilepsy was investigated in our epilepsy monitoring unit due to uncontrolled epilepsy, compatible with sleep-related hypermotor epilepsy. Electroclinical and polygraphic physiological recordings revealed left frontal epileptiform discharges and prominent peri-ictal hypotension. Normal MRI using an epilepsy protocol prompted a search for a genetic epilepsy, which revealed a likely pathogenic mutation in the *STX1B* gene. The patient remained seizure-free after treatment optimization with carbamazepine. This case suggests that a sleep-related hypermotor epilepsy phenotype can be associated with syntaxin-1B gene mutation, and testing for this gene should be considered in such patients. Furthermore, it may also be concluded that autonomic dysfunction, characterized by peri-ictal hypotension, can also occur in this discorder. [*Published with video sequences on www.epilepticdisorders.com*]

Key words: sleep-related hypermotor epilepsy, *STX1B*, hypermotor seizures, peri-ictal hypotension, frontal lobe epilepsy

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STX1B is a gene that encodes syntaxin-1B. It is involved in the release of glutamate and GABA (Mishima *et al*., 2014) and plays a role in the regulation of fast synaptic vesicle exocytosis. *STX1B* mutations have recently been implicated in fever-associated epilepsy syndromes (Schubert *et al*., 2014). However, these have not been previously reported in sleep-related hypermotor epilepsy (SHE, or nocturnal frontal lobe epilepsy [NFLE]) (Tinuper *et al*., 2016). Autonomic disturbances in general, and seizure-induced hypotension in particular,

have not been described in either SHE or cases with *STX1B* mutations. We present a case of epilepsy probably due to a *STX1B* mutation with both sleep-related hypermotor seizures and autonomic instability.

Case study

A 20-year-old, right-handed man with a difficult-to-control epilepsy was admitted through the emergency room to the epilepsy monitoring unit, with a cluster of uncontrolled partial seizures. He first developed non-febrile *grand mal* seizures during infancy. He was treated with carbamazepine and was seizure-free until 15 years of age, at which point his medication was withdrawn. Soon after, he began having daily episodes of brief, bilateral, repetitive involuntary leg movements accompanied by vocalizations that occurred mainly during the night and lasted approximately 30 seconds. The patient had no relevant past medical history, but had a strong paternal family history of epilepsy (affecting his father, both paternal grandparents, paternal uncle, paternal great aunt, and paternal first cousin; *see figure 1*), for which more details were unavailable. An MRI with epilepsy protocol revealed no abnormalities. Electroclinical and polygraphic physiological recordings were carried out; video-EEG and 3-channel ECG were recorded using the Nihon Kohden (Tokyo, Japan) Neurofax EEG-1100A system, oximetry with an Oximax N-600X machine (Covidien PLC, Dublin Ireland), respiratory movements with Ambu Sleepmat (Ambu Ltd, Copenhagen, Denmark) abdominal and thoracic belts, and continuous, beat-to-beat, non-invasive BP recordings with CNAP (CNSystems Medizintechnik AG, Graz, Austria).

Results

At the time of admission, the patient had 4-16 seizures per day, confirmed during his 13-day stay at the unit. His seizure semiology consisted of 10-30-second duration hypermotor seizures (predominantly pedalling movements and vocalizations), with preserved consciousness and no post-ictal symptoms (including no hypotension-related symptoms) (*video sequence 1*). These seizures occurred predominantly out of sleep. After reintroduction of carbamazepine, the semiology changed notably into subtle generalized tonic seizures, which then subsided with dose increases. No inter-ictal discharges were recorded. The ictal pattern consisted of rhythmic 4-5-Hz activity arising from the left frontal regions, maximum at Fp1 (*figure 2*). CNAP system recordings of continuous beat-to-beat blood pressure during seizure periods revealed evidence of autonomic instability, as evidenced by significant hypotension before, during, and after hypermotor seizures. *Figure 3* shows cardiovascular changes during a typical hypermotor seizure. A brief period of elevation of blood pressure precedes the seizure (MAP rises from approximately 80 to 100 mmHg over four seconds), and after the end of the seizure, a profound and prolonged drop in blood pressure can be observed. A minimum MAP of 54 mmHg is observed, and slow recovery to pre-seizure BP values occurs after 34 seconds. All seizures recorded consistently had the same blood pressure pattern.

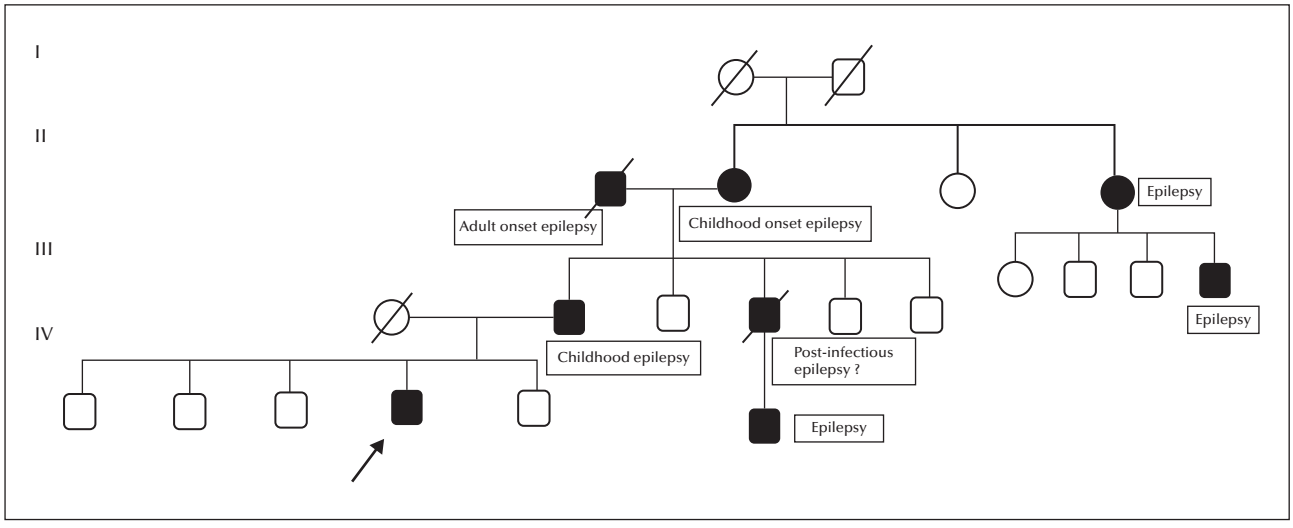

Figure 1. Family history of the patient.

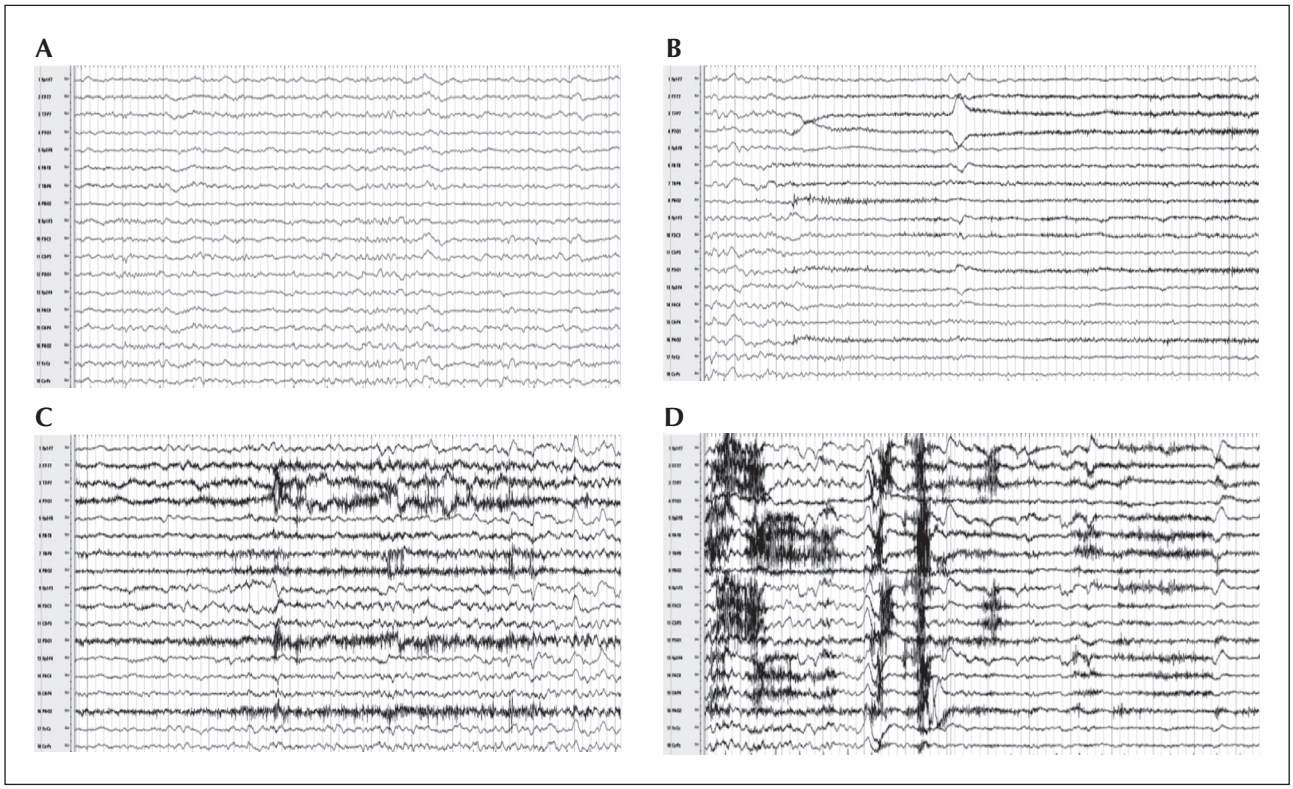

Figure 2. Longitudinal bipolar montage, 15-second page, with sensitivity: 7 uV; HPF: 0.5 Hz; LPF: 70 Hz; and Notch: 60 Hz. (A) Stage 2 sleep. (B) Arousal. (C) Seizure onset showing rhythmic activity in the theta range (5-Hz), arising from the left frontal regions, maximum at Fp1, spreading to the ipsilateral hemisphere and later to the contralateral side, with slight increase in frequency to 7 Hz. (D) Seizure end.

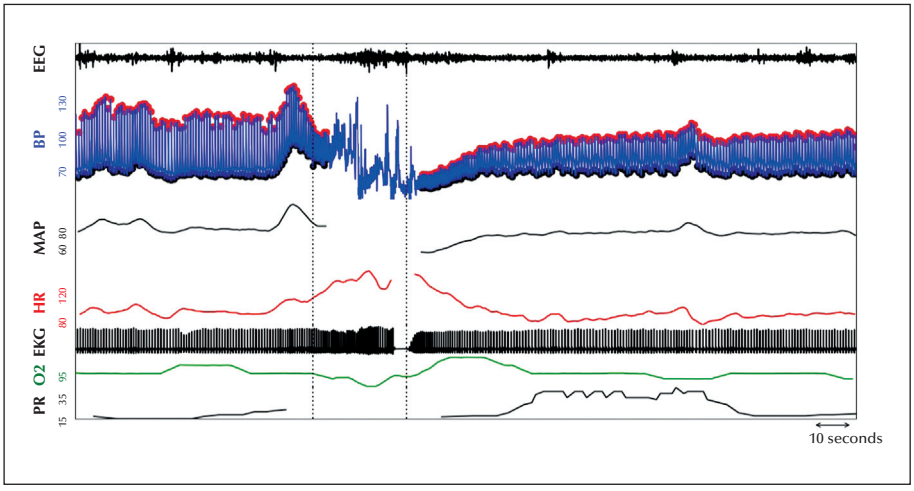

Figure 3. A 30-second hypermotor seizure was recorded (between dotted lines) with a brief period of relative pre-ictal hypertension (MAP rising from ~80 to 100 mmHg), followed by a profound drop in blood pressure immediately after the seizure to a minimum MAP of 54 mmHg, with a slow recovery to the pre-ictal MAP. All seizures recorded consistently had the same blood pressure pattern. BP: blood pressure; MAP: mean arterial pressure; HR: heart rate; RR: respiratory rate; EEG: electroencephalogram; EKG: electrocardiogram.

An extensive genetic panel (EpilepsyNext, Ambry Genetics) was performed. The following genes were evaluated: *ALDH7A1, ARHGEF9, ARX, ATP13A2, ATP1A2, CACNA1A, CASK, CDKL5, CHD2, CHRNA2, CHRNA4, CHRNB2, CLN3, CLN5, CLN6, CLN8, CNTNAP2, CRH, CSTB, CTSD, CTSF, DCX, DEPDC5, DNAJC5, DNM1, DYNC1H1, DYRK1A, EEF1A2, EPM2A, FLNA, FOLR1, FOXG1, GABRA1, GABRB3, GABRG2, GAMT, GATM, GNAO1, GOSR2, GRIN1, GRIN2A, GRIN2B, GRN, HCN1, HNRNPU,IQSEC2, KCNA2, KCNC1, KCNJ10, KCNQ2, KCNQ3, KCNT1, KCTD7, KIAA2022, LGI1. MECP2. MEF2C, MFSD8, NHLRC1, NRXN1, PCDH19, PIGA, PLCB1, PNKP, PNPO, POLG, PPT1, PRICKLE1, PRRT2, PURA, SCARB2, SCN1A, SCN1B, SCN2A, SCN8A, SIK1, SLC13A5, SLC25A22, SLC2A1, SLC35A2, SLC6A1, SLC9A6, SMC1A, SNAP25, SPTAN1, ST3GAL3, STX1B, STXBP1, SYN1, SYNGAP1, SZT2, TBC1D24, TBL1XR1, TCF4, TPP1, TSC1, TSC2, UBE3A, WDR45, ZEB2*.

This revealed a likely pathogenic variant in the *STX1B* gene (c.106-2A>G). A variant of unknown significance in the *PPT1* gene (c.433G>C, p.G145R) was also found (MAF threshold of 0.1% for dominant conditions and 1% for recessive conditions).

Considering the likely genetic aetiology of the epilepsy, the patient was no longer considered a surgical candidate.

After treatment optimization with carbamazepine, 400 bid, the patient remained seizure-free at the last follow-up visit.

Discussion

SHE is the recently proposed name for the syndrome formerly known as NFLE (Tinuper *et al*., 2016). The rationale for the nomenclature change is based on the following: seizures are associated with sleep rather than time of day, they may arise from sites other than the frontal lobe, and motor aspects of the seizures exhibit hypermotor semiology as defined by Lüders *et al*. (1998). The main clinical features of SHE (Tinuper *et al*., 2016) are:

– brief (less than two minutes) seizures with intra-individual stereotypic motor patterns with abrupt onset and offset;
– hypermotor events;
– occurrence predominantly during sleep.

In the majority of cases, the aetiology of SHE remains unknown; some may have structural and/or genetic causes. In this particular case, the normal MRI and the strong family history prompted a search for a genetic origin, including genes described to be associated with SHE (*CHRNA4*, *CHRNB2*, *CHRNA2*, *KCNT1*) (Wang *et al*., 2017). This revealed a previously unreported association between SHE and *STX1B*. This particular *STX1B* mutation has not been reported in population-based cohorts, namely the Exome Sequencing Project, in 6,497 samples with coverage of this position. Using prediction tools (ESEfinder and BDGP), this mutation is predicted to abolish the native splicer acceptor site, which is expected to cause aberrant splicing resulting in abnormal protein or a transcript that is subject to nonsense-mediated mRNA decay. Further confirmatory techniques, such as functional assays to interpret whether splicing is affected and mRNA decay tests, were not performed due to technical limitations and *STX1B* expression being limited to the brain. Family members were not available, therefore segregation studies were not performed. Nevertheless, even with these limitations, we believe this report is of importance to alert geneticists and epileptologists of a possible association between *STX1B* gene mutation and the described phenotype.

The genetic panel also led to detection of a variant of unknown significance (VUS) in the *PPT1* gene. Pathogenic mutations in this gene are associated with neuronal ceroid lipofuscinosis, which is an autosomal recessive, neurodegenerative disorder. This particular variant has been seen in 0.01% of alleles in the NHLBI Exome Sequencing Project. Its frequency in African American alleles is 0.02%.

Autonomic symptoms, including hypotension, can occur in the peri-ictal period (Bozorgi *et al*., 2013; Hampel *et al*., 2017). Continuous non-invasive beat-to-beat blood pressure monitoring (CNAP) is a reliable method for the detection of blood pressure changes in the epilepsy monitoring unit. The true incidence of ictal hypotension is unknown. Jaychandran *et al*. (2016) found it to be a relatively rare phenomenon, occurring in 8.8% of polygraphic-monitored patients with refractory epilepsy. Its possible value for lateralizing or localizing the epileptogenic zone is also unknown, but some recent advances have been made. Lacuey *et al*. (2017) recently reported their results from human brain stimulation studies that pointed to Brodmann area 25 (BA25; anterior subcallosal grey matter) as a likely site to drive hypotension. Extended polygraphic monitoring of this patient revealed consistent post-ictal hypotension (Bozorgi *et al*., 2013) (*figure 3*). Such changes have not been previously reported in the literature in association with SHE. The frontal seizure discharge in our patient and the frontal seizure semiology raise the possibility of significant involvement of Brodmann area 25, thus producing the hypotension noted. Further investigation of peri-ictal autonomic phenomena through polygraphic monitoring is probably important to understand their possible role in clinical practice.

In conclusion, this case suggests that a SHE phenotype can be associated with syntaxin-1B gene mutation, and the testing of this gene should be considered in

such patients. Furthermore, it may also be concluded that autonomic dysfunction, characterized by peri-ictal hypotension, can also occur in this disorder. □

Legend for video sequences

Video sequence 1.

Brief hypermotor seizure arising from sleep with preserved consciousness (Seizure 1).

Video sequence 2.

Brief hypermotor seizure arising from sleep with preserved consciousness (Seizure 2).

Key words for video research on www.epilepticdisorders.com

Phenomenology: hypermotor seizures
Localization: frontal lobe
Syndrome: sleep-related hypermotor epilepsy (SHE), formerly known as Nocturnal Frontal Lobe Epilepsy (NFLE)
Aetiology: genetic - STX 1B mutation (probable)

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.

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TEST YOURSELF

(1) What are the main clinical features under the new term "sleep-related hypermotor epilepsy"?

(2) Which genes are so far associated with the SHE phenotype?

(3) Which brain area has recently been proposed as a possible symptomatogenic zone for peri-ictal hypotension?

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".