Sleep-related hypermotor epilepsy with genetic diagnosis: description of a case series in a tertiary referral hospital

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ABSTRACT

INTRODUCTION: Sleep-related hypermotor epilepsy (SHE) is characterized by asymmetric tonic/dystonic posturing and/or complex hyperkinetic seizures occurring mostly during sleep. Experts agree that SHE should be considered a unique syndrome.

PURPOSE: We present 8 cases of SHE for which a genetic diagnosis was carried out using a multigene epilepsy panel.

METHODS: We retrospectively screened familial and isolated cases of SHE in current follow-ups in our center.

RESULTS: We included 8 (5F/3M) patients, 5 of whom had a positive familial history of epilepsy. We identified a pathogenic mutation in CHRNA4, CHRN2, and 3 different pathogenic changes in DEPDC5.

CONCLUSIONS: Awareness of SHE needs to be raised, given its implications for finding an appropriate treatment, its relationship to cognitive and psychiatric comorbidities, and the opportunity to prevent the disorder in the descendants. We present our series with their clinical, radiological, electroencephalographic, and genetic characteristics, in which we found 3 pathogenic mutations in the DEPDC5 gene but not previously reported in the literature. Identifying new pathogenic mutations or new genes responsible for SHE will facilitate a better understanding of the disease and a correct genetic counseling.

KEYWORDS: nocturnal frontal lobe epilepsy, sleep-related hypermotor epilepsy, genetics

Introduction

Sleep-related hypermotor epilepsy (SHE) was initially confused with a motor disorder of sleep.¹ First described in 1981, SHE was known as “nocturnal paroxysmal dystonia”²; in 1990, the epileptic origin of the episodes was demonstrated,³ and the condition was termed “nocturnal frontal lobe epilepsy.” In 2014, the Consensus Conference in Bologna, Italy, recognized its possible extrafrontal origin, and the condition was renamed as SHE.⁴

With an estimated minimum prevalence of 1.8/100,000 individuals, the true incidence of SHE is unknown but is believed to be uncommon.⁵ The first gene related to SHE was CHRNA4,¹ identified in a large Australian family with an autosomal dominance inheritance.¹⁶ CHRNA4 was found to encode alpha-4, a neuronal acetylcholine nicotinic receptor subunit, which led to the discovery of mutations in other genes such as CHRNA2 and CHRN2 coding for other subunits (alpha 2 and beta 2). The application of next-generation sequencing led to the discovery of 4 additional main genes. To date, at least 7 different genes have shown an association with SHE⁷ (CHRNA4, CHRN2, CHRN42, KCNT1 (potassium sodium-activated channel subfamily T member 1), DEPDC5 (DEP domain containing 5), NPRL2 (NPRL2-like protein), and NPRL3 (nitrogen permease regulator-like 3)). Other genes, such as corticotropin-releasing hormone (CRH) and prolinerich membrane anchor 1 (PRIMA1), have been anecdotally implicated.⁸,⁹

These mutations only account for 30% of known families with SHE.¹ Correctly characterizing the clinical syndrome and

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Table 1. Summary of the case series.

| CASE  | GENE   | SEX | CLINICAL HISTORY | C.NA NUCLEOTIDE CHANGE | PROTEIN AMINOACID CHANGE | MUTATION TYPE | ACMG CLASSIFICATION | ONSET AGE/ PRESENT AGE | VIDEO-EEG | MRI | PREVIOUS TREATMENT | CURRENT TREATMENT |
|-------|--------|-----|------------------|-------------------------|--------------------------|---------------|---------------------|-----------------------|------------|-----|-------------------|-------------------|
| 1 (confirmed) | CHRNA4 | F | HS | c.839 C>T | p.S280 F | Missense | Pathogenic | 12 y/34y | None | Ictal pattern with anterior right discharges | (3T) normal | CBZ, CLB, VPA, PB, OXC, and LTG. | TPM. |
| 2 (possible) | CHRNA4 | F | HS | c.859 G>A | p.V827 M | Missense | Pathogenic | 3 y/39y | First-degree relatives (confirmed SHE). Second- and third-degree relatives (possible SHE) | Not performed (1.5 T) normal | CBZ, OXC, and LTG. | ZNS and PB. |
| 3 (confirmed) | DEPDC5 | F | HS | c.1287+1G>A | - | Splicing | Pathogenic | 20 y/59y | None | Interictal bilateral frontal spike with left predominance | (3T) normal | LTG, LEV, CBZ, OXC, VPA, VGB, TPM, ZNS, PER, ESL, PHT, GBP, and PRM. | VPA, PER, CLB, and BRV. Surgery and VNS rejected |
| 4 (possible) | DEPDC5 | M | HS | c.301 G>T | p.(Glu101*) | Nonsense | Pathogenic | 11 y/46y | Second-degree relatives (possible SHE). Third-degree relative (West syndrome) | Not performed (1.5 T) normal | PB and CBZ. | CBZ. |
| 5 (confirmed) | DEPDC5 | M | ADPA | c.723dupA | p.I242Nfs | Frameshift | Pathogenic | 2 y/63y | First- and second-degree relatives with another type of epilepsy | Ictal pattern with left frontal discharges | (3T) normal | LTG, LEV, CBZ, VPA, VGB, TPM, ZNS, PRM, and CLB. | ESL, ZNS, PER, and BRV. Surgery and VNS rejected |

(Continued)
| CASE       | GENE | SEX | CLINICAL HISTORY | CDNA NUCLEOTIDE CHANGE | PROTEIN AMINOACID CHANGE | MUTATION TYPE | ACMG CLASSIFICATION | ONSET AGE/PRESENT AGE | EPILEPSY FAMILIAL HISTORY | VIDEO-EEG | MRI | PREVIOUS TREATMENT | CURRENT TREATMENT |
|------------|------|-----|------------------|-------------------------|--------------------------|---------------|---------------------|------------------------|--------------------------|------------|----|-------------------|-------------------|
| 6 (confirmed) | F    | HS  |                   |                         |                          |               |                     | 2 y/42y                 | Ictal pattern with right frontal discharges | (3T) normal | CBZ, VGB, LTG, VPA, TPM, ZNS, CLB, GBP, and LEV. | ESL and CLB. Pending VNS |
| 7 (confirmed) | F    | ADP |                   |                         |                          |               |                     | 16 y/45y                | Ictal pattern with right frontal discharges | (3T) normal | VPA, TPM, CLB, LTG, ZNS, LEV, CBZ, and ESL. | LCM, BRV, ZNS, and CLB. Surgery and VNS rejected |
| 8 (confirmed) | M    | HS  |                   |                         |                          |               |                     | 0.5 y/49y               | Ictal pattern with left frontal discharges | (3T) normal | VPA, TGB, TPM, PB, CBZ, and PER. | TPM, LEV, and ESL. |

Gene mutations type, protein changes, and pathogenicity likelihood according to pathogenicity classification is made according to the American College of Medical Genetics and Genomics (ACMG).

Clinical, radiological, VEEG, and treatment features: F: female; M: male; HS: hyperkinetic seizure; ADP: asymmetric dystonic posturing; PA: paroxysmal arousal; Y: years; CBZ: carbamazepine; OXC: oxcarbazepine; LTG: lamotrigine; PB: phenobarbital; ZNS: zonisamide; LCM: lacosamide; PER: perampanel; LEV: levetiracetam; VGB: vigabatrin; ESL: eslicarbazepine; PHT: phenytoin; GBP: gabapentin; PGB: pregabalin; PRM: primidone; BRV: brivaracetam; VNS: vagus nerve stimulation.
investigating the underlying genetic cause are essential, given their implications for therapeutic management, prognosis, and genetic counseling. Given the scarcity of reported cases with positive genetic testing, we aim to present a systematically investigated case series of SHE.

Materials and methods
We enrolled patients currently in follow-up at our hospital since 2015 to 2020 who met the diagnostic criteria for SHE,4 that as part of their clinical care agreed to undergo a genetic analysis. Our epilepsy unit attends about 2200 adult patients per year out of a reference population of 558,000.

We used next-generation sequencing employing a multigene panel that included the main known SHE genes (CHRNA4, CHRNB2, CHRN42, KCNT1, DEPDC5, CRH, and PRIMA1) and confirmation by Sanger sequencing for those variants of possible clinical relevance.

All patients underwent a comprehensive clinical evaluation and complementary study, including 1.5 T or 3 T magnetic resonance imaging (MRI) with an epilepsy protocol.10 Six patients turned out to have confirmed SHE after undergoing video electroencephalography (VEEG). The other 2 were possible SHE patients (core clinical features were reported by eyewitnesses), but they rejected VEEG because their epilepsy was controlled. Psychiatric and cognitive comorbidity was formally evaluated in patients who required it.11

Results
We included 8 patients, 3 of whom were male (37.5%). The mean age of onset was 8.3 years and the mean present age is 47.1 years. All but 3 patients had a positive familial history of epilepsy, defined as at least 1 third-degree relative with a clinical diagnosis of epilepsy. Patients 1, 2, 3, 4, 6, and 8 had hyperkinetic seizures (HS), and patients 5 and 7 had asymmetric dystonic posturing (ADP); the patient 5 also had multiple paroxysmal arousals (PA).

The VEEG carried out in 6 of the patients showed a frontal origin of the seizures. All seizures registered occurred during sleep, most of them onset during NREM sleep.

As for the MRI evaluation, it was normal in all patients. We found a single mutation in CHRNA4, CHRNB2, and 3 patients had mutations in the DEPDC5 gene. Two (40%) mutations were found to be pathogenic, as previously described in the literature, 3 (60%) variants were found to be pathogenic based on their association with other epilepsy syndromes (DEPDC5-associated familial focal epilepsy with variable foci [MIM#604364] or with loss of function of the protein. Table 1 summarizes the main characteristics of the genetic tests and the clinical, radiological, electrophysiological, and treatment features of the case series.

We performed a family segregation study in 3 cases. In case 1, the mutation was not found in the patient’s healthy mother; the father who had third-degree relatives with possible SHE was an asymptomatic carrier. In case 2, we were only able to study the son and daughter, who were symptomatic carriers with confirmed SHE. In case 3, we only studied the daughter, who was an asymptomatic carrier.

Half of the patients presented cognitive and psychiatric comorbidity. Patient 1, with CHRNA4 mutation, had a previous history of depression and personality disorder with impulse control disorder and poor social skills. Patient 3, who had a DEPDC5 gene mutation, had a personal history of major depression requiring follow-up with psychiatry. Patient 6 had moderate intellectual disability, and patient 8 had impairment of executive function (impairment of working memory, cognitive flexibility, and phonological verbal fluency).

In terms of treatment, 2 patients (patient 1 and 4) achieved seizure control using just one drug. Patient 2 and 8 presented decrease of seizure greater than 50% with 2 and 3 drugs. The other 4 patients had a refractory epilepsy and surgical treatment or vagus nerve stimulation (VNS) were proposed. Patients 3, 5, and 7 rejected both treatments because of their current age, and patient 6 is waiting for VNS implantation.

Discussion
Identifying patients with SHE1 and performing directed genetic testing are of utmost importance because they help solve the diagnostic process and find new phenotypes, and are essential for optimizing each patient’s treatment and the potential implications for their relatives. Regarding descendants, genetic counseling could be recommended.

Knowledge of the disease’s genetics aids in the search for new therapeutic strategies, such as that gained from the trials with nicotine, fentanyl, and furosemide on mutations in the CHRNA4 gene, quinidine in patients with a KCNT1 gene mutation, and the opportunity to investigate rapamycin in patients with a DEPDC5 gene mutation.12

Approximately one-third of patients experience drug-resistant seizures,13 which is consistent with the findings in our series, with the condition being refractory in 50% of the patients. Recent studies have proposed surgical treatment, with frontal resection according to presurgical investigations and cortical resection in focal cortical dysplasia, achieving seizure control in selected cases with a positive MRI study in presurgical evaluation.12 To our knowledge, the effectiveness of VNS in these cases has only been evaluated in one patient in whom an 80% reduction in seizures was observed.14 We found VNS as a suitable alternative in our cases.

Studies focusing on neuropsychology have reported disorders in almost half of the patients, such as cognitive impairment affecting memory, executive function, and visual impairment, with 22.4% of the patients presenting lack of inhibitory control.15 We found cognitive impairment in 3 patients.

The main limitation of our series is the limited number of patients and that not all of the relatives underwent a segregation study, despite the study having been recommended; however,
for most older patients, relatives cannot be found for the genetic study, or the relatives simply do not want to be tested.

### Conclusion

SHE is a serious disorder, and awareness of the condition needs to be raised, given its implications for finding an appropriate treatment, its relationship to psychiatric comorbidities, its impact on quality of life, and the opportunity to prevent the disorder in descendants.

We present our series of patients with SHE in whom we found 3 pathogenic mutations in the DEPDC5 gene due to loss of function of the protein not previously reported in the literature. Description of new genes or new mutations and their associated phenotype will help to correctly identify patients with SHE.

SHE is a heterogeneous genetic syndrome, and our findings suggest that at least 3 genes could be responsible for the syndrome. DEPDC5 appears to play a fundamental role in the pathogenesis of SHE, with new genes shedding light on its heterogeneity.

We believe that our study increases the current knowledge of the genetic causes of SHE and can help identify other patients and families who would benefit from comprehensive genetic testing and counseling.

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