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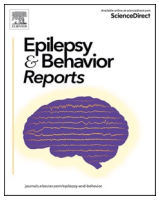

Nonsense mutation in DEPDC5 gene in a patient with carbamazepine-responsive focal epilepsy

Grainne Mulkerrin [a,*], Michael J. Hennessy [a]

[a] Department of Neurology, Galway University Hospital, Ireland

Introduction

Frontal lobe epilepsy is primarily a clinical diagnosis in modern practice. Brief, bizarre, hypermotor seizures commonly occurring from sleep and sometimes in clusters are characteristic [1]. Inter-ictal and even ictal-EEG may be normal, owing to relative inaccessibility of the deep gyri of the frontal lobe by standard scalp-EEG electrodes. The syndrome of sleep-related hypermotor epilepsy (SHE) has a considerable number of associated genes, including CHRNA4, CHRNA2, CHRNB2, KCNT1, DEPDC5, NPRL2, NPRL3 and PRIMA1 [2]. Thus genetic testing is often supportive of the diagnosis of frontal lobe epilepsy syndromes. As clinical experience with different genetic causes of epilepsy increases, trends in specific-drug-responsiveness are emerging.

In this case we describe the case of a gentleman with a long-standing diagnosis of unclassified drug-refractory epilepsy. After extensive work up, he was found to have autosomal dominant sleep-related hypermotor epilepsy (AD-SHE) caused by a DEPDC-5 (disheveled Egl-10 and pleckstrin domain containing protein 5) gene mutation. His recurrent nocturnal frontal lobe seizures completely subsided on re-commencement of carbamazepine. To our knowledge, this is the first described case of carbamazepine-responsiveness in a DEPDC-5-related epilepsy.

Case description

This case concentrates on a 41-year-old right-handed man with a long-standing diagnosis of epilepsy. He had his first seizure at 12 years of age. For many years, the working diagnosis was that he had two seizure types: the first being focal myoclonic seizures of the right hand with retained awareness, whereas the second was presumed to be focal to bilateral tonic-clonic seizure, most often occurring at night-time. He himself would report that increasing frequency of the myoclonic seizures would herald an increasing frequency of the generalised seizures. The hypothesised generalised seizures had been unwitnessed and he would report myalgia and excessive fatigue in the mornings.

His early medical records noted a normal birth and uneventful early developmental milestones. He had no history of febrile convulsions, central nervous system infection or head injuries. There is no family history of epilepsy. In childhood, and again at the age of 20, his MRI brain and routine EEG were both reported as normal. He successfully completed all standard education including university at a high level and was working full-time in a highly-skilled profession.

Over many years he remained largely seizure-free on carbamazepine monotherapy. However, he had suffered from severe symptomatic hyponatremia with significant somnolence requiring hospitalisation on several occasions. Hence trials of related anti-seizure medications notably oxcarbazepine and eslicarbazepine were introduced but these failed to control seizures. Further trials of lamotrigine and clobazam were equally unsuccessful and he reverted to carbamazepine. By early 2022 he had been seizure-free for 2 years on carbamazepine monotherapy.

In mid-2022 he was hospitalised with increasing confusion, somnolence and severe hyponatremia. Following comprehensive workup, he was diagnosed with syndrome of inappropriate antidiuretic hormone (SIADH) secondary to carbamazepine. Consequently, he was fluid-restricted and his carbamazepine was slowly discontinued and replaced with lacosamide. This failed to control seizures. Subsequent combinations of lacosamide with sodium valproate, levetiracetam, brivaracetam and perampanel elicited similar unsuccessful responses. Within six months, seizure frequency had increased to daily focal myoclonic seizure activity of the right-hand continuously lasting hours. Nocturnal events were reportedly occurring on a nightly basis with concomitant deleterious effects on sleep and quality of life. Whilst he was aware of these events in the manner of waking up at their onset multiple times per night, they were unwitnessed and hence difficult to characterise.

The patient was admitted to the video-EEG-unit, in an effort to quantify and diagnose the aetiology of these episodes. At the time he was taking a combination of lacosamide, brivaracetam and perampanel. Stereotyped events during his admission each night in the early hours of

* Corresponding author.
E-mail address: mulkerrg@tcd.ie (G. Mulkerrin).

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sleep were recorded. These events were characterised by sudden arousal from sleep, a rapidly developing tonic seizure with version of the head and body to the right. Tonic posturing of the upper limbs was initially symmetrical, then becoming asymmetrical with flexion at the left elbow and extension of the right arm in a 'figure-of-four sign'. Events lasted approximately a minute with rapid recovery, followed by a return to sleep. He reported awareness of the events the following morning. Eight events were captured over three nights (2–3 events per night). While no definite epileptic correlate was isolated on EEG, the semiology of events is consistent with frontal lobe seizures, specifically localising to seizures arising from the supplementary motor area. Of note, the EEG immediately prior to seizure onset reveals a six second decrement in EEG activity with rhythmic theta activity in the frontal leads; lending weight to the hypothesis that the frontal lobe was the seizure focus (Fig. 1). The interictal EEG was normal.

The presumed focal myoclonic seizures were also captured during admission. Clinically, this was a continuous focal myoclonus of the thumb and fingers of the right hand with retained awareness. There was no EEG correlate. This is felt to represent cortical myoclonus arising from a restricted area of cortical hyperexcitability, and is likely the same focus as the nocturnal seizures and thus not captured by the scalp-EEG.

An updated 1.5 Tesla MRI brain was normal. More advanced imaging techniques were not utilised in this case.

Whole genome sequencing revealed a pathogenic nonsense variant in the DEPDC5 gene, consistent with a diagnosis of AD-SHE. The specific genetic abnormality was c.3694C > T; p.Gln1232* in a heterozygous state, encoding a premature stop codon that leads to nonsense-mediated decay of the mRNA transcript. This specific genetic variant has not been previously described but the loss of protein is a known pathomechanism for DEPDC-5-related epilepsies.

Carbamazepine was re-introduced on day 4 of admission, leading to immediate cessation of the seizures. Lacosamide, brivaracetam and perampanel were weaned to stop and he is maintained on carbamazepine monotherapy at a dose of 400 mg mane and 1000 mg tarde. Four months later he is seizure-free, reporting no nocturnal arousals. While video-EEG could not be repeated, this is supported by improved sleep quality, absence of cortical myoclonus on exam and therapeutic serum carbamazepine levels.

Discussion

The case of a gentleman with a long-standing diagnosis of unclassified epilepsy which was drug-refractory is described. Following detailed inpatient assessment, a diagnosis of AD-SHE caused by a DEPDC-5 gene mutation was made.

Hereditary epilepsies were postulated in the literature and subsequently identified since the mid-1990s. In 1995, Scheffer et al first described the syndrome of SHE, formerly known as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), in five families who presented with recurrent nocturnal frontal lobe seizures [3]. In fact, the first causative gene in any focal epilepsy was identified in the same syndrome later that year. This was a missense variant in CHRNA4, which encodes the nicotinic acetylcholine receptor α4 subunit [4]. The ensuing 10 years were dominated by the discovery of new channel-related genes for various epilepsies; 'the channelopathy era' of neurogenomics: for example, SCN2A and LGI were implicated in self-limited familial neonatal-infantile epilepsy and autosomal dominant epilepsy with auditory features, respectively [5 6]. The advent of next generation sequencing in the 2010s led to the identification of a new wave of epilepsy genes in quick succession.

Dibbens isolated germline mutations in DEPDC5 in 2013 [7], and these have since been identified in such focal epilepsy syndromes as familial focal epilepsy with variable foci (FFEVF), SHE, and familial mesial temporal lobe epilepsy (FMTLE) [2]. Along with NPRL2 and NPRL3 genes, DEPDC-5 encodes the GATOR1-complex which is a negative regulator of the mTORC1 pathway. Mutations in these genes over-activate the mTORC1 pathway leading to excessive cell proliferation, migration and growth. Epilepsies caused by these mutations are collectively known as 'GATOR-1-related epilepsies' or 'GATORopathies'. The mutation is inherited in an autosomal dominant fashion. Incomplete penetrance and phenotypic variation are recognised features and, in our case, may explain this patient's lack of family history. Like tuberous sclerosis (TS), which also has its pathogenic basis via excessive mTORC1 activation, GATOR-1-related epilepsies are known to cause both lesional and non-lesional epilepsies [8,9]. Where lesional, this would tend to be a focal cortical dysplasia [8]. Non-lesional cases, such as in our patient, may well have covert focal cortical dysplasias too small to be appreciated by clinical MRI. GATOR-1-related epilepsies are known to have higher rates of drug-resistance and a higher incidence of

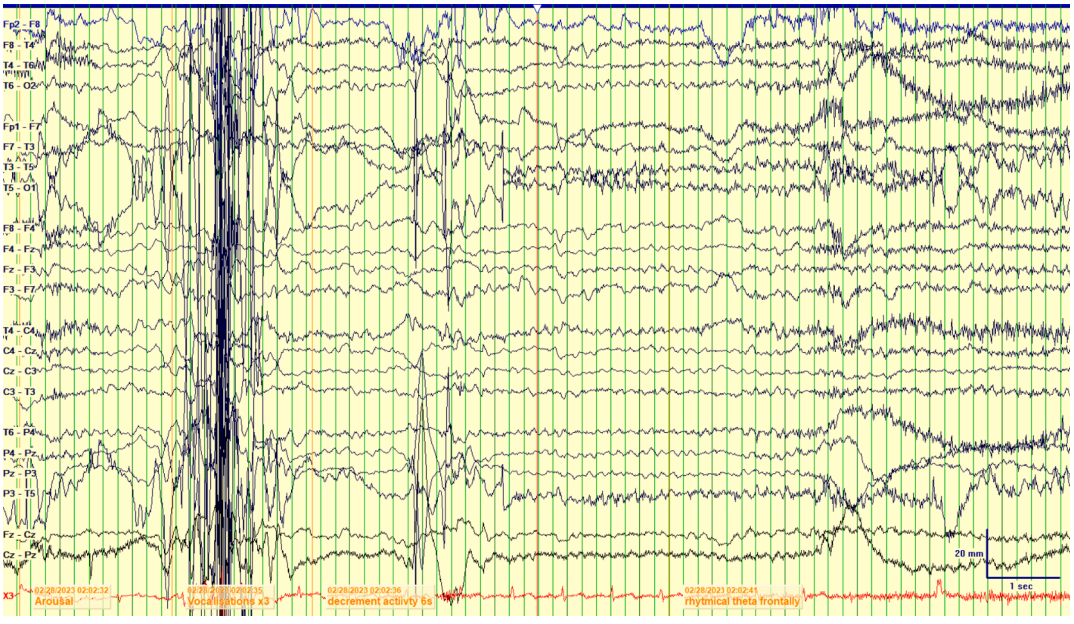

Fig. 1. EEG immediately prior to seizure onset recorded on a bipolar montage right-over-left with a sensitivity of 10 μV/m, demonstrating a decrement of activity for six seconds followed by rhythmic theta activity in the frontal leads.

sudden-unexplained death in epilepsy (SUDEP); occurring in 54 % and 10 % respectively in one large study [9]. The authors did not attribute any specific rationale for this nor are the reasons for this well-understood as yet. On a practical level, it does highlight that seizure freedom should be an important goal for affected patients.

Carbamazepine is one of the oldest anti-seizure medications available, first marketed in the 1960 s. It is a member of the 'sodium-channel blocker' class of drugs, specifically exerting its anti-seizure properties by slowing the recovery of inactivation of voltage-gated sodium-channels thereby reducing action potentials [10]. While its use is sometimes limited by an undesirable side-effect profile, carbamazepine continues to have an important role in the modern treatment of epilepsies.

Carbamazepine-responsiveness is an accepted feature of SHE. In the initial case-series describing the syndrome, 39 % of seizure-free patients were found to be on carbamazepine monotherapy [3]. More recent data suggested 68 % of patients with SHE have a significant response to carbamazepine; in this cohort of 100 patients, 20 % were seizure-free on carbamazepine and a further 48 % of cases demonstrated a seizure frequency reduction of >50 % [11]. Of note, these cohorts were genetically heterogenous.

Early speculation on carbamazepine-responsiveness in SHE largely focused on channelopathies as the aetiology of the epilepsy, whereby the mutated n-acetylcholine receptors are felt to be more sensitive to carbamazepine [12]. Such a hypothesis would not however explain the dramatic response to carbamazepine in our patient.

Referencing other mTOR-pathway-related epilepsies, TS-related seizures are also noted to be carbamazepine-responsive with one large study demonstrating 55 % of TS patients were seizure-free on carbamazepine [13]. Another case-report describes carbamazepine-responsiveness in TSC1-associated SHE [14].

Ultimately the biological basis of carbamazepine-responsiveness in our patient with a DEPDC-5 mutation is not clear. Anecdotally, it is our experience and clinical practice that carbamazepine is frequently successful in drug-refractory epilepsy syndromes where other anti-seizure medications, including other sodium-channel blockers, have failed.

For now, our patient remains seizure-free on carbamazepine monotherapy and with tight fluid restriction. He now has mild chronic, but asymptomatic hyponatremia. Undoubtedly, symptomatic, severe hyponatremia may develop in the future. The incidence of hyponatremia with carbamazepine is quoted as up to 40 % [15]. Symptomatic hyponatremia manifests with headache, confusion, somnolence and, in severe cases, seizures. Indeed asymptomatic hyponatremia may cause subtle difficulties in cognition and gait [16], highlighting the need to be vigilant with assiduous monitoring. The mechanism of carbamazepine-induced hyponatremia is commonly felt to be due to SIADH. In fact, carbamazepine also has a direct stimulation effect on the vasopressin-2-receptor in the collecting duct [17]. Tolvaptan is a competitive vasopressin-2-receptor antagonist which is used in the management of refractory hyponatremia in SIADH. There would be a biological basis for its use in this scenario if needed.

Precision therapies are undergoing early evaluation in DEPDC-5-related epilepsies. If successful, these may allow a reduction in the carbamazepine dose required for seizure control in our patient. Evrolimus, an inhibitor of the mTORC1 pathway, is used as an adjunctive therapy in refractory seizures in TS. Some success has been exhibited, albeit in a small cohort with drug-refractory GATOR-1-related epilepsy [18]. Extrapolating again from success as an add-on therapy in TS [19], cannabidiol may be another therapeutic option. Additionally, Cenobamate has proven to be an effective treatment in drug-resistant [20] and ultra-drug resistant [21] focal epilepsy. Furthermore, epilepsy surgery, while challenging and requiring rigorous investigation, can be a successful option in GATOR-1-related epilepsies [2].

Conclusion

A case of a patient with a germline nonsense mutation in DEPDC-5 gene causing AD-SHE, which is remarkably carbamazepine-responsive despite being refractory to other anti-seizure medications, is discussed.

Limitations

We acknowledge the limitation in this case is the lack of availability of repeat video-EEG to confirm the clinical impression of seizure-freedom, on the basis that patient reports of seizure-freedom in frontal lobe epilepsy can be unreliable.

Ethical statement

The authors obtained informed consent from the patient included in this case report.

Information in the case report has been anonymised insofar as is possible.

CRediT authorship contribution statement

Grainne Mulkerrin: Writing – original draft, Conceptualization. **Michael J. Hennessy:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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