Late-onset cluster seizures and intellectual disability associated with a novel truncation variant in SMC1A

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1. Introduction

1.1 Genetic diagnosis and counselling for the monogenic epilepsies is critical because not all are caused by de novo dominant variants. An important example is the epilepsy associated with PCDH19, on the X chromosome. PCDH19 variants cause an epilepsy with clusters of focal-onset and fever-sensitive seizures, primarily restricted to females and within a spectrum of cognitive impairment and psychiatric comorbidity [1,2]. This is phenotypically similar to the presentation of women with pathogenic variants in another X chromosome gene, SMC1A [3].

1.2 The SMC1A gene, Xp11.22, encodes a subunit of the cohesin complex. This complex has several functions including the holding together of sister chromatids, thereby ensuring chromosome segregation during cell replications, modulation of gene expression, and DNA repair [4]. De novo variants in SMC1A were first known to be a rare cause of Cornelia de Lange Syndrome (CdLS) which encompasses a clinical spectrum of intellectual disability, dysmorphic features (long or thick eyebrows, a hypomorphic philtrum and small nose) and, in some cases, epilepsy. More recently, SMC1A truncating variants have been described as the cause of a neurodevelopmental disorder with early-childhood onset drug-resistant epilepsy with seizures that occur in clusters, similar to that seen in PCDH19-related epilepsy, but without the classical features of CdLS. Here, we report the case of a 28-year-old woman with a de novo heterozygous truncating variant in SMC1A who unusually presented with seizures at the late age of 12 years and had normal development into adulthood.

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2. Case report

2.1 This 28-year-old woman first presented to the pediatric neurology service aged 12 years with unprovoked presumed generalized onset tonic-clonic seizures. She was the product of an uncomplicated pregnancy and spontaneous delivery at term. She had normal development prior to seizure onset, although was described as having clumsy gross motor skills and being poor at sports at the age of 12. There was no impairment of fine motor or language development. Examination identified bilateral pes cavus, hyporeflexia in the lower limbs, and a broad-based gait, non-progressive peripheral neuropathy, and a mild degree of facial asymmetry.

2.2 Her seizures were initially characterized by clusters of presumed generalized tonic-clonic seizures in the context of a febrile illness. She commenced phenytoin, supplemented by topiramate without control of seizures. She also developed focal seizures characterized by impaired awareness and right upper limb motor spasms, as well as occasional generalized myoclonic seizures. By 16 years of age, she developed monthly clusters of seizures, with a catamenial tendency, resulting in multiple admissions to critical care due to convulsive status epilepticus. At this point her anti-seizure medication was changed to levetiracetam and phenytoin, due to a metabolic acidosis caused by topiramate, and she commenced levonorgestrel/ethinylestradiol to halt ovulation in the hope that this would aid seizure control. This coincided with 18 months of seizure freedom, during which she was able to start undergraduate studies in college, which she completed with a passing grade at the age of 21.

At the age of 20, she developed focal autonomic seizures. These were stereotyped episodes of flushing, followed by deep inspiration, increasingly loud and repetitive speech, and an appearance of being vacant. These occurred in addition to clusters of generalised tonic-clonic seizures of unknown onset occurring five to eight times per day. Clobazam and lamotrigine were introduced in addition to levetiracetam and phenytoin. By this time, her cognitive function measured in an interictally had declined, and an Addenbrooke’s Cognitive Examination – Revised (ACE-R) was 79/100 [14]. She continued to present to hospital monthly with predominantly convulsive, but also episodes of non-convulsive, status epilepticus. Her medications were changed to phenobarbital, phenytoin, and lacosamide, in addition to buccal midazolam and rectal paraldehyde in the event of status epilepticus. Her medications were changed to phenobarbital, due to a metabolic acidosis caused by topiramate, and subsequently allopregnanolone, are implicated in the pathophysiology of catamenial epilepsy. Allopregnanolone is a positive allosteric modulator of GABA A neurotransmission and therefore shows significant overlap with the PCDH19 phenotype. This prominent clustering of seizures mirrors the clusters seen in PCDH19-related epilepsy, which similarly, is also characterised by fever-sensitive seizures, and a spectrum of cognitive features [17]. Whilst dysmorphic features are less common in PCDH19-related epilepsy and seizures are markedly fever sensitive, our case shows significant overlap with the PCDH19 phenotype.

There is no evidence that any particular antiseizure medication is preferred for this group of patients. However, there has been reported benefit from ketogenic or the modified Atkins diet in three people reported in the literature [3,13].

The patient described in this case developed an eighteen-month period of seizure freedom coinciding with the introduction of levonorgestrel/ethinylestradiol to treat a catamenial tendency. There is evidence that neurosteroids, particularly the progesterone metabolite allopregnanolone, are implicated in the pathophysiology of catamenial epilepsy. Allopregnanolone is a positive allosteric modulator of GABA A neurotransmission and therefore withdrawal of progesterone, and subsequently allopregnanolone, during the menstrual cycle is thought to be related to the observed increase in seizure frequency [18]. The ketogenic diet has also been associated with altered neurosteroid metabolism, in particular neurosteroidogenesis and subsequent potentiation of GABA. This is thought to be a possible mechanism underpinning the use of the ketogenic diet in epilepsy [19]. Given the previous reports of improvement with a ketogenic or modified Atkins diet in three patients with SMCA associated epilepsy and the initial hypometabolism most evident in the frontal and parietal lobes. Echocardiography has shown a small ventricular septal defect at the apex of the left ventricle. Nerve conduction studies were consistent with a mild, likely axonal neuropathy. Electroencephalographic (EEG) examinations have demonstrated intermittent focal and multifocal epileptiform activity in various locations including the right anterior quadrant, the anterior hemispheres, and the parietal regions, alongside profound encephalopathy. Other typical EEGs showing generalised ictal changes are shown in Fig. 1.

2.5 Plasma amino acids, urine amino acids, acylcarnitines and organic acids, cerebrospinal fluid examination for intermediary metabolites were normal as were neuronal antibodies and genetic testing with comparative genomic hybridisation array, karyotyping for ring chromosomes, mitochondrial disorders, and single gene tests (BTD, SCN1A). A whole exome sequencing panel (GEMINI, Cambridge University Hospitals NHS Foundation Trust) identified a heterozygous c.3312C > A, p.(Tyr1107Ter) truncating variant in SMCA, which is absent from population databases. X-inactivation studies were not performed. Her parents were not available to assess de novo status.

3. Discussion

3.1 All previously reported cases of epilepsy due to truncating SMCA variants describe a drug-resistant epilepsy with an onset in early childhood and moderate to severe intellectual disability, without the characteristic craniofacial dysmorphic features of CdLS and consistent with a DEE. This would be in keeping with the predominant mode of ascertainment of cases, the DDD project [3]. In this case, we hypothesize that the late age of seizure onset is concordant with the milder and later onset of neurocognitive compromise. Although similar to previously reported cases, she has a drug-resistant epilepsy with clustering of seizures and fever sensitivity, she does not display the characteristic dysmorphic features of CdLS. She has shown cognitive regression without atrophy detectable by MRI, temporally associated with frequent and intractable clusters of seizures/status epilepticus, in keeping with an epileptic encephalopathy [16].
| Year          | Seizure Frequency                        | Episodes of Status Epileptics | Anti-Seizure Medications                                      | Adjunctive Therapies                           |
|--------------|------------------------------------------|-------------------------------|-------------------------------------------------------------|----------------------------------------------|
| 2005         | March – first and second seizure         | N                             | Convulsive SE                                               | Sodium valproate and carbamazepine –        |
|              |                                          |                               |                                                             | stopped due to Stevens-Johnson syndrome.    |
|              | April – SE                               | Convulsive SE                 | Topiramate – stopped due to metabolic acidosis              |                                              |
|              | May – “frequent seizures”                 | N                             |                                                             |                                              |
|              | June – one generalized seizure           | N                             | Levetiracetam                                               |                                              |
| 2006         | Seizure-free                             | N                             | Convulsive SE                                               |                                              |
| 2007         | Predominantly seizure-free               | N                             | Levetiracetam                                               | N                                            |
| 2008         | Increased seizure frequency (monthly clusters) | N                             | Levetiracetam                                               | Levonorgestrel/ Ethynylestradiol             |
|              | June – SE                                | Convulsive SE                 | Levetiracetam                                               |                                              |
|              | August                                   | N                             | Levetiracetam and phenytoin                                |                                              |
|              | Oct – SE                                 | Convulsive SE                 |                                                             |                                              |
| 2009         | Seizure-free                             | N                             | Levetiracetam and phenytoin                                | Levonorgestrel/ Ethynylestradiol             |
| 2010         | Seizure-free                             | N                             | Levetiracetam and phenytoin                                | Levonorgestrel/ Ethynylestradiol             |
| 2011         | Seizure-free                             | N                             | Levetiracetam and phenytoin                                | Levonorgestrel/ Ethynylestradiol             |
| 2012         | July – one generalized seizure           | N                             | Levetiracetam and phenytoin                                | Levonorgestrel/ Ethynylestradiol             |
| 2013         | March – focal autonomic seizures         | N                             | Convulsive SE                                               | Levetiracetam and phenytoin                |
|              | July – SE                                | Convulsive SE                 | Levetiracetam and phenytoin                                | Medroxyprogesterone acetate                  |
|              | Sept – monthly seizure clusters          | N                             | Lamotrigine, levetiracetam and phenytoin                   |                                              |
|              | Oct – monthly seizure clusters           | N                             | Lamotrigine, levetiracetam and phenytoin                   |                                              |
|              | Nov – monthly seizure clusters           | N                             | Lamotrigine and phenytoin                                  |                                              |
|              | Dec – monthly seizure clusters           | Convulsive SE                 | Lamotrigine, phenytoin, zonisamide                          | Medroxyprogesterone acetate                  |
| 2014         | Jan-July – monthly seizure clusters      | N                             | Phenytoin and zonisamide Feb – April. Perampanel added May.| Medroxyprogesterone acetate                  |
|              | Aug – SE                                 | N                             |                                                             |                                              |
|              | Sept-Dec – monthly seizure clusters      | Convulsive SE                 | Perampanel and phenytoin                                   |                                              |
| 2015         | Jan-Dec – monthly seizure clusters       | N                             | Perampanel and phenytoin                                   | Medroxyprogesterone acetate Jan-April.       |
|              |                                          |                               |                                                             |                                              |
| 2016         | Jan-Sept – 8 admissions with seizure clusters | N                             | Convulsive SE – Feb                                          | Levetiracetam and phenytoin                |
|              | Oct-Dec – 3 admissions with seizure clusters | N                             | Convulsive SE – Jan, March, April, May.                     | Lacosamide, levetiracetam and phenytoin     |
| 2017         | Jan-May – 6 admissions. 1 with a single seizure, 1 with a seizure cluster, 4 with SE | N                             | Convulsive SE June, July, NCSE July.                       | Lacosamide, levetiracetam and phenytoin     |
|              | June-July – 4 admissions. 1 with a single seizure, 3 with SE. | N                             | Brivaracetam, lacosamide, phenytoin                         |                                              |
|              | Aug-Sept – 5 admissions. 1 with a single seizure, 3 with seizure clusters, 1 with SE. | Convulsive SE Aug.            | Lacosamide, levetiracetam and phenytoin                     |                                              |
|              | Sept-Oct – 4 admissions. 1 with a seizure cluster, 3 with SE. | Convulsive SE Oct. NCSE Sept, Oct. | Levetiracetam and phenytoin. |                                              |

(continued on next page)
Table 1 (continued)

| Year       | Seizure Frequency                                      | Episodes of Status Epilepticus | Anti-Seizure Medications | Adjunctive Therapies |
|------------|--------------------------------------------------------|--------------------------------|--------------------------|----------------------|
| Nov-Dec – 4 admissions. 2 with seizure clusters, 2 with SE. | Convulsive SE Nov, Dec. |                            | Levetiracetam, phenobarbital, phenytoin. |                      |
| 2018 Jan-March – 4 admissions with seizure clusters. | N                       |                               | Brivaracetam, phenytoin and phenobarbital. Single dose eslicarbazepine caused rash. | Medroxyprogesterone acetate |
| April-Dec – 19 admissions. 8 with singles seizures, 9 with seizure clusters, 2 with SE. | Convulsive SE July and Dec. |                     | Lacosamide, phenytoin and phenobarbital | Medroxyprogesterone acetate |
| 2019 Jan – 1 admission with a single seizure. | N                       |                               |                          |                      |
| Feb-March – 2 admissions with seizure clusters. |                         |                               |                          |                      |
| April-Dec – 15 admissions with seizure clusters. | N                       |                               | Phenytoin                |                      |
| 2020 Jan – Dec – 21 admissions. 13 with single seizures, 4 with seizure clusters and 4 with SE. | N                       |                               | Levetiracetam and phenytoin | Medroxyprogesterone acetate |
| 2021 Jan-July – 11 admissions. 5 with single seizures, 5 with seizure clusters, 1 with SE. | Convulsive SE Jan |                     | Levetiracetam and phenytoin | VNS June onwards Medroxyprogesterone acetate |
| Aug-Dec – 13 admissions. 8 with single seizures, 5 with seizure clusters. | N                       |                               | Cenobamate, levetiracetam and phenytoin |                      |

SE (Status epilepticus). No (N), VNS (vagal nerve stimulator).
NB – Clobazam used short term throughout.

Fig. 1. EEG recording. A. Typical EEG when well. Routine EEG performed before any episodes of status, age 20. Alpha rhythm present at 10–11 Hz. B. Generalized tonic-clonic seizure occurring during a period of status epilepticus. Patient unresponsive. Age 26. Build-up of generalized rhythmic 10 Hz activity with subsequent EMG and movement artefact. C. Nonconvulsive status epilepticus. Patient partially responsive (opened eyes to sound but not closing them on request, moving head when asked but otherwise appeared vacant). Age 27. Repetitive high amplitude generalized sharp waves and spikes seen. D. Encephalopathic post-seizure. Patient partially responsive (turned head in response to name being called but otherwise vacant and unresponsive). Age 26. Diffuse high amplitude theta and delta activity, occasional multifocal sharp waves were noted. E. Also encephalopathic post-seizure. Patient drowsy but responding appropriately. Age 25. Diffuse theta and delta activity. Vertex phenomena also noted. Note differences between panel C and D; patient in an apparently similar clinical state but EEG in C shows continuous repetitive sharp waves/spikes. These are not present in panel D.
improvement in our patient with levonorgestrel/ethinylestradiol we speculate that neurosteroid modulation may have a role in the treatment of SMC1A associated epilepsy.

The mechanism by which heterozygous truncating SMC1A variants cause the observed phenotype is unknown. The absence of reports documenting truncation SMC1A variants in men or boys, suggests that in these truncating variants may be incompatible with life — no predicted loss of function variants (such as protein truncating variants) are documented in gnomAD, indicating high constraint [20]. SMC1A is known to variably escape X-inactivation, with women shown to express twice as much SMC1A mRNA as men [21,22]. This suggests that if SMC1A largely escapes X-inactivation in those with truncating SMC1A variants, haploinsufficiency is unlikely to be the cause of the observed phenotype as these women would have the equivalent expression of SMC1A to that of a normal male. Thus, mutant SMC1A may, instead, exert a dominant negative effect. Alternatively, there may be differences in biology between males and females that mean that lower levels of SMC1A can be better tolerated by women than men. However, if X-inactivation of truncating SMC1A variants does occur to some degree, this could lead to brain function in which there is significant cellular heterogeneity in SMC1A biology, with enough cells containing sufficient SMC1A to be viable, albeit predisposed to epilepsy and neurodevelopmental disorders. Conversely, the uniform loss of SMC1A function in male fetuses carrying hemizygous protein truncating variants may have more severe consequences that cannot be tolerated.

4. Conclusion

This case broadens the spectrum of SMC1A associated epilepsy in people without CDLS and with a DEE to include an adult female with normal neurodevelopment prior to seizures starting in late childhood. Truncating SMC1A variants may be considered as a potential cause of epilepsy with seizure clusters associated with drug-resistant epilepsy, and occur in adults with normal development prior to seizure onset.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: R.H.T. reports Honoraria from Arvelle, Bial, Eisai, GW Pharma, Sanofi, UCB Pharma, UNEEG and Zogenix. R.F., M.E., D.L.-S., A.W., and M.R.B. have nothing to declare.

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