



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



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ARTICLE INFO

Article history:

Received 17 October 2021

Revised 8 May 2022

Accepted 31 May 2022

Available online 2 June 2022

Keywords:

SMC1A

Epilepsy

PCDH19

Clustering seizures

ABSTRACT

SMC1A variants are known to cause 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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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); (4–6 % of CdLS patients). CdLS encompasses a spectrum of clinical features characterized predominantly by intellectual disability, facial dysmorphism, growth restriction,

hypertrichosis, and congenital defects of the upper limbs, gastrointestinal tract, heart, and genitourinary tract [5]. Epilepsy is present in approximately 20% of people with CdLS, typically with focal-onset seizures which are relatively easily controlled with antiseizure medications [6]. CdLS attributed to variants in *SMC1A* generally manifests a milder or less classical phenotype than when attributed to variants in the most common cause, *NIPBL* [7].

More recently, protein truncating variants in *SMC1A* have been reported in association with a developmental and epileptic encephalopathy that can occur with or without midline brain defects (DEE85, OMIM: 301044). These cases are associated with a distinct phenotype of neurodevelopmental disorders and drug-resistant epilepsy but without the typical features of CdLS, or with features suggestive of Rett syndrome [3,8,9,7,10–13]. These include a case series of 10 female people with moderate to severe developmental impairment and drug-resistant seizures, which showed a clustering pattern [3]. In all these previously reported cases with epilepsy, seizures presented in early childhood and usually in infancy.

1.3 We report the case of a 28-year-old woman with drug-resistant epilepsy and normal neurodevelopment who developed seizures late, at the age of 12 years, and who carries a novel *de novo* heterozygous truncating variant in *SMC1A*.

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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, 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. At the age of 28, she underwent a neuropsychological assessment which included assessments of premorbid intellectual function and current intellectual ability (assessed using Wechsler adult intelligence scale- IV in an interictal period [15]). Her IQ was estimated to be 68 (2nd percentile) and there was particular difficulty noted with delayed recall, attention control, executive function, and verbal and category fluency. Her current therapy consists of a vagus nerve stimulator, levetiracetam 750 mg b. d. and phenytoin 175 mg b.d. with seizure recurrence every 2 to 3 weeks. Cenobamate is currently being introduced. There does not appear to have been any clear relationship between anti-seizure medications and seizure frequency. See Table 1 for a summary of seizure frequency, medication, and adjunctive treatments to date.

2.4 Multiple magnetic resonance imaging (MRI) examinations of the brain since presentation at age 12 years have been normal with a notable lack of atrophy. Positron emission tomography-computed tomography at the age of 25 years showed mild, relatively diffuse, left cerebral hemisphere

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.(Tyr1107-Ter) truncating variant in *SMC1A*, 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 *SMC1A* 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].

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 diets 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 *SMC1A* associated epilepsy and the initial

Table 1

Year	Seizure Frequency	Episodes of Status Epilepticus	Anti-Seizure Medications	Adjunctive Therapies
2005	March – first and second seizure	N		N
	April – SE	Convulsive SE	Sodium valproate and carbamazepine – stopped due to Stevens-Johnson syndrome.	
	May – “frequent seizures”	N	Topiramate – stopped due to metabolic acidosis	
	July – one generalized seizure	N	Levetiracetam	
2006	Seizure-free	N	Levetiracetam	N
2007	Predominantly seizure-free	N	Levetiracetam	N
2008	Increased seizure frequency (monthly clusters)	N	Levetiracetam	Levonorgestrel/ Ethinylestradiol
	June – SE	Convulsive SE	Levetiracetam	
	August	N	Levetiracetam and phenytoin	
	Oct – SE	Convulsive SE	Levetiracetam and phenytoin	
2009	Seizure-free		Levetiracetam and phenytoin	Levonorgestrel/ Ethinylestradiol
2010	Seizure-free		Levetiracetam and phenytoin	Levonorgestrel/ Ethinylestradiol
2011	Seizure-free		Levetiracetam and phenytoin	Levonorgestrel/ Ethinylestradiol
2012	July – one generalized seizure	N	Levetiracetam and phenytoin	Levonorgestrel/ Ethinylestradiol
2013	March – focal autonomic seizures	N	Levetiracetam and phenytoin	Levonorgestrel/ Ethinylestradiol
	July – SE	Convulsive SE	Levetiracetam and phenytoin	
	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
	Jan-July – monthly seizure clusters	N	Phenytoin and zonisamide Feb – April. Perampanel added May.	Medroxyprogesterone acetate
2014	Aug – SE	Convulsive SE	Perampanel and phenytoin	
	Sept-Dec – monthly seizure clusters	N	Perampanel and phenytoin	
	Jan-Dec – monthly seizure clusters	N	Levetiracetam and phenytoin	Medroxyprogesterone acetate Jan-April.
2015	Jan-Sept – 8 admissions with seizure clusters	Convulsive SE – Feb	Levetiracetam and phenytoin	Levonorgestrel/ Ethinylestradiol May onwards.
	Oct-Dec – 3 admissions with seizure clusters	N	Lacosamide, levetiracetam and phenytoin	Levonorgestrel/ Ethinylestradiol
2017	Jan-May – 6 admissions. 1 with a single seizure, 1 with a seizure cluster, 4 with SE	Convulsive SE – Jan, March, April, May.	Lacosamide, levetiracetam and phenytoin	
	June-July – 4 admissions. 1 with a single seizure, 3 with SE.	Convulsive SE June, July. NCSE July.	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.	Levonorgestrel/ Ethinylestradiol

(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
2019	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
	Jan – 1 admission with a single seizure.	N	Lacosamide and phenytoin	Medroxyprogesterone acetate
	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 NCSE Feb, July, Oct	Levetiracetam and phenytoin 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	VNS

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

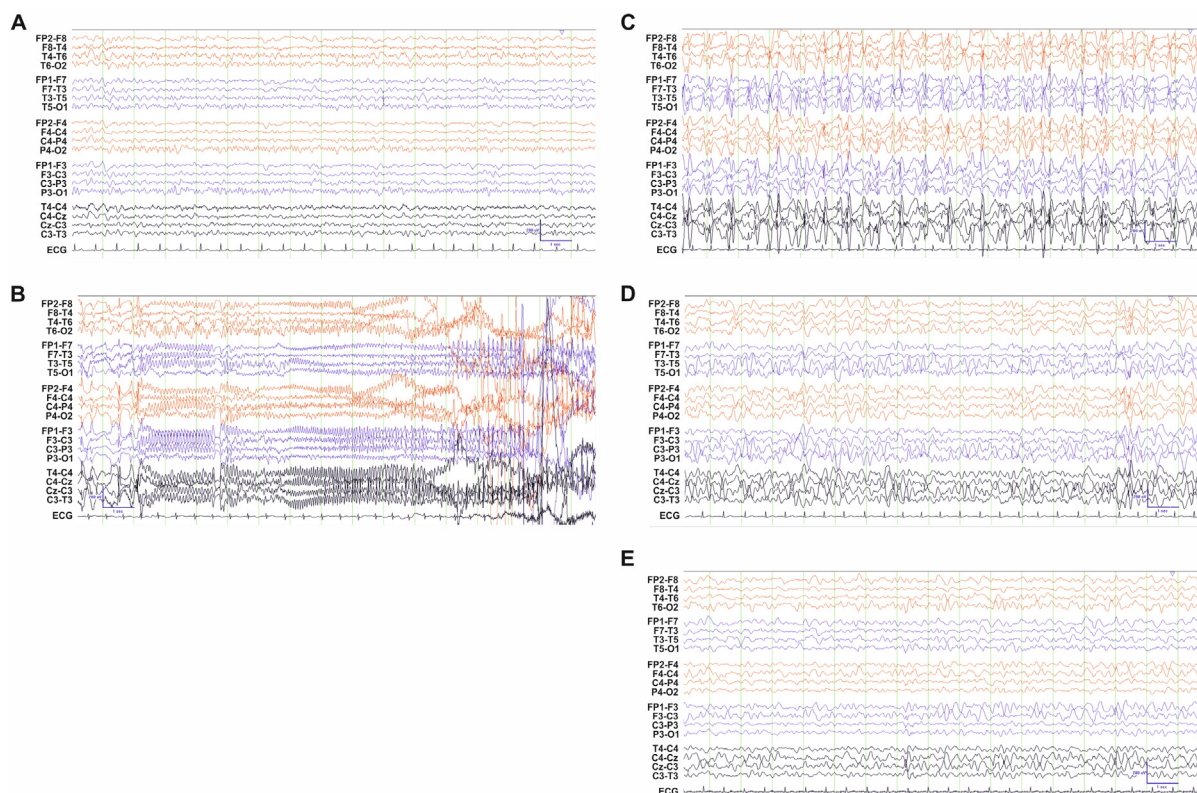


Fig. 1. EEG recording. A. Typical EEG when well. Routine EEG performed before any episodes of status, age 20. Alpha rhythm present at 10–11 Hz. B. Generalized tonic-clonic seizure occurring during a period of *status epilepticus*. Patient unresponsive. Age 26. Build-up of generalized rhythmic 10 Hz activity 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 truncating *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.

Acknowledgements

D.L.-S. is a Wellcome Clinical PhD Fellow funded through the 4ward North Clinical PhD Academy [203914/Z/16/Z]. This research was funded in whole, or in part, by the Wellcome Trust [Grant number 203914/Z/16/Z]. For the purpose of open access, the author

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