Seizure: European Journal of Epilepsy 65 (2019) 62–64

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Clinical letter

Early infantile *SCN1A* epileptic encephalopathy: Expanding the genotype-phenotype correlations

Carlotta Spagnoli[a,*], Daniele Frattini[a], Susanna Rizzi[a], Grazia Gabriella Salerno[a], Carlo Fusco[a,b]

[a] Department of Pediatrics, Child Neurology Unit, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[b] Pediatric Neurophysiology Laboratory, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

ARTICLE INFO

Keywords:
SCN1A
Early infantile epileptic encephalopathy
Movement disorder
Refractory epilepsy
Dravet syndrome

SCN1A-related disorders include Dravet syndrome (DS), genetic epilepsy with febrile seizures plus (GEFS +), and familial hemiplegic migraine as the main phenotypes [1]. However, a novel phenotype with early onset epileptic encephalopathy, profound developmental delay and an hyperkinetic movement disorder has been recently described, mainly in association with the missense mutation p.Thr226Met [2].

We report on a 6-years-old boy, born from healthy unrelated parents at 35 weeks of gestational age following uneventful pregnancy and delivery. At 20 h of life he was admitted to the neonatal intensive care unit because of stiffness, multiple contractures, hip dysplasia and talipes. He also presented with frequent episodes of tonic spasms occurring mainly in response to tactile stimuli since the first hours of life. As serial EEGs were unremarkable, hyperekplexia was suspected and clonazepam introduced with unsatisfactory results. Carbamazepine progressively controlled these episodes. Neonatal brain MRI and EMG were negative. At 8 months of age he presented with a prolonged hemiclonic seizure, followed by Todd's paralysis. He developed severe psychomotor delay with absent speech, and a severe, pharmacoresistant epileptic encephalopathy with multiple seizure types (atypical absences, focal motor and bilateral tonic-clonic seizures, episodes of myoclonic status epilepticus), with fever susceptibility. He is severely hypotonic (unable to sit) with proximal limb retractions and displays a very poor voluntary motor repertoire. From 20 months of age, he has also developed a prominent hyperkinetic movement disorder (choreoathetosis and distal myoclonic jerks, with paroxysmal exacerbations accompanied by dystonia). Follow-up EEGs demonstrate focal epileptiform discharges over the anterior regions (Fig. 1a) and a progressive deterioration of background activity (Fig. 1b) paralleling the progressive development of cortical atrophy on brain MRIs.

Negative genetic investigations include direct sequencing of: *GLRA1*, *CRFL1*, *SCN4A*, *PRRT2*, *SCN2A*, *CLCN1*, *ARHGEF9*, *SLC2A1*, *ATP1A3*, *CACNA1A*, *POLG1*, *UBE3A*, and *KCNQ2*. Array-CGH is non-contributory. He underwent an extended neurometabolic work-up: ammonia, serum and CSF lactate, urinary organic acids and mucopolysaccharides, plasma aminoacids, acylcarnitines, sialo-transferrins and very long chain fatty acids, CSF neurotransmitters, serum auto-antibodies (anti-NMDAR, LG1, CASPR and GABA2), skin and muscle biopsy (histology and mitochondrial respiratory chain activity): all normal. Clinical, genetic and brain MRI data are summarized in Table 1.

Molecular testing for the *SCN1A* gene documented the heterozygous, de novo missense c.628 T > C (p.Ser228Pro) variant, classified as likely pathogenic. Whole exome sequencing with deletions/duplications (Copy Number Variants, CNV) analysis, independently performed by a different laboratory and targeting all protein coding exons, exon-intron boundaries (± 20bps) and selected non-coding clinically-relevant variants, confirmed this finding with no additional variants in previously established disease genes. Results are validated by bidirectional direct Sanger sequencing. The variant is absent from Genome Aggregation Database, predicted to be deleterious by the in silico prediction tools SIFT and MutationTaster (while PolyPhen predicts it as tolerated) and reported in ClinVar as likely pathogenic (ID375512).

Our case shares various clinical features with early infantile *SCN1A* epileptic encephalopathy: early-onset, severe developmental encephalopathy resulting in profound developmental delay (non-verbal as

* Corresponding author at: Child Neurology Unit, Presidio Ospedaliero Provinciale Santa Maria Nuova, AUSL-IRCCS di Reggio Emilia, viale Risorgimento 80, 42123 Reggio Emilia, Italy.
E-mail address: carlotta.spagnoli@ausl.re.it (C. Spagnoli).

https://doi.org/10.1016/j.seizure.2019.01.002
Received 31 October 2018; Received in revised form 6 December 2018; Accepted 2 January 2019

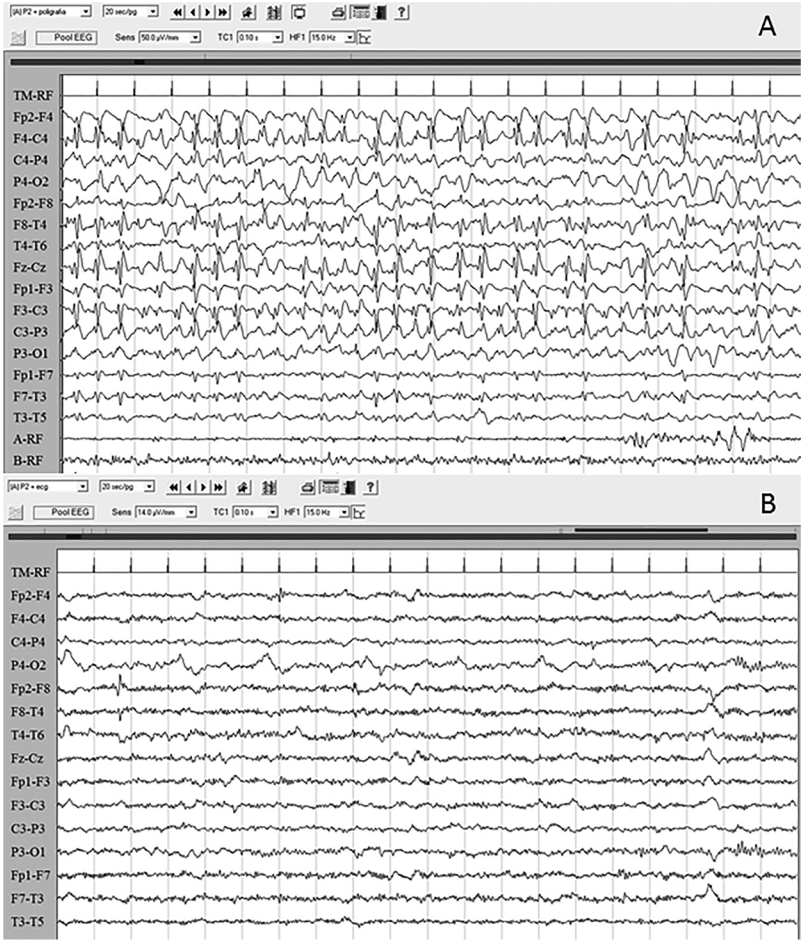

Fig. 1. Awake EEG at 2 years of age showing spike-and-wave discharges over the fronto-central regions (A). Awake EEG showing severely abnormal low-voltage background activity with superimposed fast rhythms (B).

in 8/9 cases in [2] and not sitting unsupported, due to hypotonia - unusual in DS, but encountered in 9/9 cases in [2]), pharmacoresistant epilepsy with multiple seizure types, a prominent hyperkinetic movement disorder, and non-specific neuroimaging findings (normal neonatal MRI followed by cortical atrophy, present in 2/9 in [2]).

However, there are also some differences to highlight: first, onset occurred in the first hours of life compared to the early-infantile period, and was characterized by tonic spasms mainly induced by tactile stimulation, in the absence of clear-cut EEG changes, which led to suspect hyperekplexia.

Second, the presence of diffuse stiffness, clubfeet, hip dysplasia and multiple contractures is unreported (only scoliosis/kyphoscoliosis were reported in 2/9 cases)2.

Third, our mutation is different from the ones so far associated with early infantile *SCN1A* encephalopathy. Sadleir and colleagues described a total of 9 cases, 8 carrying the c.677C > T (p.Thr226Met) variant [2], and the remaining one the c.4033C > T (p.Pro1345Ser) [2] variant. One more case (retrospectively thought to have a phenotype consistent with early-infantile *SCN1A* encephalopathy) carryied the c.1264 G > T (p.Val422Leu) variant [3].

However, our view is that the mutation we found, classified as likely pathogenic and occurring de novo, should be regarded as causative of our patient's phenotype, although with previously unreported, peculiar features when compared to early infantile *SCN1A* encephalopathy. Having performed whole exome sequencing with deletions/duplication analysis and CGH-array in addition to a targeted NGS, a contribution of additional genetic variants or CNV is to be considered unlikely, although it is not possible to completely exclude a pathogenic contribution by uncoding regions not covered by our test or by other yet undetectable epigenetic factors.

Table 1
Clinical, laboratory and neuroimaging data of our patient.

Pathogenic variant	Age at seizure onset	Seizure type at onset	Seizure types during F/U	Seizure triggers	Medication trials	Additional clinical features	Age at MD onset	Type of MD	Neurologic examination	Negative genetic investigations	Negative metabolic investigations	Brain MRI
de novo missense c.628 T > C (p.Ser228Pro)	8 mo.	hemiclonic	atypical absences, focal motor and bilateral tonic-clonic seizures, myoclonic SE	fever	Phenobarbital, vitamin B6, magnesium, clonazepam, carbamazepine, topiramate, acetazolamide, phenytoine, levetiracetam, pyridoxal-phosphate, stiripentol, valproate, nitrazepam, ketogenic diet, felbamate	Neonatal-onset tonic spasms (mainly in response to tactile stimuli), stiffnes, multiple contractures, hip dysplasia, talipes	20 mo.	hyperkinetic (choreoathetosis, distal myoclonic jerks with paroxysmal exacerbations accompanied by dystonia)	severely hypotonic (unable to sit), proximal limb retractions, very poor voluntary motor repertoire	*GLRA1*, *CRFL1*, *SCN4A*, *PRRT2*, *SCN2A*, *CLCN1*, *ARHGEF9*, *SLC2A1*, *ATP1A3*, *CACNA1A*, *POLG1*, *UBE3A*, *KCNQ2*, array-CGH	ammonia, serum and CSF lactate, urinary organic acids and mucopolysaccharides, plasma aminoacids, acylcarnitines, sialo-transferrins, VLCFA, CSF neurotransmitters, serum auto-antibodies (anti-NMDAR, LG1, CASPR and GABA2), skin and muscle biopsy	Progressive cortical atrophy

Study funding

No funding was secured for this study.

Disclosure

The authors report no disclosures.

Conflict of interest

The Authors declare that they do not have any conflict of interest to disclose and that no funding was secured for the completion of this study.

References

[1] Miller IO, Sotero de Menezes MA, et al. Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, editors. GeneReviews® [internet]. Seattle (WA): University of Washington, Seattle; 2018. p. 1993–2018. SCN1A-Related Seizure Disorders.

[2] Sadleir LG, Mountier EI, Gill D, et al. Not all SCN1A epileptic encephalopathies are Dravet syndrome: early profound Thr226Met phenotype. Neurology 2017;89:1035–42.

[3] Ohashi T, Akasaka N, Kobayashi Y, et al. Infantile epileptic encephalopathy with a hyperkinetic movement disorder and hand stereotypies associated with a novel SCN1A mutation. Epileptic Disord 2014;16:208–12.