

Electroclinical history of a five-year-old girl with *GRIN1*-related early-onset epileptic encephalopathy: a video-case study

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Received December 17, 2017; Accepted July 01, 2018

ABSTRACT – *De novo* mutations in the *GRIN1* gene have been recently reported as the molecular cause of a broad-spectrum early-onset neurological phenotype. Here, we describe a five-year-old girl with an early-onset epileptic encephalopathy associated with an infantile hyperkinetic movement disorder and oculomotor abnormalities. Whole-exome sequencing identified a novel p.Met641Leu *de novo* variant in the *GRIN1* gene as the cause of the phenotype. *In silico* analysis suggested that the p.Met641Leu variant would alter the gating property of the ion channel, with the involved methionine residue facing towards the ion pore. Long-term systematic video-EEG allowed us to report on the electroclinical history and, specifically, on the semiology of the hyperkinetic movement disorder and oculomotor abnormalities resembling oculogyric crises in our patient. Our findings and a review of the recent literature reinforce the notion of *GRIN1*-encephalopathy as a recognizable neurological phenotype that should be suspected in early-onset epilepsy associated with hyperkinetic movement disorders. [Published with video sequence on www.epilepticdisorders.com]

Key words: *GRIN1* gene, epileptic encephalopathy, oculogyric crisis, hyperkinetic movements, NMDA receptors



VIDEO ONLINE

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Early-onset epileptic encephalopathies (EOEEs) represent a group of severe neurological disorders characterized by refractory epileptiform activity, cognitive regression (or arrest), and poor prognosis

(Scheffer *et al.*, 2017). NMDA receptors are cationic channels permeable to Na⁺, K⁺, and Ca²⁺ that play a crucial role in excitatory neurotransmission throughout the central nervous system (CNS)

(Lemke *et al.*, 2016). The *GRIN1* gene encodes the GluN1 subunit, structurally involved in all NMDA receptors and recently implicated in neurodevelopmental disorders, in association with both *de novo* and biallelic variants (Lemke *et al.*, 2016; Rossi *et al.*, 2017). Although the combination of some clinical features might help in differentiating this condition from other similar epileptic encephalopathies, a specific phenotypic associated with *GRIN1*-related disorders remains to be clarified. Here, we report on detailed systematic video-EEG and clinical evolution of a patient carrying a *GRIN1* *de novo* variant, presenting with EOEE and infantile movement disorder.

Case study

The patient was a five-year-old girl born at 36 weeks of gestation from pregnancy complicated by threatened abortion. At birth, growth parameters were all within normal range. No perinatal pathology was disclosed. At 43 days of life, daily seizures appeared, characterized by unilateral eyelid and perioral myoclonus, cyanosis affecting the lips, tonic posture of the upper limbs, and clonic jerks of the lower ones, followed by facial rush, eructation, and flatulence. These seizures usually appeared after meals. At that time, the neurological examination evidenced poor reactivity to sounds and visual stimuli and axial hypotonia. Auditory and visual evoked potentials were unremarkable. By 12 months of age, the frequency of seizures significantly increased. The girl presented with sudden weeping, staring, and tonic hyperextension of the upper limbs, mainly when she was falling asleep. Throughout the following months, seizures were daily and prolonged, characterized by eye deviation and a scared gaze, generalized increased tone, and psychomotor agitation. Several antiepileptic drugs were tried such as levetiracetam, valproate, lamotrigine, carbamazepine, barbiturates, hydrocortisone, and ACTH, with poor results. At present, the patient presents with several

daily oculomotor abnormalities resembling oculogyric crises, most of which are induced by visual fixation (see *video sequence*).

Global psychomotor delay was observed early in infancy. The patient never achieved head control or the ability to sit or stand and did not gain any language skills. Severe axial hypotonia and distal dystonic posturing (mainly affecting the fists and ankles) were observed since the first months of life. She presented with choreoathetoid and stereotyped movements (see *video sequence*).

At the last examination, at five years of age, she still presented with poor reactivity to sounds and visual stimuli. The patient showed severe axial hypotonia with absent head and trunk control, as well as feeding difficulties. Dystonic posturing of the hands (claw hands), equinovarus deformity, and brisk osteotendinous reflexes were evident upon neurological examination. Brain MRI, performed at two months and three years of age, revealed non-progressive paratrigonal white matter hyperintensity with partial involvement of the tapetum and left hippocampal atrophy (*figure 1A-D*). Extensive diagnostic and metabolic work-up was unrevealing, and the patient also underwent molecular investigation including array comparative genome hybridization (array-CGH) and panel sequencing for 96 EOEE-causing genes that were both reported as normal.

Neurophysiological investigations

Normal EEG background activity was recorded at the onset of seizures with isolated and sporadic unusual spiky theta waves, mainly during quiet sleep (see *video sequence*). A neonatal electrical pattern persisted during sleep up to two months of corrected age (*figure 2A*). The onset of deterioration of EEG activity occurred at the age of two years with an appearance of unusual slow, low-voltage activities with superimposed high-voltage spikes on bilateral central regions, with no

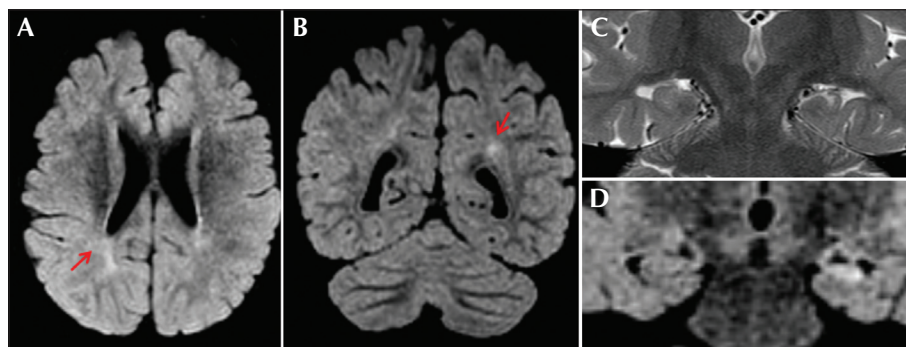


Figure 1. (A) Axial and (B) coronal fluid-attenuated inversion recovery (FLAIR) MRI images showing paratrigonal white matter hyperintensity with partial involvement of the tapetum (red arrows). (C) Coronal T2 and (D) FLAIR MRI showing left hippocampal atrophy with increased T2 signal.

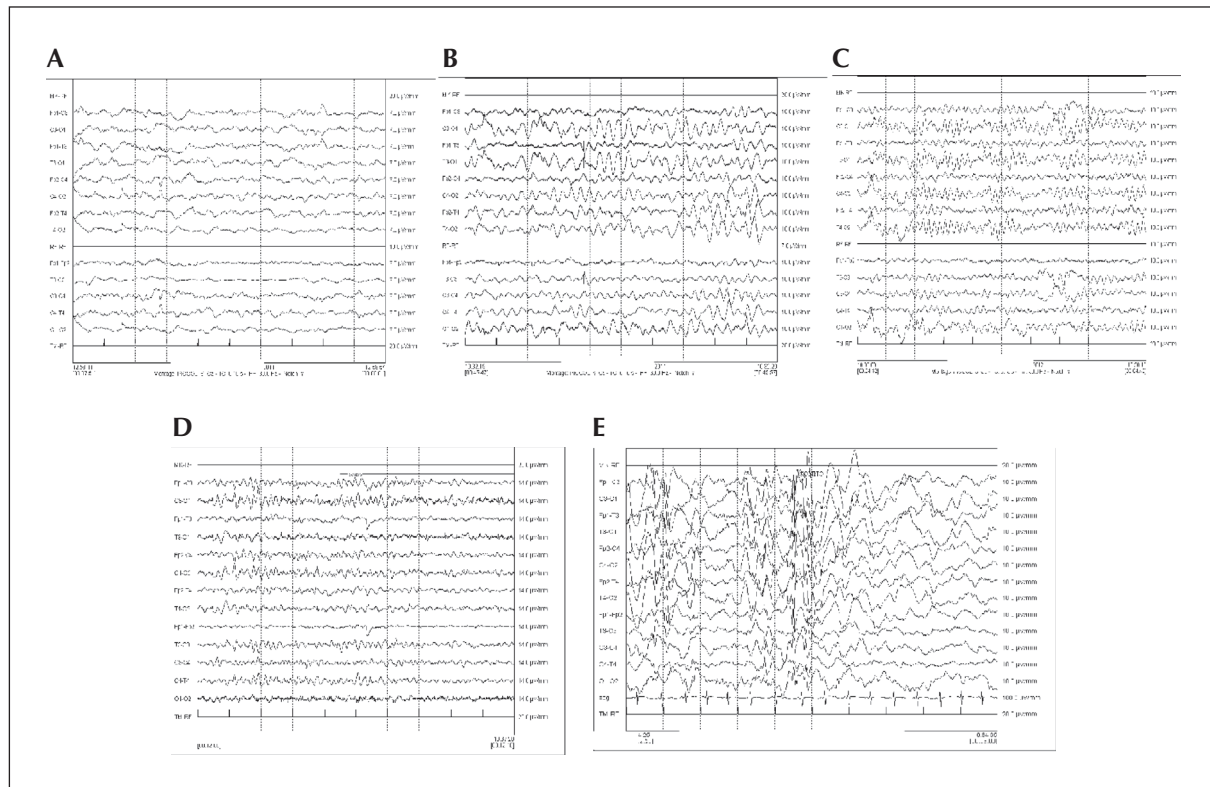


Figure 2. (A-E) Evolution of EEG in the patient: (A) quiet sleep state at 46 days of life, with diffuse and continuous slow, low-medium-voltage activity with recurrent superimposed theta sharp waves and spindle-like sequences on right fronto-central regions; (B) awake/drowsy state at three months of age, with recurrent, high-voltage delta waves on bilateral occipital regions, mostly asynchronous; (C) awake/drowsy state at 12 months of age, with recurrent, synchronous, high-voltage delta waves on bilateral posterior regions; (D) during sleep at two years of age, showing diffuse slow, low-voltage activity with isolated high-voltage spikes on bilateral central regions, with no evidence of spindles; and (E) during sleep at four years of age, showing recurrent interictal high-voltage, bilateral spike-wave discharges at 1-1.5 Hz on bilateral centro-temporal regions, followed by brief sequences of slow delta activity, interspersed with brief tracts of diffuse background slowing with a “quasi-periodic” pattern. The physiological figures of Stage 2 sleep (spindles and vertex spikes) are poorly organised.

evidence of spindles during Stage 2 sleep (figure 2B-D). At four years of age, the EEG during sleep showed recurrent, interictal, high-voltage, bilateral spike-wave discharges at 1-1.5 Hz on bilateral centro-temporal regions, followed by brief sequences of slow delta activity, interspersed with brief tracts of diffuse background slowing, with a multifocal “quasi-periodic” pattern (figure 2E).

Whole-exome sequencing

Clinical whole-exome sequencing (WES) was performed for the proband and her unaffected parents (figure 3). The Nextera Rapid Capture Enrichment kit (Illumina) was used according to the manufacturer's instructions. Libraries were sequenced with an Illumina HiSeq3000 using a 100-bp paired-end protocol. Sequence alignment with the human reference genome (UCSC hg19) and variants call and annotation were performed using an in-house pipeline, as

described elsewhere (Mencacci *et al.*, 2016). The raw data of single nucleotide variants (SNVs) and indels was then filtered. Only exonic and donor/acceptor splicing variants were considered. In accordance with the pedigree and phenotype, priority was given to rare variants (<1% in public databases, including the 1000 Genomes project, NHLBI Exome Variant Server, Complete Genomics 69, and Exome Aggregation Consortium [ExAC v0.2]) that fit a recessive or a *de novo* model and are located within genes previously associated with EOOE.

The *de novo* GRIN1 variant identified by WES in the proband (c.1921A>T; p.Met641Leu) was confirmed by traditional Sanger sequencing. The detailed conditions for sequencing analysis are available upon request.

Discussion

We report the clinical and video-EEG history of a patient presenting with EOOE, severe psychomotor

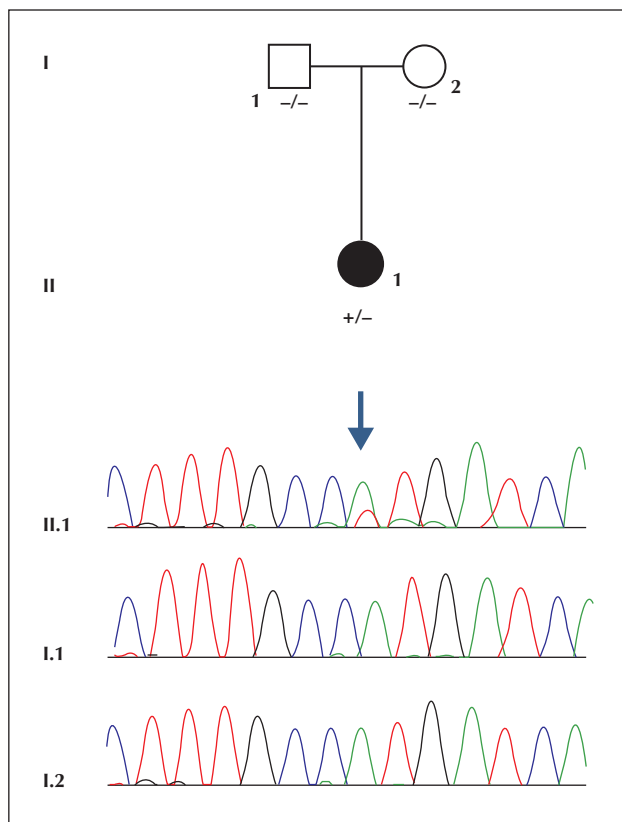


Figure 3. Clinical whole-exome sequencing (WES) for the proband (II-1) and her unaffected parents (I-1, I-2).

delay, and a complex hyperkinetic movement disorder with stereotypies, carrying a *de-novo* (novel) p.Met641Leu heterozygous variant in the *GRIN1* gene, as detected by WES trio analysis. In contrast to the majority of the reported cases, although our patient presented with neonatal-onset seizures with an early immature and atypical EEG pattern, onset of multifocal “quasi-periodic” discharges was not evidenced before the age of five years. Choreo-athetoid movements and motor stereotypies were mostly evident within infancy, but became less evident at the last visit at five years, when oculogyric crises were predominant. Global EEG background activity later became disorganized with loss of physiological sleep architecture at the age of five years. However, the onset of a multifocal “quasi-periodic” pattern and seizure worsening did not induce any neurodevelopmental and/or epileptic course modifications. According to these findings and in the light of the newly updated International League Against Epilepsy (ILAE) Classification, *GRIN1* encephalopathy might be defined as “developmental and epileptic encephalopathy” (Scheffer et al., 2017). The role of NMDAR is increasingly emphasized in neurodevelopment (Lemke et al., 2016; Chen

et al., 2017; Zehavi et al., 2017). Moreover, *GRIN1* variants are likely to affect function of both NMDA and dopamine D1 receptors, thus likely explaining the associated extrapyramidal symptoms (Lee et al., 2002). To date, more than 30 patients with *GRIN1* mutations and epilepsy have been reported; the majority with *de novo* heterozygous variants and three unrelated families with inherited homozygous variants (Ohba et al., 2015; Lemke et al., 2016; Rossi et al., 2017; Zehavi et al., 2017). Despite the core clinical phenotype including developmental delay, muscular hypotonia, hyperkinetic movements (including chorea and dyskinesia), and oculomotor abnormalities (Ohba et al., 2015; Lemke et al., 2016; Zehavi et al., 2017), some features such as epilepsy and a degree of cognitive and behavioural dysfunction appear to be relatively heterogeneous. Although 19 patients previously presented with epilepsy with a different age at onset and severity, only four patients were reported to present with unclassified EOE according to Ohba et al. (2015) and three presented with infantile spasms according to Lemke et al. (2016). Non-specific neuroradiological findings in previous patients, as in ours, did not seem to influence clinical severity.

As in our case, *de novo* pathogenic variants mostly cluster in the transmembrane domains of the gene, however, no clear-cut genotype-phenotype correlation has so far been ascertained. A variant involving the same Met641 residue (p.Met641Ile) has been previously reported in a 14-year-old male showing a different phenotype from that observed in our case. Breath-holding attacks were the main seizure type. Abnormal eye movements, tonic posture of unilateral limbs, severe intellectual disability, and hyperreflexia were further phenotypic features. Focal epileptiform discharges were evident on the EEG from the onset of seizures, at the age of three months (Lemke et al., 2016). The overlapping phenotypes of several EOEs may complicate their systematic categorization. Detailed reports of electroclinical features and evolution, as well as neurodevelopmental outcomes, are mandatory in order to define novel syndromic entities and may further support clinical work-up, parent counselling, and treatment options. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.

None of the authors have any conflict of interest to declare.

Legend for video sequence

(A) EEG recorded at the age of one month and 22 days during sleep shows diffuse and continuous slow, low-medium-voltage activity with recurrent superimposed theta sharp waves and spindle-like sequences on right fronto-central regions. (B) Oculogyric movements, sucking automatisms, and choreoathetoid and stereotyped movements of the four limbs while awake, concomitant with posterior medium-voltage, 4-5-Hz activity with no epileptiform discharges (at two years and five months). (C) Persistence of oculogyric, choreoathetoid, and stereotyped movements, associated with diffuse background slowing and artefacts, with no clear epileptiform discharges. (D) Oculomotor movements, resembling oculogyric crises (right upward eye deviation, converging movements, blinking with pupil dilation, and some opsoclonic jerks), mostly induced by visual fixation, are associated with high-voltage, bi-triphasic spikes and polyspikes on right centro-temporal-occipital regions (at five years and four months).

Key words for video research on
www.epilepticdisorders.com

Phenomenology: oculoclonic seizures, hypermotor seizure

Localization: posterior cortex (right)

Syndrome: not applicable

Aetiology: genetic disorder

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