CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Pathogenic *DNM1* Gene Variant Presenting With Unusually Nonsevere Neurodevelopmental Phenotype: A Case Report

Elaine Choi, MD, MSc, Breanne Dale, MSc, Rajesh RamachandranNair, MD, FRCPCH, FRCPC, and Resham Ejaz, MD, FRCPC, FCCMG

Correspondence
Dr. Ejaz
ejazr@mcmaster.ca

Neurol Genet 2021;7:e618. doi:10.1212/NXG.0000000000000618

Abstract

Background and Objectives

To date, all reports of pathogenic variants affecting the GTPase domain of the *DNM1* gene have a clinically severe neurodevelopmental phenotype, including severe delays or intractable epilepsy. We describe a case with moderate developmental delays and self-resolved epilepsy.

Methods

The patient was followed by our neurology and genetics teams. After clinical examination and EEG to characterize the patient's presentation, we conducted etiologic workup including brain MRI, chromosomal microarray, genetic and metabolic investigations, and nerve conduction studies. Subsequently, we arranged an Intellectual Disability Plus Trio Panel.

Results

Our patient presented with seizures at 2 days old, requiring phenobarbital. She also had hypotonia, mild dysmorphic features, and mild ataxia. Although initial workup returned unremarkable, the trio gene panel identified a de novo heterozygous pathogenic missense variant in the *DNM1* GTPase domain. Now 4 years old, she has been seizure-free for 3 years without ongoing treatment and has nonsevere developmental delays (e.g., ambulates independently and speaks 2-word phrases).

Discussion

Our case confirms that not all individuals with *DNM1* pathogenic variants, even affecting the GTPase domain, will present with intractable epilepsy or severe delays. Expanding the known clinical spectrum of dynamin-related neurodevelopmental disorder is crucial for patient prognostication and counseling.

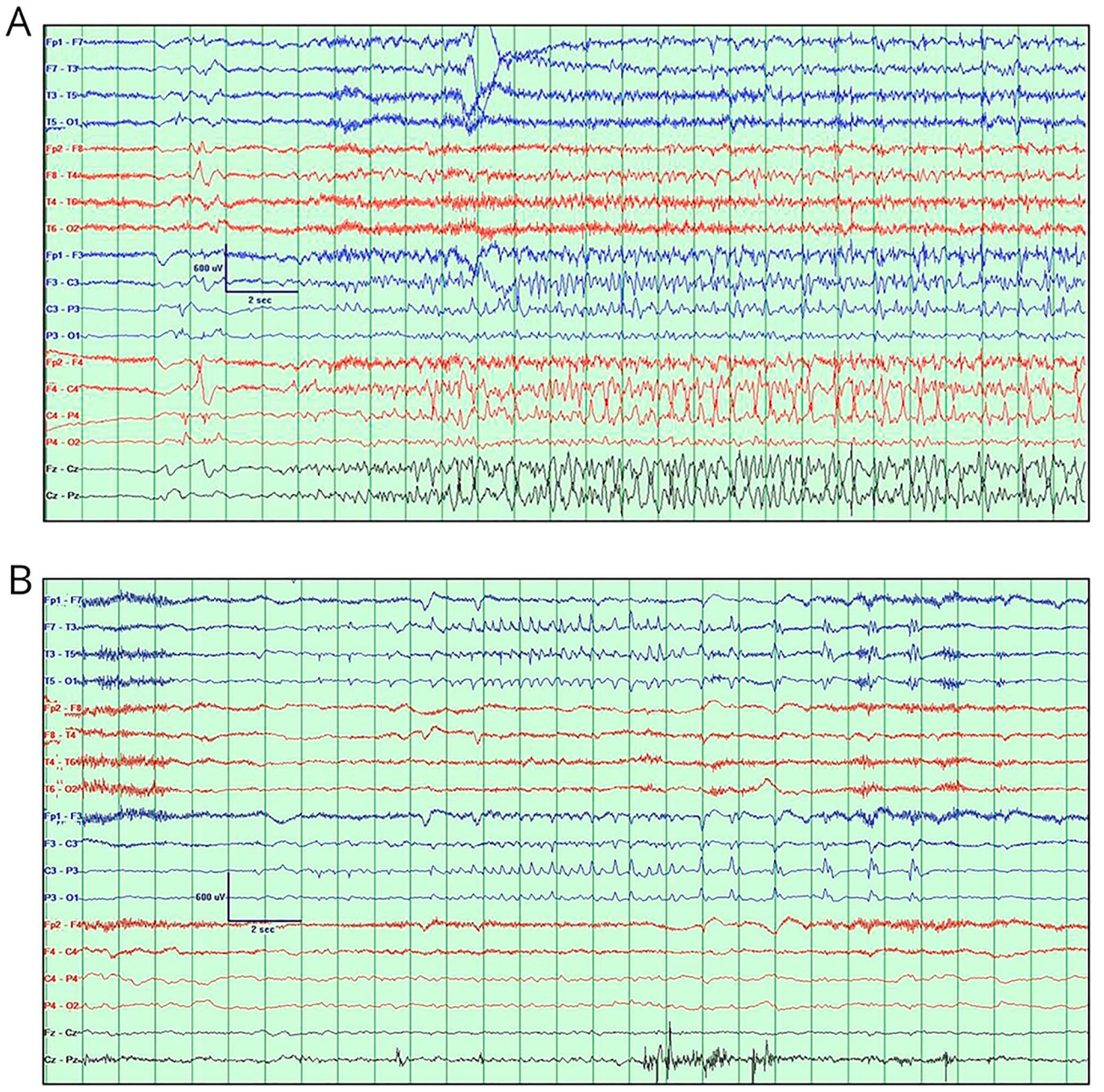
From the Division of Neurology (E.C., R.R.), and Division of Genetics (B.D., R.E.), McMaster Children's Hospital, Hamilton, ON, Canada.

Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Up to 2% of patients with developmental epileptic encephalopathies (infantile-onset refractory epilepsies with neurodevelopmental delays) have pathogenic variants in the *DNM1* gene (MIM: 616346).[1] *DNM1* encodes dynamin, a brain-expressed GTPase essential for neurotransmitter vesicle recycling after fusion with the presynaptic neuronal membrane.[2] *DNM1* has 5 domains: a GTPase domain to fuel vesicle scission, GTPase effector and middle domains for oligomerization, and pleckstrin homology and proline-rich domains for protein interactions.[2] Most reported pathogenic *DNM1* variants have dominant-negative effects on the GTPase domain,[1,3] where dysfunctional vesicle recycling results in synaptic dysfunction, leading to seizures and developmental delays.[4] All reported patients with pathogenic variants affecting the GTPase domain have severe neurodevelopmental phenotypes, with severe-to-profound intellectual disability, global developmental delay (GDD), and treatment-refractory seizures.[4,5] In 2 cases with milder phenotypes, the variants did not involve the GTPase domain.[6] We present an individual with a *DNM1* pathogenic variant affecting dynamin's GTPase domain, with a nonsevere phenotype.

Figure 1 EEG Findings



Awake EEG in anterior-posterior bipolar montage, showing (A) generalized seizure and (B) a 17-second seizure from the left temporal region.

Figure 2 Genetic Testing Findings

Read depth encompassing the missense variant (red/green squares, chr9 g.130965888G>A) in the next-generation sequencing from the patient (top) as compared with that from her parents (bottom two). Vertical gray lines indicate read depth. Horizontal blue and red lines indicate sequence reads aligned to hg19 reference genome. Original image obtained from Fulgent, edited by authors.

Methods

The individual was assessed by our neurology and genetics teams over 9 visits. We conducted prolonged EEG, brain MRI, chromosomal microarray, metabolic workup (plasma amino acids, acylcarnitines, urine organic acids, very long chain fatty acids, creatine kinase, urine creatine metabolites, and urine purines/pyrimidines), testing for Angelman and Rett syndromes, nerve conduction studies, and Intellectual Disability Plus Trio Panel (Fulgent, Temple City, CA). Parental consent to disclose was received.

Results

Our patient is a 4-year-old girl, born at term to consanguineous, healthy parents after an unremarkable pregnancy. At 2 days old, she developed weekly focal motor seizures lasting 30 seconds. By 1.5 months old, the episodes progressed to twice daily with bilateral tonic-clonic convulsions. An initial examination revealed hypotonia. Family history included 11 healthy siblings.

Prolonged EEG captured 2 seizures (Figure 1) and interictal epileptiform discharges from the left temporal region. The brain MRI was normal at 2 months old. She was started on phenobarbital. After a 1-year seizure-free period, she was weaned off phenobarbital, soon after which she experienced 2 further seizures; family declined restarting medication. Currently, she has been seizure-free for 3 years while off medication, so repeat EEG has not been conducted.

She sat unsupported, crawled, and walked at age 18 months, 2 years, and 3 years, respectively. She still used a palmar grasp at age 2 years but scribbled at 4 years. She had 2 words at age 2 years and 25 words at age 4 years, including 2-word phrases. Developmental pediatric assessment at age 3.5 years confirmed GDD, with a 12–15-month functioning. At age 4 years, she understands 2-step commands, makes eye contact, reciprocates facial expressions, waves goodbye, and plays with siblings. She uses utensils, recognizes animals, and washes hands unassisted. She is not toilet-trained and cannot copy shapes or dress herself. There have been no regressions.

At age 4 years, head circumference was 50.1 cm (73rd percentile), height 95.8 cm (9th percentile), and weight 14.1 kg (21st percentile). She had deep-set eyes, broad nose, tall

forehead, open mouth, borderline low-set ears, single palmar creases, and mildly wide-based gait.

Nerve conduction studies, repeat brain MRI at age 2 years, metabolic workup, and testing for Angelman and Rett syndromes were unremarkable. Chromosomal microarray revealed a 226-kb deletion on chromosome 6q12, likely benign. Multiple stretches of homozygosity were identified, consistent with consanguinity.

Intellectual Disability Plus Trio Panel revealed a de novo heterozygous pathogenic missense variant in *DNM1* (c.139G>A, p.Val47Met) (Figure 2).

Discussion

Our case illustrates that *DNM1* pathogenic variants do not consistently result in intractable epilepsy or severe delays. Similar to previous descriptions of *DNM1* variants,[1] our patient's presentation included seizures, hypotonia, and ataxia. However, unlike reported cases,[3] her seizures resolved without ongoing treatment, and her developmental delay is neither profound nor progressive.

Her specific variant results in a conservative amino acid change in *DNM1*'s GTPase domain. This variant has been reported in 2 other individuals, both more clinically severe. One has ongoing seizures, moderate intellectual disability, speech delay, macrocephaly, and hypotonia.[7] The other has epileptic encephalopathy, GDD, cerebellar ataxia, hypotonia, and stereotypy (ClinVar). Our patient may have milder phenotype because of various factors, including biological (e.g., potential gene interactions resulting in differential dynamin expression) and environmental (e.g., early interventions maximizing developmental potential) factors. Detailed molecular and functional analyses were not possible for this clinical report.

In summary, we report a case of nonsevere developmental delays and self-limited seizures associated with a pathogenic variant affecting the GTPase domain of *DNM1*. This study expands the clinical spectrum of dynamin-related neurodevelopmental disorders, suggesting that milder phenotypes may be underreported. Understanding the variable phenotype associated with *DNM1*, even within the same genotype, is instrumental for accurate prognostication and counseling because not all individuals have severe delays or intractable seizures.

Acknowledgment

The authors thank the patient and her parents, who provided consent for case report publication.

Study Funding

No targeted funding reported.

Disclosure

E. Choi, B. Dale, R. RamachandranNair, and R. Ejaz report no disclosures relevant to the manuscript. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* March 24, 2021. Accepted in final form June 28, 2021.

Appendix Authors

Name	Location	Contribution
Elaine Choi, MD, MSc	McMaster University, Hamilton, Ontario, Canada	Drafted the article for intellectual content
Breanne Dale, MSc	McMaster University, Hamilton, Ontario, Canada	Interpreted the data and revised the article for intellectual content
Rajesh RamachandranNair, MD, FRCPCH, FRCPC	McMaster University, Hamilton, Ontario, Canada	Interpreted the data and revised the article for intellectual content
Resham Ejaz, MD, FRCPC, FCCMG	McMaster University, Hamilton, Ontario, Canada	Interpreted the data and revised the article for intellectual content

References

1. EuroEPINOMICS-RES Consortium, Epilepsy Phenome/Genome Project, Epi4K Consortium. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. *Am J Hum Genet.* 2014;95(4):360-370.
2. Boumil R, Letts V, Roberts M, et al. A missense mutation in a highly conserved alternate exon of dynamin-1 causes epilepsy in fitful mice. *PLoS Genet.* 2010;6(8):e1001046.
3. Von Spiczak S, Helbig K, Shinde D, et al. DNM1 encephalopathy: a new disease of vesicle fission. *Neurology.* 2017;89(4):385-394.
4. Li H, Fang F, Xu M, et al. Clinical assessments and EEG analyses of encephalopathies associated with dynamin-1 mutation. *Front Pharmacol.* 2019;10:1454.
5. The Deciphering Developmental Disorders Study. Large-scale discovery of novel genetic causes of developmental disorders. *Nature.* 2015;519(7542):223-228.
6. Brereton E, Fassi E, Araujo GC, et al. Mutations in the PH Domain of DNM1 are associated with a nonepileptic phenotype characterized by developmental delay and neurobehavioral abnormalities. *Mol Genet Genomic Med.* 2018;6(2):294-300.
7. Bowling K, Thompson M, Amaral M, et al. Genomic diagnosis for children with intellectual disability and/or developmental delay. *Genome Med.* 2017;9(1):43.