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Epileptic Disorders

CLINICAL COMMENTARY

Abnormal axonal development and severe epileptic phenotype in Dynamin-1 (DNM1) encephalopathy

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Abstract

Dynamin-1 (DNM1) is involved in synaptic vesicle recycling, and *DNM1* mutations can lead to developmental and epileptic encephalopathy. The neuroimaging of DNM1 encephalopathy has not been reported in detail. We describe a severe phenotype of DNM1 encephalopathy showing characteristic neuroradiological features. In addition, we reviewed previously reported cases who have *DNM1* pathogenic variants with white matter abnormalities. Our case presented drug-resistant seizures from 1 month of age and epileptic spasms at 2 years of age. Brain MRI showed no progression of myelination, progression of diffuse cerebral atrophy, and a thin corpus callosum. Proton magnetic resonance spectroscopy showed a decreased N-acetylaspartate peak and diffusion tensor imaging presented with less pyramidal decussation. Whole-exome sequencing revealed a recurrent de novo heterozygous variant of *DNM1*. So far, more than 50 cases of DNM1 encephalopathy have been reported. Among these patients, delayed myelination occurred in two cases of GTPase-domain DNM1 encephalopathy and in six cases of middle-domain DNM1 encephalopathy. The neuroimaging findings in this case suggest inadequate axonal development. DNM1 is involved in the release of synaptic vesicles with the inhibitory transmitter GABA, suggesting that GABAergic neuron dysfunction is the mechanism of refractory epilepsy in DNM1 encephalopathy. GABA-mediated signaling mechanisms play important roles in axonal development and GABAergic neuron dysfunction may be cause of white matter abnormalities in DNM1 encephalopathy.

KEYWORDS

axonal development, delayed myelination, developmental epileptic encephalopathy, DNM1, hypomyelination, white matter abnormalities

1 | INTRODUCTION

Developmental and epileptic encephalopathy (DEE) has been shown to be caused by various genetic abnormalities due to the widespread use and technological development of whole-exome sequencing.[1,2] Dynamin-1 (DNM1) is involved in synaptic vesicle recycling and plays an important role in clathrin-mediated endocytosis and neurotransmitter release into the synaptic cleft. Since *DNM1* was reported to be a causative gene for DEE in 2014,[1] a series of case reports

have emerged, establishing DNM1 encephalopathy as a new disease concept.[2,3] The *DNM1* gene is divided into five domains: the GTPase domain, middle domain, pleckstrin-homology (PH) domain, GTPase effector domain (GED), and proline-rich domain (PRD). Among the five domains, mutations have been reported in the GTPase, middle, and PH domains, and cases with DEE phenotypes are those with mutations in the GTPase and middle domains. Pathogenic *DNM1* variants have dominant-negative effects[1,3] and presents with drug-resistant epilepsy (mainly infantile epileptic spasm syndrome) from the neonatal period and early infancy.[2,3] Classical DNM1 encephalopathy is characterized by various neurological symptoms such as severe or profound developmental delay, hypotonia, and movement disorders.[1–3] The neuroimaging of DNM1 encephalopathy has not been reported in detail. We report the characteristic neuroimaging of DNM1 encephalopathy with delayed myelination and summarized previous reported cases with white matter abnormalities.

2 | CASE PRESENTATION

The pregnancy course was uneventful, and the patient was born at 42 weeks age of gestation without asphyxia. The birth weight was 3300 g. There were no apneic episodes and seizure in the neonatal period. There was no family history of epilepsy. Echocardiography revealed an atrial septal defect. She presented with clonic and tonic seizures at 1 month of age. Interictal EEG at 2 months of age showed multifocal irregular spikes and polyspikes. At 2 months of age, oral feeding was maintained, and there were no other abnormal neurological findings including cranial nerve functions and reflexes except for generalized muscle hypotonia without decreased muscle strength. She acquired fixation at 4 months but has not acquired vision pursuit since then. As for the motor function, she never acquired neck control. At 6 months, she developed swallowing difficulty during feeding, but her swallowing function did not deteriorate significantly. At 8 months, she started weaning food and was able to eat normal food at 1 year of age. The seizures were resistant to various antiepileptic medications including adrenocorticotropic hormone therapy and ketogenic diet. Blood testing, CSF analysis, metabolic screening, and funduscopy showed no abnormal findings. Chromosomal examination including G-banding showed 46, XX and array-comparative genomic hybridization failed to achieve a definite diagnosis. Brain MRI at 2 months showed no structural abnormalities in the brainstem and cerebellum, and only the brainstem and posterior limb of the internal capsule were myelinated, suggesting hypomyelination (Figure 1). The corpus callosum and anterior commissure were hypoplastic, and the length and width of the olfactory bulb were 3 mm and 4 mm, respectively. Auditory brainstem responses showed mild to moderate sensorineural deafness: The hearing thresholds in her left and right ears were 50 and 40 dB, respectively, with a prolonged V wave in both ears. At 2 years and 3 months of age, epileptic spasms in clusters appeared. Interictal EEG showed multifocal irregular spikes and polyspikes. Epileptic spasms occurred with generalized slow waves and superimposed fast activity, followed by voltage attenuation (Figure 2). Based on this EEG pattern, the patient was diagnosed with late-onset epileptic spasms. In addition to epileptic spasms, she presented with other seizures such as focal seizure and generalized tonic–clonic seizures (Figure 2). Follow-up MRI showed slight progression of myelination but marked delayed myelination. Progression of diffuse cerebral atrophy and a thin corpus callosum were observed (Figure 1). Proton magnetic resonance spectroscopy (MRS) detected a decreased N-acetylaspartate (NAA) peak consistently at 1, 2, 3, and 14 years of age (Figure 1). Diffusion tensor imaging presented with less pyramidal decussation (Figure 1). ^{18}F-fluorodeoxyglucose positron emission tomography revealed hypermetabolism in the bilateral frontal lobes (Figure 1). After obtaining approval from the institutional ethical committee and informed consent from the family, whole-exome sequencing identified a heterozygous *DNM1* splice-site variant in the middle domain (c.1197-8G > A). This variant was not observed in the parents and was considered de novo. This variant was classified as the pathogenic cause of this patient's condition, based on the American College of Medical Genetics variant classification guideline. Although there was no developmental regression from middle childhood to early adolescence, her development did not improve. Oral intake was maintained, and she did not require tube feeding. There were no abnormal neurological findings other than hypotonia. Although she has hypotonia, she has normal deep tendon reflexes and response to pain. Moreover, she does not have muscular atrophy and lingual fasciculations. She remained with refractory epilepsy and had profound intellectual disability at 14 years of age.

3 | DISCUSSION

The presented patient showed clinical features of DEE from early infancy and was considered to have a severe phenotype. In DNM1 encephalopathy, epileptic spasms develop in early infancy; however, the present patient showed late-onset epileptic spasms, which have not been reported previously, indicating the possibility of a variety of epileptic seizure types in DNM1 encephalopathy. Her MRI showed delayed myelination and decreased NAA

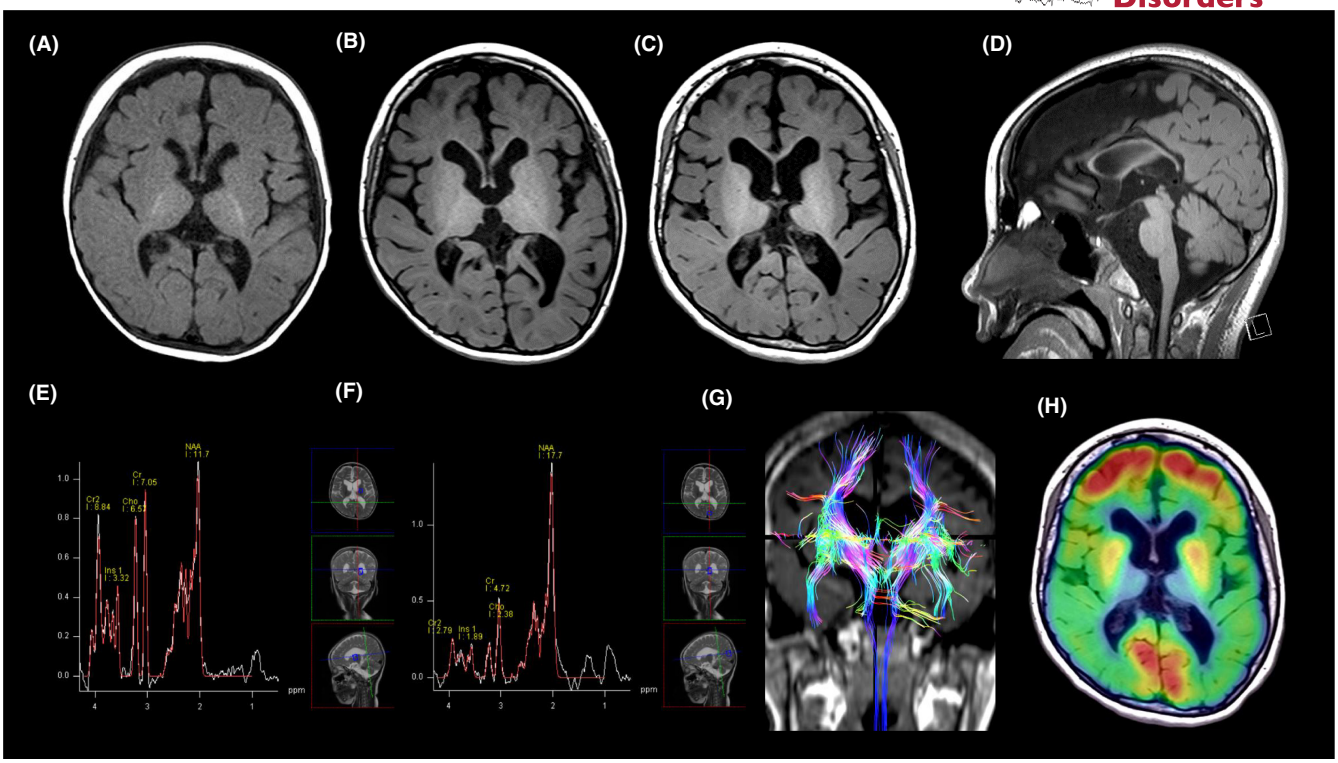

FIGURE 1 Neuroimaging of the presented patient. T1-weighted brain MRI shows hypomyelination at 5 months (A), 3 years (B), and 6 years (C), respectively. Moreover, a thin corpus callosum is revealed on the sagittal sequence (D). Magnetic resonance spectroscopy shows a decreased N-acetylaspartate peak (NAA) peak without an elevated choline peak in the basal ganglia (E), but an increased NAA peak on the occipital lobe (F). Diffusion tensor imaging shows less pyramidal decussation (G). Interictal ^{18}F-fluorodeoxyglucose positron emission tomography shows hyperaccumulation in the bilateral prefrontal and occipital regions, but hypoaccumulation in other regions (H).

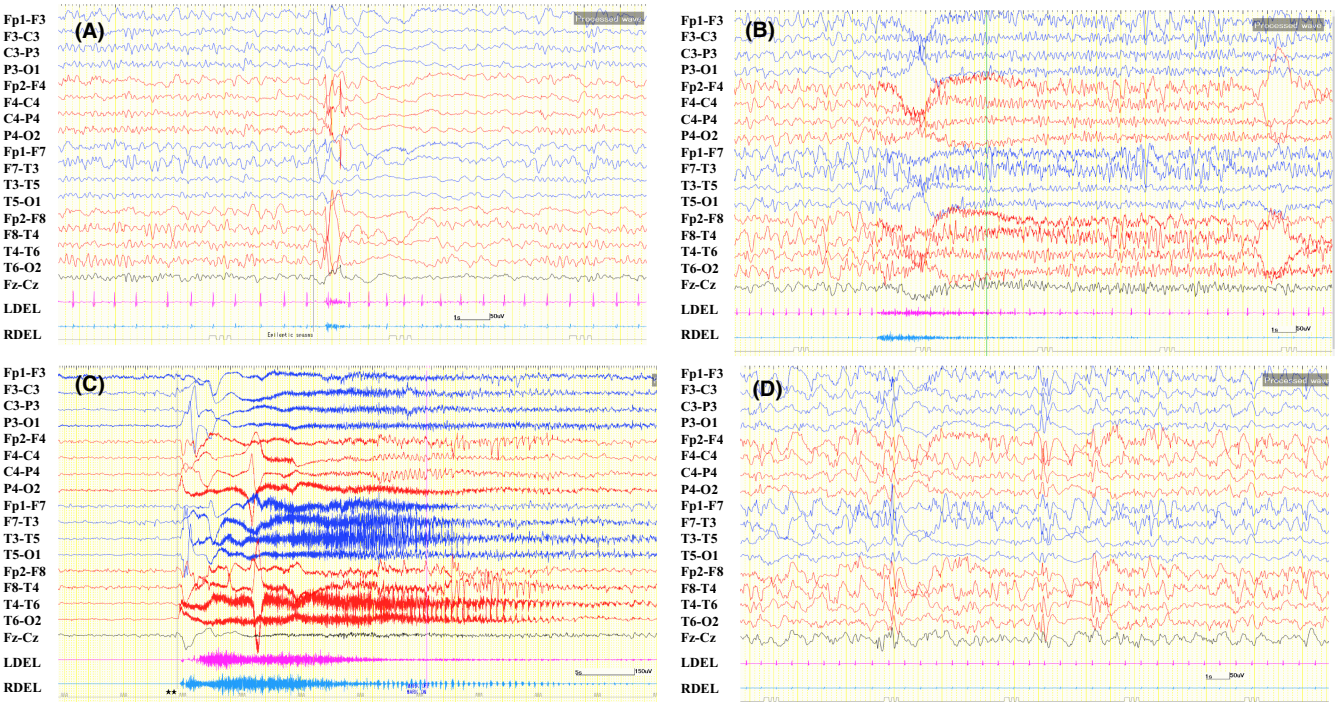

FIGURE 2 EEG findings of the presented patient. Ictal EEG findings showed irregular slow waves followed by generalized attenuation, which is indicative of epileptic spasms at the age of 3 years (A). Moreover, rhythmic slow waves originate from the frontal region in focal seizures (B), and generalized spikes and waves continue in generalized tonic–clonic seizures (C). Interictal EEG findings demonstrate frequent multifocal widespread spikes and polyspikes at the age of 6 years (D).

peak on MRS. Hyperaccumulation of bilateral frontal lobe on FDG-PET indicates the intensity of epileptogenicity. In addition, this case presented with less pyramidal decussation in diffusion tensor imaging, suggesting abnormal axonal development.

More than 50 cases of DNM1 encephalopathy have been reported to date.[4] To the best of our knowledge, eight cases, including our case, have been reported with white matter abnormalities such as delayed myelination or hypomyelination.[2,5–9] While two cases with GTPase-domain mutations show white matter abnormalities,[2,5] six cases with middle-domain mutations have been reported,[5–9] suggesting a relationship between the site of gene mutation and the presence of white matter abnormalities. However, there were cases of GTPase- and middle-domain pathogenic variants without delayed myelination, suggesting the presence of factors other than the mutated region. The c.1197-8A > G variant observed in this case was first reported by Devanna et al.[10] in a patient with severe intellectual disability, severe psychomotor retardation, epilepsy, and severe hypotonia. White matter abnormalities were reported in two cases with c.1197-8G > A, with one presenting as dysmyelination[8] and the other as delayed myelination.[9] However, not all patients with c.1197-8G > A exhibit white matter abnormalities.

There is no report to date that mentions the pathogenesis of delayed myelination in DNM1 encephalopathy. DNM1 is involved in the release of synaptic vesicles with the inhibitory transmitter GABA,[11] suggesting that GABAergic neuron dysfunction is the mechanism of refractory epilepsy. In various neurological diseases that cause epilepsy, changes in the synaptic ratio of excitatory/inhibitory afferents are involved in epileptogenicity.[12] Interestingly, a recent study on DNM1 using zebrafish strongly demonstrated that the *dnm1a* gene plays a role in both axon and synapse formation.[13] The primary transcript expressed in the human brain has been shown to be exon 10a, not exon 10b, and variants causing severe disease affect exon 10a in the DNM1a isoform.[9] In addition, it has also been reported that c.1197-8G > A, as seen in this case, affects exon 10a and presents a clinical picture of typical DEE of DNM1 encephalopathy.[9] Recent studies have demonstrated that GABA-mediated signaling mechanisms play important roles in the development and function of oligodendrocyte precursor cells, and GABA receptors have been indicated to be involved in the maturation and myelination of oligodendrocytes.[14,15] In DNM1 encephalopathy, abnormal synaptic vesicle fission may cause GABAergic neuron dysfunction, which may be the cause of delayed myelination. However, mutations at the same site do not always result in delayed myelination, and epigenetic factors other than genetic mutations may be involved. Characteristically, this case also showed less pyramidal decussation in diffusion tensor imaging. Axonal pathfinding has progressed not only during embryonic period but also after birth. Moreover, fetal and neonatal hypocalcemia is known to impair axonal growth and synapse synaptogenesis, resulting in clinical symptoms.[16] Generally, axonal growth requires neurofilaments and microtubules, which are produced within the neuron and transported distally by axoplasimic flow.[16] The corticospinal tract is typically bilateral at birth and progresses to a predominantly unilateral crossed projection in early childhood.[17] Therefore, the decreased pyramidal decussation in this case may indicate that the formation of axons and synapses was impaired by the DNM1a variant and that motor neurons running in the corticospinal tract did not develop normally. One case of MRS has been reported in which choline was increased compared with the NAA peak and demyelination was suspected to be involved.[8] In our case, the patient consistently showed a decreased NAA peak without an increase in the choline or lactate peaks during the course of the disease, and insufficient axonal development as well as delayed myelination may be associated with the pathogenesis of DNM1 encephalopathy.

This case report has a limitation. Among cases with the same variant, some cases exhibited white matter abnormalities, but some did not; we were unable to thoroughly discuss the reasons for this variability.

4 | CONCLUSION

We present a severe case of a female patient with DNM1 encephalopathy who had recurrent mutations in the middle domain of *DNM1*. Her neuroimaging revealed characteristic findings such as delayed myelination and less pyramidal decussation. White matter abnormalities have been reported in several cases of DNM1 encephalopathy, and more frequently in those with middle-domain mutations than in cases with GTPase-domain mutations. In DNM1 encephalopathy, abnormal GABA signaling is thought to underlie the pathogenesis and may affect myelination and axonal development.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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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;95:360–70.
2. Epi4K Consortium. De novo mutations in SLC1A2 and CACNA1A are important causes of epileptic encephalopathies. Am J Hum Genet. 2016;99:287–98.
3. Nakashima M, Kouga T, Lourenço CM, Shiina M, Goto T, Tsurusaki Y, et al. De novo DNM1 mutations in two cases of epileptic encephalopathy. Epilepsia. 2016;57:e18–23.
4. Kim J, Teng LY, Shaker B, Na D, Koh HY, Kwon SS, et al. Genotypes and phenotypes of DNM1 encephalopathy. J Med Genet. 2023;109233:1076–83.
5. Allen NM, Conroy J, Shahwan A, Lynch B, Correa RG, Pena SD, et al. Unexplained early onset epileptic encephalopathy: exome screening and phenotype expansion. Epilepsia. 2016;57:e12–7.
6. von Spiczak S, Helbig KL, Shinde DN, Huether R, Pendziwiat M, Lourenço C, et al. DNM1 encephalopathy: a new disease of vesicle fission. Neurology. 2017;89:385–94.
7. Kolnikova M, Skopkova M, Ilencikova D, Foltan T, Payerova J, Danis D, et al. DNM1 encephalopathy - atypical phenotype with hypomyelination due to a novel de novo variant in the DNM1 gene. Seizure. 2018;56:31–3.
8. Sahly AN, Krochmalnek E, St-Onge J, Srour M, Myers KA. Severe DNM1 encephalopathy with dysmyelination due to recurrent splice site pathogenic variant. Hum Genet. 2020;139:1575–8.
9. Parthasarathy S, Ruggiero SM, Gelot A, Soardi FC, Ribeiro BFR, Pires DEV, et al. A recurrent de novo splice site variant involving DNM1 exon 10a causes developmental and epileptic encephalopathy through a dominant-negative mechanism. Am J Hum Genet. 2022;109:2253–69.
10. Devanna P, van de Vorst M, Pfundt R, Gilissen C, Vernes SC. Genome-wide investigation of an ID cohort reveals de novo 3'UTR variants affecting gene expression. Hum Genet. 2018;137:717–21.
11. Asinof S, Mahaffey C, Beyer B, Frankel WN, Boumil R. Dynamin 1 isoform roles in a mouse model of severe childhood epileptic encephalopathy. Neurobiol Dis. 2016;95:1–11.
12. Sarnat HB, Flores-Sarnat L. Excitatory/inhibitory synaptic ratios in Polymicrogyria and down syndrome help explain Epileptogenesis in malformations. Pediatr Neurol. 2021;116:41–54.
13. Bragato C, Pistocchi A, Bellipanni G, Confalonieri S, Balciunie J, Monastra FM, et al. Zebrafish dnm1a gene plays a role in the formation of axons and synapses in the nervous tissue. J Neurosci res. 2023;101:1345–59.
14. Serrano-Regal MP, Bayón-Cordero L, Ordaz RP, Garay E, Limon A, Arellano RO, et al. Expression and function of GABA receptors in myelinating cells. Front Cell Neurosci. 2020;14:256.
15. Moura DMS, Brennan EJ, Brock R, Cocas LA. Neuron to oligodendrocyte precursor cell synapses: protagonists in oligodendrocyte development and myelination, and targets for therapeutics. Front Neurosci. 2022;15:779125.
16. Sarnat HB. Axonal pathfinding during the development of the nervous system. Ann Child Neurol Soc. 2023;1:13–23.
17. Kaye HL, Gersner R, Boes AD, Pascual-Leone A, Rotenberg A. Persistent uncrossed corticospinal connections in patients with intractable focal epilepsy. Epilepsy Behav. 2017;75:66–71.

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