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DNM1 encephalopathy – atypical phenotype with hypomyelination due to a novel *de novo* variant in the *DNM1* gene

Miriam Kolnikova[a,1], Martina Skopkova[b,1], Denisa Ilencikova[c], Tomas Foltan[a], Jaroslava Payerova[a], Daniel Danis[b], Iwar Klimes[b], Juraj Stanik[b,c], Daniela Gasperikova[b,*]

[a] Department of Pediatric Neurology, Medical Faculty of Comenius University and Children Faculty Hospital, Bratislava, Slovakia
[b] Laboratory of Diabetes and Metabolic Disorders, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
[c] Department of Pediatrics, Medical Faculty of Comenius University and Children Faculty Hospital, Bratislava, Slovakia

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1. Introduction

Epileptic encephalopathies due to mutations in the *DNM1* gene are a new severe childhood neurologic disorder typically characterized by intractable epilepsy beginning with infantile spasms, developmental delay and movement disorder [1]. The *DNM1* gene (MIM 602377, 9q34.11, NM_004408.3, 22 exons, 864 amino acids) encodes dynamin 1, a GTPase which plays a crucial role in the catalysis of clathrin-mediated endocytosis and synaptic vesicle recycling. DNM1 is organized into five domains: a) a G domain that binds and hydrolyzes GTP; b) a middle domain that is involved in oligomerization; c) a pleckstrin homology domain; d) a GTPase effector domain, and e) a proline-rich domain. During receptor-mediated endocytosis, dynamin molecules assemble into tetramers and form helical polymers at the necks of budding vesicles. Upon GTP hydrolysis, the DNM1 helices undergo a conformational change that leads to membrane constriction and scission of the vesicles from the membrane. Defective recycling causes depletion of GABA-containing synaptic vesicles resulting in decreased inhibitory neurotransmission in mice [2]. To date, 27 patients from 26 families with epileptic encephalopathy carrying *DNM1* mutations have been described in the literature (Suppl. Table). Seventeen different *de novo* missense mutations with autosomal dominant inheritance have been reported so far. Eight of the 27 patients had the recurrent p.Arg237Trp mutation (Suppl. Table).

Here we describe a case of a patient with an encephalopathy due to a novel *de novo* in frame-insertion in the *DNM1* gene.

2. Case description

We report a girl from the 3rd low-risk pregnancy, born in the 40th week of gestation (birth weight 4030 g, birth length 53 cm, Apgar score 5/8/10) requiring a short-term ventilation support after the birth. Multifocal myoclonus and tonic seizures were present since the 1st day of life treated with phenobarbital. EEG was without epileptiform discharges. Myoclonus persisted and infantile spasms manifested from the 6th week of life. The EEG showed an abnormal activity of background, irregular sharp waves and spike and waves complexes followed by attenuation. Next treatment started at the 2nd month of life and included valproate, levetiracetam, and clobazam gradually. The evolution of EEG changes is shown in Fig. 1A and B. Later, at 10 months of age, nonepileptic myoclonic jerks were dominant, both isolated and generalized, shown on several EEG recordings (Fig. 1C). Hypomyelinating leukoencephalopathy and ventriculomegaly were visible since the 6th month of age on the MRI. At the age of 4

* Corresponding author at: DIABGENE & Laboratory of Diabetes and Metabolic Disorders, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences Dubravska cesta 9, 84505, Bratislava, Slovakia.
E-mail address: daniela.gasperikova@savba.sk (D. Gasperikova).
[1] Equally contributed.

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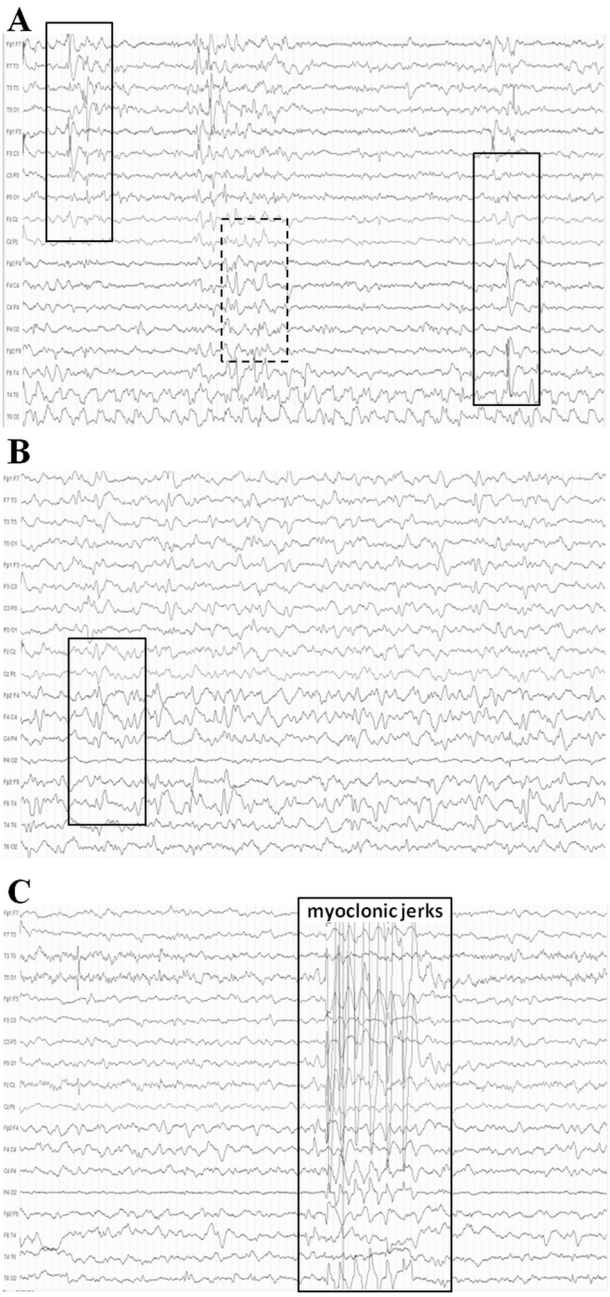

Fig. 1. Electroencephalogram of the proband on various occasions. A. EEG at the age of 2 months: abnormal activity of background, irregular sharp waves (dashed frame) and spike and waves complexes (solid frame) followed by attenuation, predominant over the right hemisphere; B. EEG at the age of 6 months: interictal EEG complexes of sharp and slow waves (frame), abnormal background, and right-side asymmetry; C. Ictal EEG during non-epileptic general myoclonic jerks at the age of 2 years (frame).

years, her brain myelination status matched to a healthy child aged 10 months (Fig. 2).

Currently, at the age of 5 years, she suffers from profound psychomotor developmental delay, without verbal expression, unable to roll over or sit alone. Due to problems with feeding a percutaneous endoscopic gastrostomy was inserted. Sever hypotonic syndrome with hyporeflexia remained unchanged since birth. Generalized myoclonic jerks in series are present along with nocturnal tonic seizures.

With the aim of identification of the etiology of the disease, we have performed a selective metabolic screening including

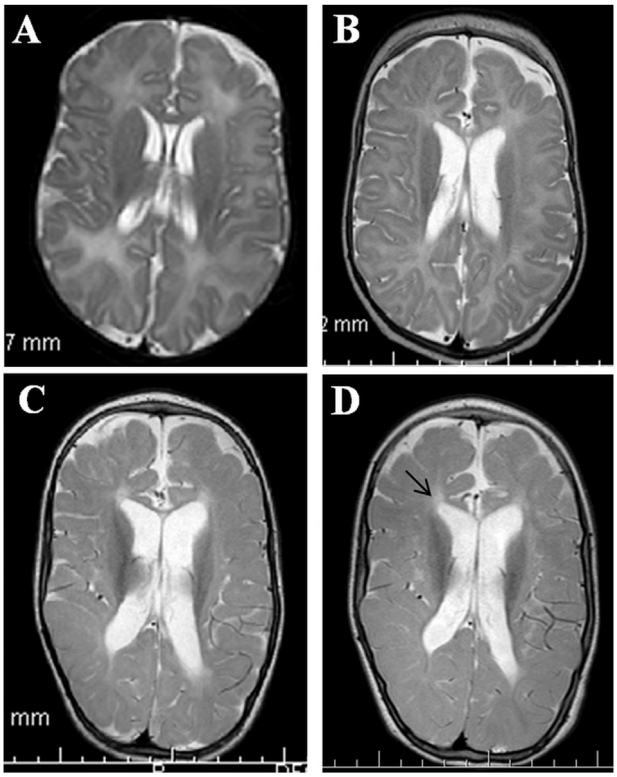

Fig. 2. MRI of the proband at the age of 6 weeks, 6 months, 27 months, and 4 years respectively. A. MRI (T2W TSE NEO) at age of 6 weeks, myelination of white matter corresponds to the 1st month, leukoencephalopathy in frontal and occipital areas without acute changes; B. MRI (T2W) at the age of 6 months, white matter myelination is slightly delayed – corresponds to the 2nd–3rd month of life; C. MRI (T2W) at the age of 27 months, myelination corresponds to the 6th–7th month of life; D. MRI (T2W) at the age of 4 years: white matter myelination significantly delayed, corresponds to the 10th month of life, periventricular leukoencephalopathy is discernible (arrow). Ventriculomegaly was present from 6 months (B–D).

cerebrospinal fluid evaluation, TORCH screening, and DNA analysis to exclude spinal muscular atrophy type I; all with negative results. Arylsulphatase-A enzyme testing was negative, and dermal fibroblast examination showed normal mitochondrial enzyme activities.

Whole exome sequencing of the patient's DNA revealed the presence of an in-frame insertion c.1089_1090insCTTCCA in exon 8 of the *DNM1* gene (NM_004408.3) in the heterozygous state. This mutation should cause an insertion of leucine and proline between Asn363 and Arg364 (p.Asn363_Arg364insLeuPro) in the middle domain of the protein. Parental analysis of exome 8 revealed the *de novo* nature of the patient's mutation (confirmed by paternity testing). Variant c.1089_ 1090insCTTCCA was not described in the literature and is not included in public population databases (dbSNP150, EVS, ExAC).

3. Discussion

We have found a novel *de novo* variant in the *DNM1* gene in a girl with the infantile epileptic encephalopathy. Since the *DNM1* gene came as a candidate from a study of *de novo* mutations in large cohorts of epileptic patients [3], together 28 patients from 27 families with 18 different pathogenic variants (including our patient) have been described (Suppl. Fig.). All pathogenic variants found in the *DNM1* patients so far were missense mutations created *de novo*. Our patient has a novel *DNM1* variant, the first in-frame insertion identified until now in the *DMN1* gene. The *DNM1* gene has a high gene constraint Z-score = 5.97 and maximal

loss-of-function intolerance probability score pLI = 1.0, indicating extremely high intolerance to both missense and loss-of-function variants [4]. Together with its *de novo* nature and the specific phenotype matching with other *DNM1* patients, we consider this variant most likely pathogenic.

Our patient has one of the most severe forms of *DNM1* encephalopathy when compared to other reported patients. In the recent Spiczak study [1] only one in 21 patients had delayed myelination on MRI. The location of his mutation was in the middle domain of the dynamin 1. This could be attributed to the in-frame insertion that might have a stronger impact on the protein structure than missense mutations. The previously reported mutations were found mainly in the GTPase domain (Suppl. Fig.); six mutations, including the one found in our patient, are located in the middle domain. Comparing the clinical course of reported cases, patients with middle domain *DNM1* mutations seem to have a more atypical phenotype. The symptom of epilepsy is variable and in two patients, including ours, we found a non-epileptic myoclonus and delayed myelination on MRI. Moreover, the severity of features can be influenced by other genetic or environmental factors [1,3].

In our case, hypomyelination was an important MRI feature since the first year of life of the patient, while it was reported in only two other *DNM1* patients [1].

In conclusion, in conjunction with prior reports (Suppl. Table) we suggest that mutations in the *DNM1* gene cause a severe form of epileptic encephalopathy including the serious global developmental delay of variable severity, hypotonia, non-epileptic myoclonus and possible serious changes on MRI.

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Contribution statement

All authors contributed to the study design and reviewed the manuscript critically and approved the final version. M.K. and M.S. researched data and wrote the manuscript; D.I., T.F, J.P.and D.D. researched data, and I.K., J.S, and D.G. reviewed/edited the manuscript.

Disclosure statement

The authors have nothing to disclose.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2018.01.020.

References

[1] von Spiczak S, Helbig KL, Shinde DN, Huether R, Pendziwiat M, Lourenco C, et al. DNM1 encephalopathy: a new disease of vesicle fission. Neurology 2017;89:385–94.
[2] Ferguson SM, De Camilli P. Dynamin, a membrane-remodelling GTPase. Nat Rev Mol Cell Biol 2012;13:75–88.
[3] Appenzeller S, Balling R, Barisic N, Baulac S, Caglayan H, Craiu D, et al. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. Am J Hum Genet 2014;95:360–70.
[4] Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60, 706 humans. Nature 2016;536:285–91.

Web resources

dbSNP150: http://www.ncbi.nlm.nih.gov/SNPEVS:http://evs.gs.washington.edu/EVSExAC:http://exac.broadinstitute.org.