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A Rasmussen encephalitis, autoimmune encephalitis, and mitochondrial disease mimicker: expanding the *DNM1L*-associated intractable epilepsy and encephalopathy phenotype

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ABSTRACT – Dynamin-1-like protein (*DNM1L*) gene variants have been linked to childhood refractory epilepsy, developmental delay, encephalopathy, microcephaly, and progressive diffuse cerebral atrophy. However, only a few cases have been reported in the literature and there is still a limited amount of information about the symptomatology and pathophysiology associated with pathogenic variants of *DNM1L*. We report a 10-year-old girl with a one-year history of mild learning disorder and absence seizures who presented with new-onset focal status epilepticus which progressed to severe encephalopathy and asymmetric hemispheric cerebral atrophy. Differential diagnosis included mitochondrial disease, Rasmussen's encephalitis, and autoimmune encephalitis. Disease progressed from one hemisphere to the other despite anti-seizure medications, hemispherectomy, vagus nerve stimulator, ketogenic diet, and immunomodulators. Continued cerebral atrophy and refractory seizures evolved until death four years after initial presentation. Post-mortem whole-exome sequencing revealed a pathogenic *DNM1L* variant. This paper presents a novel case of adolescent-onset *DNM1L*-related intractable epilepsy and encephalopathy.

Key words: developmental delay, seizure, refractory epilepsy, cerebral atrophy, encephalopathy congenital, *DNM1L*

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The advent of next-generation sequencing is rapidly expanding the already genetically and phenotypically heterogenous category of mitochondrial disorders. Epilepsy gene panels are now identifying novel nuclear mitochondrial pathologic variants, including those in the *DNM1L* (dynamin-1-like, MIM*603850) gene.

DNM1L is a nuclear mitochondrial gene that encodes dynamic-related protein 1 (DRP1) and plays a critical role in mediating the mitochondrial fission process and in regulating peroxisomal fission (Archer, 2013; Lackner, 2014). *DNM1L*-related disorders present during infancy with early-onset diffuse cerebral abnormalities, microcephaly, optic atrophy, lactic acidosis, hypotonia, and death within early infancy (Waterham *et al*., 2007). Recently, there have been reports of *DNM1L*-related disorders that include: developmental delay, refractory epilepsy, normal brain MRI, and prolonged survival (Vanstone *et al*., 2016); childhood-onset epileptic encephalopathy with diffuse cerebral atrophy (Fahrner *et al*., 2016); postnatal microcephaly, developmental delay, and pain insensitivity (Sheffer *et al*., 2016); or progressive neurological disease, characterized by mild cognitive impairment, cerebellar and pyramidal signs, and ocular involvement (Nasca *et al*., 2016).

Here, we report a patient with disease progression that mimicked Rasmussen encephalitis, autoimmune encephalitis, and mitochondrial disease. Onset of absence seizures at age nine was followed by focal status epilepticus in early adolescence at age 10, with development of severe encephalopathy, progressive hemiparesis, developmental regression, refractory focal epilepsy, and notably asymmetric progressive cerebral atrophy. The asymmetric atrophy was concerning for Rasmussen encephalitis, autoimmune encephalitis, or mitochondrial disease that did not improve with typical therapies. Post-mortem whole-exome sequencing was diagnostic for a pathogenic *DNM1L* variant (c.1207C>T [p.R403C]; a heterozygous *de novo* mutation) (Fahrner *et al*., 2016) associated with *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 (OMIM #614388).

Case study

The proband was a right-handed Caucasian female who had an uneventful birth and appropriate development, aside from a mild learning disorder. She had no prior history of traumatic brain injury, abnormal birth history/development, personal/family history of seizures, nor family history of epilepsy. She was diagnosed with typical absence seizures at age nine that initially responded to ethosuximide. One year after her initial diagnosis, at 10 years of age, the proband experienced new-onset frontal headache for one week before suddenly developing left neck twitching. This progressed to involve her left arm and leg, followed by sudden left hemibody loss of sensation. She presented to the emergency department (ED) and clinically demonstrated non-resolving rhythmic left arm and leg twitching with altered awareness. Continuous EEG revealed electroclinical status epilepticus with right hemispheric 2-Hz spike and wave discharges, alternating with diffuse background slowing. Her seizures continued despite escalating treatment with lorazepam, diazepam, and levetiracetam; she was intubated and placed on a propofol infusion. Her seizures continued and she was further treated with a midazolam infusion, fosphenytoin, phenobarbital, and ethosuximide. Pentobarbital infusion was started and a burst suppression pattern was obtained with resolution of electrographic seizures.

Initial magnetic resonance imaging (MRI) demonstrated extensive areas of restricted diffusion within the right cerebral hemisphere, predominantly at the vertex and involving the right frontal and parietal lobes, right insular cortex, and right thalamus with corresponding increased T2/FLAIR signal and cortical edema. The findings were suggestive of changes seen with status epilepticus (*figure 1*). Magnetic resonance spectroscopy demonstrated decreased n-acetyl aspartate (NAA) and minimally increased choline peaks of the right cerebral hemisphere compared to the contralateral side. Magnetic resonance perfusion images demonstrated overall symmetric perfusion, bilaterally. At this time, hemispheric presentation was most concerning for a mitochondrial disorder versus an autoimmune etiology, such as Rasmussen-type phenomena. Initial CSF studies were unrevealing.

Unfortunately, right hemispheric electroclinical seizures returned following pentobarbital discontinuation despite treatment with IVIG. An outside center evaluated and performed a right hemispherectomy 13 days after her initial presentation, sparing portions of the right thalamus and medial right basal ganglia. Seizures reoccurred almost immediately post-operatively, presenting with right facial twitching, nystagmus, and right hemibody twitching. Continuous EEG now demonstrated left hemispheric and multi-focal left hemispheric epileptiform discharges, in addition to expected post-surgical right hemispheric attenuation. She exhibited epilepsia partialis continua clinically as well as electroclinical left frontotemporal focal seizures. At that time, she was maintained on levetiracetam, lacosamide, clobazam, and topiramate. An autoimmune encephalopathy panel revealed elevated anti-glutamic acid decarboxylase (GAD) antibodies, furthering the concern for autoimmune encephalitis. She was started on monthly IVIG and high-dose steroids as well as

zonisamide and phenobarbital with minimal clinical improvement. Perampanel caused clinical worsening of seizure frequency. A vagus nerve stimulator (VNS) was placed with a decrease in seizure frequency but was complicated by sinus bradycardia and first-degree atrioventricular block requiring device removal.

Repeat MRI, seven months post-hemispherectomy, now demonstrated restricted diffusion along the cortex of the left anterior frontal lobe extending into the anterior insula with sparing of the medial most portion of the frontal lobe. There was similar cortically based restricted diffusion in the left parietal lobe extending into the medial left occipital lobe and minimal portions

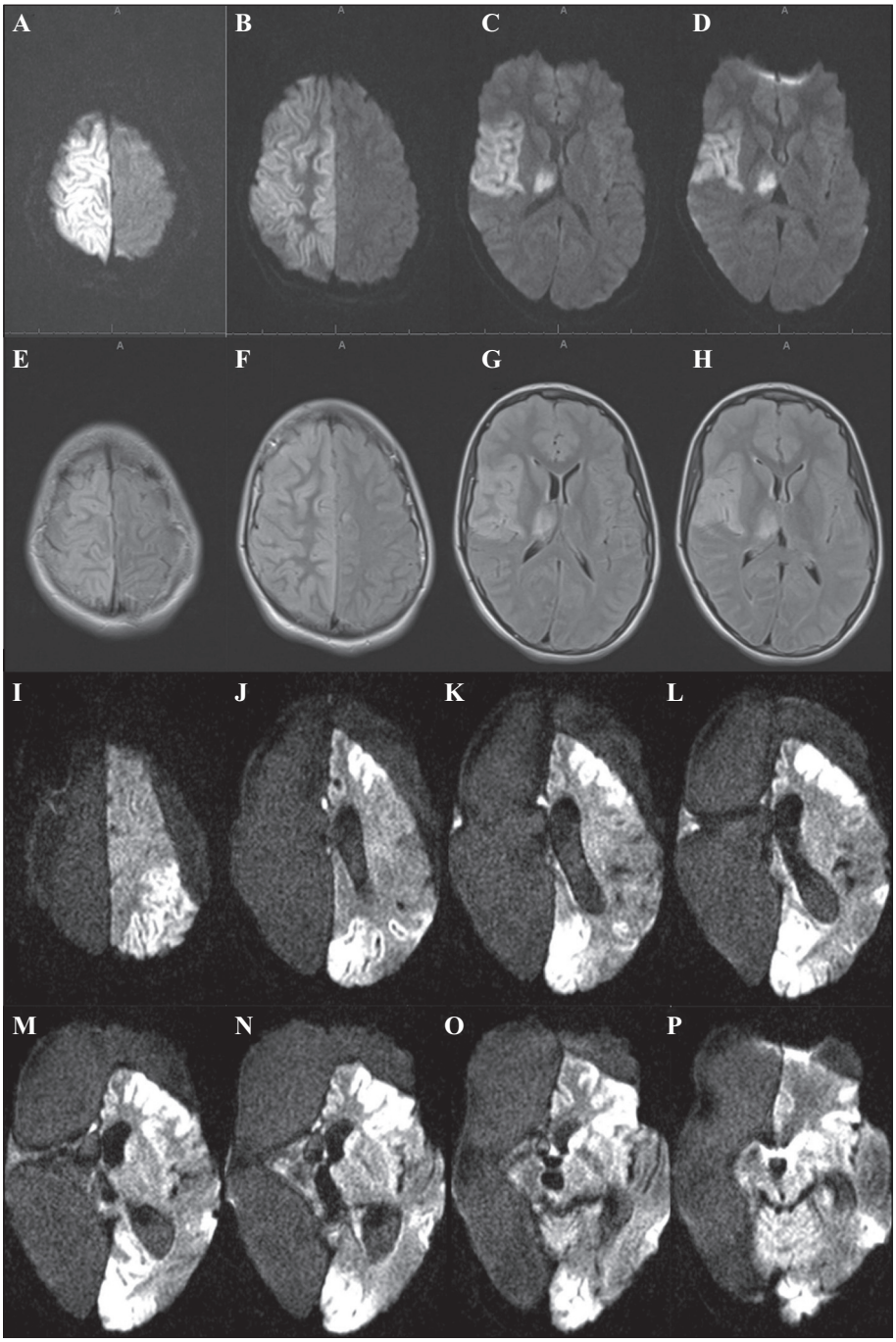

Figure 1. Initial MRI demonstrating extensive areas of restricted diffusion within the right cerebral hemisphere, predominantly at the vertex and involving the right frontal and parietal lobes, right insular cortex, and right thalamus with corresponding increased T2/FLAIR signal and cortical edema.

of the left temporal lobe. The appearance of the diffusion restriction was relatively similar in appearance to the abnormalities seen in the right cerebral hemisphere on the initial MRI prior to the patient's right hemispherectomy (*figure 1*).

The patient's clinical status continued to deteriorate from difficulty performing functional activities (*e.g.* grooming, dressing, bathing, toileting) to requiring maximal assistance for bilateral hemiparesis, aphasia, contractures of the hip and knees, and severe muscle wasting requiring a wheelchair and gastrostomy tube. Twenty months after initial EPC presentation at age 12, the patient became ventilator-dependent due to chronic respiratory failure. Repeat MRI now revealed ventricular enlargement and progressive left hemisphere atrophy. Magnetic resonance spectroscopy (MRS) showed high lactate peaks in her basal ganglia (*figure 2*). Despite multiple anti-seizure drugs, she continued to have daily breakthrough seizures complicated by recurrent pneumonia and urinary tract infections. The patient was eventually admitted to a hospice due to decreasing quality of life and died four years and three months after initial EPC presentation.

Autopsy revealed atrophy of the right cerebellar hemisphere and right pyramidal tracts, and areas of neuronal loss in the left visual and temporal lobe cortex and in the left pons. Muscle biopsy revealed only neuropathic changes. No myopathic features were present and no morphologic evidence of metabolic myopathy was present. Post-mortem whole-exome sequencing in the patient identified a *de novo* heterozygous pathogenic variant in the *DNM1L* gene (c.1207 C>T [p.R403C]). The *DNM1L* variant identified correlated with the proband's clinical presentation and provided a likely genetic diagnosis of *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 (OMIM #614388). Written informed consent for this case report could not be obtained from the patient because the patient deceased before the conception of this manuscript.

Discussion

DNM1L-related biologic function in mitochondrial and peroxisomal fission has been well described in the literature, yet the associated disease spectrum is only beginning to be clarified. The majority of reported cases presented during infancy or within the first few years of life (Waterham *et al.*, 2007; Chao *et al.*, 2016; Nasca *et al.*, 2016; Sheffer *et al.*, 2016; Vanstone *et al.*, 2016; Yoon *et al.*, 2016). There has been one case report of two individuals presenting at four and five years of age, respectively (Fahrner *et al.*, 2016). Our case report describes a *de novo* variant in the *DNM1L* gene (c.1207 C>T [p.R403C]) in a patient with initial typical early-adolescent absence epilepsy that quickly progressed to refractory epilepsy with severe encephalopathy, asymmetrically progressive cerebral atrophy, and eventual death. To our knowledge, our

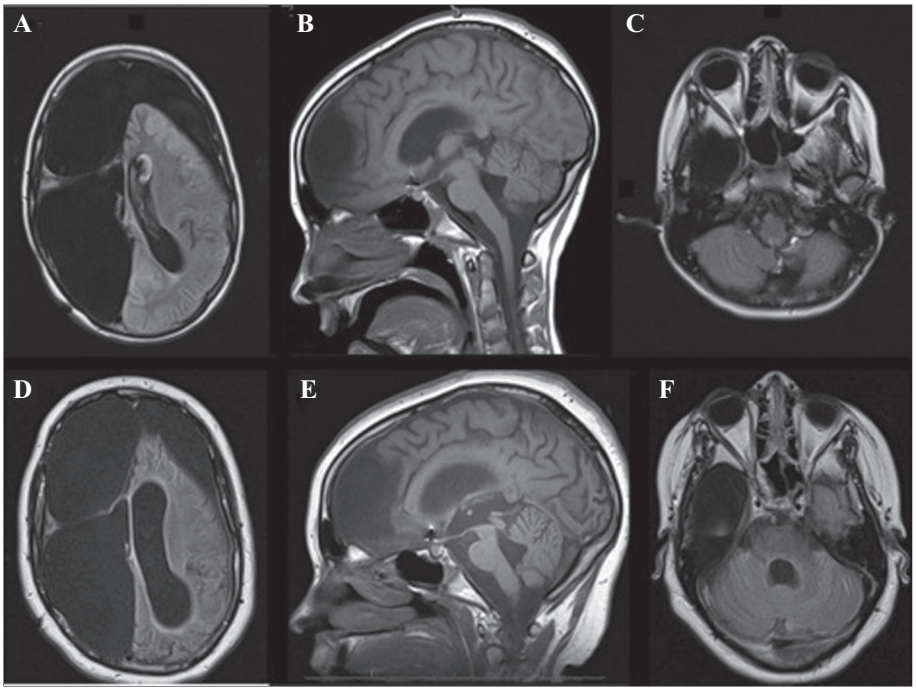

Figure 2. MRS showing high lactate peaks in the basal ganglia.

patient had the latest onset of encephalopathy at age 10, compared to the described infantile onset of *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 (OMIM #614388), expanding the described age of presentation for this disorder. This case report also suggests that *DNM1L*-related disorders may initially present with a more seemingly benign presentation, such as absence epilepsy, which is not atypical in this age range.

In addition to this patient's relatively late onset, this case was notable due to the shifting focal hemispheric predominance of the status epilepticus. This is the first report of *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 that presented with focal hemispheric findings initially, as opposed to global atrophy. This suggests that in patients with rapid progression of hemispheric refractory epilepsy, an underlying genetic etiology should be considered in conjunction with autoimmune etiologies. Typical first-step genetic testing, chromosomal microarray (CMA), and epilepsy panels are not sufficient in such cases. Indeed, in our case, reported negative first-line genetic testing and the etiology was not revealed until post-mortem whole-exome sequencing was performed. If *DNM1L*-related refractory epilepsy had been identified during that initial testing, the expected prognosis may have drastically changed management or provided parental guidance during a challenging time. In refractory epilepsy patients, especially those who demonstrate rapid clinical deterioration, whole-exome sequencing should be considered early in the diagnostic process.

To conclude, this case report presents a patient with a novel DNM1L R403C variant and clinical findings of early-adolescent-onset refractory seizures with severe encephalopathy and progressive asymmetric cerebral atrophy associated with *DNM1L*-associated lethal encephalopathy due to defective mitochondrial peroxisomal fission 1. This patient's presentation not only expands the phenotypic age range of the disorder but also demonstrates how the initial presentation can show focal findings that may mimic an autoimmune disorder such as Rasmussen's encephalopathy. □

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

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TEST YOURSELF

(1) Name a disorder that can mimic *DNM1L*-associated lethal encephalopathy.

(2) If chromosomal microarray and a gene panel are negative, what genetic test should be considered next in the investigation?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".