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GENETIC DISORDERS

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GENETIC DISORDERS

Epileptic Encephalopathy Due to *BRAT1* Pathogenic Variants

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Related Article: Horn D, Weschke B, Knierim E, Fischer-Zirnsak B, Stenzel W, Schuelke M et al. BRAT1 mutations are associated with infantile epileptic encephalopathy, mitochondrial dysfunction, and survival into childhood. Am J Med Genet A 2016 Sep;170(9):2274–81.
Keywords: Intractable Epilepsy; Microcephaly; Hypertonia; Apnea; *BRAT1*

Investigators from Institut für Medizinische Genetik und Humangenetik have highlighted the role of compound heterozygous *BRAT1* variants in two German brothers with variable presentations of intractable epilepsy, poor development, postnatal microcephaly, hypertonia, apnea, and infantile/childhood death. The older brother (Pt 1) died at 5.75 years, while the younger brother (Pt 2) died at 2 months. Seizure onset occurred at 5 months in Pt 1 and at birth in Pt 2 (and possibly in utero). Seizures were myoclonic, refractory to treatment, and accompanied by apnea, bradycardia (Pt 2), and focal/multifocal epileptiform discharges. Microcephaly was severe. Pt 1 achieved some turning and Pt 2 acquired no milestones. Appendicular hypertonia was present in both. Pt 2's brain MRI was normal; Pt 1's brain MRI showed corpus callosum thinning, enlarged CSF fluid spaces, and delayed myelination. Next-generation sequencing (NGS) of the disease-associated genome (~2800 genes) revealed a compound heterozygous variant in *BRAT1* [c.638_639insA (p.V214fs189*); c.1134+1G>A], confirmed in both siblings. The frameshift variant, which was maternally inherited, is a known change associated with lethal neonatal rigidity and multifocal seizure syndrome (RMFSL). The other variant, which was paternally inherited, alters splicing, evident by reduced *BRAT1* mRNA expression in the father. Skeletal muscle biopsy from Pt 2 revealed myofiber immaturity, decreased cyclooxygenase staining, and decreased cytochrome c oxidase activity. [1]

COMMENTARY. This study expands the knowledge surrounding *BRAT1*-related disorders, particularly its clinical heterogeneity. Some of the first reports of this disorder characterized it as a particularly severe, rapidly progressive, intractable epileptic encephalopathy with age of presentation at birth or shortly thereafter [2,3]. While these earlier investigations suggested it is lethal in the first few months of life, this present report points to increased survival into childhood (Pt 1) as one of the features of the disorder. Moreover, other manifestations in Pt 1 – later onset of epilepsy, postnatal microcephaly, and hypertonia – suggest a less affected phenotype. In fact, in addition to the severe lethal form known as RMFSL, both mild and moderate forms of *BRAT1*-related disorders may exist. Mildly affected individuals may present with intellectual disability without epilepsy/seizures, ataxia, cerebellar atrophy, and continued survival through late childhood [4]. Given the phenotypic differences seen with siblings, intrafamilial variability can occur.

This study also demonstrates that mitochondrial dysfunction may be a hallmark of *BRAT1*-related disorders. Pt 2's skeletal muscle biopsy showed evidence of impaired mitochondrial energy production. In another study, BRAT1 knockdown resulted in cells with increased glucose requirements, increased reactive oxygen species levels, and decreased ATP production [5]. Defects in mitochondrial metabolism, combined with defects in some of the other roles of BRAT1 including DNA repair and cell growth [6], may account for some of the presentations of this disorder.

Finally, this study highlights the role of NGS in diagnosing causes of epileptic encephalopathy. Depending on the laboratory, *BRAT1* may not be one of the genes sequenced as part of an epileptic encephalopathy panel. Increased awareness of this disorder, combined with utilization of NGS, may lead to earlier diagnoses.

Disclosures

The author(s) have declared that no competing interests exist.

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Ocular Manifestation of *CACNA1A* Pathogenic Variants

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Related Article: Tantsis EM, Gill D, Griffiths L, Gupta S, Lawson J, Maksemous N et al. Eye movement disorders are an early manifestation of CACNA1A mutations in children. Dev Med Child Neurol 2016 Jun;58(6):639–44.
Keywords: *CACNA1A*; Ocular Manifestation; Global Developmental Delay

Investigators from The Children's Hospital at Westmead in New South Wales; The Queensland University of Technology in Brisbane; Sydney Children's Hospital in New South Wales and Laboratoire de Genetique in Paris investigated children with a proven heterozygous missense pathogenic variant in the *CACNA1A* gene. The *CACNA1A* gene encodes the alpha-1 subunit of the voltage-gated calcium channel. Expression of these channels is particularly high in neuronal tissue, especially in the cerebellum. The literature on *CACNA1A* disorders in children is relatively modest, and the focus of the range of ocular presentations in childhood remains rare. The authors reviewed retrospectively nine children from Children's Hospital at Westmead over a 10-year period (2005–2015). All of them had confirmed heterozygous mutation in the *CACNA1A* gene. Eye movement disorders like paroxysmal tonic upgaze (PTU), strabismus, and abnormal saccades were the presenting feature in eight of the nine children. There was a wide range in the age of presentation of the first sign (2mo–10y), though six of the nine children demonstrated the eye movement disorder in the first 2 years of life. None of them followed a 'benign' course. The children presenting with ocular abnormalities had additional problems including hypotonia, cerebellar ataxia, or epilepsy. Six patients were diagnosed with global developmental delay within 2 years of their initial presentation, including all three patients with PTU. In total, 5 patients had an abnormal brain MRI - cerebellar or generalized mild cerebral atrophy. Based on the previously described findings, the authors suggest that an eye movement disorder may be a clue to the underlying mutation in the *CACNA1A* gene, especially if there is evidence of developmental delay or cerebellar or cerebral atrophy on MRI. [1]

COMMENTARY. This interesting overview of children with heterozygous missense pathogenic variants in the *CACNA1A* gene gives a new perspective on the disease course. Since the concept of a 'pre-symptomatic' eye movement disorder was previously described in children [2, 3] and adults diagnosed with SCA6 [4], the suggestion that all children with PTU, and an ocular motor apraxia or strabismus (especially when associated with developmental delay or cerebellar atrophy), should be considered for *CACNA1A* genetic testing.

Importantly, a study like this calls attention to the wide phenotypic spectrum of patients with *CACNA1A* mutations. Moreover, we have recently described two sibs with bi-allelic *CACNA1A* pathogenic variants, which cause early onset epileptic encephalopathy, cerebral, cerebellar atrophy and optic nerve atrophy [5]. All this additional information could lead to better counselling regarding the prognosis at the time of diagnosis (e.g. episodes of severe hemiplegic migraine) as well as implementing more targeted therapies like verapamil [6].

As the authors pointed out, the weakness of their study is that it is retrospective with small number of patients and quite short period of follow-up. A multicenter research study with gene sequencing of all children with aforementioned eye movement disorders would identify the true frequency of the *CACNA1A* pathogenic variants in this cohort.

Disclosures

The author(s) have declared that no competing interests exist.

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Neurocognitive Functions and Behavior in Joubert Syndrome

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Related Article: Bulgheroni S, D'Arrigo S, Signorini S, Briguglio M, Di Sabato ML, Casarano M et al. Cognitive, adaptive, and behavioral features in Joubert syndrome. Am J Med Genet A 2016 Dec;170(12):3115–24.
Keywords: Joubert syndrome; Cognitive functions; Behavior

Investigators from multiple Italian pediatric neurology and neurogenetics departments studied cognitive functions, behavior, and adaptive functioning in large cohort of 54 patients with Joubert syndrome (JS) as part of a prospective, multi-center study. The authors applied standardized, age-appropriate tests to assess development, intelligence, behavior, and adaptive functioning. A global developmental delay was found in 44 (81%) patients. Cognitive functions have been assessed in 49 patients: intelligence (IQ) or general quotient ranged from 15 to 129 (mean 58) and was normal in six (11%) patients. Performance IQ (mean 59) was lower than verbal IQ (mean 67). Scores on subtests of arithmetic and verbal comprehension items were particularly low representing deficits in working memory. A psychiatric diagnosis was reached only in four (7.4%) subjects, but 21 (39%) of 54 patients showed inattention, hyperactivity, social withdrawal, and atypical behaviors affecting daily life. Internalizing problems (anxiety and sociality) were more common than externalizing problems. Adaptive functioning revealed that the motor domain was the area of greatest vulnerability, with a negative impact on personal care, social, and academic skills, while communication skills were relatively preserved. [1]

COMMENTARY. JS is a rare mid-hindbrain malformation that results in the pathognomonic molar tooth sign and hypodysplasia of the cerebellar vermis [2]. JS is genetically heterogeneous and is caused by pathogenic variants in more than 30 genes encoding proteins of the primary cilium [3]. Hypotonia, an abnormal neonatal respiratory pattern including apnea and tachypnea, ocular motor apraxia, and ataxia are typical clinical features observed in children with JS. Cognitive impairment and intellectual disability are common in JS and only few patients with JS and normal IQ have been reported so far. The current study adds to the knowledge about cognitive functions in children with JS and shows that cognitive functioning is extremely variable in JS, ranging from severe disability to normal and correlating well with adaptive function. In addition, up to 40% of the children showed behavioral changes, although a psychiatric diagnosis was made only in a few children. Impairment in cognitive functions and behavioral abnormalities in children with JS is in line with the "cerebellar cognitive affective syndrome", which includes impairments of executive function, deficits in visuospatial skills, linguistic deficiencies, and inappropriate behavior and affect [4]. Knowledge about the type and variability of cognitive functions and behavior in children with JS is important for prognostic and counseling purposes as well as for early initiation of targeted, supportive, rehabilitation therapies to improve functioning and quality of life; however, this may be challenging within the context of the degree of cognitive impairment frequently observed among individuals with JS. As such, use of a combination of standardized neurocognitive measures in conjunction with more experimental methods of examining the developmental trajectories of specific neurocognitive functions will be beneficial. Future studies should also evaluate these outcomes on both types of neurocognitive measures in children with JS, and the relationship with neuroimaging findings and genetic causes.

Disclosures

The author(s) have declared that no competing interests exist.

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