Decreased level of consciousness in a toddler with overgrowth syndrome

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ABSTRACT
Physicians caring for patients with rare diseases face unique challenges in managing symptoms, ordering diagnostic tests, and providing patients and families with anticipatory guidance. We describe the case of a toddler with overgrowth syndrome, and previously known ophthalmological and neurological findings, presenting with decreased level of consciousness (LOC) following a fall. We highlight the extensive workup undertaken in a patient with symptoms spanning multiple systems but lacking a unifying diagnosis. In this case, rapid whole exome sequencing identified a de novo CACNA1A gene mutation encoding a calcium channel subunit, located within chromosome region 19p13.13. We explore 19p13.13 Microdeletion Syndrome and compare our patient's presentation to the cases described in the literature. Although our patient had several symptoms consistent with 19p13.13 Microdeletion Syndrome, others remain unexplained. This highlights the difficulty in determining a definitive diagnosis or treatment plan in the realm of rare diseases and emphasizes the need for further research into the disease process and development of novel therapies.

PATIENT PRESENTATION
A 2 years 10 months old male presents to hospital with decreased LOC following an unwitnessed fall. He was found face-down by a caregiver who described unusual movements but no clear seizure activity. Emergency medical services brought him to the nearest tertiary care centre, where he remained intubated for 10 days. After successful extubation he was transferred to a general paediatric inpatient unit for further work-up and management.

INVESTIGATIONS AND MANAGEMENT
On initial presentation to the PCCU, the patient was started on empiric broad-spectrum antibiotics and antiviral treatment for possible meningitis or encephalitis. Infectious workup, including cultures of urine, blood, and cerebral spinal fluid (CSF), were negative. CSF polymerase chain reaction (PCR) was negative for enterovirus and herpes.

A computed tomography (CT) of the head ruled out any acute intracranial abnormality. Magnetic resonance imaging (MRI) of the head identified restricted diffusion involving parietal and occipital cortices bilaterally in a symmetrical fashion. Repeat MRI head 4 weeks later was normal. Ophthalmologic examination was unchanged from previous.

Electroencephalogram (EEG) findings were nonspecific but suggested moderate to diffuse encephalopathy with left occipital spike and wave discharges associated with increased risk of focal seizures. Paediatric neurology started the patient on phenytoin and levetiracetam following seizure in the PCCU. During hospitalization, he developed moderate choreiform movements of all four limbs and oculogyric phenomena involving the upward rolling of the eyes. Phenytoin was discontinued and valproic acid started. Levetiracetam was weaned in discussion with his family due to concern that the anti-epileptic was contributing to the patient’s chorea.

Although the patient was feeding orally prior to his acute change in LOC, in hospital he developed feeding intolerance on nasogastric (NG) tube feeds and ultimately required gastrostomy tube insertion.

Previous genetic testing included normal chromosomal microarray, Fragile X testing, Simpson-Golabi-Behmel testing, isoelectric focusing, very long chain fatty acids, Bardet-Biedl and Alström panels, and GeneDx overgrowth panel. While in hospital, the patient was followed by the medical genetics team who recommended several additional investigations. Acylcarnitine profile and urine organic acids were normal. Skeletal survey was unremarkable with no dysplasia, metabolic bone disease, congenital malformation, or trauma identified. Muscle biopsy was performed for mitochondrial studies with results pending. Rapid whole exome sequencing identified a de novo pathogenic variant in CACNA1A, the gene responsible for calcium voltage-gated channel subunit alpha 1A.

DIAGNOSIS AND FOLLOW-UP
Despite the identification of a de novo CACNA1A gene mutation, there is an association between overgrowth syndrome and mutations in this gene region. CACNA1A loss-of-function mutations have been associated with symptoms including cognitive impair-
Deletions in the 19p13 region are exceed
Another case was published in the same year of
CACNA1A encodes the main alpha 1A subunit of a volt
Some of this patient's symptoms
In addition, the devel
Additional cases have been described of children with
microdeletions spanning the 19p13.12 to 19p13.2 region (which in
syndrome 2), which present with features such as developmental delay,
ciostosis, epilepsy, and mental retardation.
mutations have been associated with epilepsy and implicates in episodic ataxia
type 2, spinocerebellar ataxia type 6, and familial hemiplegic migraine.2,7
With the description of another 5 cases of 19p13.13 microdeletion, each with similar presentations, including overgrowth, macrocephaly, intellectual delay and gastrointestinal problems, a unique syndrome was proposed, termed 19p13.13 Microdeletion Syndrome.10,11 Additional cases have been described of children with microdeletions spanning the 19p13.12 to 19p13.2 region (which includes the CACNA1A gene) who presented with syndromic craniosynostosis, epilepsy, and mental retardation.12

Microdeletions of neighboring region 19p13.12 have been associated with similar phenotypes such as Malan syndrome (Sotos syndrome 2), which present with features such as developmental delay, macrocephaly, central nervous abnormalities, overgrowth, and cephalic malformations.13,14 Deletions in the 19p13 region are exceedingly rare; as such, only five case reports have been described.15-17
But they, and this case, present a unique opportunity for research into the roles of genes such as CACNA1A in normal physical and intellectual development.

This case report describes a 2 years 10 months old male with a unique constellation of symptoms including developmental delay, overgrowth with undetermined etiology, retinal cone dysfunction, peripherally hypogammunated fundus, hypotonia, and autistic features. On admission to hospital he was found to have seizure activity on EEG and developed choreiform movements of all four limbs and oculargic phenomena. Through rapid whole exome sequencing, a variant in CACNA1A, the gene encoding calcium voltage-gated channel subunit alpha-1A, was identified.

A limited number of case reports describing CACNA1A loss-of-function mutations have found associations between these mutations and episodic ataxia type 2, spinocerebellar ataxia type 6, and familial hemiplegic migraine.2,7 Some of this patient's symptoms are consistent with previous reports, including developmental delay, hypotonia, and overgrowth syndrome.2 In addition, the development of seizure activity is supported by literature as CACNA1A mutations have been associated with epilepsy and febrile seizures.1,2 However the patient had other symptoms that remain unexplained. The clear retinal findings in this patient have not been previously reported in the literature. Additionally, his movement disorder is not a previously described finding, though it's resolution post-discharge may imply it is not associated with a CACNA1A mutation.

As limited literature exists on CACNA1A loss-of-function mutations, this genetic finding brought little clarity to the underlying disease process causing the patient's symptoms. In addition, there is still much that remains unknown, including the expected long-term progression of this patient's disease.

This case report highlights the complexities parents and families of children with rare diseases often face as they search for a diagnosis. Children with rare diseases often require frequent medical visits with specialists and are subjected to many diagnostic investigations, as presented in this report. This can be both emotionally and financially stressful for families as they care for their loved one without receiving a clear definitive diagnosis or treatment plan. This is made more stressful by the fact that rare diseases are associated with high morbidity and mortality.15,16

REFERENCES


