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Novel *MYT1L* gene mutation and cerebral palsy: A case report

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Abstract

Over the last decade, a body of genes that may underlie cerebral palsy causation has been elaborated. The objective of this case report is to highlight the possible implication of a loss-of-function pathogenic variant in myelin transcription factor-1 like *(MYT1L)* gene, not associated with cerebral palsy in prior literature, in the development of cerebral palsy. Our patient is a 22-month-old female referred for specialty evaluation of developmental delay who was subsequently diagnosed with spastic quadriplegic cerebral palsy. Normal magnetic resonance imaging and the finding of microcephaly prompted genetic analysis, which revealed a *MYT1L* pathogenic variant. Based on the critical function of *MYT1L* in brain development and based on the reported phenotypes associated with *MYT1L*, we conclude that a *MYT1L* pathogenic variant could contribute to the development of cerebral palsy. We therefore recommend that in cases of cerebral palsy where no acquired causes are identified and where, despite neurological findings beyond cerebral palsy (i.e., microcephaly), magnetic resonance imaging is normal, a genetic etiology should be suspected. In these cases, genetic testing should include testing specifically for the *MYT1L* gene as well as the other genes known to be associated with cerebral palsy.

Keywords: Cerebral palsy; *MYT1L*; case report

Abbreviations: CP: Cerebral Palsy; CNS: Central Nervous System; KANK1: KN motif and ankyrin repeat domains 1; GAD1: Glutamate Decarboxylase 1; MRI: Magnetic Resonance Imaging; *MYT1L*: Myelin Transcription Factor-1 like

Introduction

Cerebral Palsy (CP) is the most common childhood-onset physical disability with an estimated prevalence of 17 million affected individuals worldwide [1]. It is attributed to the maldevelopment of the brain or to an injury of the developing brain, which results in a wide spectrum of clinical manifestations invariably including motor limitations and often also featuring intellectual disability, epilepsy and varied sensory impairments [2]. Multiple risk factors are associated with CP development including premature birth, difficult delivery, maternal tobacco use, maternal illicit drug use, diabetes, preeclampsia, low Apgar scores, and infant weight [3]. While the emphasis has been traditionally on acquired risk factors, recently there is an emerging body of evidence that genetic factors may also be associated with the development of CP.

This case report highlights a 22-month-old girl that was referred for specialty evaluation of developmental delay. Clinical assessment led to the diagnosis of spastic quadriplegic cerebral palsy. After a normal brain imaging study, a gene panel revealed a mutation in the myelin transcription factor-1 like *(MYT1L)* gene. *MYT1L* is a transcription factor that is expressed in the developing brain and *MYT1L* loss-of-function pathogenic variants have previously been associated with intellectual disability and autism spectrum disorder but not CP as of yet [4].

The objectives of this case report are to highlight the possible implication of a *MYT1L* loss-of-function variants in the development of cerebral palsy and to highlight the emerging evidence for genetic contribution to CP causation.

Case Presentation

The patient is a 22-month-old female who was referred for specialty evaluation of developmental delay. The mother's reason for initial consultation was concern about her daughter first walking independently only at the age of 21 months and saying her first words only at 18 months.

The patient is the youngest of three children of her parents. Both of her older siblings have a normal development and no comorbidities. The parents are both 34-year-old, in good physical health, and of Middle Eastern heritage. The father was recently diagnosed with bipolar disorder. Parental consanguinity was denied and could not be inferred. There is no family history of neurological problems on either side of the family.

The mother's pregnancy with the patient was uncomplicated without any maternal illnesses or untoward events. Alcohol, drug and tobacco use was denied during the pregnancy. The patient was born at 39 weeks of gestation via an elective repeat cesarean section. Her birthweight was 3.3 kg and Apgar scores were 9 and 9 at 1 and 5 minutes respectively. No neonatal difficulties were noted, and the patient was discharged home with the mother at three days of age.

The patient's past medical history is unremarkable with no hospitalizations or surgical procedures. The patient is on no current medications and has no known drug allergies.

Regarding the patient's gross motor development, the mother reports that the patient walked late at the age of 21 months without first progressing through a crawling phase on flat surfaces. She was able to crawl up the stairs, but not go down the stairs. She was just beginning to run at the time of the initial assessment and was doing so somewhat awkwardly. She did not demonstrate the ability to jump. She tended to be up on her tiptoes when ambulating. Regarding her language development, she said her first words at 18 months of age. At 22 months of age, the patient had a vocabulary of 5 words. Regarding her fine motor development, the patient was using a spoon, a fork and a cup, and was able to eat independently, however she was not yet scribbling. She was described as a sociable child who engaged in pretend play and reciprocity with others.

On examination, the head circumference was 45 cm, which is at the second percentile for age and female sex. Birth head circumference was 33.5 cm, which is around the tenth percentile for term gestation and female sex.

Motor examination revealed mildly increased tone in all four extremities. There were symmetrical antigravity movements. Stretch reflexes were brisk diffusely with spread. There were a few beats of clonus at both ankles. Plantar responses were indifferent to equivocal.

Following this assessment, a cranial MRI was ordered. The 3T MRI results were interpreted as normal. Due to these normal findings with concurrent microcephaly and spastic quadriparesis, a gene panel study ("Cerebral Palsy Xpanded Panel") from GeneDx was undertaken. The panel revealed a heterozygous frameshift variant in exon 17 of the *MYT1L* gene (NM_015025.2:c.2554dup, p.R852Kfs*58), considered pathogenic based on ACMG criteria [5]. This frameshift variant is absent in public control databases such as the genome Aggregation Database (gnomAD) and has never been previously reported in patients. It is predicted to result in protein truncation and nonsense mediated decay imparting a loss-of-function for *MYT1L*. Haploinsufficiency of *MYT1L* has been associated with intellectual disability, speech delay, behavioral problems, obesity, postnatal short stature, microcephaly and macrocephaly [6,7]. Of note, trio genetic testing was offered to the parents, but they did not consent for it.

Discussion and Conclusion

While environmental risk factors associated with CP – including infection, trauma, hypoxia, ischemia – have been described extensively, the current literature suggests emerging awareness of a genetic susceptibility to CP causation. For instance, linkage analysis and microsatellite typing have identified that pathogenic variants in GAD1, which codes for L-glutamate decarboxylase that catalyzes the conversion of the inhibitory neurotransmitter GABA to the excitatory neurotransmitter glutamate, can contribute to the development of CP. Mutations in KANK1, a gene involved in actin polymerization and cell migration, have been identified through linkage analysis and were noted to be pathogenic. Furthermore, SNP microarray, comparative genomic hybridization, and DNA sequencing have revealed pathogenic copy number variants in approximately 10 to 20% of CP cases [8].

This case report describes a loss-of-function variants of the *MYT1L* gene that appears to contribute

to the pathogenesis of cerebral palsy in our case.

The MYT1L gene encodes the *MYT1L* transcription factor, which peak levels of expression occur during fetal development in a subset of neural progenitor cells of specific regions of the Central Nervous System (CNS), particularly the cortex. *MYT1L* is central for the maturation of neural stem cells and for the differentiation and proliferation of oligodendrocyte precursor cells. It allows for the myelination and re-myelination processes of the CNS to occur [9]. The disruption of this function can appear to plausibly be associated with later manifestations of a phenotype consistent with CP.

A literature review of 40 patients presenting with pathogenic variants of *MYT1L* found that 78% of the patients had motor delay, 81% had fine motor disorders, 20% had an unsteady gait, and the median age of independent walking was 22 months [9]. No mention was made in this study of objective findings consistent with a diagnosis of CP (e.g., spasticity, dyskinesias). Although this study did not investigate specifically the prevalence of CP in individuals with a *MYT1L* pathogenic variants, this study documented features often associated with CP including motor delay, fine motor disorders and unsteady gait.

To conclude, this case report characterizes a new gene that may underlie CP causation. The current clinical challenge focuses on when to do genetic testing and what genes to test for. This case reinforces an emerging consensus that a genetic etiology should be suspected when there is no historical evidence for an acquired cause and when detailed MRI studies fail to detect an abnormality despite neurological findings beyond CP (i.e., microcephaly). Documentation of a loss-of-function MYT1L pathogenic variant in this case suggests that this gene should be specifically tested for as a potential causal agent when circumstances suggest a possible genetic etiology, using targeted gene panels as a testing modality.

References

1. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, Damiano DL, et al. Cerebral palsy. Nat. Rev. Dis. Primers. 2016; 2.

2. Lewis SA, Shetty S, Wilson BA, Huang AJ, Jin SC, Smithers-Sheedy H, et al. Insights From Genetic Studies of Cerebral Palsy. Front Neurol. 2021;11.

3. Rouabhi A, Husein N, Dewey D, Letourneau N, Daboval T, Oskoui M, et al. Development of a Bedside Tool to Predict the Diagnosis of Cerebral Palsy in Term-Born Neonates. JAMA Pediatr. 2023; 177: 177-186.

4. Chen J, Yen A, Florian CP, Dougherty JD. MYT1L in the making: emerging insights on functions of a neurodevelopmental disorder gene. Transl Psychiatry. 2022; 12.

5. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015; 17: 405-424.

6. De Rocker N, Vergult S, Koolen D, Jacobs E, Hoischen A, Zeesman S, et al. Refinement of the critical 2p25.3 deletion region: the role of MYT1L in intellectual disability and obesity. Genet Med. 2015; 17: 460-466.

7. Windheuser IC, Becker J, Cremer K, Hundertmark H, Yates LM, Mangold E, et al. Nine newly identified individuals refine the phenotype associated with MYT1L mutations. Am J Med Genet A. 2020; 182: 1021-1031.

8. Shevell M. The evolution of our understanding of the conceptualization and genetics of cerebral palsy: Implications for genetic testing. Mol. Genet. Metab. 2022; 137: 449-453.

9. Coursimault J, Guerrot AM, Morrow MM, Schramm C, Zamora FM, Shanmugham A, et al. MYT1L-associated neurodevelopmental disorder: description of 40 new cases and literature review of clinical and molecular aspects. Hum. Genet. 2022; 141: 65-80.

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