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Case Report

Early Childhood Onset Vanishing White Matter Disease with Multiple Cranial Nerve Enhancement: A New Consensus Criteria?

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Abstract

Vanishing White Matter Disease (VWM), also known as Childhood Ataxia with Central Nervous System Hypomyelination (CACH), although a rare neurological condition, is a prevalent hereditary leukoencephalopathy with a characteristic phenotype of gradual neurologic deterioration with ataxia being a prominent feature. It is characterized by a wide range of onset, from antenatal and infantile periods to early childhood and later adulthood periods. The early childhood form is considered the prevailing form, characterized by a preceding phase of normal development until the second or 3rd year of life, followed by progressive neurologic deterioration, accentuated by certain stressors, such as infections or minor trauma. Diagnosis is achieved based on the clinical pretext combined with distinctive MRI brain features, confirmed by DNA analysis detection of elf2B mutation. Our case is a healthy 18-month-old male who after a preceding upper respiratory tract infection, developed an ataxic gait, encephalopathy, and recurrent generalized seizures. Physical assessment revealed signs of generalized spasticity and hyperreflexia. Neuroimaging revealed diffuse symmetric supratentorial and infratentorial diffuse white matter hypomyelination. Interestingly, there was notable enhancement of the 3rd and 5th cranial nerves. Differential diagnosis included acute demyelinating leukoencephalopathies; and neuromatobolic disorders with acute presentations (including leukodystrophies, hypomyelinating disorders, and mitochondrial encephalopathies). In the early course of his management, he received immunomodulatory therapy in the form of pulse steroids, intravenous immunoglobulins, and oral tapering course of steroids. He had limited response to these interventions. Whole exome sequencing yielded a homozygous mutation in EIF2B3, confirming the diagnosis of VWMD/CACH. The presence of enhancing cranial neuropathies represent an atypical phenotype reported in other case reports and should alert the physician to avoid unnecessary intervention with immunosuppressive therapies.

***Keywords:** VWMC, CACH, Hypomyelination, ELF2B3, Leukoencephalopathies.*

Introduction

VWMD is a hereditary disease of heterogenous range of onset and presentations. Its neuroimaging features although distinct, have shown features still not fully explained by its underlying pathogenesis. A number of case reports have described unusual enhancements involving multiple cranial nerves. [1]

Case Presentation

Our proband is an 18-month-old male with previously healthy, and appropriately matched developmental milestones, who, after a few days following an upper respiratory prodrome, started to manifest with acute developmental regression, ataxic gait and episodes of generalized seizures. Examination revealed truncal ataxia, generalized hyperreflexia and spasticity with mild cognition delay.

Neuroimaging studies showed diffuse bilateral symmetric supratentorial and infratentorial white matter low T1 signals, and T2 hyperintensity signals, involving the subcortical U fibers, white matter long tracts at the brainstem, and deep cerebellar white matter. There was notable enhancement of the 3rd and 5th cranial nerves. (Figure 1) Spectroscopy revealed no abnormal peaks. For his encephalopathic state, and suspected parainfectious pathology, he received immunotherapy in the form of pulse steroids, intravenous immunoglobulins, and oral steroids. The neuroimaging findings suggested a differential diagnosis encompassing acute demyelinating leukoencephalopathies; and neurometabolic disorders with acute presentations (including leukodystrophies, hypomyelinating disorders, and mitochondrial encephalopathies). Whole exome sequencing yielded a homozygous pathogenic variant mutation in EIF2B3, designated as c.32G>T p.(Gly11Val), confirming the diagnosis of VWMD/CACH (Vanishing White Matter Disease/Childhood Ataxia, with Central Nervous System hypomyelination).

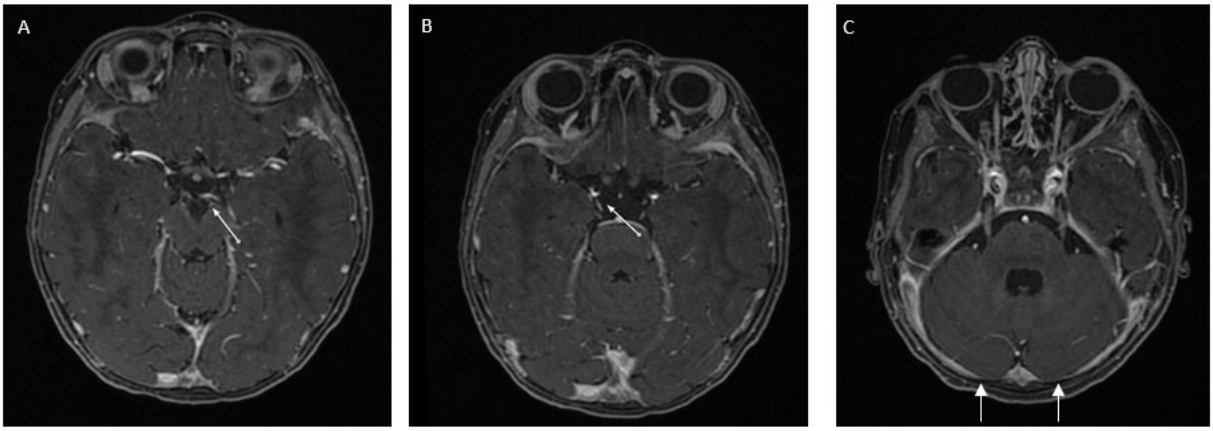

Figure 1. *Brain MRI with contrast, FLAIR sequence. Brain MRI at age of 18 months revealed abnormal enhancement involving the bilateral oculomotor (A, B) as well as the trigeminal cranial nerves (C).*

Discussions

The widely used proposed MRI criteria for the diagnosis of VWM has been divided into obligatory and suggestive criterions. Neither criterion includes cranial nerves enhancements in the genotypic and/or phenotypic correlation [2]. In a similar reported case with similar findings of cranial nerves involvement, VWM/CACH, along with other leukodystrophies (i.e. metachromatic leukodystrophy; Krabbe's disease) were suggested to be considered, based on clinical context and neuroimaging features [3]. Interestingly, Singh et al. [1] demonstrated a case of VWM with multiple cranial nerves enhancement, with resolution after immunotherapy. Herein we emphasize the importance of considering certain neurometabolic disorders with acute presentations, that may mimic neuroinflammatory demyelinating disorders, such as mitochondrial encephalopathies (Leigh Syndrome, leukoencephalopathy with brainstem and spinal cord involvement), biotin-responsive basal ganglia disease (BBGD), acute familial necrotizing encephalopathy due to RANBP2 gene mutation, POLG-leukodystrophies, and VWM.

Conclusion

Presence of cranial and/or spinal nerve enhancement may in the future be considered as part of the neuroimaging consensus for VWMD/CACH.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

Dr. Saleh Alzaid is the first author for this case report, assisted by Dr. Muneer Almutairi, Dr. Fahad Albassam is the Pediatric Neurology Consultant, and Neuroinflammatory Subspecialist, and is the principal investigator, who reviewed the formatting and content of the manuscript, including the imaging content.

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