International Journal of Contemporary Pediatrics
Aly A et al. Int J Contemp Pediatr. 2023 Jun;10(6):946-950
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20231506

Case Report

Vanishing white matter disease: a case of combined saposin deficiency

Aly Aly[1]*, Maria Theresa Villanos[1], Emily Zientek[2], Malini Riddle[2], Ittay Moreno[1]

[1]Department of Pediatric, Texas Tech University Health Sciences Center, El Paso, Texas, USA
[2]Texas Tech University Health Sciences Center, Paul L. Foster School of Medicine, El Paso, Texas, USA

Received: 21 April 2023
Revised: 16 May 2023
Accepted: 19 May 2023

***Correspondence:**
Dr. Aly Aly,
E-mail: aly.aly@ttuhsc.edu

ABSTRACT

Vanishing white matter disease (VWMD) is an autosomal recessive neurodegenerative disease often present during childhood and is exacerbated by trauma and other stressors. VWMD is caused by EIF2B gene mutation, which encodes eukaryotic initiation factor 2 B (EIF2B), a transcription factor activated by insulin that is a major protein synthesis regulator during the integrated stress response. Autosomal recessive combined saposin deficiency is a metachromatic leukodystrophy, a progressive neurological disorder characterized by motor delay, regression of gained skills, and nerve demyelination. Here, we present the case of an 11-year-old Hispanic male presenting with ataxia, dysphagia, and global developmental delay which was found to have VWMD on imaging. A genetic panel reveals the PSAP gene, a novel presentation in the setting of VWMD.

Keywords: Ataxia, Developmental delay, EIF2B gene mutations, Leukoencephalopathy, White matter disorders

INTRODUCTION

Vanishing white matter disease (VWMD) has the dichotomy of being an incredibly rare condition while also one of the most common inherited childhood leukoencephalopathies.[1] Clinical presentation, coupled with imaging, genetic testing, or both, has proven successful in identifying patients with VWMD. However, the factors affecting the onset and degree of morbidity remain unknown. Unfortunately, the mortality rate is high within a few years of symptom onset, and a potential cure has yet to be discovered.[2] The primary characteristics of VWMD are progressive neurological deterioration, cerebellar ataxia, and spasticity.[3] Due to its rare nature, it is often not considered among the differential diagnosis for developmental delay. In this case, we will not just discuss a rare presentation of developmental regression but also advocate for diagnosis-orientated parental education and informed decision-making, especially in patients with social and financial challenges.

CASE REPORT

An 11-year-old Hispanic male presented to the hospital with profound global developmental regression over the past two years. His parents reported that he had been developmentally appropriate until two years ago when he sustained a head injury due to an unprovoked fall at school. The mother endorsed that after this head injury, the patient began regressing developmentally, becoming nonverbal, oppositional, incontinent for urine and stool, and progressive dysphagia. Upon a detailed review of his developmental milestones, we discovered that he has a global developmental delay.

The patient was a cheerful and playful child without syndromic features. He was reasonably cooperative with our physical examination. He was only able to verbalize his name and ‘mama’. There was significant muscular atrophy of the lower extremities with spastic muscular tone. He had a tip-toe gait with significant ataxia that required two-person support. We estimated his development to be consistent with a 1-year-old child at verbal and communication and a three to four-year-old at motor skills. He showed no signs of failure to thrive with age-appropriate growth percentiles.

A speech consult and video fluoroscopic swallowing study revealed a significant delay in the oral and pharyngeal phases of swallowing without any anatomical defects. Physical therapy indicated that the patient required moderate assistance to ambulate. Laboratory investigations were within normal limits, including complete blood count, complete metabolic panel, and ammonia levels. Laboratory panel for inborn error of metabolism, urine amino acids, and organic acids showed elevation in urine aspartic acid, 3-hydroxybutyrate, and acetoacetate in the absence of acidosis or hyperglycemia. Lumbar puncture was unremarkable, with cerebrospinal fluid studies demonstrating normal levels of myelin basic protein and lactic acid and no growth on culture. Magnetic resonance imaging (MRI) revealed severe diffuse profound white matter disease extending from the subcortical white matter to the deep white matter, involving the cerebellum and cerebrum with relative sparing of the temporal lobes (Figure 1).

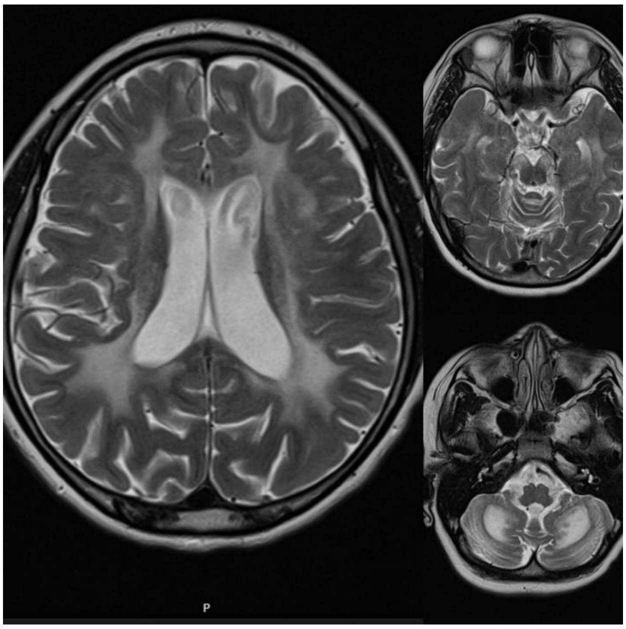

Figure 1: MRI brain with contrast shows severe diffuse profound white matter disease extending from the subcortical white matter to the deep white matter involving the cerebellum and cerebrum with relative sparing of the temporal lobes.

Diagnosis

Given the clinical presentation and relative temporal lobe sparing, patient's radiological findings were concerning for vanishing white matter disease. However, such cases have a very broad differential such as inborn errors of metabolism disorders, severe demyelinating disease, leukodystrophies, nonketotic hyperglycemia, 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency, urea cycle disorders, collagen vascular diseases, viral infections, and end-stage white matter disease. The patient was later found to have the PSAP gene associated with autosomal recessive combined saposin deficiency.

Social needs awareness

Our patient and his family live in a trailer in an unincorporated community miles away from the nearest specialty care center. The family requires food stamps and other state-sponsored assistance to supplement the mother's income and make ends meet. Despite initial adherence to treatment plans, his mother appeared to have significant gap in understanding the severity of his developmental regression and the specialized care he required, which led to a relapse in his case. Over a series of finely scheduled follow-ups and well-established interdisciplinary team planning led by our team with neurology, genetics, and ophthalmology, the patient's mother finally realized the diagnosis and its prognosis, which made inclusive parental decision-making more adherent to the general plan. That orientation allowed for more cooperation from the parents which helped facilitate the patient to receive therapies such as occupational, physical, and speech. In addition, social workers were continuously involved ensuring the patient's parents were not met with financial burdens from the extensive therapies.

Patient course

Over the course of a few months after diagnosis, the patient's disease progression worsens as expected. However, adherence to therapies remains, and close monitoring via scheduled physical exams and virtual visits to ensure any acute deterioration is met with appropriate, timely intervention. As the patient clinically progresses, further discussions to prepare the parents for long-term plans are being routinely done. The importance of palliative care in pediatric patients such as ours and parental education on its roles and values is one of the core pillars in understanding and establishing a long-term management plan.

DISCUSSION

One of the most important cornerstones in such rare diseases is an early index of suspicion that leads to appropriate diagnosis and early onset intervention. Palliative care medicine's role and value in pediatrics and early discussion about prognosis is always essential to set realistic goals and expectations for not just the parents and patients but also for the multiple care providing team.

VWMD hallmark characteristics are progressive neurological deterioration, cerebellar ataxia, and spasticity.[3] Additionally, seizures, late-stage optic atrophy, and progressive macrocephaly have been noted in only a handful of cases.[4,5] The typical onset is in early childhood, specifically at ages two–six years.[2] A later onset often correlates with a milder disease course. Even in the more typical early childhood presentation, the initial development of the patient is often normal, and they may achieve the most motor and mental milestones in a timely manner.[4] VWMD exhibits an autosomal recessive mode of inheritance. Eukaryotic translation initiation factor 2 B, a principal regulator of the integrated stress response, has five genes (EIF2B1-5), each encoding a unique subunit.[6] When mutated, any of these genes can cause VWMD, although EIF2B5 is the most commonly mutated.[4,7,8] The effects of mutations are predominantly observed in the brain, but there have been occasional documentation of systemic involvement.[9,10]

Owing to defects in the principal integrated stress response regulator EIF2B, the pathogenesis of VWMD involves significant vulnerability to trauma, as in our case, or other stressors, such as infection.[2] Interestingly, the first identified case of VWMD was in a 36-year-old woman with gait difficulties who demonstrated rapid deterioration after minor physical trauma.[11] Whether any intervention could have precipitated deterioration was unclear in our case. Although such measures are unlikely to prevent the disease from presenting, it has been theorized that they may decrease the severity of acute attacks that lead to rapid white matter destruction.[2]

MRI is the imaging modality of choice for VWMD. The disease has a characteristic pattern of diffuse disappearance of white matter with relative sparing of the temporal lobes, which is especially consistent among affected children.[2] MRI may be used periodically throughout the disease to assess the progression of degeneration.[12] As the disease progresses, the white matter begins to be replaced by fluid, correlating with the massive loss of myelin seen on autopsy.[9] Astrocytic dysfunction can be used as a proxy for disease severity at the cellular level. VWMD cases with more severe symptoms often present with cystic decay on imaging, whereas adequate gliosis is a sign of proper neuronal response to injury in less severe cases. Astrocytes and oligodendrocytes are glial cells that are predominantly affected by this disease.[2] Relatively few biomarkers have been proposed for VWMD. Elevated CSF glycine is a marker found in many cases of VWMD and may be derived from a primary derangement in glycine metabolism or secondary to excitotoxic damage to cells.[1,14] Decreased CSF asialotransferrin concentrations have also been proposed as biomarkers thought to arise from either abnormal turnover of CSF transferrin or reduced de novo production from local cells.[15] Upon review of the literature, we did not encounter any other documented cases of VWMD presenting with ketonuria in the absence of hyperglycemia or other evidence of diabetes. We found one case of diabetic ketoacidosis in a patient with VWMD.[16] The pathogenesis of VWMD involving mutations in EIF2B1-5 may provide a clue regarding the presence of ketonuria in our patient. EIF2B is a transcription factor vital for the initiation of protein translation. Under normal circumstances, insulin, in the presence of glucose and amino acids, activates EIF2B, leading to increased protein synthesis.[17] With a mutation in EIF2B genes, EIF2B has been shown to confer decreased resilience to oxidative stress in oligodendrocytes, astrocytes, and their progenitors, resulting in chronic low ATP status despite compensation efforts.[18] Astrocytes have been identified as primary cells capable of cytogenesis in the brain.[19] It is possible that the increased metabolic demand in these cells caused by oxidative stress in the setting of EIF2B mutation is a trigger for ketogenesis, even with adequate glucose supply. Hypoammonemia is likely secondary to ketone-induced inhibition of renal ammoniagenesis.[20] PSAP-related autosomal recessive combined saposin deficiency (PSAD), a metachromatic leukodystrophy due to saposin B deficiency, can present with severe neurological disease, hyperkinetic movement disorder, myoclonus, and respiratory insufficiency. In addition, PSAP is associated with a progressive neurological disorder characterized by motor delay, regression of gained skills, and nerve demyelination.[21] Combined saposin deficiency is an extremely rare condition that almost only reported in literature close to eleven times.[22-24] It has been described as a rapidly progressive neurovisceral lysosomal storage disorder due to accumulated substrates in visceral cell types that ultimately lead to end organ death.[25] It is reported that intact prosaposin has a neuroprotective role by preventing the aforementioned substrate accumulations in both central and peripheral nervous systems, which can lead to a neuronal survival crisis. In addition, it prevents the accumulation of glycosphingolipids in non-neuronal tissue as well. Subcortical white matter lesions and cortical atrophy have been reported on neuroimaging.[26]

Treatment and prognosis

The current state of disease management revolves around avoiding stressors that can precipitate an acute deterioration attack, such as the liberal use of antibiotics and antipyretics and avoidance of contact sports.[2] Given his advanced medical needs and poor prognosis, our patient was referred for speech, occupational, and physical therapy. In addition, a close follow-up was performed at our outpatient pediatric clinic. Early involvement in social work for assistance with referrals and obtaining necessary supplies. Our treatment focused on maintaining the current level of functioning to sustain maximal independence in activities of daily living. Although gene therapy with CRISPR/Cas-9 and targeting the integrated stress response for the treatment of VWMD are promising areas of study, there is no current treatment that can halt or slow disease progression.[27] Owing to the uncommon nature of VWMD, parents and healthcare providers may not recognize the constellation of symptoms due to progressive white matter loss. The devastating fact of VWMD is that after symptoms are present, patients like ours rarely survive for more than a few years, as proven by his rapid clinical deterioration during subsequent outpatient visits.

CONCLUSION

Medical providers' awareness with such rare progressive neurological disease is pertinent to early diagnosis and high index of suspicion. Understanding of social determinants of health come into play, as lower health literacy coupled with socioeconomic challenges and the resultant lack of access to expert care lead to difficulty obtaining services that can improve a patient's quality of life.

Recommendations

As with many neurodegenerative conditions, early diagnosis and subsequent steps to maintain the remaining function are essential in prolonging the quality of life in patients with VWMD. Early establishment of multidisciplinary care conferences with close follow-ups for both medical and social adherence to the management plan is crucial for timely interventions for acute deterioration and long-term care planning.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Knaap MS, Breiter SN, Naidu S, Hart AA, Valk J. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology. 1999;213(1):121-33.
2. Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. Lancet Neurol. 2006;5(5):413-23.
3. Vinogradsky EI, Otallah SI. Vanishing White Matter Disease Diagnosis After Athletic Concussion in an Adolescent Male Patient. Clin J Sport Med. 2021;31(4):207-9.
4. Pronk JC, Kollenburg B, Scheper GC, Knaap MS. Vanishing white matter disease: a review with focus on its genetics. Ment Retard Dev Disabil Res Rev. 2006;12(2):123-8.
5. Viñas E, Pineda M, Cusí V, López-Laso E, Del Pozo RL, Gutiérrez-Solana LG, et al. Vanishing white matter disease in a spanish population. J Cent Nerv Syst Dis. 2014;6:59-68.
6. Boone M, Wang L, Lawrence RE, Frost A, Walter P, Schoof M. A point mutation in the nucleotide exchange factor eIF2B constitutively activates the integrated stress response by allosteric modulation. Elife. 2022;11:e76171.
7. Knaap MS, Leegwater PA, Könst AA, Visser A, Naidu S, Oudejans CB, et al. Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter. Ann Neurol. 2002;51(2):264-70.
8. Leegwater PA, Pronk JC, Knaap MS. Leukoencephalopathy with vanishing white matter: from magnetic resonance imaging pattern to five genes. J Child Neurol. 2003;18(9):639-45.
9. Knaap MS, Barth PG, Gabreëls FJ, Franzoni E, Begeer JH, Stroink H, et al. A new leukoencephalopathy with vanishing white matter. Neurology. 1997;48(4):845-55.
10. Knaap MS, Berkel CG, Herms J, Coster R, Baethmann M, Naidu S, et al. eIF2B-related disorders: antenatal onset and involvement of multiple organs. Am J Hum Genet. 2003;73(5):1199-207.
11. Eicke W. Polycystic transformation of the medulla with progressive course. Atypical diff use sclerosis? Arch Psychiatrist Nerve Cr. 1962;203:4.
12. Stellingwerff MD, Al-Saady ML, Brug T, Barkhof F, Pouwels PJW, Knaap MS. MRI Natural History of the Leukodystrophy Vanishing White Matter. Radiology. 2021;300(3):671-80.
13. Knaap MS, Wevers RA, Kure S, Gabreëls FJ, Verhoeven NM, Raaij-Selten B, et alJ. Increased cerebrospinal fluid glycine: a biochemical marker for a leukoencephalopathy with vanishing white matter. J Child Neurol. 1999;14(11):728-31.
14. Sugiura C, Miyata H, Oka A, Takashima S, Ohama E, Takeshita K. A Japanese girl with leukoencephalopathy with vanishing white matter. Brain Dev. 2001;23(1):58-61.
15. Vanderver A, Schiffmann R, Timmons M, Kellersberger KA, Fabris D, Hoffman EP, et al. Decreased asialotransferrin in cerebrospinal fluid of patients with childhood-onset ataxia and central nervous system hypomyelination/vanishing white matter disease. Clin Chem. 2005;51(11):2031-42.
16. Alamri H, Al Mutairi F, Alothman J, Alothaim A, Alfadhel M, Alfares A. Diabetic ketoacidosis in vanishing white matter. Clin Case Rep. 2016;4(8):717-20.
17. Campbell LE, Wang X, Proud CG. Nutrients differentially regulate multiple translation factors and their control by insulin. Biochem J. 1999;344 Pt 2(Pt 2):433-41.
18. Herrero M, Daw M, Atzmon A, Elroy-Stein O. The Energy Status of Astrocytes Is the Achilles' Heel of eIF2B-Leukodystrophy. Cells. 2021;10(8):1858.
19. Foll C, Levin BE. Fatty acid-induced astrocyte ketone production and the control of food intake. Am J Physiol Regul Integr Comp Physiol. 2016;310(11):1186-92.
20. Lemieux G, Pichette C, Vinay P, Gougoux A. Cellular mechanisms of the antiammoniagenic effect of ketone bodies in the dog. Am J Physiol. 1980;239(5):F420-6.
21. Johns Hopkins University. Online Mendelian Inheritance in Man, OMIM®. Combined saposin deficiency, 2020. Available at: https://www.omim.org/entry/611721. Accessed on 22 April 2023.
22. Motta M, Tatti M, Furlan F, Celato A, Di Fruscio G, Polo G, et al. Clinical, biochemical and molecular

characterization of prosaposin deficiency. Clin Genet. 2016;90(3):220-9.

23. Harzer K, Paton BC, Poulos A, Kustermann-Kuhn B, Roggendorf W, Grisar T, et al. Sphingolipid activator protein deficiency in a 16-week-old atypical Gaucher disease patient and his fetal sibling: biochemical signs of combined sphingolipidoses. Eur J Pediatr. 1989;149(1):31-9.
24. Bhat V, Thergaonkar RW, Thakur M, Rajkamal T. Combined saposin deficiency: A rare occurrence. Med J Armed Forces India. 2023;79(2):238-40.
25. Hulková H, Cervenková M, Ledvinová J, Tochácková M, Hrebícek M, Poupetová H, et al. A novel mutation in the coding region of the prosaposin gene leads to a complete deficiency of prosaposin and saposins, and is associated with a complex sphingolipidosis dominated by lactosylceramide accumulation. Hum Mol Genet. 2001;10(9):927-40.
26. Sikora J, Harzer K, Elleder M. Neurolysosomal pathology in human prosaposin deficiency suggests essential neurotrophic function of prosaposin. Acta Neuropathol. 2007;113(2):163-75.
27. Hillen AEJ, Hruzova M, Rothgangl T, Breur M, Bugiani M, van der Knaap MS, Schwank G, Heine VM. In vivo targeting of a variant causing vanishing white matter using CRISPR/Cas9. Mol Ther Methods Clin Dev. 2022;25:17-25.

Cite this article as: Aly A, Villanos MT, Zientek E, Riddle M, Moreno I. Vanishing white matter disease: a case of combined saposin deficiency. Int J Contemp Pediatr 2023;10:946-50.