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Vanishing White Matter Disease- Report of two Cases

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Abstract

Vanishing white matter (VWM) disease is a chronic progressive childhood onset leukodystrophy that result in central nervous system demyelination, often precipitated by some stressful events. There is wide phenotypic variation buy typical MRI findings are diagnostic in most of the patients. Here we report two cases of vanishing white matter disease with typical MRI findings.

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Introduction

Vanishing white matter (VWM) disease is a childhood onset progressive leukoencephalopathy transmitted by autosomal recessive inheritance. Synonyms are 'childhood ataxia and central nervous system hypomyelination (CACH)[9], 'myelinopathiacentralis diffusa'[2]. It is one of the prevalent leukoencephalopathy characterized by normal or near normal early developmental period followed by an episodic and chronically progressive neurological deterioration. Though It can occur in any age from neonate to adulthood, classical and most common variant occur in childhood between age 2-6 year[3,9]. Clinically characterized by progressive cerebellar ataxia, spasticity and optic atrophy after an episode of physiologic stress like fever, freight or trauma(Ref). VWM is caused by mutation in the genes encoding the translation initiation factor eIF2B[4,5]. MRI of the brain is essential for diagnosis[6]. Management is only supportive and symptomatic, as there is no specific treatment available. We are presenting two cases of vanishing white matter disease based on typical clinical presentation and MRI findings.

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Case Report-1

A 5 years old female child, 3rd issue of non-consanguineous parents presented with progressive deterioration of motor skill and visual impairment for 2 and ½ years. Prior to this illness she had history of febrile status epilepticus followed by unconsciousness. Then she developed walking difficulty and cannot maintain balance properly. She also had history of difficulty in seeing far and near objects. Another episode of afebrile status epilepticus occurred 1 and ½ months back. There is no history of speech difficulty or memory loss .There was no history of trauma. This child was delivered by normal vaginal delivery and cried immediately after birth. She was developmentally age appropriate upto 2 and ½ years of age. She was immunized as per EPI schedule .Other family members was healthy. She was conscious, cooperative, oriented. Her vitals were stable. Anthropometrically she was well thriving. Nervous system examination shows tone increased in lower limb, deep tendon reflexes exaggerated, and planters were bilaterally extensor and

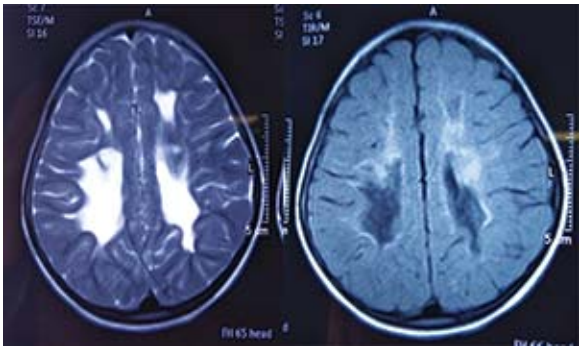

Fig.-1: T2 image showing bilateral symmetrical involvement of white matter with near CSF intensity, sparing of subcortical white matter and FLAIR image showing hypointense signal in involved white matter (case 1).

gait ataxic. All cranial nerves were intact. Ophthalmological examination showed nystagmus, optic atrophy in both eyes. Her blood picture was normal. Brain MRI shows periventricular white matter hyperintensity with near CSF intensity in T2 image. EEG shows multifocal discharge. This patient was treated with antiepileptic drugs and other supportive management. Parents were counseled about the prognosis and outcome of the disease. This patient was discharged with advice to avoid head trauma, and any stressful condition .Now she is on regular follow up.

Case Report-2

An 11 months old male child, presented with loss of acquired skill following fever .Prior to this illness the child could walk with support but now cannot stand. There was no history of trauma. He was developmentally age appropriate upto11 months of age. This child had no history of perinatal events. There is no consanguinity and no family history of such type of illness. He is immunized as per EPI schedule .On examination; he was conscious, cooperative, interested to surroundings. His Vitals were normal. Anthropometrically well thriving. Nervous system examination shows bulk of muscle was normal, tone was increased lower limbs, deep tendon reflex were exaggerated and planter was bilaterally extensor. His basic metabolic screening was normal Brain MRI shows bilateral symmetrical periventricular white matter hyper intensity .Ophthalmologic evaluation shows bilateral optic atrophy. This patient was treated with supportive management. Parents were counseled about the outcome of the disease. They were also advised to avoid head trauma, stressful condition she was advised for regular follow up.

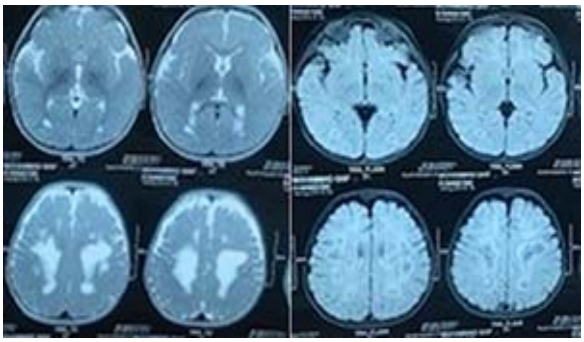

Fig.-1: *T2 image showing bilateral symmetrical involvement of white matter with near normal CSF intensity and FLAIR image showing hypointense signal due to cystic degeneration (case 2)*

Discussion

Vanishing white matter disease (Childhood ataxia and central nervous system hypomyelination) is a slowly progressive disorder of white matter. At first, Dr. Hanefeld and Dr. Schiffmann and their colleagues identified the disease in 1993-94. The precise incidence and prevalence of VWM is unknown, but it is one of the most prevalent childhood leukodystrophies8.Van dar Knapp et. Al(YEAR), described the age of onset of VWM as an infantile form (onset age 1 year), an early childhood onset form (onset age 2-4 years), a late childhood/juvenile onset form (onset age 5-15 years), and an adult onset form (onset age >15years)1. One of our reported patients presented with infantile form and another one had late childhood onset form. Infantile form is one of the fewer forms of the VWM. Infantile form constituted 8.2% of the 85 cases with mutation proved VWM(Ref). Early childhood form 57.6%, late childhood/juvenile form 29.4%, adult form 4.7% respectively10. Patient usually presents with cerebellar ataxia, spasticity, optic atrophy with loss of vision and epilepsy. Cognition is often better preserved.3,9,11.Both of our patient presented with typical clinical features including ataxia, spasticity and optic atrophy with preserved cognitive function and one also had epilepsy. Van der Knapp et. al, proposed a diagnostic criteria for ease of diagnosis of the disorder-(a) Normal or near normal Initial psychomotor development, (b) Episodic and chronic progressive neurological deterioration,(c) Spasticity and cerebellar ataxia (epilepsy and optic atrophy may also occur), (d) Magnetic resonance imaging findings of symmetrical and bilateral involvement of the cerebral white matter, with parts or all of the white matter demonstrating signal intensities similar to that of CSF over time9.Both of our patient had initial normal developmental periods followed by a chronic progressive neurological deterioration after an episode of febrile event. Some stressful conditions including fever, head trauma, and fright etc. are considered as provoking factors responsible for onset of the disease and the episodes of neurologic deterioration3,7,9,12. During acute illness

consciousness may be impaired, from somnolence to coma, and death also may occur. Otherwise acute

decompensation usually follows a slowly progressive course 3, 7,9,12. One of our patients had an episode of acute decompensation followed by mild improvement and then a slowly progressive clinical course. Though not obligatory, optic atrophy is an important feature of this condition and both of our patient developed optic atrophy. It could be a nonspecific marker of the disease progression or may occur due to environmental or genetic susceptibility13. MRI of brain is mandatory for diagnosis. MRI abnormalities are present in almost all patients with VWM, even in the asymptomatic at- risk family members1. Magnetic resonance imaging typically shows diffuse and symmetrical involvement of the cerebral white matter. Cerebellar white matter and brainstem, especially pontine tegmentam also involved. Inner rim of corpus callosum may be involved early but usually there is sparing of the U fibers. The cortical grey matter is not involved in VMD. Contrast enhancement usually does not occur14. Over time there is progressive rarefaction and cystic degeneration of the white matter and eventually it is totally replaced by CSF-like signal intensity. Van der Knapp et.al,(Year) established an MRI criteria for diagnosis15. MRI findings of both of our patients are consistent with the typical MRI features of vanishing white matter disease showing bilateral symmetric T2 hyperintensities of periventricular white matter with near CSF intensities and FLAIR image shows attenuation. Magnetic resonance spectroscopy (MRS) findings are not specific for VWM and there may be reduction of the normal metabolite peaks with the accumulation of glucose and lactate15. Biochemical markers including Cerebrospinal fluid (CSF) analysis may be done in patient with inconclusive MRI features and may demonstrate a decreased asialotransferrin: transferrin ratio. On genetic testing there may be mutation in any of five genes EIF2B1, EIF2B2, EIF2B3, EIF2B4, and EIF2B5. Mutation mostly found in EIF2B5 (68.4%) and disease with EIF2B2 mutations found to have a better course than EIF2B5 mutations14. There is no specific management for this condition. Treatment is only supportive and symptomatic as we provide to our patients.

Conclusion

Vanishing white matter disease or childhood ataxia with central hypomyelination (CACH syndrome) is a chronic and progressive white matter disorder, with unique clinical and radiological features. There is no specific treatment, but as it often exacerbated by infection or minor head trauma, avoidance of stressful condition could be important. With comprehensive multidisciplinary care the symptoms of VWM can be managed to improve the quality of life.

References

1. Van der Knaap MS, Fogli A, Boespflug-Tanguy O, Abbink TE, Schiffmann R. Childhood ataxia with central nervous system hypomyelination/vanishing white matter. 2003 Feb 20 [Updated 2019 Apr 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington,Seattle;1993-2021.BookshelfURL: https://www.ncbi.nlm.nih.gov/books/
2. Brück W, Herms J, Brockmann K, Schulz Schaeffer W, Hanefeld F. Myelinopathia centralis diffusa (vanishing white matter disease): evidence of apoptotic oligodendrocyte degeneration in early lesion development. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2001 Oct;50(4):532-6.
3. Hanefeld F, Holzbach U, Kruse B, Wilichowski E, Christen HJ, Frahm J. Diffuse white matter disease in three children: an encephalopathy with unique features on magnetic resonance imaging and proton magnetic resonance spectroscopy. Neuropediatrics. 1993 Oct;24(05):244-8.
4. Labauge P, Fogli A, Niel F, Rodriguez D, Boespflug-Tanguy O. CACH/VWM syndrome and leucodystrophies related to EIF2B mutations. Rev Neurol (Paris). 2007 Sep; 163(8-9): 793-9. French. doi: 10.1016/s0035-3787(07)91461-7. PMID: 17878805.
5. Van Der Knaap MS, Leegwater PA, Könst AA, Visser A, Naidu S, Oudejans CB, Schutgens RB, Pronk JC. Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2002 Feb;51(2):264-70.
6. Van der Lei HD, Steenweg ME, Barkhof F, de Grauw T, d'Hooghe M, Morton R, Shah S, Wolf N, van der Knaap MS. Characteristics of early MRI in children and adolescents with vanishing white matter. Neuropediatrics. 2012 Feb;43(01):022-6.
7. Van der Knaap M, Kamphorst W, Barth P, Kraaijeveld C, Gut E, Valk J. Phenotypic variation in leukoencephalopathy with vanishing white matter. Neurology. 1998;51(2):540-7. doi: 10.1212/wnl.51.2.540. PMID: 9710032.
8. Van der Knaap MS, Breiter SN, Naidu S, Hart AA, Valk J. Defining and categorizing leukoencephalopathies of

unknown origin: MR imaging approach. Radiology. 1999 Oct;213(1):121-33. doi: 10.1148/radiology.213.1.r99se01121. PMID: 10540652.

9. Van der Knaap MS, Barth PG, Gabreëls FJ, Franzoni E, Begeer JH, Stroink H, Rotteveel JJ, Valk J. A new leukoencephalopathy with vanishing white matter. Neurology. 1997 Apr 1;48(4):845-54.

10. Fogli A, Schiffmann R, Bertini E, Ughetto S, Combes P, Eymard-Pierre E, Kaneski CR, Pineda M, Troncoso M, Uziel G, Surtees R. The effect of genotype on the natural history of eIF2B-related leukodystrophies. Neurology. 2004 May 11; 62(9):1509-17.

11. Schiffmann R, Moller JR, Trapp BD, Shih HH, Farrer RG, Katz DA, Alger JR, Parker CC, Hauer PE, Kaneski CR, Heiss JD. Childhood ataxia with diffuse central nervous system hypomyelination. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1994 Mar;35(3):331-40.

12. Vermeulen G, Seidl R, Mercimek-Mahmutoglu S, Rotteveel JJ, Scheper GC, van der Knaap MS. Fright is a provoking factor in vanishing white matter disease. Ann Neurol. 2005 Apr; 57(4):560-3. doi: 10.1002/ana.20418. PMID: 15786451.

13. Barros SR, Parreira SCR, Miranda AFB, Pereira AMB, Campos NMP. New Insights in Vanishing White Matter Disease: Isolated Bilateral Optic Neuropathy in Adult Onset Disease. J Neuroophthalmol. 2018 Mar;38(1):42-46. doi: 10.1097/WNO.0000000000000565. PMID: 28902089.

14. Bugiani M, Boor I, Powers JM, Scheper GC, van der Knaap MS. Leukoencephalopathy with vanishing white matter: a review. Journal of Neuropathology & Experimental Neurology. 2010 Oct 1;69(10):987-96.

15. van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. The Lancet Neurology. 2006 May 1;5(5): 413-23.