Vanishing white matter in Saudi Arabia

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ABSTRACT

يعتبر مرض تلاشي المادة البيضاء (VWMD) هو أحد الأمراض الغير شائعة التشخيص، والتي تصيب المادة البيضاء في الدماغ لدى جميع الأعمار خصوصاً عند الأطفال. هذا المرض ينتمي إلى مجموعة متباينة الوصف من الناحية السريرية والجينية تدعى جميعا أمراض اعتلال العامل المحفز النوي 2ب (eIF2B). تم وصف هذا المرض في سلالات بشرية مختلفة، وهنا نصف – على حد علمنا – أول حالة لمرض تلاشي المادة البيضاء (VWMD) تُسجل في المملكة العربية السعودية، مع مناقشة لصفات المرض وطرق تشخيصه.

Vanishing white matter disease (VWMD) is an under-diagnosed condition that affects the brain's white matter at all ages, especially in the pediatric age group. It belongs to a clinically and genetically heterogeneous group of disorders, collectively known as eukaryotic initiation factor 2B-related disorders. The disorder has been described in different ethnic groups. Here, we describe a case of VWMD from Saudi Arabia.

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Vanishing white matter disease (VWMD) is a recently described disorder characterized by cystic degeneration and progressive loss (vanishing) of the CNS white matter due to mutations in eukaryotic initiation factor 2B. The classic presentation of the disorder is in early childhood as progressive spastic ataxia with variable seizures, optic atrophy, and late dementia. A unique feature of the disease is the development of abrupt neurologic deteriorations, including coma after a physical stress situation (such as mild head trauma or febrile illness).[1] Eukaryotic initiation factor 2B-related disorders (eIF2B) are inherited as autosomal recessive disorders due to either homozygous or compound heterozygous mutations in the 5 genes encoding subunits of the eIF2B factor.[2] We present a case of a 2-year-old Saudi girl whose disease symptoms occurred after having a febrile illness. We aim to highlight the existence of this disease in Saudi Arabia and to alert physicians to consider this entity when caring for children presenting with similar case.

Case Report. A 2-year-old girl was evaluated for episodic deterioration of level of consciousness, regression of milestones, and lately, seizures. Her prenatal and perinatal history was normal. Before referral to our center, she had a febrile illness with acute deterioration in level of consciousness at age of 15 months necessitating intensive care unit (ICU) admission. Work up including brain CT scan, and cerebrospinal fluid (CSF) studies were reportedly inconclusive, and no final diagnosis was reached. She improved and was discharged, but was still unable to talk or stand. Six months later, she developed high-grade fever due to urinary tract infection. The child again deteriorated neurologically for which she was admitted to our Pediatric ICU due to encephalopathy. Three weeks after PICU admission, the child started to have seizures that were difficult to control. Clinical examination revealed a macrocephaly with head circumference of 50 cm (>95th centile). No obvious dysmorphic features. Her pupillary reaction to light was very sluggish, but fundus examination was normal. She had positive corneal reflex but weak gag and cough reflexes. She was intubated and mechanically ventilated with no peculiar pattern of breathing. She was initially drowsy to stuporous, but became comatose after approximately 3 weeks. Her motor examination showed good muscle bulk and generalized reduced muscle tone, but with increased deep tendon reflexes in all limbs. Systemic exam did not show organomegaly, or any other masses. No abnormal skin rash or pigmentation. Investigations showed normal values of complete blood count with differential, glucose, coagulation profile, and

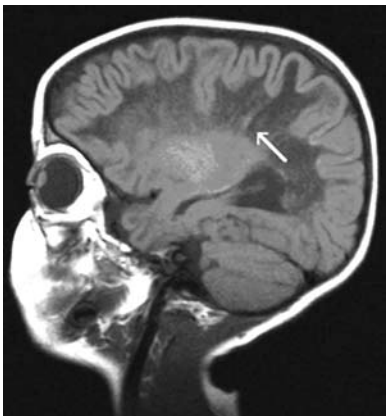

Figure 1- Sagittal T1-weighted image showing extensive white matter low signals, with evidence of white matter stripes.

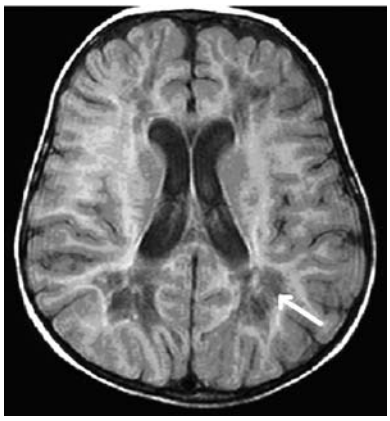

Figure 2 - Axial FLAIR showed white matter degeneration and rarefaction.

electrolytes. Her CSF study revealed white blood cells = one cell/mm^3 (normal = 0-5), red blood cells = one cell/mm^3 (normal 0-0), glucose = 4.6 mmol/l (normal: 2.2-3.9 mmol/l), protein = 572 mg/l (normal: < 440 mg/l), and lactate = 1.7 mmol/l (normal < 2mmol/l). Metabolic workup showed normal CSF glycine, normal urine organic acids, and normal blood tandem mass spectrometry. Urine test for N-acetyl-aspartic acid, to rule out Canavan disease, was negative. Initial electroencephalogram demonstrated generalized slowing compatible with encephalopathic state. Muscle biopsy showed mildly increased lipid on oil red O stain, thought to be related to patient immobility. There was no evidence of mitochondrial cytopathy, or features suggestive of lipid storage disorder. An MRI of the brain without contrast revealed diffuse and symmetrical bilateral signal abnormalities within the cerebral white matter, with a high signal on T2-weighted images and a low signal on T1-weighted images, **Figure 1**. The fluid attenuation inversion recovery (FLAIR) images revealed that part of the abnormal cerebral white matter had a low signal, suggestive of white matter rarefaction and cystic degeneration (**Figure 2**). There were no mass lesions and no features suggestive of ischemic, embolic, or inflammatory process. The imaging picture was consistent with the diagnosis of VWMD. A genetic study confirmed VWM disease. It showed that the child has homozygous mutation of EIF2B3: c.602A-G/p. Asp201Gly. Her parents were found to be carriers of the same mutation.

Discussion. Between 1962 and 1997, many case reports described a CNS disease with progressive white matter destruction and cystic degeneration found at autopsy.[1,3] In 1998, Van der Knaap et al[5] further described that disease as childhood onset progressive leukoencephalopathy with an autosomal recessive pattern of inheritance, and recognized both minor head trauma and febrile illness as provoking factors. They also concluded that MRI and magnetic resonance spectroscopy were indicative of cystic white matter degeneration rather than hypomyelination.[4] Vanishing white matter is one of the most prevalent inherited childhood white-matter disorders, although its exact incidence has not been determined. The disease seems to be particularly common in white populations, although no systematic study to assess the incidence in different populations has been carried out.[1] Clinical manifestations commonly but not always include the onset of progressive neurological deteriorations between 2-6 years, irritability, and seizures. The episodic change in level of consciousness might progress to coma and death. The sudden neurological deteriorations may be triggered by stress, febrile illness, minor trauma, or even acute fright.[1] If recovery occurs, it is usually incomplete. Most of the patients die after a few years.[1] Vanishing white matter disease was also described in infants, for whom the course of the disease is usually more aggressive, and rarely in adults with psychiatric symptoms, dementia and seizures.[5] It can involve systems other than brain white matter. The most common are the eyes, causing cataracts, and kidneys, leading to kidney hypoplasia.[6] Our patient has a unique feature, which is macrocephaly, a finding that has been reported before in 3 children aged 14-16 months old, and were found to have a heterozygous mutation in eIF2B5.[7]

Overall, the phenotypic presentation is wide both in terms of age of onset, systemic involvement or progression. Earlier onset cases tend to be more severe, and have more extra-neurological organ involvement. Genotype-phenotype correlation is an evolving area of research. Some mutations although not invariably, are associated with a mild phenotype, whereas other mutations are consistently associated with a severe phenotype. However, there is much variation between patients carrying the same mutations and between

affected siblings in the same family. Consequently, environmental and other genetic factors influence the phenotype as well.[1]

Diagnosis. An MRI of the brain is usually quite diagnostic. Diagnostic criteria have been developed that include 7 obligatory, and 3 suggestive criteria.[1] Essential criteria basically include MRI evidence of either diffuse or extensive white matter rarefaction with CSF-filled cystic degeneration of the cerebral hemispheres with relative sparing of the temporal lobes, and absence of cysts within the cerebellar hemispheres. There should be no enhancement on contrast administration. The immediate subcortical white matter may be spared. Suggestive features include stripe like appearance on coronal and sagittal T1 or FLAIR images indicative of sparring of axons with degeneration of the white matter. The inner rim of the corpus callosum and the central pontine tegmental tracts may be involved as well. Elevated CSF glycine, and low CSF asialotransferrin were recently recognized as disease markers.[8] However, because of its low sensitivity and specificity, these tests are not widely used.[1,8] Differential diagnoses of episodic encephalopathy may include acute disseminated encephalomyelitis, mitochondrial encephalopathy, and infectious processes like encephalitis. The brain MRI, however, would be a very helpful diagnostic tool in such cases. In contrast to VWM, MRI usually shows multifocal white matter lesions with an asymmetrical distribution in acute demyelinating encephalomyelitis, and variable lesions involving both white and grey matter in encephalitis. Contrast enhancement and restricted diffusion in affected areas are features of both acute demyelinating encephalomyelitis and encephalitis, but not of VWM. In patients with sub-acute or chronic neurological deterioration, and an MRI showing diffuse cerebral white matter abnormalities with rarefaction and cystic degeneration, mitochondrial leukoencephalopathies are important disorders in the differential diagnosis. In mitochondrial defects, MRI may typically show well-delineated cysts, the white-matter abnormalities tend to be less diffuse, often display focal contrast enhancement, and usually contain areas of restricted diffusion, unlike in VWM[1]. In addition, in mitochondrial encephalopathy, MR spectroscopy would show abnormal high lactate peak, and may show basal ganglia abnormality as well.

Pathophysiology. The EIF2B complex acts as a down-regulator of protein synthesis during events regarded as stress at the tissue level, such as fever. Down-regulation of protein synthesis is part of normal cellular stress response. This can explain the triggering effect of stresses.[1,4] A defect in one of the eIF2B genes leading to decreased activity of the eIF2B complex may compromise the cellular stress response, and lead to expression of the VWMD phenotype.[9] Since 1990, genetic linkage studies identified the first gene related to VWMD, which was EIF2B5. The linkage location was found to be on chromosomes 3q27 and 14q24.[1,8] The VWMD can be related to mutations in any of the 5 genes (EIF2B1-5), encoding the 5 subunits of eukaryotic translation initiation factor eIF2B (eIF2B alpha, beta gamma, delta, and epsilon).[1,8] Two thirds of patients have mutations in EIF2B5, which is the largest identified subunit.[1] Our patient was found to have an uncommon novel mutation in eIF2B3. It was postulated that some mutations in the eIF2B genes might lead to the earlier more severe form of the disease associated with multi-organ involvement.

A DNA analysis was performed in 9 patients with an early-onset leukoencephalopathy and, in some of them, there was multi-organ involvement. The findings demonstrate that patients with VWMD can have very early even antenatal onset with decreased fetal movements, intrauterine growth retardation, oligohydramnios, and at birth microcephaly and contractures. More importantly, it was clear that patients with eIF2B genes can suffer from multi-organ dysfunction like ovarian dysgenesis, kidney hypoplasia, hepatosplenomegaly, or cataract as well as leukoencephalopathy. Affected siblings showed involvement of the same organs, where siblings carrying no mutations or only one mutation did not show signs of the disease.[10]

Pathology. Light microscopy demonstrates rarefaction of the white matter with relative sparing of axons and subcortical U-fibers. Based on the histologic criteria, childhood ataxia with CNS hypomyelination appears to be a predominantly glial related disorder with relative preservation of axons noted in all 6 pathologically studied cases of childhood ataxia with CNS hypomyelination that we examined.[4,11]

Treatment. There is no specific treatment for VWM. Avoidance of stressful situations known to provoke deterioration in VWM patients is essential. Liberal use of antibiotics and antipyretics, vaccinations, and abstinence from contact sports are simple but important measures. However, they are not sufficient to prevent the onset or progression of the disease. The most important consequence of available research findings of the last 5 years is probably that prenatal diagnosis has become available for families as soon as the disease-causing mutations in the index is identified.[1]

In conclusion, it is important for pediatricians and neurologists to be aware of this disease, and to include it in the differential diagnosis of any case presenting with extensive or progressive white matter disease manifesting as episodic encephalopathy. An MRI remains the most helpful diagnostic tool. Recognition of MR imaging features is vital in reaching the correct diagnosis, and providing appropriate family counseling.

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CASE REPORTS

Case reports will only be considered for unusual topics that add something new to the literature. All Case Reports should include at least one figure. Written informed consent for publication must accompany any photograph in which the subject can be identified. Figures should be submitted with a 300 dpi resolution when submitting electronically or printed on high-contrast glossy paper when submitting print copies. The abstract should be unstructured, and the introductory section should always include the objective and reason why the author is presenting this particular case. References should be up to date, preferably not exceeding 15.