

CASE REPORT

VANISHING WHITE MATTER DISEASE: A CASE REPORT

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ABSTRACT: Vanishing white matter disease (VWM) is one of the most prevalent inherited childhood Leucoencephalopathies. We report MR imaging features of vanishing white matter disease in a 4-year-old boy, who manifested with seizures, aphasia, spastic quadriparesis and myoclonic jerks. MRI of brain showed diffuse white matter signal changes of CSF intensity in all the sequences. MR spectroscopy of white matter showed severe decrease in NAA, choline and creatine and presence of lactate peak. Additional notable findings were diffuse extensive brain stem and thalamic atrophy. The clinico-radiological correlation was consistent with the diagnosis of vanishing white matter disease. Reporting of such cases may widen the spectra of these disorders.

KEYWORDS: MRI, MRS, vanishing white matter disease.

INTRODUCTION: Vanishing white matter disease (VWM) is one of the most prevalent inherited childhood leucoencephalopathies. The disease is variably called Myelinopathia Centralis Diffusa. Childhood ataxia and diffuse central nervous system hypomyelination are the common findings. The disease is characterized by chronic progressive and episodic deterioration with ataxia, spasticity and optic atrophy.¹ VWM is caused by mutation in any of the five genes encoding the subunits of eukaryotic translation initiation factor eIF2B.^{2,3} The disease has an autosomal recessive mode of inheritance. The cause of the disease is unknown. Previously it was known that there is no biochemical marker for this disease,⁴ but recently analysis of body fluids has revealed only a few biochemical markers for VWM. The first marker found was a consistent elevation of cerebrospinal fluid glycine concentrations with an elevated ratio of cerebrospinal fluid to plasma glycine concentrations.⁵ A decreased cerebrospinal fluid concentration of asialotransferrin is a recently identified biomarker for VWM.

CASE REPORT: A 4year old male child presented with history of recurrent seizures, aphasia, spastic quadriparesis associated with myoclonic jerks. The child term born with no history of birth asphyxia. No family history of epilepsy or mental retardation. The mother gives a history of elder sibling which was born pre term and died soon after birth. On examination the child was ill looking, mildly pale, BCG mark was present. His weight was 8 kg, supine length was 73 cm (within normal limit). His motor functions, bulk, power was normal but tone was increased. All reflexes of both upper and lower limbs were exaggerated, plantar was extensor and ankle clonus was also present bilaterally. Co-ordination and gait could not be elicited. His sensory functions and cranial nerve revealed intact. He was developmentally delayed as he was not able to sit. Other system revealed normal findings. His blood picture was normal. MRI of brain showed diffuse white matter signal changes of CSF intensity in all the sequences. MR spectroscopy of

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white matter showed severe decrease in NAA, choline and creatine and presence of lactate peak. Additional notable findings were diffuse extensive brain stem and thalamic atrophy. MRI revealed bilateral symmetrical diffuse extensive signal changes in white matter similar to that of CSF signal intensity in all lobes on T1W (hypointense), PD (hypointense), FLAIR (hypointense) and T2W (hyperintense) images with a very thin boundary between CSF and white matter. There was diffuse involvement of deep and subcortical white matter, arcuate fibers, internal capsules, external capsule and corpus callosum. The cerebral cortex was thin with normal sulcal and gyral pattern. Thalamus on either side was atrophic. There was severe brain stem and cerebellar atrophy. Ventricles were dilated, likely due to white matter changes. A cavum septum pellucidum was noted. Basal ganglia were normal. In vivo localized multi-voxel proton spectrometry was done (Hybrid 2D chemical shift imaging; TE = 135 ms) from the white matter and cerebral cortex. The MRS of white matter showed severe decrease in NAA. Lactate peak was also noted. MRS of cerebral cortex showed normal spectral pattern.

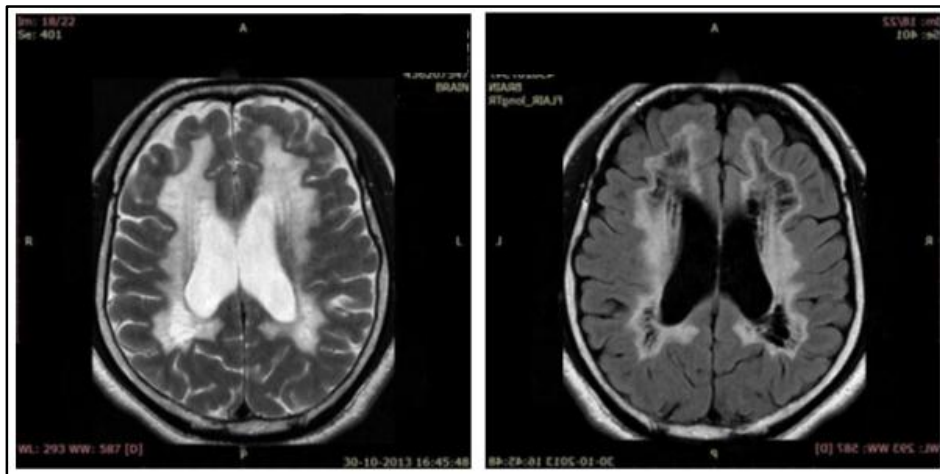


Figure 1

Figure 2



Figure 3

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Axial T2 weighted image shows diffuse white matter hyperintensity similar to CSF intensity extending from periventricular white matter to the subcortical arcuate fibres. Axial FLAIR image shows white matter vanished and replaced by near-CSF intensity fluid i.e., it attenuated. Axial T1 weighted image shows diffuse white matter hypointensity similar to CSF intensity.

DISCUSSION: The first time this disease was documented in 1962 when Eickle studied a 36 year old woman.¹ In 1993-94, Dr. Hanefeld and Dr. Schiffmann and their colleagues identified the disease. It is characterized by chronic progressive neurological deterioration with cerebellar ataxia, usually less prominent spasticity and relatively mild mental decline.^{2,3} Epilepsy is common. VWM disease has an autosomal recessive mode of inheritance. Characteristically, there are additional episodes of major and rapid deterioration following minor head trauma and especially febrile infections.^{4,5} The classical and most common variant of Vanishing white matter disease has its onset in childhood, at age 2-6 years.^{6,7} though this disease may have an early infantile or antenatal onset.⁸⁻¹⁰ that had happened in our patient. Optic atrophy with loss of vision may occur⁸ but that was not present in our patient. The baby had not a history of acute frightening that recently has been reported as another provoking factor.⁹ MRI of the brain is usually diagnostic in VWM. It shows an abnormal signal of all or almost all cerebral white matter with relatively spared U-fibers in some cases and progressive rarefaction and cystic degeneration of the affected white matter that is replaced by fluid.^{9,10,11} There have been important advances in the diagnosis of VWM because of genetics since 1996. VWM leukoencephalopathy is caused by mutations in the five genes (eIF2B1–5) encoding the five subunits of eukaryotic translation initiation factor eIF2B (eIF2B α , β , δ , γ , and ϵ).

Pathological study had shown axonal loss, hypomyelination, demyelination and gliosis, primarily involving the white matter with cortical sparing. Abnormal foamy oligodendroglial cells are identified and are unique for vanishing white matter.¹² Pontine tegmental white matter may also be involved.¹³ Increased cerebrospinal glycine level is noted and may be secondary to excitotoxic brain damage.^{13,14} Diagnostic criteria for diagnosing this disease include normal initial psychomotor development, deterioration following infection or trauma, presence of ataxia and spasticity with MR features of diffuse white matter signal changes with signal intensity of CSF on all pulse sequences.^{15,16,17} Additional features are lesions in central tegmental tracts and basis pontis. Subcortical white matter involvement is early and severe. Cerebellar or primary vermian atrophy has been documented with or without involvement of cerebellar white matter. Basal ganglia are typically spared.¹⁸ Internal and external capsules may also be spared. MRS might reveal reduced NAA, choline and creatine with mildly increased lactate and glucose peaks. In advanced disease, the white matter shows almost complete disappearance of all normal signals and presence of glucose and lactate, compatible with presence of mainly CSF and little brain tissue. Spectra of the cortex are preserved; however, signals representing lactate and glucose are described.^{19,20} Differential diagnosis on MR imaging include megalencephalic leukoencephalopathy with subcortical cysts, Canavan's disease and Alexander's disease.²¹ Age of onset and temporofrontal cysts differentiate it from megalencephalic leukoencephalopathy;^{22,23} classical phenotype of Canavan's disease along with MRS revealing elevated NAA and of Alexander's disease along frontal changes would exclude it.²⁴

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CONCLUSION: Vanishing White Matter leukoencephalopathy is one of the most prevalent hereditary diseases of white matter in childhood. Clinical and neuroimaging findings are very typical, and they suggest this diagnosis. Molecular genetic studies confirm up to 90% of affected patients. Nevertheless, it is still unknown why this disease starts up at a particular moment and why it follows an acute or chronic form. To date, no curative treatment has been found. Avoidance of stress situations known to provoke deterioration in VWM patients is essential. Liberal use of antibiotics and antipyretics, vaccinations, and abstinence of contact sports are simple but important measures. However, they are not sufficient to prevent onset or progression of the disease. The most important consequence of research findings of the last 5 years probably is that prenatal diagnosis has become available for families as soon as the disease-causing mutations in the index patient have been identified.

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