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Case Report

Atypical vanishing white matter disease with microcephaly and hepatosplenomegaly provoked after diphtheria pertussis tetanus vaccination

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Abstract. Vanishing white matter (VWM) disease is a rare leukoencephalopathy. Normal development in early childhood with regression of milestones after trauma or infection is typical clinical presentation. We are reporting a child with atypical VWM disease. A 1.5-year-old female child presented with fever followed by altered sensorium and convulsions following first booster dose of diphtheria pertussis tetanus vaccination. Her development was normal till 1 yr of age. Her weight and head size were below 3 standard deviations. She had hepatosplenomegaly. Her routine investigations including cerebrospinal fluid examination were normal. Magnetic resonance imaging (MRI) of brain shows diffuse white matter signals changes (hyperintensity on T2-weighted and hypointensity on T1-weighted images) involving the subcortical "U" fibers sparing basal ganglia. MRI shows diffuse white matter hyperintensity on T2-weighted images with areas of low signal on fluid-attenuated inversion recovery, close to the signal of cerebrospinal fluid. Based on MRI findings we diagnosed as VWM disease.

Keywords: Vanishing white matter disease, whole cell DPT vaccine, hepatosplenomegaly, microcephaly

1. Introduction

Vanishing white matter (VWM) disease is a rare leukoencephalopathy that was initially called childhood ataxia with central nervous system hypomyelinating [1,2]. The disease has an autosomal recessive mode of inheritance [1]. Normal development in early childhood with chronic progressive ataxia and spastic diplegia is the most common clinical presentation. Magnetic resonance imaging (MRI) shows diffuse white matter signal changes, with areas in which the signal intensity is close to that of cerebrospinal fluid (CSF) on all pulse sequences. Gray matter structures are spared. Magnetic resonance spectroscopy (MRS)

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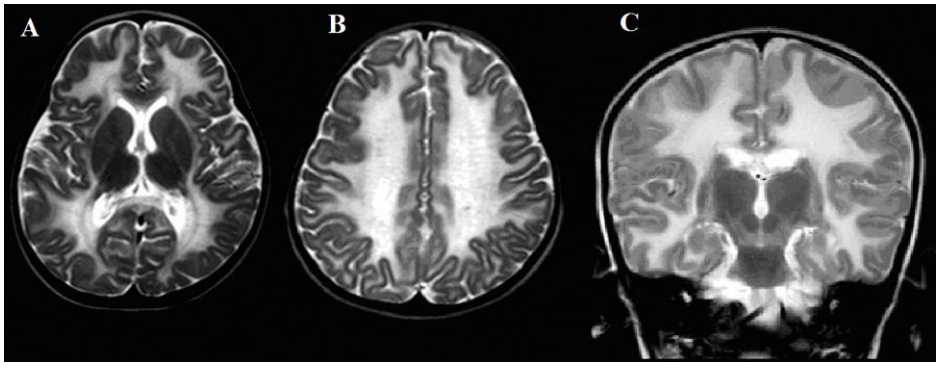

Fig. 1. (A, B and C) T2-weighted magnetic resonance images with axial sections at basal ganglia, axial sections at centrum semiovale and coronal sections respectively, shows diffuse white matter hyperintensity involving the subcortical "U" fibers sparing the basal ganglia.

shows severely reduced N-acetylaspartate, choline and creatine with elevated glucose and lactate in highly rarefied or cystic areas of the white matter [1]. The disease has an extremely wide phenotypic variation and may affect people of all ages [3].

2. Case report

A 1.5-year-old female child presented with fever followed by altered sensorium and convulsions of 2 d duration. She received first booster dose of whole cell diphtheria pertussis tetanus (DPwT) vaccination 1 d prior to the onset of fever. She was the third sibling of consanguineously married couple. She was born at full term, normal vaginal delivery with an uneventful neonatal course. Birth weight was 2.100 g. The child had 3 episodes of left complex partial seizures, each lasting for few minutes. There was no history of vomiting. Her development was normal till 1 yr of age, when she had independent walking and speaking two words with meaning. No new milestones were then achieved.

On examination, the child was hemodynamically stable with normal vital parameters. Weight was 6000 g, (below 3 standard deviations), height was 80 cm, and head circumference was 39 cm (below 3 standard deviations). Vitals were stable. Glasgow coma scale was 8/15 at the time of admission. Cranial nerves were normal. Fundus examination was normal. Tone was decreased with brisk deep tendon reflexes. There were no signs of meningeal irritations. Liver was palpable 4 cm below right costal margin with liver span of 8 cm by physical examination, spleen was palpable 2 cm below the left costal margin, and both were firm in consistency.

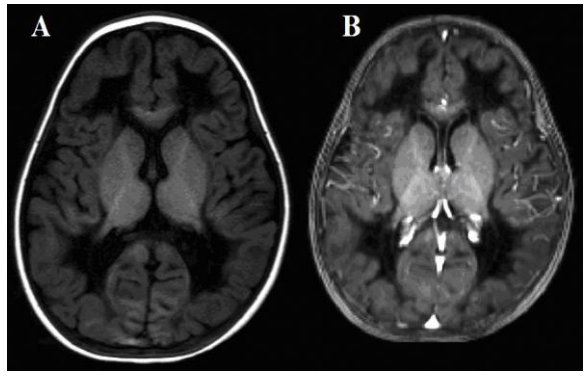

Fig. 2. T1-weighted pre (A) and post (B) contrast magnetic resonance images respectively, with axial sections at basal ganglia; shows diffuse white matter hypointensity and no abnormal contrast enhancement.

Her complete blood counts were normal. Liver function tests, renal function tests, serum electrolytes, serum calcium, arterial blood gas, lactate, and ammonia were within normal limits. Tandem mass spectroscopy for amino acids and acylcarnitine was normal. Ultrasonography of abdomen shows increased size of liver (9 cm) and spleen (8 cm). CSF examination was normal. MRI of brain shows diffuse white matter signal changes (hyperintensity on T2-weighted and hypointensity on T1-weighted) involving the subcortical "U" fibers sparing basal ganglia (Figs 1 and 2). There was no contrast enhancement (Fig. 2). MRI shows areas of low signal on fluid attenuated inversion recovery, close to the signal of CSF (Fig. 3). A diffusion weighted image and apparent diffusion coefficient MRI shows no diffusion restriction of the involved white matter (Fig. 4). MRS was not done. Based on above clinical and MRI findings we diagnosed as variant of VWM disease.

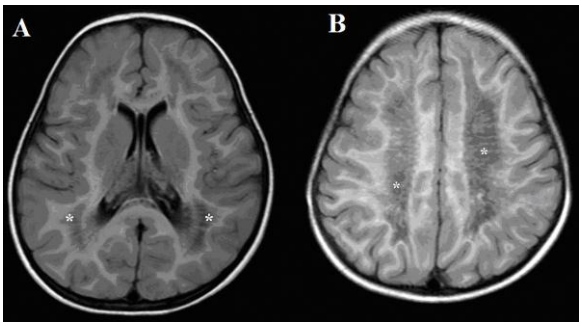

Fig. 3. (A and B) are fluid attenuated inversion recovery magnetic resonance images with axial sections at basal ganglia and centrum semiovale respectively, shows diffuse white matter hyperintensity with areas of inversion (asterix, *) whose signal intensity is that of cerebrospinal fluid.

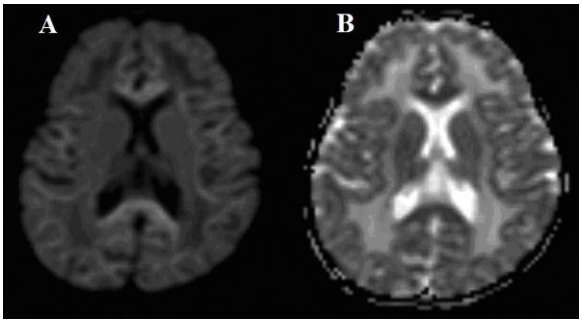

Fig. 4. (A and B) Diffusion weighted image and apparent diffusion coefficient magnetic resonance images respectively, shows no diffusion restriction of the involved white matter.

The child was treated symptomatically with anticonvulsants and partially improved over a period of 2 wk. She started sitting, and recognizing parents. However, the child deteriorated following one more febrile illness and didn't regain previous milestones.

3. Discussion

Clinical and radiological diagnostic criteria for VWM disease were proposed by Van der Knaap et al. [4] in 1998. According to these criteria, initial psychomotor development is normal or mildly delayed. Neurological deterioration shows a chronic, progressive, and episodal course. These episodes may follow minor head trauma or infection. Deterioration may lead to lethargy or coma. The main neurological symptoms are cerebellar ataxia and spasticity. On MRI, symmetric involvement is present within the hemispheres. The affected parts show signal intensity similar to that of CSF on fluid attenuated inversion recovery, proton density-weighted, T1-weighted, and T2-weighted sequences. White matter may be involved completely. Cerebellar atrophy may be mild or severe, and the vermis is primarily involved. MRS findings are not unique; they only indicate that the white matter is cystic and may be found in other cystic leukoencephalopathies as well.

The classical and most common variant of VWM disease has its onset in childhood, at age 2–6 yr [1,2]. In our child the age of onset may be before 1 yr of age, because her head size was 39 cm, and she didn't develop any new milestones after 1 yr of age. The disease is characterized by chronic progressive neurological deterioration with cerebellar ataxia, usually less prominent spasticity and relatively mild mental decline [1,2]. The episodes of major and rapid deterioration following minor head trauma and especially febrile infections had noted [2,4]. Recently, acute fright has been reported as another provoking factor [5]. These episodes may end in coma and death. This child presented at 18 mo as underlying disease was provoked by injection DPwT vaccination. If recovery occurs, it is usually incomplete. Most patients die after a few years, but some do so after a few months or decades later [1,2,4]. Our child had acute worsening following fever with development of convulsion, altered sensorium, and loss of milestones. The child recovered incompletely with symptomatic treatment again deteriorated with febrile illness.

Other disorders affecting the white matter diffusely during childhood are adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe disease, and Canavan disease [6]. In these disorders, MRI shows extensive or diffuse white matter changes, with no cystic degeneration. In Alexander disease, white matter signal changes have a frontal predominance. The cystic degeneration may affect the subcortical or deep white matter. Basal ganglia and thalamic abnormalities are frequently present. Contrast enhancement is often seen. Megalencephalic leukoencephalopathy with subcortical cysts, characterized by diffusely abnormal and mildly swollen cerebral hemispheric white matter that does not show signs of diffuse rarefaction or cystic degeneration. Subcortical cysts are almost always present in the anterior temporal lobe and often in other regions. Finally, mitochondrial disorders, including deficiencies of pyruvate dehydrogenase and pyruvate carboxylase, can mimic VWM disease. MRI abnormalities similar to those seen in VWM disease with

prominent and diffuse white matter rarefaction and cystic degeneration can be seen; however, multisystem involvement and other parameters like lactate, metabolic tests like Tandem mass spectroscopy are usually helpful in diagnosing these disorders [6].

VWM disease may have an early infantile or antenatal onset [7,8]. "Cree leukoencephalopathy" is a severe variant of VWM [9]. The disease, described among the Cree Indians, has its onset between 3 and 9 mo; death occurs before age 2 yr [10]. More severe variants of VWM may present with decreased fetal movements, oligohydramnios, growth failure, and microcephaly in the third trimester of pregnancy. Soon after birth, rapid deterioration occurs in these patients, characterized by feeding problems, vomiting, failure to thrive, irritability, apathy, axial hypotonia, limb hypertonia or hypotonia, seizures, apneic episodes, coma, respiratory failure, and death within a few months [8]. Only in the early onset, a severe variant of the disease has prominent involvement of organs other than the brain and ovaries [8]. In addition to signs of encephalopathy, these patients may display growth failure, cataracts, hepatosplenomegaly, pancreatitis, and kidney hypoplasia [8].

We evaluated for other possible causes of short stature, microcephaly, and hepatosplenomegaly. Congenital infections like toxoplasma, rubella, cytomegalovirus, herpes, simplex virus infections, syphilis, acquired immunodeficiency syndrome, and chronic systemic disorders were considered. Investigations did not suggest any evidence of above disorders.

Based on the clinical and laboratory abnormalities she was diagnosed with VWM disease. Parents were not given consent for the genetic test; hence, mutational studies were not done. This is a limitation of our report. In our child, involvement of other organs like hepatosplenomegaly and growth failure was noted. Rare findings in our case were early age of onset, growth failure, microcephaly, hepatosplenomegaly, and developmental arrest after first years of life and provocation following DPwT vaccination.

In conclusion, VWM disease should be suspected in case of microcephaly and MRI of brain showing diffuse white matter signal changes.

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