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RESEARCH ARTICLE

Rare cause of progressive spastic paraparesis with premature ovarian failure

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Abstract

Leukoencephalopathy with vanishing white matter (VWM) is a rare autosomal recessive disorder with normal early development and, usually, childhood-onset neurological deterioration. The diagnosis of VWM is based on clinical examination and findings on magnetic resonance imaging and magnetic resonance spectroscopy. We report an adult-onset leukoencephalopathy with vanishing white matter presenting with progressive weakness of lower limbs and premature ovarian failure. This is the first adult case reported from India to the best of our knowledge.

INTRODUCTION

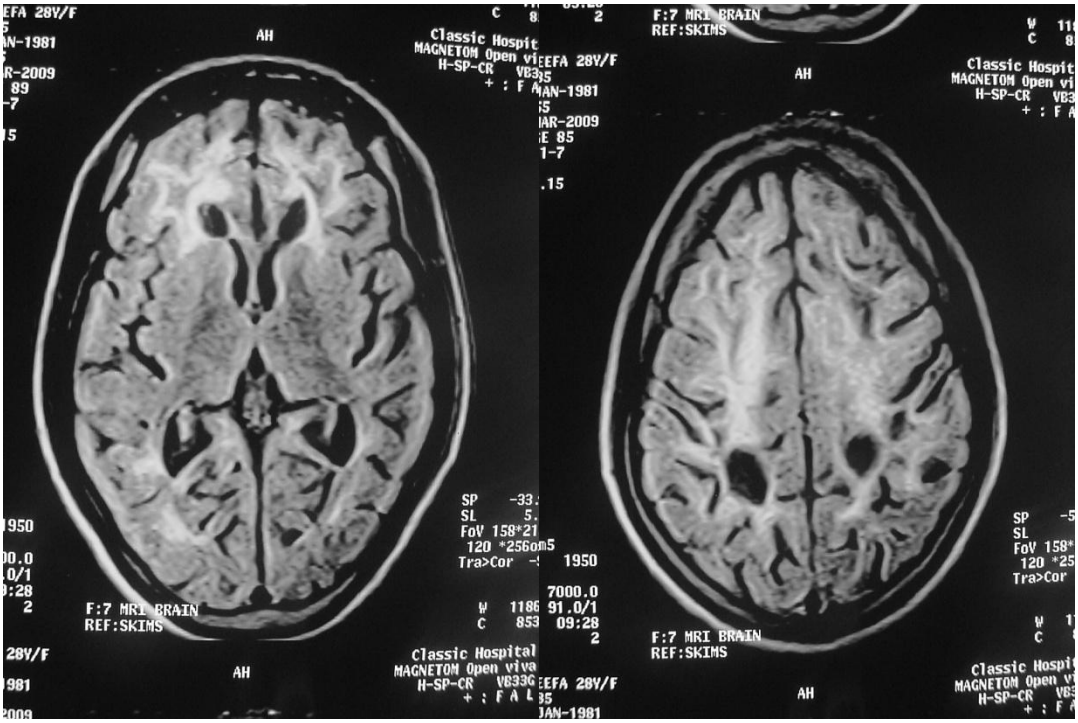
Leukoencephalopathy with vanishing white matter (VWM) is an autosomal recessive neurological disorder with chronic progression and episodes of rapid deterioration of neurodeficit, provoked by fever and minor head trauma[1]. Onset usually occurs in childhood but rarely may occur in adults[2,3]. Because of its association with premature ovarian failure, it is also known as Ovarioleukodystrophy[4]. This disease is caused by the mutation in any of the 5 genes encoding subunits of the translation initiation factor EIF-2B(Eukartyotic Initiation Factor)[5]. The diagnosis depends on the characteristic clinical and MRI findings which shows reversal of signal intensity of the white matter in the brain.

CASE REPORT:

The patient was a 32 year old female admitted to our tertiary care hospital with complaints of instability of gait, progressive weakness of lower limbs starting in right side and then the left side. Patient had difficulty in walking as her legs used to get crossed. These symptoms started abruptly about 7 months back after a minor head trauma. She was a product of consanguineous marriage with normal initial mental development. There was history of generalized tonic clonic seizures at the age of 10 years for which she was treated for 3 years. Parents noticed that her mental development was delayed as she was not able to do simple calculations and understand simple commands. There was history of secondary amenorrhea for last 8 years. There was history of neonatal death in her siblings but no similar history in any other family member. On examination, she was conscious but mentally retarded (IQ=60) and had madarosis. Cranial nerve examination including fundus examination was normal. Spasticity was present in all four limbs, more in lower limbs than upper limbs, power was grade 4(-) in both lower limbs. Deep tendon reflexes were exaggerated and plantars were downgoing. Sensations were normal. Gait was spastic. There were no cerebellar signs. Investigations revealed normal hemogram and biochemistry including kidney function tests, liver function tests, serum calcium, sodium, potassium and blood sugar were normal. Chest x-ray and USG abdomen was normal. HIV serology, CMV serology was negative. ANA, AntidsDNA was normal. Magnetic Resonance Imaging (MRI) brain showed diffuse white matter signal hyperintensity on T2-weighted images similar to CSF intensity

accompanied by hypointense areas on fluid-attenuated inversion recovery images(Fig. 1 & 2). FSH was 43.14IU/L and LH was 25.89 IU/L much higher than the normal range, suggesting the premature ovarian failure. TSH,T3,T4,testosterone and prolactin in serum were normal. In view of the typical clinical and radiological features, and after ruling out all secondary causes of white matter disease, final diagnosis of Leukoencephalopathy with vanishing white matter (VWM) with premature ovarian failure was made. Patient was discharged on supportive treatment but was lost to follow up.

Figure 1&2: Axial T2 weighted MR images showing extensive hyperintense signal changes in subcortical white matter.



DISCUSSION:

Leukoencephalopathy with vanishing white matter also known as ovarioleukodystrophy[4] is a progressive disease of central white matter, which has been described by van der Knaap et al[2,6] in 1997. The onset is common in childhood but can be extremely variable. The course is often progressive with fluctuations[6] but both early and late onset and a relatively slow progression has been seen[2,3]. This disease results due to mutation in any of the 5 genes encoding subunits of the translation initiation factor EIF-2B: EIF2B1 to EIF2B5[5].The gene for this disease is located on Chromosome 3q27[7]. There is axonal loss, hypomyelination, demyelination and gliosis on histopathology mainly involving the white matter with cortical sparing and characteristic abnormal foamy oligodendroglial cells[8].

The classical presentation is a child with normal initial growth and milestones and later development of progressive neurological deficits, provoked by fever, infection or minor head trauma. Symptoms include cerebellar ataxia, spasticity, optic atrophy, epilepsy, loss of motor functions, irritability, vomiting, and coma[1,2]. Death may occur in a few months to many years. Patients can also present in late childhood, adolescent or adults and vanishing white matter with ovarian failure (ovarioleukodystrophy)[4].

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[1,2,6]. There can be 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 may be spared[6]. MRS may show 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[1,9]. There are no real treatments, only precautions which can be taken, mainly is to reduce trauma to the head and avoiding physiological stress[1].

Leukoencephalopathy with mental retardation is non-specific. Some of the important acquired causes include HIV encephalopathy(HIVE), CMV encephalitis, HTLV infection, Progressive multifocal Leukoencephalopathy, and Vitamin B12 deficiency[10]. And some of these can lead to spastic paraparesis as well. Thats why before labelling a patient as having leukoencephalopathy with vanishing white matter (VWM), clinician has to rule out the common causes first and if possible a genetic study needs to be done. In our patient, presence of typical clinical features and absence of acquired causes made it possible to reach to the diagnosis.

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