Van der Knaap Disease

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ABSTRACT

Van der Knaap disease or megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare, inherited, autosomal recessive disorder. It is characterised by macrocephaly and slowly progressive ataxia, spasticity, and cognitive decline. The usual age of onset is described from birth to infancy. MLC predominantly occurs in some ethnicities where consanguinity is common. This disease is caused by mutations in the gene, which encodes a novel protein, MLC1. The characteristic MRI findings include leukodystrophy and subcortical cysts that yield diagnostic clue in most of the cases. The diagnosis can be established prenatally and genetic counseling is usually offered for future pregnancies. Herein, we chronicle a case of Van der Knaap disease from Pakistan with the classical MRI features.

Key Words: *Van der Knaap disease. Megalencephalic leukoencephalopathy. Subcortical cysts. Consanguinity. Autosomal.*

INTRODUCTION

Megalencephalic leukoencephalopathy with subcortical cysts (MLC), also known as Van der Knaap disease, is a rare inherited neurological deterioration disease. Due to the rarity of this condition, the exact prevalence is not known. It exhibits characteristic MRI features and usually has a mild clinical course.[1] Frontal and temporal subcortical cysts on imaging are the diagnostic features.[2] MLC usually presents with pyramidal spasticity (57%), cerebellar signs-like ataxia (58%), and seizures (49%).[3] Furthermore, megalencephaly is usually detected early in the course of the disease. Although neuropsychiatric manifestations are not frequent in these patients, behavioral problems and even depression have been reported.[4] In majority of patients, the causative mutations are described in the *MLC1* gene locus at chromosome 22q.[5] The diagnosis is established on the basis of consistent clinical and MRI features in patients with MLC.

Since the early existence of modern humans, consanguineous marriages have frequently been practised. Consanguinity has been shown to be an independent risk factor for different types of genetic diseases. We report a case of Van der Knaap disease from Pakistan and review pertinent medical literature. This study reemphasises the fact that education on consanguineous marriages and genetic counselling are highly recommended in Pakistan.

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CASE REPORT

A 6-year-old girl, born of first-degree consanguineous marriage, presented to our medical centre with seizures and difficulty in walking. She had complex partial seizures with secondary generalisation around 50% of the time for the last five months that occurred at a frequency of 3 to 5 times a month. She was previously initiated on benzodiazepines for her seizures and the clinical response was remarkable. Her mother reported that the patient did not have any pregestational abnormalities and she was delivered with spontaneous normal delivery without any complications. First few years of growth were uneventful, except for a progressive increase in head size. Apart from this, she had an unremarkable developmental history. She achieved normal milestones with head-holding by the age of 3 months, sitting by the age of 8 months, and walking around by the age of 16 months. She had a progressive decline of mental ability after the age of 3 years with increased difficulty in walking and progressive deterioration of motor function. She was able to comprehend, obey commands, and speak a few words.

Motor examination showed grade 3 spasticity in both the upper limbs and the left lower limb. On Ashworth scale of spasticity, grade 4 spasticity was noted in the right lower limb with a power of 4/5. Furthermore, hyper-reflexia and bilateral extensor response was present in the lower limbs. The sensory examination was normal. Bilateral cerebellar signs were present with a typical spastic gait. Head size was 60 cm, which was greater than the 95th percentile. The ophthalmoscopic fundal examination was unremarkable. Abdominal examination was also normal. Routine basic panel, electro-cardiogram, and chest radiography were inconclusive. Cerebrospinal fluid (CSF) analysis was unremarkable. The electroencephalogram (EEG) abnormalities included polyspike foci in the temporal, parietal, and frontal areas with migratory changes in waking and sleep.

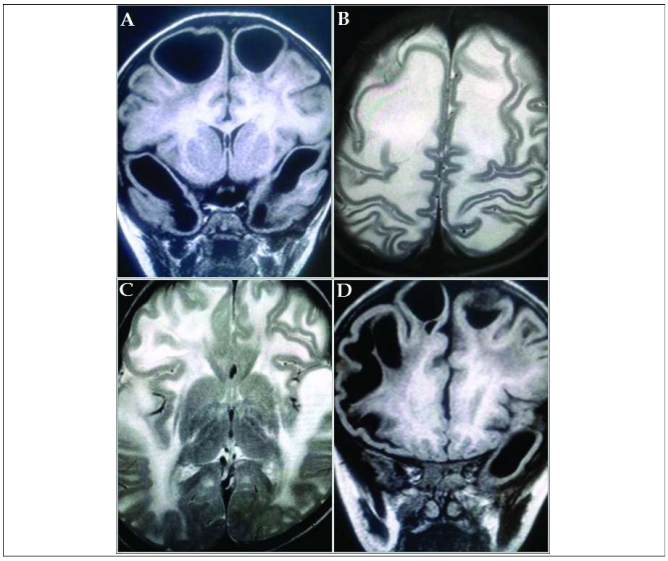

Figure 1: The classical MRI features of Van der Knaap disease. **A:** Coronal FLAIR image showing bilaterally symmetrical subcortical cysts located in anterior temporal lobes as well as in high frontal region of subcortical white matter. **B:** Axial T2W image reveals T2 bright subcortical cysts in top frontal region and diffusely increased white matter signal intensity. **C:** Axial T2W image showing bilaterally symmetrical subcortical cysts located in the anterior temporal lobes as well as in the frontal lobes and diffusely increased white matter signal intensity of subcortical white matter. **D:** Coronal FLAIR image showing bilateral subcortical cysts located in anterior temporal lobes as well as in frontal lobes with no significant hydrocephalus.

Imaging of the brain revealed bilaterally symmetrical subcortical cysts located in anterior temporal lobes as well as in the high frontal region of subcortical white matter on FLAIR MRI (Figure 1, panel A). Bright subcortical cysts were evident in the top frontal region and diffusely increased white matter signal intensity on axial T2W MR (Figure 1, panel B). Furthermore, bilaterally symmetrical subcortical cysts located in anterior temporal lobes as well as in frontal lobes and diffusely increased white matter signal intensity of subcortical white matter were present on axial T2W MR image (Figure 1, panel C). Coronal FLAIR MRI demonstrated bilateral subcortical cysts located in anterior temporal lobes as well as in frontal lobes, no significant hydrocephalus was appreciated (Figure 1, panel D).

Diffusely increased FLAIR signal intensity in the supratentorial and periventricular white matter, and centrum semiovale was noted. The white matter changes were more significant in frontal lobes. Basal ganglia, brain stem, and cerebellum were spared. No mass effect on adjacent structures was present. Macrocephaly was noted; however, there was no hydrocephalus or midline shift. Based on the consistent clinical and MRI findings, the patient was diagnosed with Van der Knaap disease.

DISCUSSION

MLC is an extremely rare disorder of the white matter. To date, only a handful of cases of this disorder are reported globally. It is known to occur commonly in communities where consanguinity is frequent.[6] The age of onset of the disease is from birth to 25 years; however, late presentation of symptoms is exceedingly rare.[6] The essential diagnostic features include macrocephaly (present at birth), motor disability (due to spasticity), ataxia, seizures, and cognitive decline.[6]

Macrocephaly is the most important and obvious feature that has been documented in all previous genetically proven cases of MLC.[7] The other commonest initial feature is the delay in developmental milestones, developmental regression, difficulty in walking, and progressive deterioration in motor and mental function.[7] In previous studies, extrapyramidal abnormalities, such as dystonia and athetosis are reported in few patients.[7] Megalencephaly is noted in infancy, as in our patient, and follows the normal growth pattern. Partial and/or generalised seizures have also been documented. Epilepsy is usually controlled on one or two antiepileptic drugs.[7] Significant disability was noted in our patient that was attributable to motor impairment.

Characteristic imaging feature is the presence of thin-walled subcortical cysts, mainly in the frontoparietal and temporal region. Deep white-matter structures, including the corpus callosum, internal capsule, and midbrain are usually spared.[8] Presence of subcortical cysts in the anterior temporal region is diagnostic in such patients. The cysts are usually thin walled and are present in bilateral symmetrical fashion without causing a significant mass effect on adjacent structures. They typically show bright on T2, whereas dark signals on T1 and FLAIR. No restricted diffusion is evident. With the passage of time, these subcortical cysts increase in size and number.[8] Diffusely increased T2 and FLAIR signal intensity may also be present in the subcortical and periventricular white matter. Moderate decrease in NAA/Cr and Choline/Cr ratios have been reported in patients with MLC on MR spectroscopy.[9]

The differential diagnosis of macrocephaly with a diffuse white matter leukoencephalopathy includes Canavan disease, Alexander disease, and infantile onset GM2 gangliosidosis. Canavan disease, unlike MLC, has diffuse white matter involvement including the thalami and globus pallidi and usually without the development of cysts. In addition, NAA is high on spectroscopy. In Alexander disease, white matter involvement is predominant in frontal regions. Alexander lesions show contrast enhancement, which is usually absent in MLC. These conditions have severely progressive course and are frequently fatal within the first decade of life; however, MLC has relatively slower loss of neurological function. Hence, MLC must be considered among the differential diagnosis of early-onset leukoencephalopathy with macrocephaly.[8,9]

In conclusion, the case of a 6-year-old Pakistani patient with MLC is presented. Although distinctive clinical and

MRI characteristics are established, the correct diagnosis of MLC is difficult during the symptomatic stage of the disease. Consanguineous marriages without genetic counselling are not uncommonly encountered in sufferers of MLC, which prompts awareness about this disease, especially in countries like Pakistan.

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