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Case Report

Van der Knaap disease

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ABSTRACT

Van der Knaap disease is a rare form of leukodystrophy, phenotypically characterized by megalencephaly, early-onset ataxia, pyramidal features, cognitive impairment, with an autosomal recessive inheritence. MRI Brain shows T1 and FLAIR hypointense subcortical cysts in mostly temporal lobes and in fronto-parietal subcortical areas. Authors report a 20 yr. girl with typical features.

Keywords: Leukodystrophy, Megalencephaly, Subcortical cysts, Van der Knaap

INTRODUCTION

Van der Knaap disease is clinically characterized by macrocephaly, mild motor developmental delay, and seizures. Later in life, patients may develop gradual onset of ataxia and pyramidal features. Mental capacities are usually preserved but there may be a mild deterioration later. A combination of clinical features and MRI features is required for arriving at the diagnosis. The condition is inherited in an autosomal recessive pattern and the gene locus is at MLC1 gene in chromosome 22q.

The condition has been originally reported from India. In a meeting in Japan in 1991, Singhal et al. described about 18 patients with features of megalencephalic leukodystrophy from India.[1] This was the first series to be reported. Van der Knapp et al. group from Netherlands later published a series of eight patients and described the clinical and MRI features.[2]

Their description earned them the eponym Van der Knaap disease first used by Cavalcanti and Nogueira.[3] A Turkish study of 12 patients soon followed and established the genetic nature of the disease with autosomal recessive inheritance and a locus at 22q.[4] From India, Gorospe, Singhal and co-workers did detailed genetic analysis and established this disease as a distinct clinicopathological entity with common locus at MLC 1 gene in all the 31 patients described in the Agarwal community.[5] Authors recently identified the disease in a 20 year old girl admitted in our hospital.

CASE REPORT

A 20-year-old Muslim girl born out of consanguineous marriage presented with progressive difficulty in walking and stiffness of all limbs. She had gross developmental delay in the form of delayed sitting and walking. She had clumsiness and frequent falls while walking.

She had complex partial seizures with semiology suggestive of right temporal lobe with secondary generalization since 4 years of age and were initially responsive to Valproate. However, Levetiracetam had to be added to prevent breakthrough seizures.

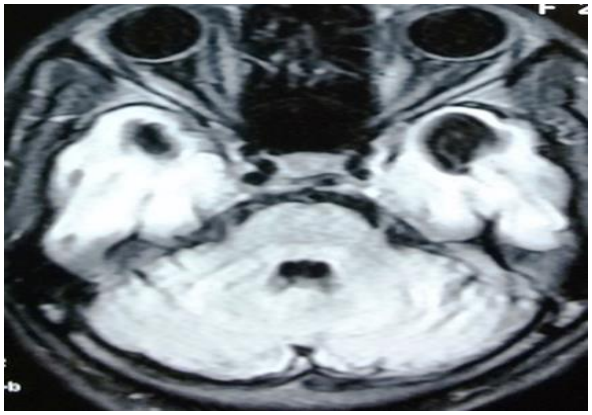

Figure 1: MRI brain T2 flair image showing bilateral temporal subcortical cysts.

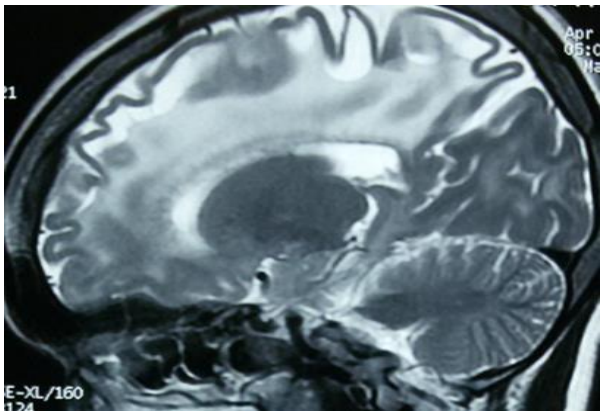

Figure 2: MRI T2W image showing white matter changes.

The child had moderate impairment of cognitive and language abilities and could not go to school. Her siblings were however not affected. Megalencephaly was evident as the head circumference was 56 cm. The mental examination was suggestive of severe language impairment. The motor system examination was suggestive of severe spasticity with grade 4 power of all limbs. She had brisk reflexes and bilateral plantar were extensor. She had severe incoordination and also had a spastic gait. Routine blood investigations, LFT, RFT, electrolytes were normal. NCS of 4 limbs were normal. Her MRI showed bilateral temporal and frontal subcortical cysts along with other characteristic features suggestive of the disease. (Figures 1,2). Genetic test was positive for MLC1 mutations. CSF was essentially normal and glycine content was normal contrary to reports from Western countries where it was found elevated.[6]

DISCUSSION

Marked heterogeneity is present in the clinical picture of Van der Knaap disease. Patient becomes symptomatic between birth and 25 years, with a median age of symptom onset is 6 months.[7] The most consistent feature is macrocephaly which has been demonstrated in all the genetically proven cases.[4,5,7] The macrocephaly is usually present at birth and after the first year follows the normal growth pattern. It remains several centimetres above the normal throughout life. Seizures may be partial or generalized. They are usually well controlled with one or two drugs and uncontrolled epilepsy is unusual. Singhal et al reported seizures in half of the patients (49%). [7,8] Van der Knaap et al reported seizures in six out of eight patients.[2] Mental retardation and cognitive regression is reported to be mild, though late progression may be noted.[7] The diagnosis is mainly based on the radiological picture. Extensive white-matter changes in the brain with subcortical cysts in temporal lobes have been considered the MRI hallmarks of the disorder. Subcortical cysts are present mainly in the anterior temporal region and often in the frontoparietal area. Later, MRI may only reveal cerebral atrophy. The size and number of the cysts may increase over time. Involvement of the frontal lobe is variable and so is the cerebellar involvement. Alexander disease, Canavan disease, and Glutaric aciduria have been considered as differential diagnosis of these MRI findings, these conditions are not associated with mild clinical course.[7] All of these conditions generally involve basal ganglia which is unlikely in Van der Knaap disease. Identification of biallelic pathogenic variants in MLC1 or HEPACAM by molecular genetic testing can confirm the diagnosis of classic MLC (MLC1 or MLC2A, respectively) - particularly important if clinical features are inconclusive - and allow for family studies. Identification of a heterozygous HEPACAM pathogenic can confirm the diagnosis of MLC with improving phenotype (MLC2B) if clinical features are inconclusive, and/or allow for family studies.[9]

CONCLUSION

Authors report a rare case of Van der Knaap disease from an ethnicity different from that noted in Indian studies. Authors believe that characteristic MRI features, large head size, ethnicity, pyramidal and cerebellar features, with a discrepantly mild clinical course and appropriate genetic study (MLC gene) are the key to diagnosing this disease in practice.

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