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Van der Knaap Syndrome: Rare Case with an Atypical Presentation: A Case Report

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ABSTRACT

Megalencephalic leukoencephalopathy with subcortical cysts, Van der Knaap Disease, is an autosomal recessive disorder seen in populations where consanguinity is common.
It is a slowly progressive neurodegenerative disorder with infantile megalencephaly, neurological symptoms like ataxia and seizures and leukoencephalopathy.
Prevalence is less than 1 in 1,000,000.
Predisposed populations are the Libyan Turks, Egyptians, Jews and the Agrawal community of India.
Here we present a case of a macrocephalic 4 month old female with infantile seizures with follow up at 8 months of age, having typical MRI findings of Van der Knaap disease and symptomatic worsening after meningitis.
The case presented being of a non-Agrawal family in India and born of a non-consanguineous marriage is an atypical and rare presentation, indicating that the syndrome may be seen in other communities as well.

Keywords: Megalencephalic leucoencephalopathy, vanishing white matter, Van der Knaap, neuroradiology, subcortical cysts, macrocephaly, developmental delay, ataxia, myelination, autosomal recessive, genetics, seizure, magnetic resonance imaging, magnetic resonance spectroscopy, brain

INTRODUCTION

Megalencephalic leukoencephalopathy with subcortical cysts (MLC), is an autosomal recessive disorder defined by macrocephaly in the neonatal period or presenting upto the first year of life. These children have associated developmental delay, mainly motor, cognitive deterioration and neurological deficits: seizures, spasticity and slowly progressive ataxia.

These features were first identified by the Dutch neurologist, Marjo Van der Knaap, thus MLC is also referred to as Van der Knaap disease. She described MRI, MRS and autopsy findings of cystic degeneration of cerebral white matter in children with leucoencephalopathy and almost complete absence of white matter intensities in advanced disease with worsening after infections and minor head trauma.[1] The typical distribution is supratentorial, hemispheric white matter with central white matter region being relatively spared. There is complete absence of gray matter involvement.

Prevalence of this disorder is less than 1 in 1,000,000 population.[2]

Genes involved are: *MLC1*, locus: 605908; *HEPACAM* gene, locus 611642.[3]

Possible pathophysiology is splitting of outer myelin lamellae and disruption of myelin compaction.

CASE DESCRIPTION

A 4 month 7 day infant girl, first by birth order of non-consanguineous marriage, of a non-Agarwal community, presented in the emergency department with complaints of fever since eight days, followed by a two day afebrile period, noisy breathing since one day and seizure activity in the morning.

This involved increased tone in bilateral upper limbs and tonic clonic activity of both lower limbs. This lasted for a duration of about 10 to 15 minutes and was associated with uprolling of eyeballs and frothing from angle of mouth. There was no loss of bowel and bladder control and complains of vomiting with no post ictal loss of consciousness or drowsiness.

The episode self aborted.

The child was born of a normal, full term vaginal delivery to a mother with hypothyroidism, controlled on medication and had a head circumference of 36 cm. There is no significant family history. The patient was admitted at three days of life with indirect hyperbilirubinemia (mother and baby blood group: A Rh positive), with Kramer zone 4, resulting from sepsis. Double surface phototherapy and antibiotics were given. Neurosonography showed no abnormalities at birth.

The patient had global developmental delay on presentation at 4 months of age with developmental quotient: 0.75; neck rigidity, seizures, controlled on injection Levetiracetam. Head circumference was 42.5 cm, between 1 and 2 SD for age. Low lying ears, sunset sign of eyes [Figure 1], and brown nevus of size 4x1 cm was present on the back. Fundus examination was normal. CSF examination showed a meningitis picture, hence appropriate antibiotic treatment was given for 21 days along with physical therapy to improve speech and motor functions.

NSG was done showing: Cystic encephalomalacia with white matter loss. Bitemporal cysts with the largest measuring: 74x26 mm.

MRI brain was done showing: Multiple large well defined, variable sized cystic areas involving bilateral temporal lobes, left cerebellar hemisphere. Left temporal lobe cyst is seen extending to adjacent parietal lobe. Diffuse white matter signal abnormality predominantly involving anterior subcortical U fibres. Features suggestive of: Megalencephalic leukoencephalopathy with subcortical cysts. [Figure 2, Figure 3, Figure 4]

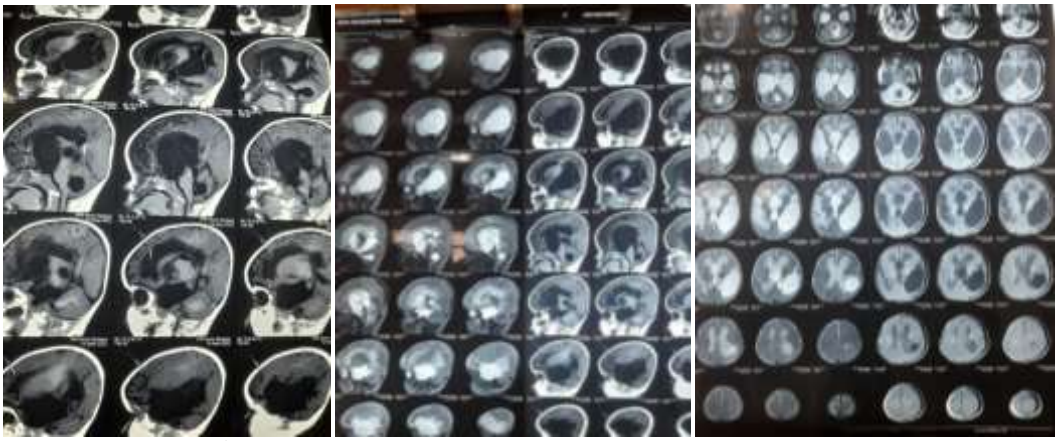
Hence, MRI findings confirmed the diagnosis of Van der Knaap syndrome.

Neurology consultation was done and referral to higher centre for fenestration of cysts was advised.

Follow up: Child was followed up at 8 months of age. Further seizure episodes were noted along with increase in head circumference to 49 cm: above 97th percentile for age [Figure 5]. Antiepileptics were upgraded.

Child was also advised to continue physical therapy and use of precautions such as helmet to prevent head trauma. Genetic counselling was done as well.

Figure 1: Child with Macrocephaly



Figures 2,3,4: MRI picture of Van der Knaap Disease showing: Megalencephalic leukoencephalopathy with subcortical cysts.

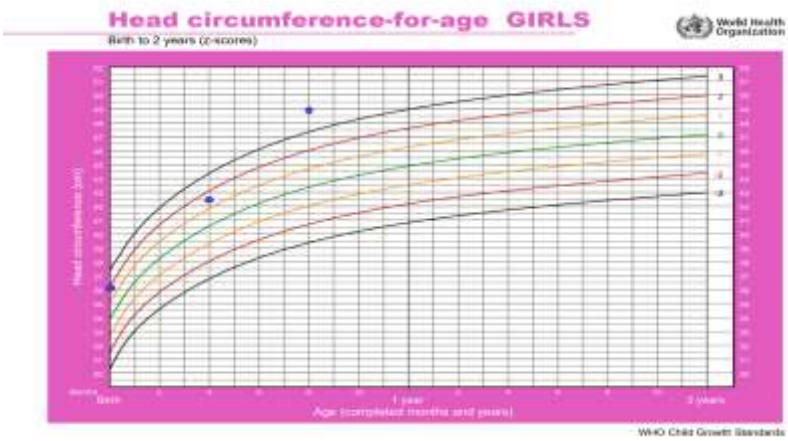


Figure 5: Head circumference charting of the patient discussed.

DISCUSSION

Diagnosis

Typical clinical features and MRI findings (abnormal cerebral hemispheric white matter, presence of subcortical cysts in the anterior temporal region and in the frontoparietal region) are diagnostic of MLC.

Molecular testing can also help establish the diagnosis in patients by identifying biallelic pathogenic variants in MLC1 and HEPACAM gene loci.[4]

Differential Diagnosis:

Canavan's disease: is ruled out because of the absence of NAA peak in MRS.

Alexander's disease: is ruled out by the absence of frontal predominance of the leukoencephalopathy.[5]

GM gangliosidosis: is ruled out by the absence of basal ganglia and thalamic predominance.[6]

There was also no cherry red spot on fundus examination and no organomegaly.

Management:

Symptomatic management: addition of antiepileptics and physical/speech therapy.

Prevention of worsening of symptoms in infants: advising helmets to prevent head trauma may be of some benefit. Prevention of meningitis by adequate vaccination and appropriate antibiotic use to prevent severity of disease is advisable.[7]

Precautions: avoiding contact sports as the child grows up to prevent further complications.

Genetic Counselling:

Van der Knaap disease is an autosomal recessive disorder (MLC 1 And MLC 2A), hence any further siblings of an affected child would have a fifty percent probability of being an asymptomatic carrier and twenty

five percent chance of having the disorder. Prenatal testing at the time of pregnancy may be performed as well with informed consent.

MLC 2B is autosomal dominant, hence each sibling would have a fifty percent chance of being affected by the disorder.

CONCLUSION

Van der Knaap disease or Megalencephalic leukoencephalopathy with subcortical cysts is an autosomal recessive disorder seen consanguineous marriages in Libyan Turks, Jews and Agrawal community members from India.[8] [9]

Typical presentation is macrocephaly with worsening neurological symptoms with MRI finding of temporal white matter abnormality with subcortical cystic degeneration.

This case report attempts to record an atypical presentation in a non-Agrawal patient born of a non-consanguineous marriage to increase awareness about the rare instance bringing forward the need for adequate diagnostic measures and genetic counselling.

Declaration by Authors

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Conflict of Interest: The authors declare no conflict of interest.

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