International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Siblings with Van Der Knaap Disease - An Atypical Presentation

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Abstract: ***Van Der Knaap Disease, or megalencephalic leukoencephalopathy with subcortical cysts (MLC), is a rare autosomal recessive leukodystrophy typically linked to consanguinity and specific ethnic groups. This case report presents two siblings from a non-consanguineous family in Lucknow, India, diagnosed with MLC, highlighting an atypical presentation. An 8-year-old girl exhibited macrocephaly, seizures, and motor regression, while her asymptomatic 3-year-old sister showed characteristic MRI findings of subcortical cysts. These cases underscore the importance of early MRI screening in children with macrocephaly, even in the absence of consanguinity, and emphasize the need for genetic counseling to inform at-risk families. This report adds to the limited literature on MLC's diverse clinical spectrum and advocates for heightened diagnostic awareness.***

Keywords: Van Der Knaap Disease, megalencephalic leukoencephalopathy, subcortical cysts, macrocephaly, genetic counseling

1. Introduction

Van der knaap disease is a rare leukodystrophy characterized by subcortical cysts.1 It has an autosomal recessive inheritance and two - third of the cases are due to mutation of MLC1 gene located on chromosome 22q[2]. Geographical distribution of MLC is global, however it occurs more commonly in some ethnicities where consanguinity is common, such as Libyan, Jewish, Turkish, Agrawal Indian community[3, 4]. It is characterized by early onset increase in the head circumference, delayed motor milestones, abnormal body movements, ataxia, spasticity, and mild mental retardation. It has a subtle clinical course characterized by typical MRI findings of white matter T2/FLAIR hyperintensity with subcortical cysts in frontotemporal region[5]. Macrocephaly with these MRI findings are often diagnostic of MLC and must be differentiated from other leukoencephalopathies. We identified a patient with this rare disease and then screened her sister for it and is now reporting two cases of Van Der Knaap syndrome not belonging to Agrawal community, born out of a "non - consanguineous" marriage in north central part of India from Lucknow District. The unique feature of this case report is the lack of consanguinity in the two reported cases, highlighting the need for early diagnosis and genetic counselling in at - risk communities.

2. Cases

Case 1
An 8 years old girl presented to our emergency department with c/o seizure for 2 days and difficulty walking since 4 and a half years. The seizures were generalized tonic clonic in nature, for which she was previously started on antiepileptic drugs. The clinical response to antiepileptics drugs was good but parents stopped the drugs abruptly. Within a month of stopping antiepileptic, patient had an episode of seizure which lasted for 5 minutes. The patient was born out of uneventful normal home delivery. She was born out of non - consanguineous marriage with one elder brother and one younger sister. First year of growth was uneventful, except for a progressive increase in head size. The abnormal large head was first noticed by parents at 7 months age. According to them the size of the head was normal at birth. On examination, the child had macrocephaly with head circumference of 58.5cm which was >95th percentile. From one and a half year of age patient had 3 episodes of fall followed by seizure episode for which medication was started. As per the mother after 3 years of age there was regression of milestones with the first features being difficulty in walking. There was progressive decline of mental ability and motor function.
She was able to speak a few words, comprehend and obey commands.

Motor examination showed spasticity in both the upper limbs with the intact muscle power.

Bilateral extensor response and hyperreflexia was present in the lower limbs. Typical spastic gait was present with bilateral cerebellar signs. The sensory examination was normal. She had no dysmorphic features or organomegaly. Her baseline investigation like complete blood count, liver and kidney function test, serum electrolytes and calcium were within normal limits. MRI was done and the imaging revealed bilaterally subcortical cysts located in temporal, frontal and parietal area (fig.1A and 1B).

Case 2
A 3 years old girl, younger sibling of our first case was noticed to have large head with head circumference of 52.7 cm. The child was asymptomatic and had no developmental delay. Since her sister was diagnosed to have Van Der Knaap disease which has genetic inheritance, MRI brain was advised for the girl. The MRI turned out to be characteristic of Van der Knaap disease i. e., subcortical cysts present in temporal and frontal area (Fig 2) and yet the patient was asymptomatic. Though rare but such presentations are described in previous literatures.

3. Discussion

Through this case, we report an uncommon disorder with atypical features. Van der Knaap disease is characterized by

variable clinical features with onset of symptoms from as early as birth to third decade of life with usual age of onset at 6 months[6]. MLC is an autosomal recessive disorder and more commonly prevalent in ethnicities where consanguinity is common, such as in the Agrawal community in India, in Libyan Jews and in Turks. However, in our case, consanguinity was not a factor, which presented an atypical feature in relation to the epidemiological pattern of the disease. Macrocephaly being the salient clinical feature, is present at birth, increases during infancy and remains constant but above 97th centile thereafter. Previous studies have documented the prevalence of seizures to be around 49 - 75%[7- 9]. It may be focal or generalized and well controlled with antiepileptics.1[0]The clinical presentation of the elder sibling is similar to the clinical features reported in the literature.9 MRI is diagnostic with typical finding of supratentorial white matter degeneration with fronto - temporal subcortical cysts with relative sparing of the deeper structures like corpus callosum, internal capsule and brain stem.[10] Due to decrease in swelling in white matter, MRI done in later stages reveals only cerebral atrophy. Both of our patients have typical MRI findings with subcortical cysts in temporal and parietal region.

MLC was eminently reported by Van der Knaap in eight children, whom he described as having severe white matter swelling on brain MRI, with a discrepantly mild clinical course.[9] Ben - Zeev et al reported 12 cases of MLC in an ethnic Jewish group with consanguinity, having classical clinical and MRI features.4 Singhal et al reported 30 patients of leukodystrophy, megalencephaly and a relatively benign course in an ethnic Agrawal group in India.[3]

Although diagnostic criteria including brain MRI findings are sufficient to confirm a diagnosis of MLC, still, molecular genetic testing should be performed whenever possible, mainly to identify the family - specific mutations for genetic counselling purposes. Also, prenatal diagnosis and preimplantation genetic diagnosis for at - risk pregnancies require prior identification of the disease - causing mutation (s) in the family similar to other genetic diseases. .[11, 12]

Other leukodystrophies are close differentials of Van der Knaap disease like Alexander disease, Canavan disease, and Glutaric aciduria. Van der Knaap disease can be differentiated from them by the presence of subtle clinical course, subcortical cysts on MRI and relative sparing of deeper brain structure.7The differential diagnosis in a case of macrocephaly and leukoencephalopathy includes Canavan disease, Alexander disease, infantile - onset GM2 and GM1 gangliosidosis. In Canavan disease, MRI shows involvement of white matter, thalamus and basal ganglia, which are spared in MLC, as seen in this case.[13] Also, Canavan disease is characterised by a marked increase in the NAA peak, which was not so in this patient. Alexander's disease also presents with megalencephaly and leukoencephalopathy. MRI may show cystic degeneration but, additionally, it shows frontal predominant abnormalities and contrast enhancement of particular brain structures, which are not features of MLC. MRI in infantile GM2 gangliosidosis is also characterised by prominent involvement of the basal ganglia and thalami in addition to the white matter abnormalities.[14] Basal ganglia and thalami were normal, as evident on brain MRI, in our patient unlike the patients with hypoxic ischemic encephalopathy.[15]

Recently a review study has enlisted 151 unique variants in MLC1, 29 unique variants in GLIALCAM, 2 in GPRC5B and 1 in AQP4.51 variants had not been discussed in literature before thus highlighting the knowledge gaps that should be filled with future research. Important questions are how MLC1 and GlialCAM regulate astrocyte osmoregulation, how they interplay with AQP4 in MLC and what the involvement of intracellular signalling cascades, potentially mediated by GPRC5B, is in this process. An answer to these key questions will be crucial in future efforts to develop curative therapy for MLC.[16]

Unfortunately, there is no current definite treatment option though trials for genetic therapy ongoing.[17]

There may be some preceding risk factors leading to poorer outcome like lack of early exposure to breastmilk, genetic defects, frequent CNS or gastrointestinal infections, home delivery and nutritional deficiency.[18 – 24] Like older children VAP is rampant in neonates as well.[25]

This case report highlights that genetic counselling for parents of offspring with this condition may be beneficial preventing cases in future offsprings. Appropriate diagnosis based on clinical characterisation and MRI features in a particular family or community may be of long term importance in genetic counselling on avoidance of customary consanguineous marriage in such families. We must focus on disease prevention by avoiding consanguineous marriages and providing proper prenatal diagnosis and genetic counselling.[6]

4. Conclusion

We report 2 cases of Vander Knaap disease with atypical features such as not belonging to more affected community or predisposed ethnicity. We suggest that any child presenting with early onset macrocephaly should be advised for diagnostic MRI since it is the main key to diagnosing the disease along with variable clinical features.

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