CASE REPORT

Van der Knaap disease: a rare disease with atypical features

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SUMMARY

Megalencephalic leukoencephalopathy with subcortical cysts (MLC), or Van der Knaap disease, is a rare autosomal recessive disorder. It is characterised by macrocephaly that either presents at birth or develops during infancy. It occurs more commonly in some ethnicities where consanguinity is common, such as in the Agrawal community in India. This disease typically presents with a history of delayed motor milestones in affected children. MRI findings including leukodystrophy and subcortical cysts are hallmarks of the disease and yield the diagnostic clue in most cases. Several cases of Van der Knaap disease with classical features have been reported in the literature. We present a case of Van der Knaap disease with classical MRI features, including a few distinctly atypical characteristics in its epidemiological, clinical and electrophysiological attributes.

BACKGROUND

Megalencephalic leukoencephalopathy with subcortical cysts (MLC), or Van der Knaap disease, is a rare autosomal recessive disease first described by Van der Knaap in 1995.¹ It is more commonly observed in some ethnic groups, such as the Agrawal community in India, where consanguinity is common.²

Clinically, it is characterised by macrocephaly, which may be present at birth or develop during the first year of life. Additionally, these patients may have delayed motor development and early onset of seizures.¹ Motor development in infancy is usually normal or mildly delayed. However, early childhood is marked by a significant delay in motor development. Later in the course of disease, patients have slow mental deterioration. Cerebral MRI shows diffusely swollen cerebral white matter and subcortical cysts.¹ White matter swelling over time may be set back by the ensuing cerebral atrophy. In approximately 70% of patients with MLC, mutations in the *MLC1* gene appear to have a causal relationship with the syndrome.³ We present a case of a 9-month-old boy born of non-consanguineous marriage in a Hindu family from eastern India, with a normal birth history, who presented to us with grossly delayed developmental milestones and increased head circumference (HC). He was diagnosed as a case of MLC on the basis of his brain MRI, which had features classically described for the syndrome. Thus, occurrence of this disease in a child of a 'non-Agrawal' community in India, born out of a non-consanguineous marriage, is unusual from its epidemiological

perspective. Furthermore, presence of gross motor developmental delay in infancy, as in this child, is rarely reported. Besides, while conducting electrophysiological studies, visual evoked potential (VEP) analysis was suggestive of bilateral prolonged P100 latencies, which is not a feature in early life. So, in this child, this rare disease manifested with some features that can be categorically considered as atypical for the disease.

CASE PRESENTATION

A 9-month-old boy born out of a non-consanguineous marriage in a Hindu family from Bihar (a state in eastern India), presented to our neurology outpatient department with a history of delayed developmental milestones. He developed a social smile at the age of 8 months. Moreover, he was not able to sit, even with support, and was not able to utter sounds, at the time of presentation. He was born out of a normal full-term delivery with an uneventful perinatal and postnatal period. His parents noticed his abnormally large head size in comparison to that of his peers, at the age of 5 months. The parents denied any history of seizures or any other behavioural problem. There was no history of prolonged fever or head trauma. Family history was not significant. On examination, the baby had macrocephaly with a HC of 48 cm (>95th centile for his age; figures 1 and 2). His fundoscopic examination was normal, without any evidence of cherry-red spot. He did not have any

Figure 1 Child with macrocephaly.

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Figure 2 Location of the child's head circumference lies above the 95th centile in the WHO growth chart 'head circumference for age 'X' boys'.

organomegaly. The rest of the general physical and systemic examination was unremarkable.

INVESTIGATIONS

Routine blood biochemistry, chest X-ray and ultrasound of the abdomen were normal. MRI showed extensive diffuse homogenous dysmyelination involving the subcortical and deep white matter of the cerebral hemispheres along with cysts bilaterally in the temporal lobe (figures 3 and 4). Cerebrospinal fluid analysis was within normal limits. EEG, brainstem auditory evoked response, nerve conduction studies of all four limbs and EMG, did not reveal any abnormality. Flash VEP testing, however, revealed prolonged P100 latencies bilaterally (139 on the left and 142 on the right side). Resting on the typical MRI findings, we kept Van der Knaap disease as our first possibility and ordered a MR spectroscopy, which was not suggestive of any abnormal N-acetylaspartate (NAA) peak, thus ruling out the possibility of Canavan disease.

DIFFERENTIAL DIAGNOSIS

Canavan disease, Alexander disease, infantile-onset GM2 and GM1 gangliosidosis.

TREATMENT

In the absence of any available treatment, the patient was discharged after genetic counselling of the parents.

Figure 3 T2-weighted brain MRI. (A) Extensive diffuse homogenous dysmyelination involving the subcortical and deep white matter of the cerebral hemispheres along with presence of cysts (arrows) bilaterally in the temporal lobe as seen on T1 weighted (B) and T2 fluid-attenuated inversion recovery (C) sequences.

OUTCOME AND FOLLOW-UP

At the time of first follow-up visit 2 months after the discharge, the patient did not show any significant clinical worsening or improvement. He was able to, however, start sitting with support.

DISCUSSION

Through this case, we report an uncommon disorder with atypical features. 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.²⁻⁴ However, in our case, consanguinity was not a factor, which presented an atypical feature in relation to the epidemiological pattern of the disease. Likewise, this child also had some peculiarities in context with the clinical features of the disease. Macrocephaly, though it may be present at birth,

Figure 4 Another T2-weighted image showing diffuse extensive dysmyelination.

more frequently develops during infancy.¹ The HC in this child was normal at birth and there was rapid growth from the early months of life. Although almost all patients have early-onset epilepsy, this child had no history of seizures to date. Early development is normal or mildly delayed, but in our case, the child had grossly delayed developmental milestones. Diagnosis of MLC can be made by MRI of the brain, which invariably shows diffuse white matter changes and subcortical cysts, in the anterior temporal region or in the frontoparietal region.¹ Later in life, white matter swelling decreases and cerebral atrophy comes into the picture. Grey and deep white matter structures such as the corpus callosum, internal capsule and brain stem, are relatively spared. MRI of the brain in our patient revealed classical features of the disease. However, on electrophysiological testing, flash VEP testing demonstrated prolonged P100 latencies bilaterally. VEP, which is a marker of optic pathway dysfunction, is deranged early in some leukodystrophies such as adrenoleukodystrophy, metachromatic leukodystrophy, Pelizaeus-Merzbacher disease and infantile Krabbe disease.⁵ In MLC, however, it is usually initially normal, and deteriorates over years, as the disease advances.⁶ Atypical findings, as evident in our case, have been reported to be a predictor of a severe and aggressive disease course.

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.¹ Ben-Zeev *et al*⁴ reported 12 cases of MLC in an ethnic Jewish group with consanguinity, having classical clinical and MRI features. Singhal *et al*² reported 30 patients of leukodystrophy, megalencephaly and a relatively benign course in an ethnic Agrawal group in India.

MLC is caused by mutations in MLC1 (75%) or HEPACAM (20%). The biallelic mutation of MLC1 is associated with the classic phenotype (known as MLC1); whereas the biallelic mutation of HEPACAM it is known as MLC2A. There is also one other phenotype, which is seen less frequently and has been classically described as an 'improving phenotype', associated with a heterozygous mutation of HEPACAM known as MLC2B. Symptomatically, the patients in the 'improving phenotype' group do better over time in terms of HC, which usually follows a line above and parallel to the 98th centile, and normalises in a few children, with normal or mildly delayed early development with improving motor function after first year of life, and easily controlled seizures without any regression of mental and motor functions.⁷

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.⁷

The 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.⁸ 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.⁹ Basal ganglia and thalami were normal, as evident on brain MRI, in our patient.

This case highlights the importance of clinicians being aware of the atypical features of MLC, and thus avoiding misdiagnosis in these cases.

Learning points

- Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is an autosomal recessive degenerative disease of the brain, without any specific treatment. It is characterised by macrocephaly that either presents at birth or develops during infancy.
- It is more commonly found in some ethnicities, such as the Agrawal community in India, where consanguinity is common.
- Classical MRI findings include leukodystrophy and subcortical cysts, which clinch the diagnosis in most cases.
- MLC with atypical presentation is a predictor of poor prognosis.
- 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.

Competing interests None declared.

Patient consent Obtained.

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