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VAN DER KNAAP DISEASE: AN UNUSUAL PRESENTATION OF A RARE VANISHING WHITE MATTER DISEASE

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ABSTRACT

Van der Knaap disease (Megalencephalic Leukoencephalopathy with Subcortical Cysts; MLC) is a rare autosomal recessive leukodystrophy with a prevalence of less than 1 in 1,000,000. We report a 2-year 8-month-old male child born of consanguineous parents who presented with progressive macrocephaly, isolated speech delay, and gait disturbance with ataxia. Neuroimaging revealed the characteristic pattern of diffuse cerebral and cerebellar white matter signal abnormality with subcortical cysts in the bilateral anterior temporal and frontoparietal lobes, confirming the diagnosis. Electroencephalography, nerve conduction studies, and brainstem evoked response audiometry were normal. No disease-modifying therapy exists; management is supportive. This case highlights the importance of MRI in establishing diagnosis and illustrates an atypical ethnic presentation outside the classically reported high-risk communities.

BACKGROUND

Van der Knaap disease, also known as Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC; OMIM #604004), is a rare autosomal recessive leukodystrophy first described by the Dutch neurologist Marjo van der Knaap in 1995. The condition has a prevalence of less than 1 in 1,000,000 and disproportionately affects populations with high rates of consanguinity, including the Agrawal community in India, Libyan Jews, Turkish, and Egyptian populations.

Pathogenic variants in two genes account for the majority of cases: mutations in *MLC1* (chromosome 22q13.33), encoding a plasma membrane protein expressed in astrocytes, account for approximately 75% of cases, while mutations in *HEPACAM* (chromosome 11q24.2), encoding the cell-adhesion molecule GlialCAM, account for a further 20%. The remaining 5% carry no identifiable mutation in either gene.[1-3]

The hallmark clinical features are macrocephaly, gradual motor deterioration with ataxia and spasticity, dysarthria, and episodic deterioration following febrile illness or minor head injury. MRI is diagnostic, demonstrating diffuse white matter signal abnormality with characteristic subcortical cysts predominantly in the anterior temporal and frontoparietal regions. No curative treatment exists.

Case Presentation

A 2-year 8-month-old male child — the second child of a consanguineously married couple — presented with a 6-month history of progressive gait disturbance characterised by swaying and frequent falls, alongside isolated speech delay noted by the mother since 9 months of age. The child was currently able to produce bisyllables only. Parents also reported progressive head enlargement relative to peers. Onset was insidious and gradually progressive; the child retained the ability to walk without support. There was no history of convulsions, behavioural change, head trauma, or prolonged fever.

He was born at full term via normal vaginal delivery with no significant perinatal or postnatal events, and was immunised according to the National Immunisation Schedule. Developmental milestones were appropriate for age until 2 years, after which regression of gross motor milestones was noted alongside isolated speech delay. The mother had a known history of childhood-onset epilepsy managed with levetiracetam 500 mg twice daily. The elder sibling was developmentally normal with a normal head circumference.

Investigations

Routine haematological and biochemical investigations were within normal limits. Abdominal ultrasonography was unremarkable.

MRI of the brain (Figures 1–5) demonstrated ill-defined T1 hypointensity with T2/FLAIR hyperintensity, without diffusion restriction or susceptibility blooming on GRE sequences, involving the cerebral and cerebellar white matter bilaterally. Multiple subcortical cysts were identified in the bilateral anterior temporal, frontal, and high posterior parietal lobes; the largest measured 4.2 × 2.1 cm in the left temporal lobe. These findings were consistent with Megalencephalic Leukoencephalopathy with Subcortical Cysts, confirming the diagnosis of Van der Knaap disease.

Electroencephalography (EEG), nerve conduction studies, and brainstem evoked response audiometry (BERA) were all within normal limits. Genetic testing for *MLC1* and *HEPACAM* mutations was not available at our centre.

Differential Diagnosis

The following conditions were considered in the differential diagnosis:

- Canavan disease — presents with macrocephaly and white matter disease but N-acetylaspartate elevation on MRS and lacks subcortical cysts
- Alexander disease — frontal-predominant white matter signal change with Rosenthal fibre deposition; *GFAP* mutation testing distinguishes
- Infantile-onset GM1 and GM2 gangliosidosis — associated with cherry-red spot, hepatosplenomegaly, and specific enzyme deficiencies
- Other metabolic leukodystrophies — excluded on the basis of biochemical and MRI profile

The characteristic MRI pattern of diffuse white matter abnormality with anterior temporal and frontoparietal subcortical cysts, together with the clinical constellation of macrocephaly, progressive ataxia, and a background of parental consanguinity, favoured MLC and established the diagnosis of Van der Knaap disease.

Treatment

No disease-modifying or curative therapy is currently available for Van der Knaap disease. Management is supportive and multidisciplinary. The child was enrolled in structured physiotherapy to address gait instability and motor regression, referred to speech therapy for language delay, and linked with special educational needs services. Caregivers were counselled regarding the natural history of the condition, the risk of episodic neurological deterioration following febrile illness or head injury, and the 25%

recurrence risk in future pregnancies given autosomal recessive inheritance.

Outcome and Follow-up

The child was discharged with outpatient follow-up in the paediatric neurology and developmental paediatrics clinics. Regular monitoring of head circumference, developmental milestones, and neurological status was planned. Parents were advised to seek early medical review during any febrile illness to prevent injury during episodes of deterioration.

DISCUSSION

MLC is a clinically and genetically distinct leukodystrophy in which MRI findings precede and often exceed the severity of clinical symptoms.[4] The characteristic neuroimaging pattern — diffuse white matter T2/FLAIR hyperintensity combined with subcortical cysts predominantly in the anterior temporal and frontoparietal regions — is considered pathognomonic and forms the basis of clinical diagnosis in the absence of genetic confirmation.

Although described across multiple ethnicities, the condition is most prevalent in communities with high rates of consanguinity.[1,2] In the present case, the child was not from the classically reported Agrawal community; however, parental consanguinity represented a clear predisposing risk factor. This underscores that MLC should remain a differential diagnosis for any child presenting with macrocephaly and white matter disease in the context of consanguinity, irrespective of specific ethnic background. Early psychomotor development in MLC is typically normal or only mildly delayed, with slow progressive deterioration thereafter.[3,5] This case illustrates a pattern consistent with the established phenotype: regression of gross motor milestones, axial hypotonia, bilateral lower limb hyporeflexia, and isolated speech delay emerging after an initially normal developmental trajectory. The absence of seizures, normal EEG, and intact nerve conduction studies further align with typical MLC presentation.

Management remains purely supportive. Emerging experimental approaches, including gene therapy targeting *MLC1* and pharmacological strategies to reduce vacuolating oedema, are under investigation but have not yet reached clinical practice.[4]

Figures

Figure 1. MRI Brain — Sagittal T1-weighted sequence demonstrating diffuse hypointensity of the cerebral white matter.

Figure 2. MRI Brain — Axial FLAIR sequence showing bilateral white matter hyperintensity and subcortical cysts in the anterior temporal lobes.

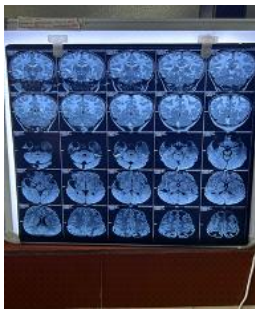

Figure 3. MRI Brain — Coronal FLAIR sequence demonstrating enlarged subcortical cysts, largest in the left temporal lobe (4.2 × 2.1 cm).

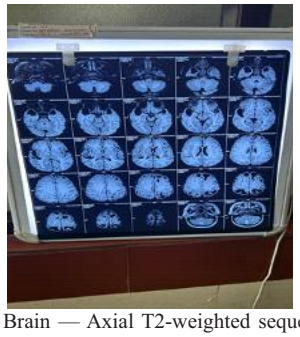

Figure 4. MRI Brain — Axial T2-weighted sequence showing the extent of bilateral cerebral and cerebellar white matter involvement.

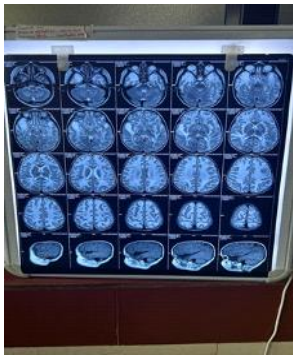

Figure 5. MRI Brain — Additional axial sequence confirming involvement of the posterior fossa white matter.

Patient Consent for Publication

Consent obtained from parent(s)/guardian(s) of the minor participant. Ref: [Consent reference number].

Competing Interests

None declared.

Contributors

[Author 1]: conception, data collection, drafting of manuscript. [Author 2]: critical revision of manuscript. All authors approved the final version.

Ethics Statement

This case report was prepared in accordance with the CARE guidelines for case reports. Patient data have been anonymised. Institutional ethics committee approval was not required for a de-identified single case report per local guidelines.

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