

Van der Knaap Disease: A Case Series Highlighting Clinical and Radiological Features

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ABSTRACT

Megalencephalic Leukoencephalopathy (MLC) presents with enlarged head circumference, delays in developmental milestones, and recurrent seizures. The present case series, was conducted over ten years, and assessed Magnetic Resonance Imaging (MRI) and clinical features in familial and non-familial cases of van der Knaap disease. Twelve patients were evaluated, of whom five were familial and seven non-familial, 8 males and 4 females. Macrocephaly was invariably present along with delays in gross motor milestones in six of the 12 cases (50%), and a seizure disorder was present in eight of the 12 cases (66.7%). Of the eight patients with seizures, 7 (87.5%) had generalised tonic-clonic seizures, while simple partial seizures were observed in only 1 (12.5%) case. Motor and intellectual impairment were more severe in patients with extra-temporal lobar subcortical cysts, present in seven of the 12 (58.3%) cases. The classical MRI features include diffuse white matter involvement (T2/FLAIR hyperintensity) with subcortical cysts in the anterior temporal region (rarely in the frontoparietal region), sparing of deeper structures, and varying degrees of cerebral atrophy; diffuse white matter involvement and anterior temporal subcortical cysts were observed in 100% of our cases. Early MRI should be considered for asymptomatic siblings of an affected family to enable early diagnosis and treatment initiation. Clinicians should maintain a high index of suspicion for van der Knaap disease; when clinically suspected, MRI of the brain should be performed for diagnosis. Screening of other family members should also be advised to detect asymptomatic cases. Because the MRI features are highly suggestive of van der Knaap disease, further investigations beyond genetic testing may be avoided. As it is an autosomal recessive disorder, patients and their relatives should be counseled to prevent consanguineous marriages and thereby reduce transmission of the disease.

Keywords: Consanguineous marriage, Diffuse white matter involvement, Leukodystrophy, Magnetic resonance imaging, Paediatric neuroradiology

INTRODUCTION

Megalencephalic Leukoencephalopathy (MLC) presents with enlarged head circumference, delays in developmental milestones, and recurrent seizures. The disease shows a slow progression with variable motor and cognitive impairment [1]. In later stages, ataxia and spasticity may occur. It has an autosomal recessive pattern of inheritance; the mapped gene locus is MLC1 on chromosome 22q [2]. Many factors seem to affect the course and severity of the disease; even siblings with the same mutation may have differences in its phenotypic expression [3].

The disease has the highest incidence among the Indian Aggarwal community [4,5] and the Turkish population [6]. MRI is used as a diagnostic modality of choice, along with clinical and epidemiological attributes, to arrive at a diagnosis. Typical MRI features include diffuse bilateral symmetric T2/FLAIR white matter hyperintensity giving a characteristic swollen appearance, with relative sparing of the deep and cerebellar white matter [7,8]. Bilateral subcortical cysts of CSF intensity affecting the temporal regions and frontoparietal lobes are also seen [9].

CASE SERIES

Between December 2012 and November 2022, 12 cases of van der Knaap disease based on MRI and clinical features were identified. Each case was assigned a case number and categorised into familial and non-familial groups. Cases belonging to the same family were grouped into two familial subsets. Due to unavailability, genetic tests such as MLC1 and HEPACAM were not performed in these cases. Metabolic and leukodystrophy panels were done to rule out other imaging differentials such as Canavan disease and Alexander disease, etc.

Of the familial cases, three patients belonging to subset one were from the Aggarwal community of India. All three were siblings from the same parents. The younger patient, a 14-year-old male, presented with seizures, learning difficulties, and behavioural abnormalities. MRI of all three siblings showed the typical features of van der Knaap disease [Table/Fig-1].

The comparative clinical features between familial and non-familial cases of van der Knaap disease are presented in [Table/Fig-1]. Two other patients from a different family, a father and daughter also presented with megalencephaly and other described features [Table/Fig-1] and had white matter involvement and subcortical cysts consistent with van der Knaap disease on MRI. The father also had cerebellar involvement with peridentate T2/FLAIR hyperintensity.

The comparative MRI features between familial and non-familial cases of van der Knaap disease are presented in [Table/Fig-2]. The other seven non-familial cases had varied clinical presentations in terms of motor and intellectual development, with megalencephaly as a common feature. They all had diffuse white matter involvement with subcortical cysts in different locations [Table/Fig-3].

DISCUSSION

The disease presents more frequently during the first two years of life, as observed in the above cases. Macrocephaly has been observed in all of the cases. Two cases presented with ataxia in individuals aged over 18 years and belonging to the familial subset, representing late presentation of the disease. Diffuse white-matter involvement (T2/FLAIR hyperintensity) in the brain with subcortical

Cases	Age/sex	Motor development	Intellectual development	Age of onset of seizure	Head circumference (percentile)	Macrocephaly	Birth history	Cerebellar signs
Familial cases								
Subset-1								
Case 1	14 years/male	Delayed	Learning difficulty with behavioural abnormality	2 years- Generalised tonic clonic seizure (GTCS)	96 th	Present	Uneventful	No such sign
Case 2	29 years/male	Normal	Normal	No seizure	97 th	Present	Uneventful	Ataxia
Case 3	18 years/female	Normal	Normal	No seizure	96 th	Present	Uneventful	No such sign
Subset-2								
Case 4	2 years/female	Delayed (Not started walking at the time of presentation)	Delayed (impaired speech development)	No seizure	97 th	Present	Uneventful	No such signs
Case 5	25 years/male	Normal	Normal	2 years (simple partial type)	96 th	Present	Uneventful	Ataxia
Non-familial cases								
Case 6	5 years/female	Delayed	Learning difficulty with delayed speech development	6 months of age (GTCS)	97 th	Present	Uneventful	No such signs
Case 7	2 years/female	Delayed	Delayed speech development	2 months of age (GTCS)	97 th	Present	Uneventful	No such signs
Case 8	3 months/male	Normal for age	Normal for age	1 month of age (GTCS)	98 th	Present	Uneventful	No such signs
Case 9	24 days/male	Normal for age	Normal for age	No seizure	99 th	Present	Didn't cry at birth	No such signs
Case 10	2 years/male	Delayed	Delayed speech development	1 month of age (GTCS)	96 th	Present	Uneventful	No such signs
Case 11	3 months/male	Normal for age	Normal for age	Since birth (GTCS)	97 th	Present	Uneventful	No such signs
Case 12	26 days/male	Delayed (no neck holding)	Normal for age	Since birth (GTCS)	96 th	Present	Uneventful	No such signs

[Table/Fig-1]: Comparative clinical features between familial and non-familial cases of Van der Knaap disease. Subset 1 and Subset 2 represent familial cases of Van der Knaap disease.

Cases	White matter involvement	Subcortical cyst	Cerebellar white matter involvement	Grey matter involvement	Cerebral atrophy
Familial cases					
Subset-1					
Case 1	Diffuse involvement	Bilateral temporal cyst and left frontal cyst	Not involved	Not involved	Mild diffuse atrophy
Case 2	Diffuse involvement	Bilateral temporal cyst	Not involved	Not involved	Moderate diffuse atrophy
Case 3	Diffuse involvement	Bilateral temporal cyst	Not involved	Not involved	Moderate diffuse atrophy
Subset-2					
Case 4	Diffuse involvement	Bilateral temporal cyst and bilateral frontoparietal cyst	Not involved	Not involved	Severe diffuse atrophy
Case 5	Diffuse involvement	Bilateral temporal cyst, bilateral parietal cyst and right frontal cyst	T2 / FLAIR hyperintensity in bilateral peridentate region	Not involved	No atrophy
Non-familial cases					
Case 6	Diffuse involvement	Bilateral temporal cyst	Not involved	Not involved	No atrophy
Case 7	Diffuse involvement	Bilateral temporal cyst and bilateral frontal cyst	Not involved	Not involved	Bilateral marked frontal atrophy
Case 8	Diffuse involvement	Bilateral temporal cyst	Not involved	Not involved	No atrophy
Case 9	Diffuse involvement	Bilateral temporal cyst	Not involved	Not involved	No atrophy
Case 10	Diffuse involvement	Bilateral frontal and bilateral parietal cyst	Not involved	Not involved	Mild diffuse atrophy
Case 11	Diffuse involvement	Bilateral temporal cyst, bilateral frontal and parietal cysts	Not involved	Not involved	No atrophy
Case 12	Diffuse involvement	Bilateral temporal cyst and bilateral frontal cyst	Not involved	Not involved	No atrophy

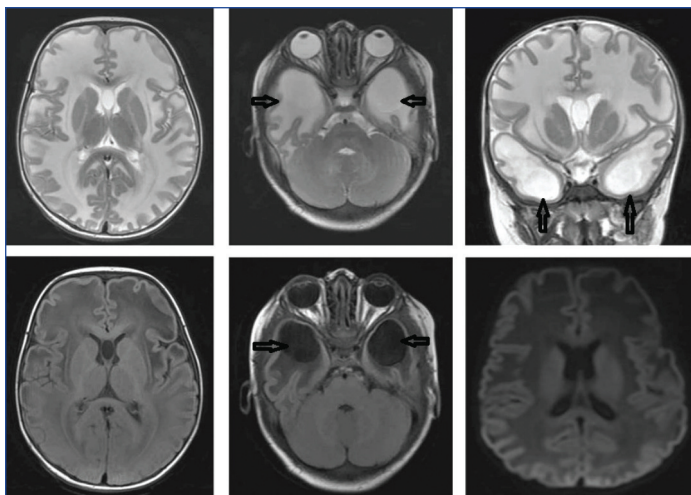
[Table/Fig-2]: Comparative MR Imaging features between familial and non-familial cases of Van der Knaap disease.

cysts, sparing of the deeper structures, has been considered the classical MRI feature of the disorder [10].

Differential diagnosis of MLC with subcortical cysts includes Glutaric aciduria type 1, Canavan's disease, and Alexander disease; however, these conditions do not have such a mild clinical course. None of these conditions has subcortical cysts on MRI, and all of these diseases involve the basal ganglia, unlike MLC with subcortical cysts.

In a study by Sharma A. et al., a 27-year-old male born of a non-consanguineous marriage in a Sikh community in Haryana, India, presented with ataxia and seizures beginning at age eight, with MRI

features consistent with van der Knaap disease [11]. In another study by Batla A. et al., four patients were described. Seizures were seen in all of these patients. One of these four patients had moderately severe depression. All patients were diagnosed by MRI features and responded well to symptomatic treatment [12]. Singhal BS et al., described 18 patients with megalencephalic leukodystrophy from India [5]. From India, Singhal BS et al., conducted detailed genetic analyses and established this disease as a distinct clinicopathological entity with a common locus at the MLC1 gene in all 31 patients described in the Aggarwal community [4].



[Table/Fig-3]: Axial and Coronal T2 images reveal symmetrical hyperintensity in subcortical white matter. Axial FLAIR images show subcortical cysts in bilateral temporal lobes (marked by arrowheads). DWI shows no diffusion restriction in the involved white matter.

In a case report by Ramzan Y. et al., van der Knaap disease was described in a case from the Bhat family. The patient had delayed motor milestones, ataxia, increasing head circumference, and abnormal body movements. MRI of the brain showed diffuse white matter hyperintensities in the bilateral cerebral hemispheres, predominantly in the frontotemporoparietal areas, with cyst formation [13]. Kumar MK and Singh BB described three siblings belonging to a non-Aggarwal Hindu family affected with MLC, presenting with early onset macrocephaly and gradual onset ataxia [1].

However, the lack of genetic testing was a limitation in the present diagnostic work-up. Also, the cases were not followed for a long duration, and management aspects were not covered. Early MRI should be considered in asymptomatic siblings of the same family for early diagnosis and initiation of treatment. Screening of other family members should be advised to diagnose asymptomatic cases.

CONCLUSION(S)

Patients with megalencephaly, clinical findings suggestive of MLC, and characteristic MRI changes such as diffuse white matter involvement with a subcortical cyst should raise suspicion for van der

Knaap disease, especially in communities where consanguineous marriages are common. However, an increasing number of non-familial sporadic cases is being reported from different communities. Clinicians should remain vigilant regarding the possibility of van der Knaap disease and advise MRI when clinically suspected for prompt diagnosis and early initiation of treatment.

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