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Megalencephalic leukoencephalopathy with subcortical cysts: A report of two cases with a brief review of literature

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Abstract: Megalencephalic leukoencephalopathy with subcortical cysts (MLC) , also known as van der Knaap disease is a rare neurodegenerative disorder first described by van der Knaap et al. in 1995. It is characterized by early-onset macrocephaly with mild motor developmental delay, gradual onset ataxia, spasticity, seizures and usually late onset mild cognitive deterioration. Majority of cases have been reported from the Aggarwal community in India. We report two cases of this disease, both are from non- Aggarwal family with a brief review of literature. We diagnosed this disease at an earlier age by clinical features and characteristic MRI findings.
Keywords: megalencephalic leukoencephalopathy, Macrocephaly, subcortical cysts, van der Knaap disease, MLC1 gene.

INTRODUCTION

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a relatively new entity of dysmyelinating disorder. This disease is inherited mostly in an autosomal pattern and in approximately 75% cases caused by mutations in the MLC1 gene mapped to chromosome 22q. Clinically it is characterised by early-onset macrocephaly with mild motor developmental delay, gradual ataxia and slow course of neurological deterioration. Macrocephaly is the consistent feature and the degree of macrocephaly is variable [1,2,3]. Though this disease bears the name of van der Knaap, it was first reported by Singhal et al. from India who presented a series of 18 patients at 8th Asian and Oceanian Congress of Neurology at Tokyo in 1991. Later ,Van der Knaap et al. from Netherlands later published a series of 8 patients and described the clinical and MRI features [4]. There is no definite treatment available and it is mostly supportive in the form of physiotherapy and psychomotor stimulation. Early rehabilitation may prolong ambulatory life.

CASE REPORTS

Case-1

A one and half year old female child presented with progressive increasing head size from five months of age. She was born of non-consanguineous marriage. She had uneventful birth history. She attained social smile by 3 months and head control by 6 months. She is not able to stand without support. She had two episodes of generalized tonic clonic seizures at the age of 1 year.

On examination she had macrocephaly with head circumference of 55cm(> 95th percentile) . She was able to say few words. Her sensory and cerebellar examination was normal.

Case-2

This 1-year-old female presented with increasing head size since 2 months of age as noticed by her mother. She was first order child with normal birth history and born of non-consanguineous marriage. She had no developmental delay or seizures. She was able to say bisyllables.

On examination , her head circumference was 50 cm. Motor, sensory and cerebellar examination was essentially normal.

IMAGING FINDINGS

MRI in both cases showed diffuse supratentorial white matter T2 and FLAIR **(**Fluid attenuation inversion recovery) hyperintensity , T1 hypointensity with temporal subcortical cysts. Case -1 in addition showed bilateral fronto-parietal cysts. These cysts showed CSF signal intensity and were suppressed on FLAIR. There was sparing of internal capsules , corpus callosum, brain stem and cerebellar white matter. (Fig 1 & 2)

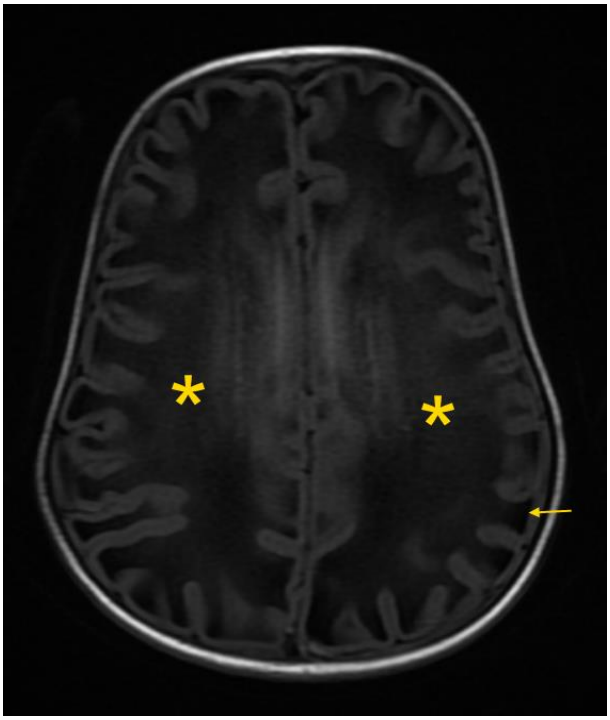

Fig 1A: Axial T1 MRI showing bilateral symmetrical diffuse white matter hypointensity (*) with involvement of subcortical U fibres (arrow).

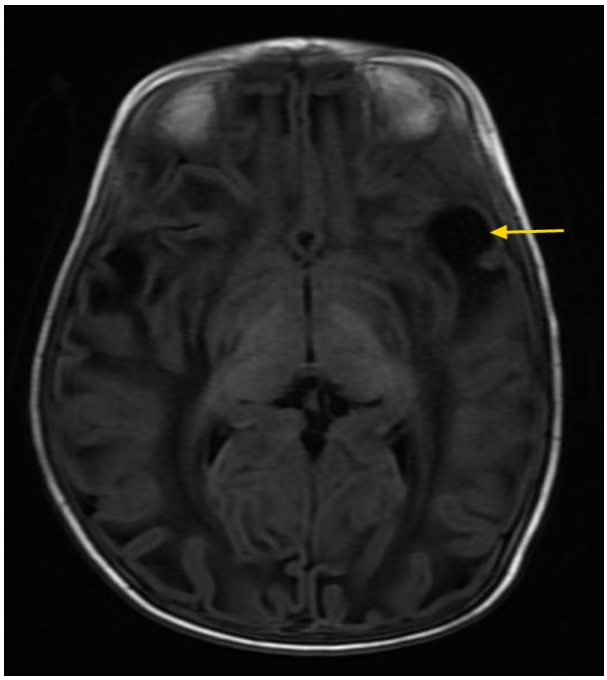

Fig 1B : Axial T1 MRI showing a CSF intense cyst in left temporal lobe subcortex (arrow).

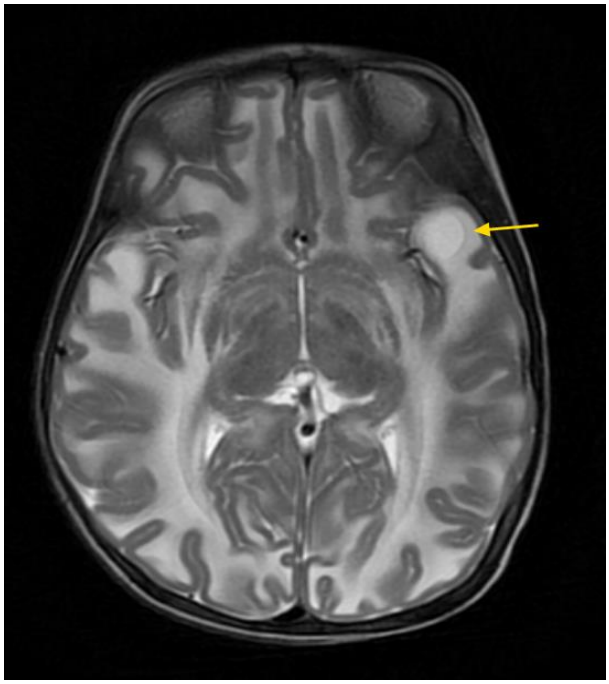

Fig 1C : Axial T2 MRI showing same cyst (arrow) which is CSF intense.

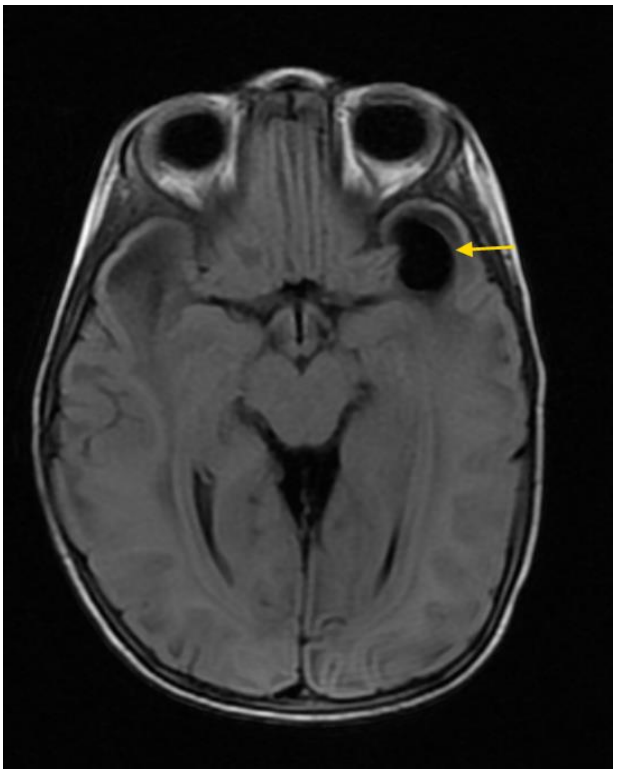

Fig 1D : The cyst (arrow) suppresses fully on FLAIR.

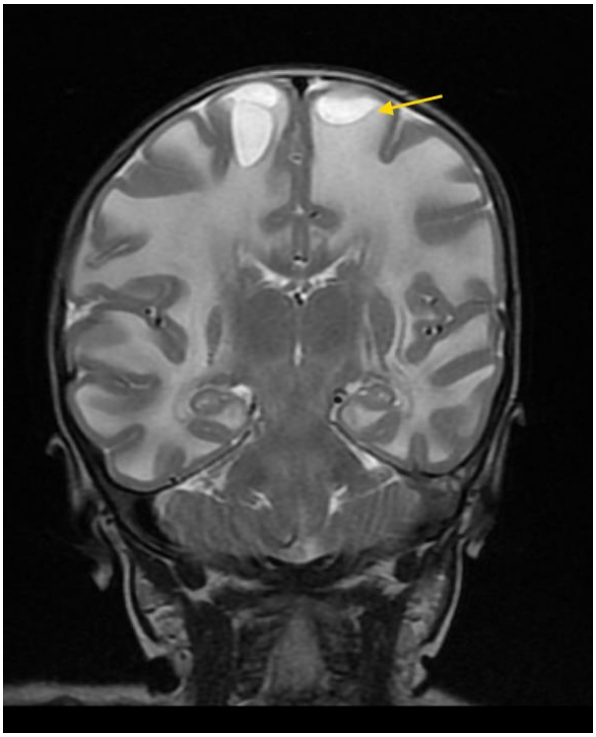

Fig 1E :Coronal T2 image showing subcortical cysts in bilateral frontoparietal region (arrow).

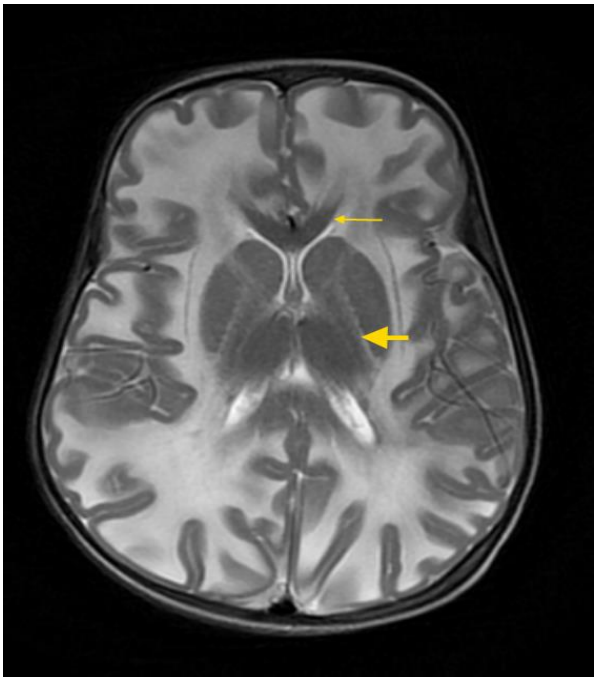

Fig 1F : Axial T2 MRI showing sparing of internal capsule (thick arrow) , corpus callosum (thin arrow).

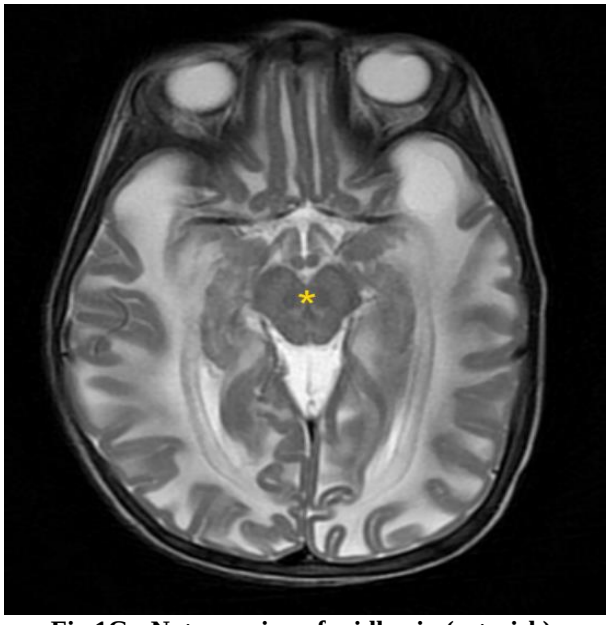

Fig 1G : Note sparing of midbrain (asterisk).

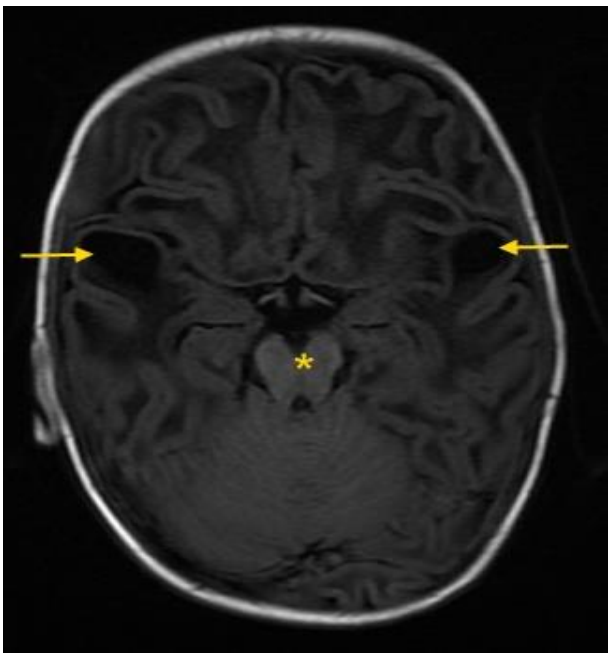

Fig 2A : Axial T1 MRI brain showing bilateral temporal subcortical cysts (arrows) which are CSF intense. Note sparing of midbrain (asterisk)

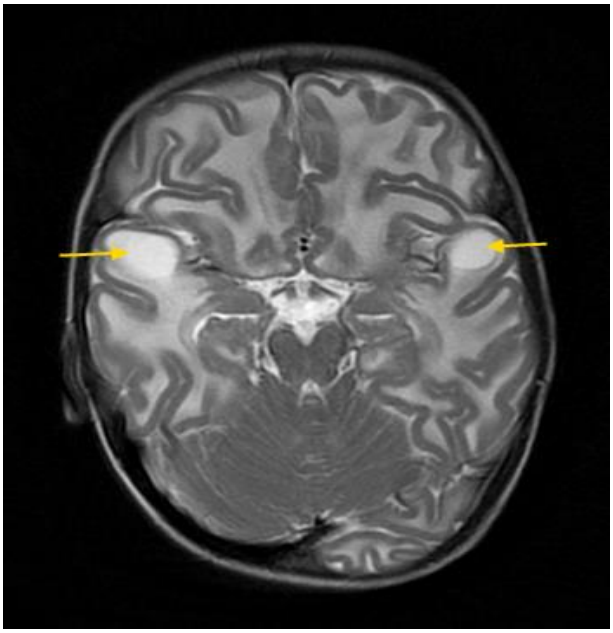

Fig 2B : These cysts follow CSF signal in T2 MRI also (arrows)

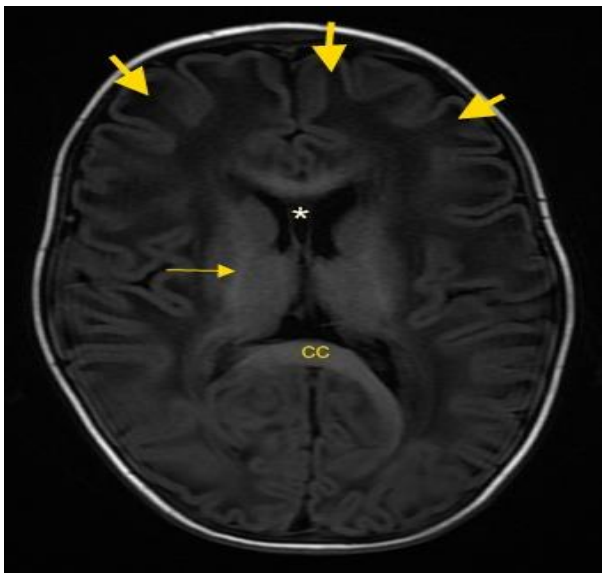

Fig 2C : Axial T1 MRI showing sparing of corpus callosum (CC) , internal capsules (arrow). Involvement of subcortical U fibres (thick arrows) is noted. Note the cavum septum pellucidum(*).

DISCUSSION

Megalencephalic leukoencephalopathy with subcortical cysts(MLC) is a rare dysmyelinating disorder first described by van der Knaap et al. in 1995. It is inherited mostly as an autosomal recessive disorder (MLC1 gene mutation) with low carrier rate .It has characteristic MRI features and a variable but mild clinical course. It is characterized by early-onset macrocephaly with mild motor developmental delay, gradual onset ataxia, spasticity, seizures and usually late onset mild cognitive deterioration. The disease has a high incidence in populations in which consanguinity is common and in certain ethnic groups(Agarwal community in India, Jewish community) [1,2,3].

Genetics

Approximately 75% of cases are caused by mutations in the MLC1 gene mapped to chromosome 22q13.33. The physiological function of the protein is at present not known. It is probably an integral membrane protein located in astrocyte-astrocyte junction. Rest of the cases show mutation in HEPACAM (hepatocyte cell adhesion molecule) gene encoding for glialCAM protein. It is located on chromosome 11q24 and called MLC2A. A newly described heterozygous HEPACAM mutation (MLC2B) is transmitted as autosomal dominant form and has improving phenotype as compared to MLC1 and MLC2A [4, 5].

Clinical features

Age at symptom onset varies widely ranging from birth to 25 years with median age of onset at 6 months [3].

Macrocephaly is present in all cases. The degree of macrocephaly is variable and can be as much as 4-6 SD above the mean. Macrocephaly develops in first 6 months in 24% cases and 70% in second six months. After the first year of life, head growth rate becomes normal and growth line is above and parallel to 98th centile [4,5,6].

Early development is normal or mild delayed. Slow deterioration of motor function with cerebellar ataxia and spasticity occurs in early childhood or later. Dysphagia and dysarthria may develop. Extrapyramidal symptoms (dystonia, athetosis) can occur in some individuals. Mental decline is usually milder than motor decline .Most individuals have epileptic seizures which are easily controlled on medication. This disease follows a slow benign course except in some patients when minor head trauma may induce temporary deterioration most commonly observed as seizures, prolonged unconsciousness, acute motor deterioration with gradual improvement [3,4,6,7].

MRI findings

MRI findings are often diagnostic in MLC. MRI shows swollen supratentorial hemispheric white matter with high signal intensity in T2 and FLAIR. There is relative sparing central white matter structures like the corpus callosum, internal capsule, brainstem. Subcortical cysts are invariably present in anterior temporal region and also frequently in frontoparietal region. Cerebellar white matter is minimally involved or spared. White matter swelling decreases over time and cerebral atrophy may ensue. The size and number of subcortical cysts may also increase over time. The magnetic resonance spectroscopy may reveal mild decrease in N- acetyl aspartate(NAA) to choline and choline to creatine ratios [3,4,6,7,8].

The differential diagnosis of MLC includes Canavan disease, Alexander disease, Infantile onset GM2 gangliosidosis, occasionally Infantile onset GM1 gangliosidosis, L-hydroxy glutaric aciduria and Merosin-deficient congenital muscular dystrophy. These conditions are quite unlikely to have mild clinical course as in MLC [6,7,8]

Canavan disease almost always involves globus pallidus,thalamus; does not develop typical subcortical cysts though white matter may show cystic changes and shows a large NAA peak on MRS.

Alexander disease leads to megalencephaly and leukoencephalopathy with frontal white matter predominance. Contrast enhancement occurs unlike in MLC. Deep frontal white matter may show cystic degenerations.

MRI in infantile gangliosidosis shows prominent involvement of the basal ganglia and thalami (absent in MLC) in addition to the white matter abnormalities.

Glutaric aciduria type 1(GA 1) shows macrocrania , bilateral widened (open) sylvian fissures, bilaterally symmetric basal ganglia lesions. Severe GA1 may show diffuse hemispheric white matter abnormalities.

Subcortical cysts are absent in congenital muscular dystrophy and patients have weakness and hypotonia which are absent in MLC.

Prenatal diagnosis is possible by identifying MLC1 mutations in fetal cells from amniocentesis or chorionic villus sampling [6,7].

Treatment is mostly supportive and includes antiepileptics, physiotherapy and psychomotor stimulation. Early diagnosis and treatment may prolong ambulatory life [6].

CONCLUSION

MLC is the most common leukodystrophy with megalencephaly observed in India especially in Aggarwal community. Our patients didn't belong to this community. We observed phenotypic variations in above cases. It should be placed in the differential diagnosis of infantile onset macrocephaly with white matter disease [8]. MRI is diagnostic and genetic testing is not necessary. Diffuse supratentorial white matter abnormalities with temporal or frontoparietal subcortical cysts are hallmark imaging features.

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