ORIGINAL RESEARCH PAPER

Radio Diagnosis

MEGALOENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS – MR IMAGING: PICTORIAL REVIEW

KEY WORDS:

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ABSTRACT

Megalencephalic leukoencephalopathy (MLC) with subcortical cysts is a rare disease first described by Van der Knaap et al, in 1995 [1]. MLC is a relatively new entity of neurodegenerative disorder characterized by infantile onset macrocephaly, cerebral leucoencephalopathy and mild neurological symptoms and an extremely slow course of functional deterioration. MLC is a rare disease with autosomal recessive inheritance more prevalent in the theagarwal community in India[2]. MLC must be distinguished from other IMDs with Macrocrania. Patients with megalencephaly and MR changes that show extensive white matter changes with temporal cysts should raise suspicion for MLC.

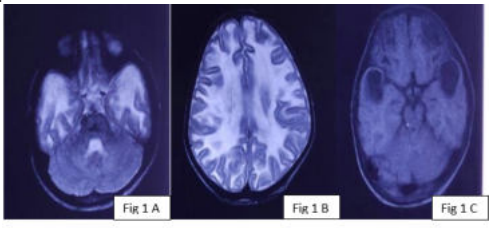
CASE REPORTS :

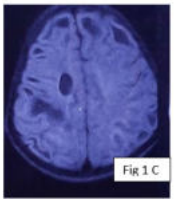
CASE 1 :

The first patient is a 4-year-old boy, born out of non-consanguineous marriage with uneventful birth history, presented with progressively increasing head size noticed from 1 year of age. He attained a social smile by 3 months and head control by 7 months of age. He was not able to sit or walk himself.

On examination, there was macrocephaly with head circumference of 61 cm, which is greater than the 97th percentile for age. The sensory system was normal, and there were no cerebellar signs. Other systems examinations were unremarkable.

MRI of brain revealed characteristic swollen appearance of the supratentorial white matter with equal affection of periventricular, deep and subcortical white matter .The lesions are extensive, bilaterally symmetrical and are hypointense on T1W ,hyperintense on T2W and FLAIR images suggestive of extensive demyelination. Additionally, large well defined symmetrical subcortical cysts were noted in bilateral anterior temporal lobe and frontal lobes which are hypointense on T1W,hyperintense on T2W and suppressed on FLAIR images. There is characteristic sparing of grey matter and infratentorial brain which consistent with a diagnosis of MLC.



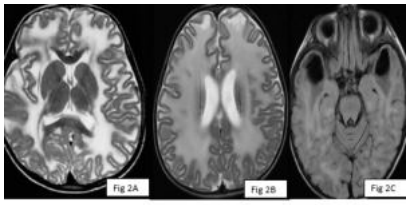


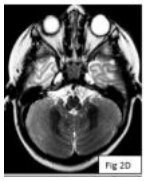
These are axial T2W (1A,1B) AND FLAIR (1C & 1D) images showing characteristic hyperintense swollen appearance of the supratentorial white matter with equal affection of periventricular ,deep and subcortical white matter with bilateral symmetrical subcortical cysts in bilateral anterior temporal lobe and frontal lobes.

Case 2 :

The second patient is a 3-year girl, born out of non-consanguineous marriage, admitted with symptoms of increasing head size since birth with delay in speech acquirement and inability to walk without support. Her head circumference was 60 cm, which is greater than the 97th percentile for age; other system examinations and laboratory investigations were unremarkable.

On MRI, there was increased T2 signal in the cerebral white matter, sparing the corpus callosum and internal capsule. Subcortical cysts were seen in the bilateral anterior temporal and frontal lobes with sparing of grey matter, corpus callosum, and infratentorial brain parenchyma, consistent with the diagnosis of MLC.

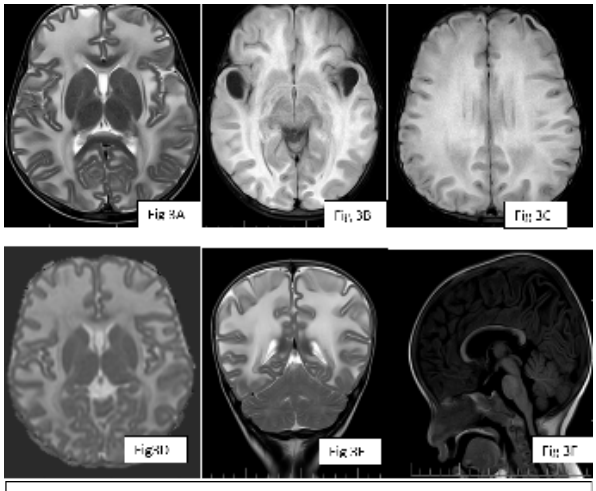




These are axial T2W (3A,3B,3 D)and axial T1 W images showing characteristic hyperintense appearance of the supratentorial white matter with subcortical cysts noted in bilateral anterior temporal lobe and frontal lobes. Sparing of grey matter, internal capsule ,corpus callosum and infratentorial brain noted.

Case 3 :
The third patient is a 2-year girl child, the second sibling of a non-consanguineous marriage, was admitted with symptoms of delay in speech acquirement and inability to walk without support. The child had a big head since birth, but the acquisition of motor milestones in infancy was normal. There was no history of seizures or visual disturbances. Her head circumference was 54.5 cm, which is greater than the 97th percentile for age, other system examinations and laboratory investigations were unremarkable.

The MR features were strikingly abnormal with diffuse involvement of the cerebral white matter. On T1W images, the involved white matter was hypointense and had a characteristic swollen appearance. On T2w and FLAIR sequences, these areas were hyperintense. Diffusion-weighted imaging shows increased diffusivity with high apparent diffusion coefficient values. The peripheral and periventricular white matter were equally involved with sparing of some central white matter structures like the corpus callosum and internal capsule and bilateral optic radiations. The cortical and central gray matter and the cerebellum were uninvolved. Large, well-defined, oval cystic lesions, which followed CSF intensity on all sequences, were seen symmetrically in subcortical locations of bifrontal and bitemporal lobes. Persistentcavum septum pellucidum was noted. These findings were consistent with a diagnosis of MLC.



These are axial T2W (2A),FLAIR (2B,2C) ADC(2D) T2W coronal(2E) and T1W axial(2F) images showing bilaterally symmetrical T2 FLAIR supratentorial white matter with increased diffusivity (2D)and subcortical cysts were noted in bilateral anterior temporal lobe and frontal lobes sparing of grey matter , internal capsule ,corpus callosum and infratentorial brain noted. Persistent cavum septum pellucidum noted (2A,2D).

RESULTS :
All the three cases presented to us are born out of non-consangious marriage and did not belong to Agarwal community. Macrocephaly in the first year of life was the most common first disease sign and had been present in all patients in infancy. All the children had minimal neurological symptoms in contrast to the extensive changes observed on imaging. No associated CNS or any other system anomalies/abnormalities were noted in any of our cases. Characteristic subcortical cysts were noted in the anterior temporal lobe in all our cases with additional cysts in the frontal lobe in 2 out of three cases. Sparing of cortical and deep grey matter infratentorial brain parenchyma with relative sparing of central white matter was noted in all cases.

DISCUSSION :
MLC is also known as vacuolating megaloencephalic leukoencephalopathy, formally called Van der Knaap disease or vacuolating megaloencephalic leukoencephalopathy with benign slowly progressive course. MLC is a rare autosomal-recessive disorder with characteristic MR features and a variable but mild clinical course. MLC is a genetically heterogeneous disorder. Approximately 75%of cases are caused by mutations in the MLC1 gene located on Chr. 22q(tel).MLC1 is an oligomeric membrane protein located in astrocyte-astrocyte junctions. A newly described mutation in the HEPACAM gene that encodes for the Glia lCAM protein, an IgG-like hepatic and glial cell adhesion molecule, may account for the remaining cases[3].

Both defects lead to abnormal cell junction trafficking with associated disturbed water homeostasis and osmotic balance and functional disturbance in volume-regulated anion channels (i.e., impaired osmoregulation).

Gross pathology shows a swollen cerebral hemispheric WM, relative occipital sparing, variable involvement of the subcortical arcuate fibers, frequent involvement of the external capsules, and sparing of the internal capsules with multiple variably sized subcortical cysts often initially involving the temporal lobes. The basal ganglia are spared. In the few reported cases of MLC with histopathology, extensive vacuolation is seen in the outer layers of myelin sheaths, accounting for the characteristic swollen appearance of the WM on MR.

MLC is distinguished clinically from other leukoencephalopathies by its remarkably slow course of neurologic deterioration. Infantile-onset macrocephaly is characteristic, but neurologic deterioration is often delayed. Age at symptom onset varies widely, ranging from birth to 25 years; median age of onset of prominent clinical symptoms is 6 months. Pyramidal and cerebellar signs are common. Therefore, early motor developmental delay, gait ataxia, and hypotonia may be observed. Eventually, progression to spastic tetraparesis occurs. Seizures are variable. Intellectual skills are typically preserved early in the disease, but slow cognitive decline is observed as the disease progresses. Although the geographical distribution of MLC is global, increased population isolates of MLC have been reported among Libyan Jewish, Turkish, and Agrawal Indian communities.

MRI IMAGING :
The diagnosis of MLC is typically established by MR. Most patients undergo MRI of the brain in the first year because of rapidly increasing macrocephaly. Commonly, the magnitude of MR abnormalities appears much worse than the clinical appearance of the child. Macrocephaly with diffuse confluent WM T2/FLAIR hyperintensity in the subcortical WM is typical. The affected subcortical WMappears "watery" and swollen. The overlying gyri seemingly stretch over the swollen WM.

Characteristic CSF-like subcortical cysts develop in the anterior temporal lobes, followed in frequency by frontoparietal cysts. Unlike the "watery" WM, which exhibits T2/FLAIR hyperintensity, the cysts approximate the signal intensity of CSF on FLAIR. The number and size of thecysts may increase over time. The abnormal WM and cysts do not enhance on T1 C+.

On DWI/DTI, the increased water content within the interstitial spaces leads to reduced anisotropy and increased ADC values.MRS shows mild to moderate reduced NAA and NAA: Cr ratio. Myoinositol is normal, with or without lactate. Cystic regions show a reduction of all neurometabolites.

CONCLUSION :
MLC must be distinguished from other IMDs with Macrocrania. Patients with megalencephaly and MR changes that show extensive white matter changes with temporal cysts should raise suspicion for MLC[4].The differential diagnosis of MLC includes Canavan's disease, Alexander disease, infantile-onset GM2 and GM1 gangliosidosis. These conditions have relentlessly progressive infantile onset

leukoencephalopathy that is frequently fatal within first decade of life however, MLC has remarkably slow course of deterioration in neurologic function. MLC must be included in differential diagnosis of macrocephaly with early onset leukoencephalopathy.

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