Multimodal MRI findings of Megalencephalic Leukoencephalopathy with subcortical cysts

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Aims and objectives

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare autosomal recessive disease characterized by macrocephaly and slowly progressive clinical course and caused by mutations in the gene MLC. In patients with typical clinical findings, brain MRI is diagnostic. The aim of our study is to review MRI diagnostic criteria defined by van der Knaap and discuss the differential diagnosis of leukodystrophy with macrocephaly.
Methods and materials

We conducted a retrospective review of 4 patients (3 females /1 male) with genetically confirmed MLC followed in our institution from 2011 to 2014. The average age was 16 years old (ranging from 5 to 35). Multimodal brain MRI (3 Tesla Magnetom, Siemens) was performed in all patients using T1 Weighted Spin Echo (WSE), T2WSE, FLAIR and diffusion sequences. MR Spectroscopy (MRS) was performed in 1 patient.
Results

The 3 females were born of a consanguineous marriage. All patients presented with increased head size since birth with a delayed onset of mild neurological symptoms consisting of ataxia, pyramidal tract signs, seizures and a slow course of functional deterioration. All patients were born at term without a significant antenatal or prenatal history.

Cytogenic study in all patients showed a mutation of MLC1 gene on chromosome 22qtel.

MR scans showed diffusely abnormal white matter. The involved white matter showed diffuse T1WSE hypointensity Fig. 1 on page 6 and T2WSE Fig. 2 on page 6 and FLAIR Fig. 3 on page 7 hyperintensity and had a characteristic "swollen appearance" with obliteration of the peripheral sulcal spaces and thinning of the overlying cortex. Peripheral and periventricular white matter were equally involved with sparing of some central white matter structures like the corpus callosum Fig. 4 on page 8, anterior limb of the internal capsule Fig. 5 on page 9 and bilateral posterior occipital radiations. Mild to moderate dilatation of the ventricular system is noticed. Well defined cysts were noted in the subcortical white matter of temporal poles and of frontal and parietal lobes characterized by T2 hyperintensity which nulled on the FLAIR images, differentiating them from the rest of the expansile white matter change Fig. 6 on page 10, Fig. 7 on page 11. There was sparing of the central gray matter. The brainstem was spared. Mild T2WSE and FLAIR hyperintensity in the bilateral cerebellar hemispheres were noted in only one patient Fig. 8 on page 12. Diffusion tensor imaging showed an increased apparent diffusion coefficient in affected white matter Fig. 9 on page 13, Fig. 10 on page 14. White matter MRS demonstrated a mild decrease in N-acetylaspartate Fig. 11 on page 15.

Discussion

Megalencephalic leukoencephalopathy with subcortical cysts also known as Van der Knaap disease, refers to a rare inherited autosomal recessive disease characterised by diffuse subcortical leukoencephalopathy associated with white matter cystic degeneration [1].

MLC is known for its mild neurological signs and symptoms in the setting of very abnormal MR findings. Macrocephaly is present at birth or, more commonly, develops within the first year of life in all patients. Early development is normal or mildly delayed. Slow deterioration of motor functions with cerebellar ataxia and mild spasticity usually starts in early childhood. Some patients have extrapyramidal movement abnormalities with dystonia and athetosis, usually as a late finding. Mental decline occurs later and is much milder than motor decline. Most patients have epileptic seizures [1].
Initially the disease has been assigned to the gene, MLC1, and is localized on chromosome 22qtel [2]. Later, it has been shown that when associated with biallelic mutation of MLC1, the classic phenotype is known as MLC1; when caused by biallelic mutation of HEPACAM it is known as MLC2A. Pathogenic variants in MLC1 are observed in approximately 75% of persons with MLC; pathogenic variants in HEPACAM are found in approximately 20% [3].

When the clinical and MRI findings are characteristic of MLC, the absence of identified MLC1 or HEPACAM pathogenic variants does not exclude the diagnosis of MLC because [3] the MLC1 or HEPACAM pathogenic variants may not be identifiable with testing methods used or [4] the MLC phenotype may be the result of pathogenic variants in another as-yet unidentified gene.

In typical cases, the MR findings are often diagnostic of MLC. MR shows 'swollen white matter' and diffuse supratentorial symmetrical white matter changes in the cerebral hemispheres with relative sparing of central white matter structures like the corpus callosum, internal capsule, and brain stem. Subcortical cysts are almost always present in the anterior temporal region and are also frequently noted in frontoparietal region. Grey matter is usually spared. Gradually the white matter swelling decreases and cerebral atrophy may ensue. The subcortical cysts may increase in size and number. Moderate decrease in NAA/ Cr and Choline/Cr ratios have been reported in patients with MLC on MR spectroscopy [5].

The differential diagnosis of MLC includes Canavan's disease, Alexander disease and glutaric aciduria. 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. None of these conditions have subcortical cysts on MRI and all of these involve basal ganglia unlike megalencephalic leukoencephalopathy with subcortical cysts. The main differential diagnosis is Metachromatic leukodystrophy; however, not all symmetrical leukodystrophies are MLD. If U-fibers or cysts involved, MLC is considered [6].
Fig. 1: MRI T1 weighted axial image, showing the diffuse low signal of white matter lesions and subcortical frontal cysts.

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Fig. 2: MRI T2 weighted axial image, showing the diffuse high signal of white matter lesions and subcortical frontal cysts.

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Fig. 3: MRI FLAIR weighted axial image, showing the diffuse high signal of white matter lesions and subcortical frontal cysts.

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**Fig. 4:** MRI T2 weighted sagittal image, showing the diffuse high signal of white matter lesions sparing the corpus callosum.

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Fig. 5: MRI T2 weighted axial image, showing the diffuse high signal of white matter lesions sparing the anterior limbs of internal capsules.

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Fig. 6: MRI FLAIR weighted axial image, showing diffuse hyperintense lesions of the white matter, with bitemporal subcortical cysts.

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Fig. 7: MRI FLAIR weighted coronal image, showing diffuse hyperintense lesions of the white matter, with bitemporal subcortical cyst

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**Fig. 8:** MRI FLAIR weighted coronal image, showing a mild hyperintensity in the bilateral cerebellar hemispheres. Note the presence of parietal subcortical cysts.

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**Fig. 9:** Diffusion weighted imaging.

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Fig. 10: Apparent Diffusion Coefficient (ADC) mapping.

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Fig. 11: White matter MRS demonstrated a mild decrease in N-acetylaspartate.

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Conclusion

MRI provides specific findings of MLC characterized by diffuse white matter lesions 'swollen white matter' with symmetrical cystic changes in the cerebral hemispheres. In typical cases MRI findings are sufficient for the diagnosis.
References


