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Case Report

The Role of MRI in the Diagnosis of Megalencephalic Leucoencephalopathy with Subcortical Cysts

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Abstract

Megalencephalic leukoencephalopathy with subcortical cysts, or Van der Knaap disease, is a rare genetic disorder characterized by the mutation of the MLC1 gene. It is most commonly observed in ethnicities with a high rate of consanguinity. Symptoms typically appear around 6 months of age and include macrocephaly, ataxia, spasticity, and psychomotor deterioration. MRI scans show swollen cerebral white matter and subcortical cysts in the anterior temporal and fronto-parietal regions. MRI spectroscopy shows decreased levels of normal neuronal white matter metabolites and a decreased NAA/Cr ratio. Similar symptoms of leukoencephalopathy and early onset macrocephaly can also be found in other conditions such as Canavan disease, Alexander disease, and infantile-onset GM2 and GM1 gangliosidosis.

Keywords: *Megalencephalic Leukoencephalopathy; Subcortical Cysts; Van der Knaap; MRI Spectroscopy; Macrocephaly*

Introduction

Megalencephalic leukoencephalopathy with subcortical cysts, also known as Van der Knaap disease, is an uncommon autosomal recessive disorder first described by Van der Knaap in 1995, due in 75% of cases to a mutation in the MLC1 gene located on chromosome 22q. This condition is more prevalent in some ethnic groups where consanguinity is common, and most cases have been described in Libyan, Jewish, Turkish or Agarwal Indian communities [4]. Neurological symptoms are typically mild, commencing at around six months of age, and the course of degeneration progresses very slowly [5]. Patients commonly manifest macrocephaly, ataxia, spasticity, and psychomotor deterioration. Characteristically, MRI scans show swollen cerebral white matter and subcortical cysts. We describe two cases of megalencephalic leukoencephalopathy in a Moroccan cohort and review the radiological aspects of this condition.

Observations

Case 1

We report a case study of a 3-year-old girl born to non-consanguineous parents who exhibited symptoms of epilepsy in conjunction with a pyramidal syndrome and cerebellar ataxia. The clinical examination revealed a progressive increase in head circumference. Brain MRI showed extensive, symmetrical white matter changes indicating demyelination, which were hypointense on T1 weighted images and hyperintense on T2/FLAIR images (Figure 1a). And it also showed characteristic bilateral temporal and frontal subcortical cysts (Figure 1b and 1c). The basal ganglia and thalami were spared. Spectroscopic analysis displayed a decreased N-Acetylaspartate/Creatine ratio

(Figure 1d) consistent with the diagnosis of Van der Knaap's disease.

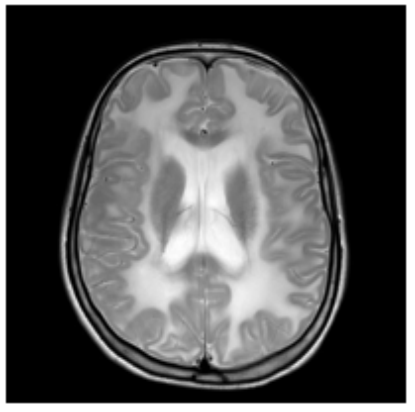

Figure 1a: *Extensive and bilateral increased signal of the white matter on axial T2-WI.*

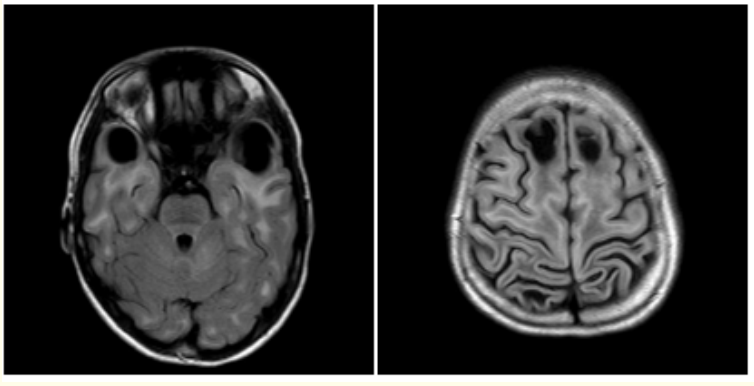

Figure 1b and 1c: *Axial FLAIR images showing subcortical temporal and frontal cysts.*

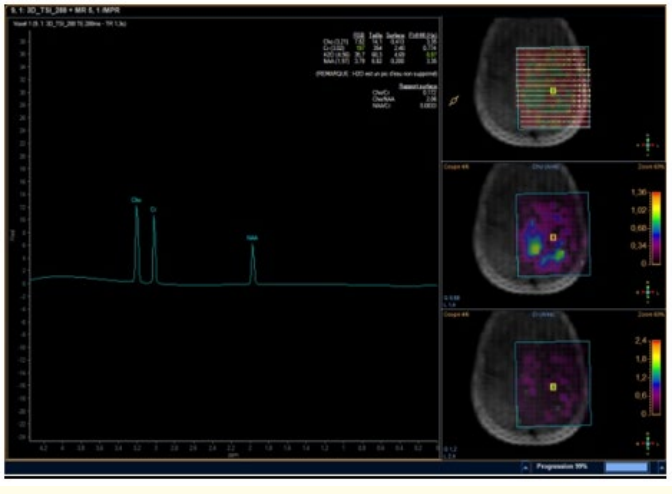

Figure 1d: *MR spectroscopy showing a decreased N-Acetylaspartate and N-Acetylaspartate-creatine ratio.*

Case 2

An 2 year-old child, born of consanguineous parents, presented with delayed developmental milestones and one episode of abnormal movements. The MRI showed bilateral and symmetrical white matter changes (Figure 2a) and subcortical temporal cysts (Figure 2b and 2c). Spectroscopy MRI demonstrated a decreased N- Acetylaspartate/Creatine ratio and an elevated lactate peak, all features characteristic of Van der Knaap's disease (Figure 2d).

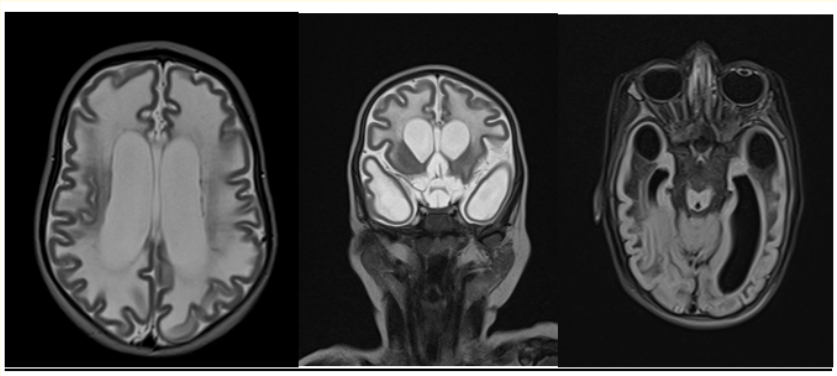

Figure 2a-2c: *Extensive and bilateral increased signal of the white matter on axial T2-WI (Figure 2a), with subcortical temporal cysts with the same signal as CSF on T2 WI (Figure 2b) and FLAIR (Figure 2c).*

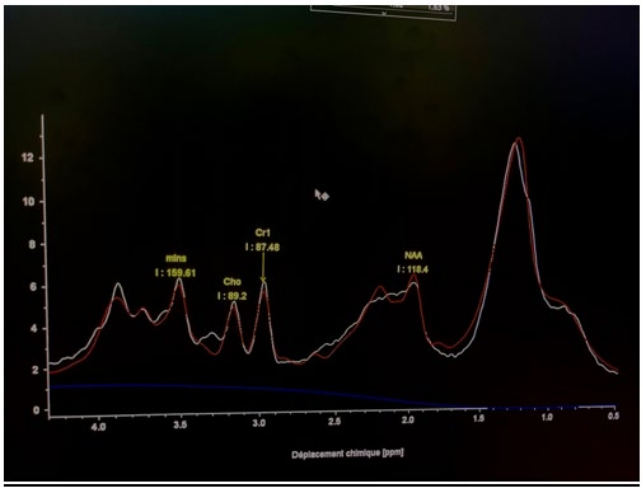

Figure 2d: *MR spectroscopy showing a decreased NAA-Creatine ration and a lipid-lactate peak.*

Discussion

Megalencephalic leukoencephalopathy with subcortical cysts, described by Van der Knaap in 1995, is a rare disease with autosomal recessive transmission and a low carrier rate. The responsible gene is located on Chr. 22q and is called MLC1. More than 50 mutations in the MLC1 gene have been reported in the literature. It seems to affect more frequently certain populations where consanguinity is quite significant [2].

Van der Knaap's disease is characterised by mild symptoms that contrast with highly abnormal imaging features on MRI, predominantly affecting the white matter [2].

Although macrocephaly may be present at birth, it typically develops within the first year of life. A clinical presentation during the second year of life, with a slight delay in stone development, is also possible. Over time, patients demonstrate a gradual decline in their motor abilities, accompanied by cerebellar ataxia and mild spasticity. Intellectual function deterioration is less severe and manifests at a later stage. Moreover, more patients develop epileptic seizures [2].

When clinically suspected, an MRI can confirm the diagnosis in typical cases by symmetrical changes and signal abnormalities in the subcortical white matter, which appear swollen and hyperintense on T2-weighted imaging, with associated gyri enlargement. With age, the swelling decreases and cerebral atrophy ensues. The second characteristic feature are subcortical cysts that almost always develop first in the anterior temporal region, and subsequently in fronto-parietal regions. They are bilateral and symmetrical, and their signal is that of CSF. Progressive enlargement and multiplicity of these structures can be witnessed over time.

Additionally, central white matter structures such as the corpus callosum, the internal capsule and the brainstem are relatively preserved [1,2]. Some grey matter structures may exhibit mild atrophy, whereas the thalami and basal ganglia remain unaffected. The presence of a cavum septum pellucidum is a commonly observed occurrence [3].

MRI spectroscopy reveals a decrease in normal neuronal white matter metabolites such as N-Acetylaspartate, choline and creatine, and therefore a decreased N-Acetylaspartate/Creatine ratios [3]. Myo-Inositol may be normal, increased or decreased depending on the severity of the disease.

Leukoencephalopathy and early-onset macrocephaly are also present in pathologies such as Canavan disease, Alexander disease, and infantile-onset GM2 and GM1 gangliosidosis. While these conditions are characterized by a progressive infantile onset that is often fatal within the first decade of life, the neurological decline in MLC is relatively slow. While these conditions are characterized by a progressive infantile onset that is often fatal within the first decade of life, the neurological decline in MLC progresses slowly [1]. MRI characteristics can assist in distinguishing MLC from these pathologies [2,5]:

- Basal ganglia and thalami that are spared in MLC are found to be involved in Canavan disease. And a marked increase in the NAA peak usually ads up.
- In Alexander's disease, MRI shows in addition to cystic degeneration frontal abnormalities and contrast enhancement.

In infantile GM2 gangliosidosis, MRI shows involvement of the basal ganglia and thalami adding up to white matter abnormalities.

Conclusion

Van Der Knaap's disease is an autosomal recessive disorder which is characterized by macrocephaly, epilepsy, and a progressive cerebellar-spastic syndrome. On MRI scans, diffuse white matter involvement can be observed, as well as the presence of frontal and temporal subcortical cysts, with the basal ganglia and thalami being spared. MRI spectroscopy shows decreased levels of normal neuronal white matter metabolites and a decreased NAA/Cr ratio.

Conflict of Interest

We declare that there is no financial interest or any conflict of interest.

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