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Case Report

Megalencephalic Leukodystrophy with Subcortical Cysts: A Case Report

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Abstract

Megalencephalic leukodystrophy is a rare neurodegenerative disorder which is characterized by macrocephaly in early infancy, slowly progressive neurologic deterioration and epilepsy. It was first described by Van der knaap in 1995. We present evolution of the imaging findings from 11 months to 10 years of age.

Introduction:

Leukodystrophy is a heterogeneous group of inherited metabolic disorders with one common denominator; abnormalities of the white matter of the central nervous system. A progressive mental regression with motor abnormalities is the most frequent clinical finding. In addition to the classic leukodystrophies such as Canavan disease and Alexander disease that have been extensively delineated, almost half of patients with leukodystrophies are of unknown cause. In the past few years, neuroimaging, especially cranial MRI, has played a major role in the identification of a number of new clinico-pathologic entities. Megalencephalic leukodystrophy with subcortical cyst is one of the novel leukodystrophies described by Van der knapp in 1995 by its characteristic clinical and MRI findings. We report a case with characteristic clinical and radiological findings including sequential imaging from infancy to adolescence.

Case Report

The patient is a child of healthy unrelated white parents, delivered normally at term after an uneventful pregnancy. Birth weight was 8-9 lbs. Head circumference at birth was normal. In the course of his 1st year of life, macrocephaly developed. His occipito-frontal circumference (OFC) at the age of 4 years was above the ninety-eight percentile at 58 cm. His development was delayed. He walked at 2 years of age. He spoke only one word ("mom") at 4 years of age. He has history of minor head trauma at the age of 16 months, history of murmur at birth, which spontaneously resolved, and history of asthma also resolved. The patient has 3 healthy unaffected siblings. He was referred for seizure work up at the age of 4 years. The episode consisted of eye blinking, face twitching, and tremor-like activity of the upper extremities, lasting 10 minutes, followed by an extended post-ictal period. Neurological examination revealed generalized hypotonia with normal muscle bulk. Antiepileptic drug treatment was initiated. He was seizure free for 4 years on antiepileptic drugs. He remained seizure free for 2 years off antiepileptic drugs before the focal seizures returned at the age of 10 years. His motor function deteriorated after he had seizures.

At the age of 9 years, he developed generalized spasticity, progressive dysphagia, ataxia of the limbs; particularly of the left upper extremity. Clonus and Babinski's signs were positive. By 10 years of age, he was unable to walk.

Laboratory investigations, including CBC, BUN/Cr, Electrolytes, blood glucose, liver function test, urine biochemical profile analysis, ammonium level were normal. Metabolic screening of a 24-hr sample of urine for amino acids, organic acids, oligosaccharides, mucopolysaccharides was normal. Assessment of lysosomal enzyme, B12, folate and vitamin E were normal. EMG was normal. Peripheral motor and sensory nerve conduction velocity for left peroneal and left sural nerve were normal. EEG revealed abnormal continuous left temporal slowing and frequent epileptiform discharges over the left temporal region which is indicative of a structural abnormality with epileptogenic potential in that region.

Cranial computed tomographic (CT) examinations were performed in 1994, 1995, 1997 and 2004 at the age of 10 months, 1.5, 4 and 10 years, respectively. The first CT at 10 months of age (Fig.1a) showed diffuse low density with mild expansion of the cerebral white matter bilaterally and symmetrically with a left anterior temporal subcortical cyst. The second CT performed at 18 months of

age was unchanged. The CT, performed at 4 years of age (Fig. 1b) showed the development of volume loss as indicated by increase prominence of the cortical sulci and ventricles with stable left anterior temporal subcortical cyst. The CT performed in 2004 showed (Fig. 1c) slight progression of atrophy but stable left anterior temporal subcortical cyst.

Cranial MRI in 1998, 2002 and 2004 performed at 4, 8 and 10 years of age respectively demonstrated diffuse, symmetric T1 and T2 signal prolongation within the cerebral white matter bilaterally. Subcortical cysts were present in the left frontal and both anterior temporal lobes (Fig. 2-5). These cystic lesions were isointense to CSF on both T1- and T2-weighted

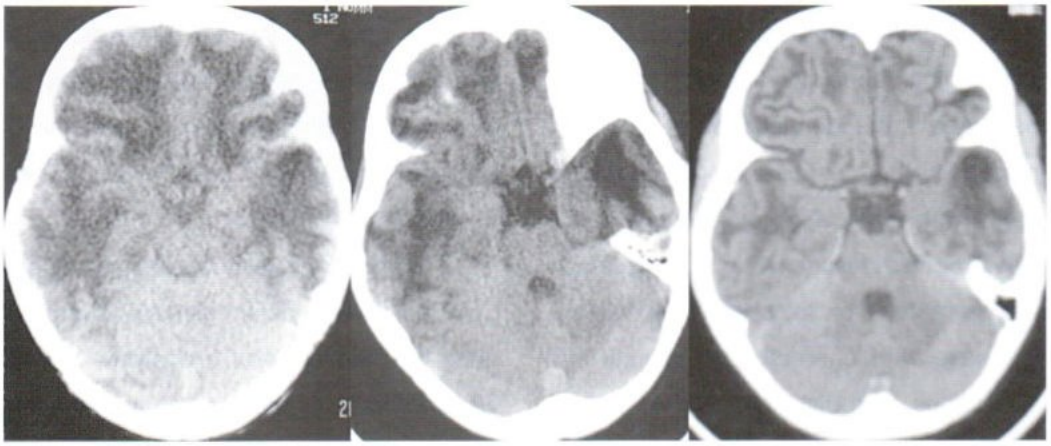

Fig.1 Transaxial CT in 1994 (a), 1997 (b) and 2004(c) (from left to right) shows diffuse cerebral white matter low density with a left anterior temporal subcortical cyst and progression of cerebral atrophy.

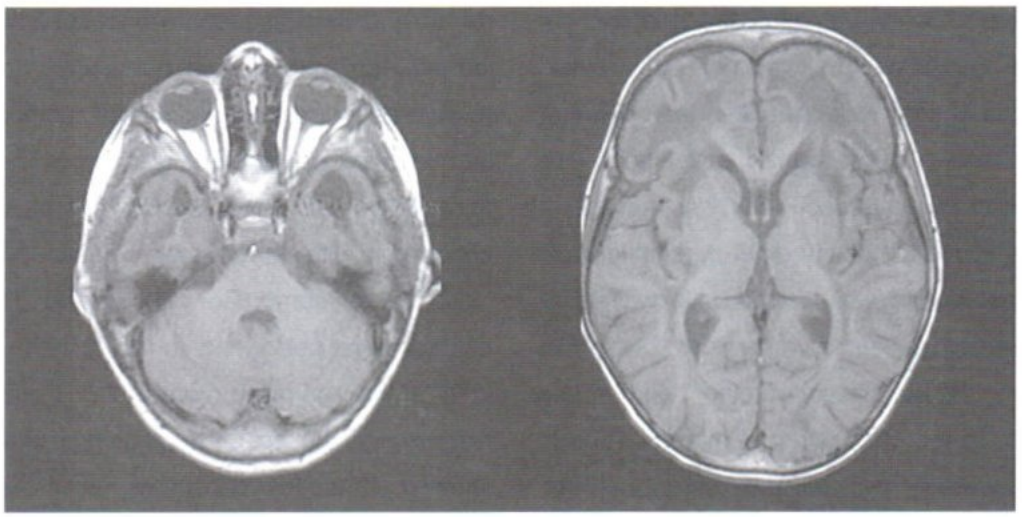

Fig.2 Axial T1-weighted images (TR.450 ms; TE.14 ms) shows diffuse T1 prolongation of the cerebral white matter predominantly at the frontotemporal lobes with anterior temporal subcortical cysts.

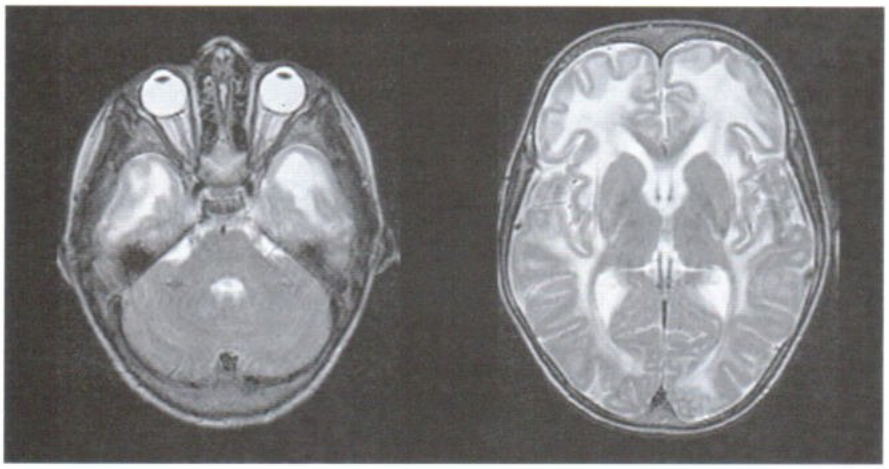

Fig.3 Axial T2-weighted (TR.3000 ms/TE.105 ms) images show diffuse T2 prolongation of the cerebral white matter predominantly at the frontotemporal lobes with anterior temporal subcortical cysts. Note increased T2 prolongation of the dentate nuclei (asterisk) and dorsal pons (black arrow).

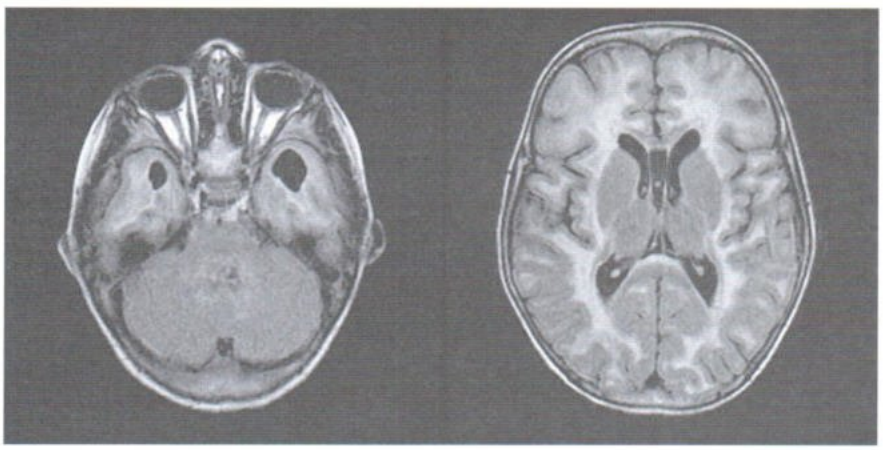

Fig.4 Axial FLAIR images show diffuse abnormal hyperintensity of the cerebral white matter predominantly at the frontotemporal lobes with anterior temporal subcortical cysts. Note increased signal of the dentate nuclei and dorsal pons.

images. There was no swelling of the gyri. The cerebral sulci and ventricular system appeared slightly prominent. There was sparing of central white matter structures, including corpus callosum, anterior limb of the internal capsule, a periventricular rim of the occipital white matter (optic radiation), and some subcortical white matter, especially in the occipital lobes (Fig. 2-4). The cerebellar white matter was spared, but there was increased T2 signal of the dentate nuclei and dorsal pons bilaterally (Figure 3-4). There is no significant difference among these three MRI studies. Proton magnetic resonance spectroscopy (MRS) using PRESS technique with TE 35 and 288, performed at the age of 8 years

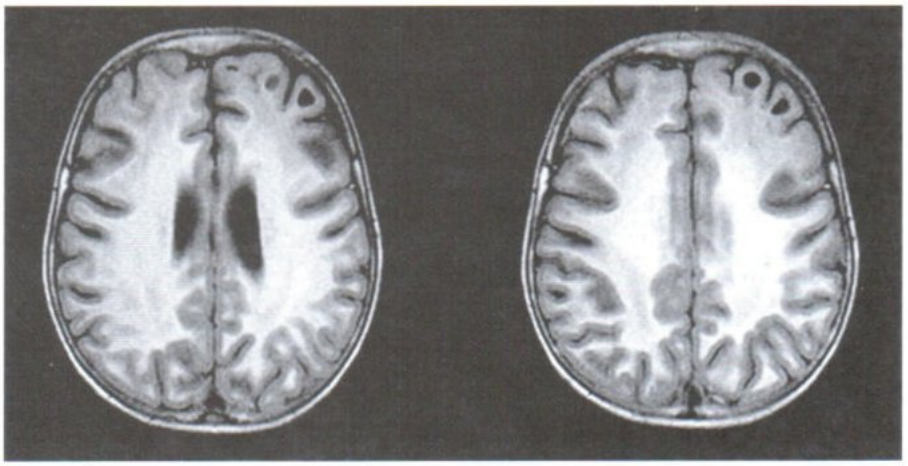

Fig.5 Axial FLAIR images show diffuse abnormal hyperintensity of the cerebral white matter with several left frontal subcortical cysts.

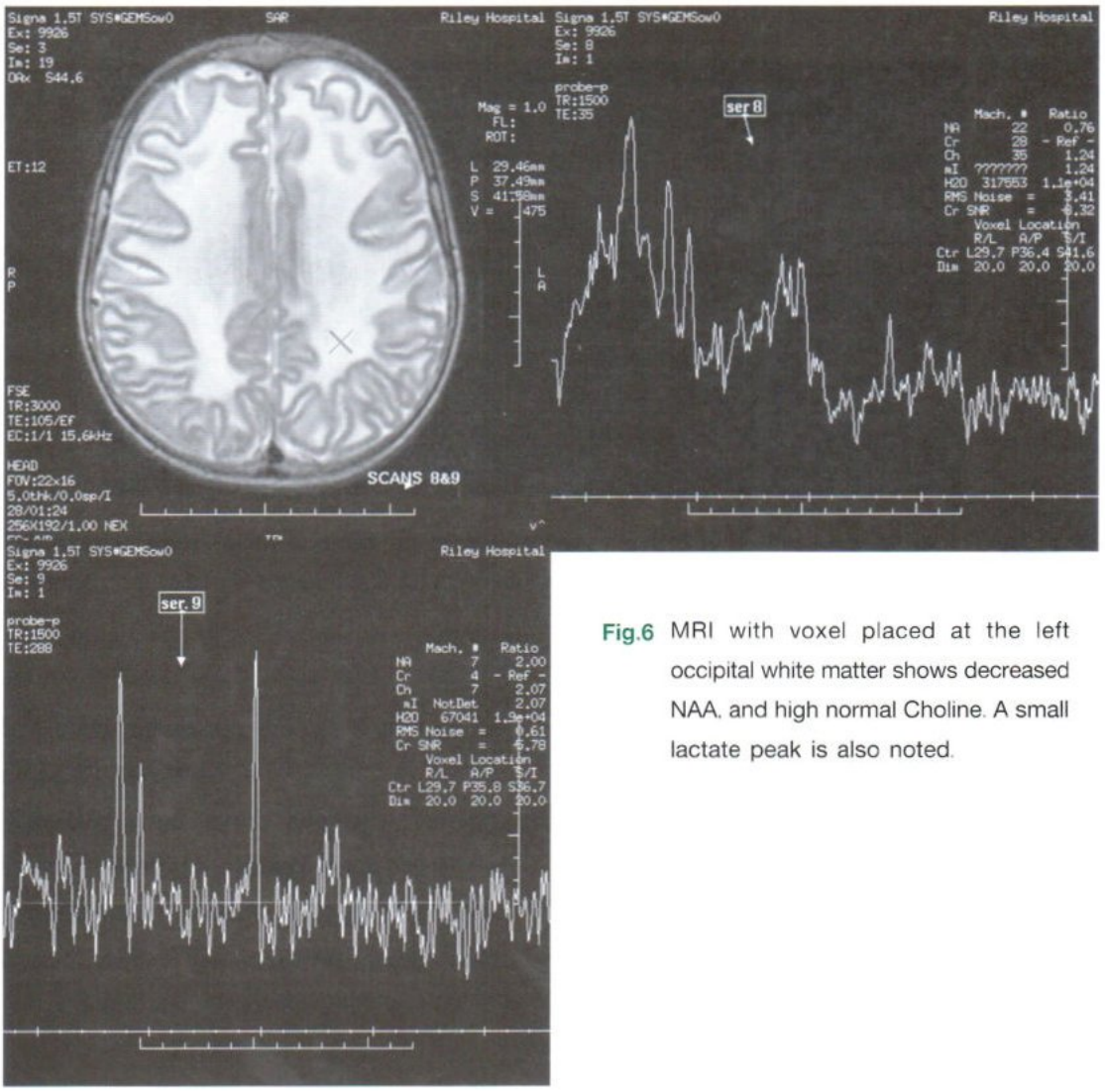

Fig.6 MRI with voxel placed at the left occipital white matter shows decreased NAA, and high normal Choline. A small lactate peak is also noted.

showed decreased NAA. Choline at the upper limits of normal and high Myo-Inositol in the white matter (Fig. 6) with normal spectrum of the basal ganglia.

Discussion and Literature Review

The first two reported cases of infantile onset megalencephaly and leukodystrophy syndrome were reported by Harbord et al. in 1990. There was no mention of subcortical cysts and no MRI study was performed.

In 1995, van der knaap et al. described detailed distinctive clinical and radiological characteristics of this new syndrome based on eight cases. Subsequently, there has been many reports of similar cases[2,3,5,6]. This novel leukodystrophy has been synonyms: leukoencephalopathy with macrocephaly and mild clinical course. Van der knaap disease and Vacuoliting megalencephalic leukoencephalopathy. It is characterized by the development of macrocephaly within the first year of life. Early infantile development is usually normal or minimally delayed. However, after a delay of several years, a slow deterioration of motor function occurs with ataxia and spasticity. Cognitive function is less affected. Seizures occur in most patients but are usually easily controlled with medication. Screening for inborn errors of metabolism that causes either megalencephaly or white matter disease is negative.

Since the report by Van der knaap in 1995, further family studies in several ethnic groups have suggested an autosomal recessive mode of inheritance. The disease occurs with relatively high frequency in an Asian-Indian tribe[3] and Turkish populations[6]. A locus of MLC was mapped to chromosome 22qtel[7]. Several mutations in the MLC1 gene, which encodes a putative CNS membrane transporter have been identified[8-11].

Histologically, the disease is characterized by the presence of numerous vacuoles between the outer lamellae of myelin sheaths suggesting splitting of these lamellae along the intraperiod line or incomplete compaction of the outermost myelin lamellae[4].

There is no biochemical diagnostic test for detection of the disease in asymptomatic stage. Only DNA test can be used for diagnosis, however it is not commercially available at the present time. And unfortunately, there is no specific treatment for this rare leukodystrophy.

Currently Magnetic Resonance Imaging is the most readily available diagnostic tool for evaluating this disease. The MRI features are characteristic and specific[1-3,5,6]. MRI typically demonstrates bilateral diffuse abnormal and swollen supratentorial hemispheric white matter,and subcortical cysts which are invariably present in the anterior-temporal, and often the frontoparietal regions.

Characteristic sparing of central white matter structures (corpus callosum, anterior limb of the internal capsule, occipital periventricular white matter, partially posterior limb of the internal capsule) and some sparing of subcortical white matter have been described[1,6]. No abnormal enhancement has been reported. Radiologists should be aware of this disorder since they may be the first to suggest the diagnosis based on the characteristic imaging findings. This may further prompt definitive genetic studies to confirm the diagnosis. On the basis of clinical and MRI criteria, our case is a typical example of Megalencephalic leukodystrophy with subcortical cysts. The clinical and MRI findings in our case are

similar to those previously described. However, we have serial imaging studies showing progression of cerebral atrophy with time. Swelling of the white matter was present in the early stage with gradual development of cerebral atrophy in late stage.

MRI is better than CT in identifying the white matter abnormality and subcortical cysts. However, MR findings do not reflect the clinical severity of disease (no change of follow up MRI studies, despite clinical progression of disease). In the study of van der knaap et al., MRS in four patients revealed decreased N-Acetyl aspartate (NAA), high Choline and normal myo Inositol (mI). In our case, NAA is decreased, Choline at the upper limits of normal, mI was not detected and a very small lactate doublet was identified (Figure 6). This MRS may be explained by loss of neurons, and tissue destruction.

The differential diagnosis of MLC includes other leukodystrophies that present with megalencephaly, cognitive decline and motor disability. Whereas megalencephaly is seen in the infantile form of Alexander disease, imaging studies are quite distinct, showing a frontal region preponderance of white matter change with abnormal enhancement and basal ganglia involvement, and the clinical course is much more rapidly progressive. Patients with Alexander disease can be diagnosed by GFAP (glial fibrillary acidic protein) gene mutation screening.

Canavan disease can present as megalencephaly and spasticity but is often accompanied by cortical blindness and much smaller subcortical cysts that are not as easily identifiable as the larger cysts seen in MLC. Canavan disease can also have involvement of basal ganglia and thalami. A deficiency of the enzyme aspartoacylase in cultured fibroblasts or characteristically high NAA peak on Magnetic Resonance Spectroscopy is diagnostic of Canavan Disease. Canavan disease also has rapid clinical course.

Similarly, glutaric aciduria type I can present with megalencephaly and variable clinical presentation (normal or slightly delayed development, dyskinesia, spasticity) but can be easily distinguished from MLC by the metabolic abnormality (metabolic acidosis/ketosis, hypoglycemia, aciduria) and MRI findings (Deep gray matter abnormality).

Conclusion

Megalocystic leukodystrophy is a rare disorder of infancy and childhood. The MR imaging findings are characteristic. The radiologist should therefore suggest this diagnosis when these classically located cysts are present in the setting of a leukodystrophy. MRS may also be helpful in making the diagnosis.

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