

Global Developmental Delay in a Mexican Patient With Megalencephalic Leukoencephalopathy With Subcortical Cysts

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Introduction: Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a neurologic disorder characterized by macrocephaly within the first year of life and the delayed onset of motor function deterioration with ataxia and spasticity. Magnetic resonance imaging of the brain is diagnostic and shows diffusely abnormal, mildly swollen cerebral white matter and subcortical cysts. MLC exhibits an autosomal recessive mode of inheritance. Two genes have been associated with MLC. The first and most important gene is MLC1. The other gene involved is HEPACAM.

Case Presentation: We studied a Mexican patient with a compatible diagnosis of MLC. The patient exhibited the c.353C > T, p.Thr118Met mutation, and both parents were carriers for the same mutation. To the best of our knowledge, no other cases of MLC have been reported in Mexican patient. This patient exhibited rapid deterioration of motor function.

Conclusions: A diagnosis of MLC, which can be facilitated by imaging studies, should be considered in all patients who exhibit global developmental delay.

Keywords: Global Developmental Delay; Megalencephalic Leukoencephalopathy; Leukoencephalopathy; Subcortical Cysts; Van der Knaap Disease

1. Introduction

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a neurologic disorder characterized by macrocephaly within the first year of life and a delayed onset of motor function deterioration with ataxia and spasticity and mild cognitive decline (1-3).

MLC exhibits an autosomal recessive mode of inheritance. Two genes have been found to be associated with MLC, including MLC1, which is present in 80% of cases (4). There is no knowledge about the incidence of MLC. MLC is a rare disease with a low carrier frequency, and inbreeding and consanguinity contribute to its occurrence. This could be the reason for the occurrence in our patient, because both parents come from a small town of 346 individuals (5).

The progression of the disease is usually very slow, in contrast to many other leukodystrophies (6). Magnetic resonance imaging (MRI) of the brain is diagnostic and

shows diffusely abnormal, mildly swollen cerebral white matter as well as subcortical cysts, especially in the anterior-temporal region (7).

We present a Mexican patient with clinical manifestations and MRI images compatible with the diagnosis of MLC. This diagnosis was corroborated by a molecular exam.

The aim of this study is to emphasize the importance of MRI as a diagnostic tool in patients with global developmental delay.

2. Case Presentation

We studied a patient who was 5 years 6 months of age and exhibited global developmental delays. She was a native and resident of an inbred community of 346 inhabitants in the municipality of Villa Victoria in Mexico. Her parents denied consanguinity. A personal history of

apparent congenital hydrocephalus and mental retardation was reported in one paternal 14-year-old cousin.

The patient, who was born at 40 weeks of gestation was the product of a third pregnancy. The mother presented with a urinary infection with nonspecific treatment and diminished fetal movements. The patient presented with Apgar scores of 8/9, height of 51 cm, weight of 3300 gr, and slight jaundice at birth. The patient exhibited psychomotor retardation, which was dominant in the language area. In her first evaluation, at 3 years 9 months of age, the patient had not developed independent walking or speech with sentences, used only a few words, and did not have sphincter control. Her current disease is congenital, but was not treated until she was 1 year 10 months of age. Upon physical examination, we observed a height of 100.5 cm (50th percentile), head circumference of 56.5 cm (> 97th percentile), apparent age equal to chronologic age, autistic behavior, easily irritable and uncooperative, assisted walking with an ataxic component and wide base support, macrocephaly without other dysmorphias or malformations, limbs with discrete intention tremor, exhaustible bilateral clonus, bilateral extensor plantar responses, and slight dysmetria. A second examination one year later revealed further deterioration. In addition, the patient had less contact with people, and she was screaming and walking with the assistance of her mother at all times. An MRI and electroencephalography (EEG) had been conducted since the first examination.

A molecular study for genetic analysis was conducted after a review of the MRI results. The exons and flanking intronic regions of the gene *MLC1* were analyzed by sequence analysis at the genomic level in both the patient and her parents (2).

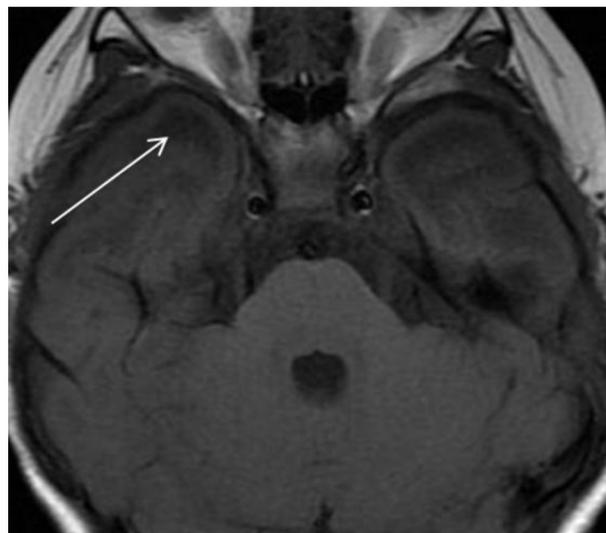
3. Discussion

The MRI showed widespread cortical atrophy, which is suggestive of delayed cerebral and cerebellar myelination. Fluid-filled cavities of varying dimensions without a noticeable membrane separating them from the rest of the white matter were observed. Those cavities were located in the rostral portion of the anterior temporal lobes (Figures 1, 2, and 3).

Based on these characteristics, MLC was considered to be the most likely diagnosis. The EEG showed no abnormal patterns. The molecular study revealed the following mutation in the patient: c.353C > T, p.Thr118Met. Both parents were carriers of the same mutation.

MRI is mandatory for patients with global developmental delays. In approximately 50% - 60% of cases, as in the present case, MRI reveals the cause of the global developmental delay (4). MLC exhibits very specific characteristics on MRI (7-11).

Figure 1. Magnetic Resonance Imaging in the Axial Plane (Sequence T1)



Fluid-filled cavities are located in the rostral portion of the temporal lobes. Other white matter is diffusely affected (areas of decreased signal in T1).

Figure 2. Magnetic Resonance Imaging in the Axial Plane (Sequence T2)



The cavities exhibit different dimensions without a noticeable membrane separating them from the rest of the white matter. The remaining white matter signal intensity is increased on T2.

Figure 3. Magnetic Resonance Imaging Axial Plane in Sequence T2 Fluid Attenuated Inversion Recovery (FLAIR)



An intensity-increased signal of white matter is observed around the subcortical cysts (which does not appear to be gliosis). This finding is indicative of delayed myelination.

The feature that distinguishes van der Knaap syndrome from other leukoencephalopathies associated with either large or normal-sized heads is the presence of temporal and frontal white matter cysts in combination with diffuse white matter abnormalities on computed tomography (CT) or MR. The presence of cystic degeneration of the white matter can be confirmed by fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (12).

The differential diagnosis of leukoencephalopathy with anterior temporal cysts includes congenital cytomegalovirus (CMV) infection, leukoencephalopathy with subcortical temporal cysts and megalencephaly, and vanishing white matter disease as well as other diseases such as Alexander disease, Canavan disease, and L-2-hydroxyglutaric aciduria. The differences with MLC are based on clinical evolution, neuroimaging, and biochemical findings (13, 14).

Two genes are involved in MLC, and the most frequent involvement is from the MLC1 gene (9). Neurological deterioration is usually slow in patients with MLC. In contrast, our patient exhibited significant deteriora-

tion over one year. Her communication and social skills were significantly affected such that she never developed language, and her attitude was that of a child with mental retardation and hyperkinesias (8-11). In general, the literature defines MLC by normal to mildly decreased cognitive capacity initially, with increases in deterioration over several years. It has also been reported that communication and social skills remain generally unaffected. In contrast, our patient had significant affection since birth (15).

The MR images from our patient are not consistent with the clinical evolution in either our patient or others from the literature. The cysts in our patient were small in comparison to findings in other patients, but the affection was worse than the majority of other patients that have been reported (16). There are many different phenotypes that have been described in the literature with no apparent presence of a genotype-phenotype correlation (15, 17).

The most constant clinical findings in patients with MLC are macrocephaly, loss of motor skills, ataxic gait, and epilepsy. There are many differences in the clinical features and evolution between patients of the same family and others with the same mutation. Other clinical findings, including ataxia, spasticity, extrapyramidal signs, and mental retardation are inconsistent across cases, and when they exist, the time of onset is variable (Table 1) (6, 8, 18-23). Recently, Masuda and Ueda reported a patient without the classical features of MLC on MRI. This finding is important because these features were considered to be diagnostic of the disease. We should be suspicious of the disease based on clinical features, and not dismiss the diagnosis based on negative MRI findings (22). The evolution of the disease also depends on the mutated gene (24).

The MLC protein is involved in the chloride channel as well as in other protein complexes. The protein product is highly expressed in the brain (mainly in astrocytes). This multiple involvement of the MLC protein may explain its relation to edema as well as other functions. It is also possible that phenotype differences across patients are due to the presence of other modifier genes (16, 25, 26).

We can conclude that there are many different phenotypes associated with MLC. When global developmental delay is present, it is essential to perform an MRI, as MRI can provide either a diagnosis or additional clues. There is much yet to learn about MLC.

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Table 1. Clinical Findings and Other Data From Patients with MIC Reported in the Literature

Author	Year	Number of Cases	Sex	Mutation	Macrocephaly	Age Of Symptom Onset	Epilepsy (Seizures)	Evolution	Parental Consanguinity	Subcortical Cysts	Bibliography
Patrono et al. (18) (Italian, French, Turkish, Morocco)	2003	18 (15 families)	9F/9M	177delG, IVS2_1G_T, 848delC, 249G_T, 263G_T, 423C_A, 357insT, 880C_T, IVS5_1G_A/IVS1_0-1G_C, None identified (5)	Yes	3-12 months	Yes (15)	Mild and severe	No	Present	Neurol 2003; 6i: 534- 537
Riel-Romero M. et al. (23) (Caucasian)	2005	2 siblings	1F/1M	c.366A_G 538 + Ig>aa (compound heterozygous)	Yes	5 and 6 months	Yes (2)	Mild	No	Present	J Child Neurol /Volume 20, Number 3, March 2005
Kumar and Singh (19)	2012	3	2F/1M	Non done	Yes	All of them around the 5 years.	No	Mild	No	Present	Ann Indian Acad Neurol 2012 Jul-Sep; 15 (3): 214 - 217.
Koul et al. (20) (Arabian patients)	2013	2 siblings	1F/1M	c.432 + 1G > A mutation	Yes	1 year	No	Severe	Yes	Present	Sultan Qaboos University Med J, November 2013, Vol. 13, Iss. 4, pp. 585- 586
Kocaman et al. (8) (Turkey patient)	2013	1	Male	c.177 + 1G > T	Yes	38 years (headache)	No	Mild	No	Present	Clinical Neurology and Neurosurgery 115 (2013) 1564 - 1566
Mahmoud et al. (21) (Egyptian patients)	2014	6 (3 families)	Male 6/6	c.908-918del/insGCA and c.880 C > T	Yes	Birth, 4 months, 8 months	Yes (4)	Mild and severe	Yes (First cousins; 3 families)	Present	Pediatr Neurol 2014; 50: 140- 148
Masuda and Ueda (22) (Japanese patients)	2015	2 siblings	Female 2/2	c.393CNT (p.Ser93Leu) in exon 4 and c.823C N/A (p.Ala275Asp) in exon 10	Yes/No	3 months/2 years	Yes/No	Mild	No	1 Present/1 Absent	Journal of the Neurological Sciences 351 (2015) 211- 213
Our study	-	1	Female	c.353C > T, p.Thr118Met	Yes	Birth (psychomotor retardation)	No	Severe	Yes	Present	-

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