Megalencephalic leukoencephalopathy with subcortical cysts in all three siblings of a non-Aggarwal Indian family

Mani Kant Kumar, Brish Bhanu Singh

Department of Pediatrics, Narayan Medical College and Hospital, Jamuhar, Sasaram, Bihar, India

Abstract

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare neurodegenerative disease seen mainly in the Aggarwal community in India. It is characterized by early-onset macrocephaly with mild motor developmental delay, gradual onset ataxia, spasticity, seizures and usually late onset mild cognitive deterioration. Very few familial cases of MLC have been reported in the world literature, and to the best of our knowledge, there is no published study of all three siblings affected with MLC in a same family. Here, we are reporting three siblings belonging to a non-Aggarwal Hindu family, affected with MLC, who presented with early-onset macrocephaly and gradual onset ataxia.

Key Words

Macrocephaly, megalencephalic leukoencephalopathy, subcortical cysts, white matter degeneration

For correspondence:

Dr. Mani Kant Kumar, Department of Pediatrics, Narayan Medical College and Hospital, Jamuhar, Sasaram, Dist.- Rohtas, Bihar - 821 305, India. E-mail: manikant7@yahoo.com

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Introduction

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare neurodegenerative disease, first described by van der Knaap *et al*. in 1995.[1] It is characterized by early-onset macrocephaly with mild motor developmental delay, seizures, gradual onset of ataxia, spasticity, and sometimes extrapyramidal signs, and usually late onset of mild mental deterioration.[2] It is an autosomal recessive disease and its gene locus is situated on chromosome 22q13.3. The gene implicated in the disease process has been identified, which is known as MLC1.[3] The degree of macrocephaly is variable and can be as much as 4–6 SD above the mean. Almost all the patients have epilepsy from an early age. Some patients may die in their second and third decades, but a few may live till the fourth decade. To our knowledge, there is no case report of three affected siblings, especially belonging to a non-Aggarwal Hindu family, in the world literature. Here, we report three siblings diagnosed with this disease from a non-Aggarwal Hindu family.

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Case Report

A 9-year-old boy, the youngest of three siblings, belonging to non-Aggarwal community (Kurmi kshatriya community) and born of non-consanguineous marriage, presented with large head which was noticed since late infancy, mildly delayed mental and motor milestones, and progressive ataxia since 5 years of age. There was no history of seizures. Examination revealed stable vital signs; weight and height were within normal limits for age. The patient had macrocephaly with head circumference of 59 cm (more than 95th percentile for age). Nervous system examination showed mild cognitive impairment, no cranial nerve deficits, bilateral pyramidal signs in the form of spasticity, power >4/5 in all the four limbs, brisk deep tendon reflexes (DTRs) and extensor plantar responses. His gait was ataxic. Sensory system was normal. Both his fundi were normal. Rest of the systemic examination was unremarkable. Magnetic resonance imaging (MRI) brain [Figures 1 and 2] revealed bilaterally symmetrical white matter changes with extensive subcortical cysts in bilateral anterior temporal, frontal and parietal regions, consistent with a diagnosis of MLC. Genetic analysis for mutation study was not done due to limited availability and unaffordability as the family belonged to low socioeconomic stratum.

Second of the three siblings, an 11-year-old female, had similar complaints in the same chronology, and for last 2 years she had not been able to walk. She also had macrocephaly, spasticity in lower limbs, bilateral planter extensor and power 4/5 in all the four limbs. She had abnormal movement in the form of athetosis. Her MRI brain findings were consistent with

diagnosis. The eldest of the three siblings was a 14-year-old female, who had similar complaints, and for last 5 years she was also not able to walk. On examination, she had dystonia and dysarthric speech; otherwise, similar findings were discerned as in the other two siblings. There was no history of epilepsy in any of the three siblings. There was no history of any such neurological illness in the past two generations as shown in the pedigree analysis [Figure 3].

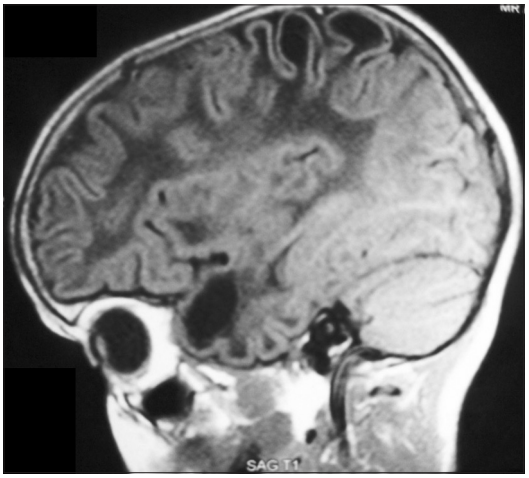

Figure 1: Sagittal T1W image shows multiple circumscribed hypointense subcotical lesions in anterior temporal lobe and parietal lobe.

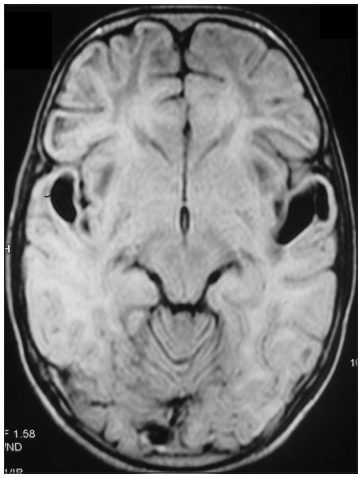

Figure 2: Axial FLAIR sequence shows well-circumscribed subcortical hypointense cystic lesion in bilateral anterior temporal lobe.

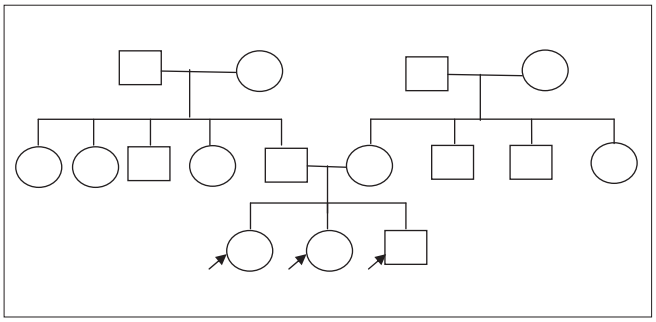

Figure 3: Pedigree chart of the cases

Routine workup that included hemogram, urine routine examination, metabolic profile, urinary metabolic screening and EEG of all the three siblings were normal. The parents were counselled regarding the prognosis and the available treatment options. All the three patients were managed with nutritional supplements and physiotherapy. Currently, the youngest sib is ambulatory and studying in III standard.

Discussion

MLC was first described by van der Knaap *et al*. in 1995.[2] MLC is a rare disease with a low carrier rate. The disease has a high incidence in populations in which consanguinity is common.[3,4] MLC is an autosomal recessive disorder due to mutations in the MLC1 gene which has its locus in chromosome 22q13.3. Severity of the phenotype does not correlate with the specific mutations found. Mutations of MLC1, encoding a putative membrane protein, cause MLC.[5] The diagnosis of MLC can be made with confidence in patients with typical clinical findings and characteristic abnormalities on cranial MRI.[2,4,6]

Typical clinical findings

Macrocephaly is present at birth or (more commonly) develops within the first year of life in all individuals. After the first year of life, head growth rate becomes normal; growth follows a line usually above and parallel to the 98th centile.

Early development is normal or mildly delayed. Most (not all) children achieve independent walking.

Slow deterioration of motor functions with cerebellar ataxia and mild spasticity usually starts in early childhood or later. The majority of affected children become wheelchair dependent in their teens. Speech can become increasingly dysarthric; dysphagia may develop.

Some individuals have extrapyramidal movement abnormalities with dystonia and athetosis, usually as a late finding. Tics may occur. Mental decline occurs later and is much milder than motor decline. Some affected individuals develop behavioral problems. Most individuals have epileptic seizures that are usually easily controlled with medication; however, some experience status epilepticus.

Minor head trauma may induce temporary deterioration in some individuals, most often observed as seizures, prolonged unconsciousness, or acute motor deterioration with gradual improvement.

MRI criteria

MRI of the brain is diagnostic.

Cerebral hemispheric white matter is diffusely abnormal and mildly swollen.

Subcortical cysts are almost invariably present in the anterior temporal region and often in the frontoparietal region.

Central white matter structures, including the corpus callosum, internal capsule, and brain stem, are better preserved than

other structures, although they are not usually entirely normal.

Cerebellar white matter usually has a mildly abnormal signal and is not swollen.

Over time, the white matter swelling decreases and cerebral atrophy ensues. The subcortical cysts may increase in size and number.

In our cases, all three siblings had early-onset macrocephaly, mild motor developmental delay and gradually progressive ataxia, and MRI findings were consistent with diagnosis of MLC. 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. Most children achieve independence in walking. Slow deterioration of motor functions with ataxia and mild spasticity usually starts in early childhood. The majority of the patients become wheelchair dependent in their teens. Some patients have extrapyramidal movement abnormalities with dystonia and athetosis, usually as a late finding. Most patients have epileptic seizures. The typical MRI findings present from about 6 months, but may occur even before that. In typical cases, MRI findings are sufficient for the diagnosis of MLC. The magnetic resonance spectroscopy [MRS] findings in this disorder include mild to moderate decreases in the N-acetyl aspartate [NAA] to choline and choline to creatine ratios.[7]

The combination of megalencephaly and leukoencephalopathy is seen in a limited number of disorders. The characteristic swollen white matter changes, as seen on MRI, have only been reported in MLC, Canavan disease, Alexander disease, infantile-onset GM2 gangliosidosis, glutaric aciduria type 1, and merosin-deficient congenital muscular dystrophy.

In Canavan disease, the MRI typically shows involvement of the thalamus and globus pallidus with relative sparing of a bilateral crescent formed by the putamen and caudate nucleus. The globus pallidus and thalamus are not involved in MLC. The white matter may be cystic in Canavan disease, but the typical subcortical cysts seen in MLC are lacking. In Canavan disease, *N*-acetyl aspartate is elevated in urine and blood and a deficiency of the enzyme aspartoacylase can be demonstrated in cultured fibroblasts.[8]

Alexander disease leads to megalencephaly and leukoencephalopathy with frontal predominance of MRI abnormalities. This predilection for the anterior parts of the brain is not shared by MLC. In Alexander disease, contrast enhancement of particular brain structures is almost invariably observed, whereas contrast enhancement is not a feature of MLC. Cystic degeneration may occur in Alexander disease, but the location of the cysts is different: The deep frontal white matter is mainly affected.[9]

MLC characteristically has an early onset and slow progression, whereas Canavan and Alexander disease have a rapid progression.

MRI in infantile GM2 gangliosidosis is characterized by prominent involvement of the basal ganglia and thalami in addition to the white matter abnormalities. MRI features in infantile GM1 gangliosidosis[10] are very similar to those of GM2 gangliosidosis. Demonstration of deficiency of betagalactosidase activity in leukocytes confirms the diagnosis.

In merosin-deficient congenital muscular dystrophy, white matter involvement resembles that observed in MLC, but the typical subcortical cysts are generally lacking. In addition, individuals with merosin-deficient congenital muscular dystrophy have prominent weakness and hypotonia, not shared by individuals with MLC.[11]

In glutaric aciduria type 1, involvement of the dentate nuclei, severe atrophy of the cerebellar vermis and less prominent white matter changes are the characteristic features on neuroimaging. Clinical course can be static, progressive or relapsing.[12]

Prenatal diagnosis is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis at 16–18 weeks gestation, or by chorionic villus sampling at about 10–12 weeks gestation. MLC is the commonest form of leukodystrophy described in India. Singhal *et al*. described 18 patients with megalencephalic leukodystrophy in a specific Indian community, namely, Aggarwals.[4,13] Although world literature has shown that seizure was present in almost all the patients with MLC but in Indian studies, seizure was uncommon. None of our patients had seizure, which correlates with other published study from India, among which seizure was uncommon. Singhal *et al*. have reported the clinical presentation in 70 patients with MLC from India. They consisted of 42 males and 28 females. The age at onset of symptoms varied from birth to 25 years. The median age at onset was 6 months. The first presenting symptom was a large head in 45 patients, developmental delay (usually delayed motor milestones) in 10 patients, seizures in 9 (12.8%) patients, and motor disability in 6 patients. Many children were able to complete schooling. Of the 46 who attended school, 6 completed graduation, 22 had an average school performance, and 18 were found to be below average.[12] So far, no curative treatment is available. Supportive therapy includes anticonvulsants if the patient has seizures. Physiotherapy is important to improve motor dysfunction. Special education is required for such children.

Conclusion

MLC is the most common leukodystrophy with megalencephaly observed in India and majority of the patients have been from the Aggarwal community. In our study, all three siblings belonged to the same family and were from Kurmi kshatriya (non-Aggarwal) Hindu community. For any patient presenting with infantile onset macrocephaly with signs and symptoms of white matter disease, MLC must be included in the differential diagnosis because it has a remarkably slow course of deterioration in neurologic function and early rehabilitation may prolong ambulatory life.

Contributors: MKK was involved in conception and drafting of the manuscript. MKK and BBS were involved in case management and critical revision of the manuscript. MKK will act as guarantor for the article.

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