CASE REPORT

Megalencephalic leucoencephalopathy with subcortical cysts: subcortical diffuse leucoencephalopathy associated with white matter cystic degeneration

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SUMMARY

Megalencephalic leucoencephalopathy with subcortical cysts (MLC) is a diffuse subcortical leucoencephalopathy with cystic white matter degeneration. Patients with MLC present with macrocephaly at the first year of life, and neurological abnormalities such as motor deterioration, ataxia, spasticity and cognitive defects progress later. MLC is caused by mutations in the gene MLC1, which encodes a novel protein, MLC1. There is no specific treatment for MLC. Management is based on physiotherapy procedures, psychomotor stimulation and treatment of seizures. We report a case of a 1-year-old boy with a normal birth and developmental history, presenting with progressive increase of head size; on further evaluation with CT and MRI of the brain, the child was diagnosed as MLC.

Figure 2 MRI of the brain reveals diffuse supratentorial white matter hypodensities with relative sparing of the basal ganglia, brain stem, cerebellum and central white matter areas, in T2-weighted images.

BACKGROUND

We report this case to emphasise the importance of paediatricians, physicians and radiologists involved in primary care of children diagnosing this rare form of leucoencephalopathy so as to offer the best management in terms of disability limitation and to prevent the occurrence of disease in future offspring through proper genetic counselling.

born at term to non-consanguineous parents and had no significant antenatal or perinatal history. His developmental milestones were normal. There was no history of seizures, neurological deficits, loss of consciousness or head trauma. There was no family history of any genetic disorder. On examination, the baby's head circumference was higher than the 95th centile for age (macrocrania); other general and systemic examinations were uneventful.

CASE PRESENTATION

A 1-year-old boy with progressive gradual increase in head size for the past 4 months, presented to the paediatric department with his parents. He was

INVESTIGATIONS

The child's routine blood work up, consisting of complete blood count, blood glucose, serum electrolytes, liver and renal function tests, was normal.

Figure 1 A photograph of the child, the volume rendered three-dimensional reconstruction of the cranium and CT of the skull clearly depicts macrocrania.

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Figure 3 Non-contrast CT of the brain showing bilateral symmetrical subcortical cysts in anterior temporal lobes, shown by arrows.

However, macrocrania was clearly demonstrated (figure 1). CT of the brain revealed diffuse supratentorial white matter hypodensities with relative sparing of the basal ganglia, brain stem and cerebellum (figure 2), with bilateral symmetrical subcortical cysts in the temporal lobes (figure 3). MRI of the brain showed increased characteristic diffuse supratentorial white matter signal intensity on T2-weighted images (figure 4), decreased signal intensity on T1-weighted images (figure 5), mild swelling of the abnormal white matter and subcortical cysts of the bilateral temporal lobes (figure 6). The patient was diagnosed as megalencephalic leucoencephalopathy with subcortical cysts (MLC) and a genetic study of the child proved the S93 L mutation in MLC1 gene—both the parents were heterozygous carriers.^{1 2}

DIFFERENTIAL DIAGNOSIS

- ▶ Canavan's disease
- ▶ Alexander's disease

- ▶ Infantile onset GM2, GM1 gangliosidosis
- ▶ Glutaric aciduria
- ▶ Merosin deficient congenital muscular dystrophy

TREATMENT

There is no definitive treatment for this disease. Management depends on using antiepileptics to prevent seizures and physiotherapy to improve motor impairment, if it occurs in the future.

OUTCOME AND FOLLOW-UP

The outcome of this child was generally poor. Most of these patients are wheelchair dependent in their early adolescence, and death occurs in the second or third decade. Only a few patients survive to the fourth and fifth decades of life.

DISCUSSION

Megalencephalic leucoencephalopathy with subcortical cysts was first described by van der Knaap *et al* in 1995. Megalencephalic leucoencephalopathy with subcortical cysts is a relatively new neurodegenerative disorder, and is characterised by infantile-onset macrocephaly, cerebral leucoencephalopathy and mild neurological symptoms, alongside an extremely slow course of functional deterioration.³ In India, the majority of these patients belong to the Agarwal community.⁴ However, our patient did not belong to that community. This disease is autosomal recessive and has been assigned to the gene MLC1, which is localised on chromosome 22qtel.⁵ In cases that do not show MLC1 mutation, HEPACAM mutations have been described.⁶ Macrocephaly develops during the first 6 months in 24% of patients and, in 70% of patients, in the second 6 months of life. In this respect, our patient had early onset of macrocephaly, before 6 months of age. The main presenting features after macrocephaly are extrapyramidal findings and ataxia, which are age dependent. Spasticity and ataxia usually develop by 5 years of age and are usually slowly progressive. Loss of independent ambulation has been seen in 38% of reported patients and occurred at an average age of 7.2 years. In all patients, early psychomotor development is normal, as was the case in our patient,^{7 8} or mildly delayed.^{5 9} Some patients have extrapyramidal movement abnormalities, with dystonia and athetosis as a late finding. Mental decline occurs later and is much milder than motor decline. The typical MRI findings are present from about 6 months, and sometimes even before that. In typical

Figure 4 MRI of the brain showing increased characteristic diffuse supratentorial white matter signal intensity on T2-weighted images.

Figure 5 MRI of the brain showing decreased signal intensity in supratentorial white matter on T1-weighted images.

Figure 6 MRI of the brain in T2-weighted and fluid-attenuated inversion recovery sequence showing diffuse white matter swelling with bilateral symmetrical anterior temporal lobe subcortical cysts.

cases, MRI findings are sufficient for a diagnosis of MLC. The MRI abnormalities that are characteristic of the disease are the discrepant severity in comparison with the clinical picture, the aspect of white matter abnormalities (diffuse homogeneous abnormality with swelling), the distribution of the abnormalities with supratentorial hemispherical white matter involvement with relative sparing of central white matter structures, the absence of grey matter involvement and the presence of cysts at a typical location. Cysts are present in the anterior temporal area and often in the frontoparietal area.¹⁰ Absence of typical bilateral cysts are also noted in some MLC cases.¹¹ Prenatal diagnosis is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis at 16–18 weeks gestation, or chronic villus sampling at about 10–12 weeks gestation.

The differential diagnosis of MLC includes Canavan's disease, Alexander's disease, infantile-onset GM2 and GM1 gangliosidosis, glutaric aciduria and merosin-deficient congenital muscular dystrophy. MLC characteristically has an early onset and slow progression, whereas Canavan's and Alexander's disease have a more rapid progression and neurological deterioration is severe, resulting in the development spasticity and seizures at a young age. In Canavan's disease, involvement of the globus pallidus and thalamus is seen, which is not the case in MLC.¹² Alexander's disease leads to a megalencephaly and leucoencephalopathy with frontal predominance, sometimes

hydrocephalus, cavitation and cystic degeneration in the frontal deep white matter and abnormal enhancement of caudate nuclei, and anterior columns of the fornices and periventricular areas.^{9 13} These findings were absent in our patient. Glutaric aciduria can be ruled out biochemically. Absence of muscle weakness and normal creatine kinase rules out congenital muscular dystrophy.¹⁰ MRI in infantile GM1 and GM2 gangliosidosis shows prominent involvement of the basal ganglia and thalami in addition to the white matter abnormalities.¹⁴

Patient's perspective

My child is very active and did not have any problems until now, except the gradual increase in his head size. He feeds and plays well, he even stands with support. As per the advice of the paediatrician, we did CT and MRI for him and doctors suspected a rare disease called MLC. We did many blood and genetic tests, which also came out positive for this disease. The doctors are saying that my boy may have problems walking, remembering things and interacting with others. The doctors also say that I should undergo genetic testing if I plan for another child and they also say that there is a 25% chance that the next child may also be affected. I am deeply saddened.

Learning points

- ▶ Megalencephalic leukoencephalopathy with subcortical cysts (MLC) should be suspected in Asian population, as a differential for macrocrania.
- ▶ Prenatal diagnostic testing, available for diagnosing MLC, should be employed in high risk families to prevent this disease.
- ▶ Family support, physiotherapy and psychological counselling are very important in the management of these patients.

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REFERENCES

- 1 Shimada S, Shimojima K, Masuda T, *et al.* MLC1 mutations in Japanese patients with megalencephalic leukoencephalopathy with subcortical cysts. *Hum Genome Variation* 2014;1:14019.
- 2 Itoh N, Maeda M, Naito Y, *et al.* An adult case of megalencephalic leukoencephalopathy with subcortical cysts with S93L mutation in MLC1 gene: a case report and diffusion MRI. *Eur Neurol* 2006;56:243–5.
- 3 Van Der Knaap MS, Barth PG, Stroink H, *et al.* Leukoencephalopathy with swelling and a discrepantly mild clinical course in eight children. *Ann Neurol* 1995;37:324–34.
- 4 Gorospe JR, Singhal BS, Kainu T, *et al.* Indian Agarwal megalencephalic leukodystrophy with cysts is caused by a common MLC1 mutation. *Neurology* 2004;62:878–82.
- 5 Pascual-Castroviejo I, van der Knaap MS, Pronk JC, *et al.* Vacuolating megalencephalic leukoencephalopathy: 24 year follow-up of two siblings. *Neurologia* 2005;20:33–40.
- 6 López-Hernández T, Ridder MC, Montolio M, *et al.* Mutant GlialCAM causes megalencephalic leukoencephalopathy with subcortical cysts, benign familial macrocephaly, and macrocephaly with retardation and autism. *Am J Hum Genet* 2011;88:422–32.
- 7 Chandrashekan HS, Guruprasad AS, Jayakumar PN, *et al.* Megalencephalic leukoencephalopathy with subcortical cysts: MRI and proton spectroscopic features. *Neurol India* 2003;51:525–7.
- 8 Saijo H, Nakayama H, Ezoe T, *et al.* A case of megalencephalic leukoencephalopathy with subcortical cysts (van der Knaap disease): molecular genetic study. *Brain Dev* 2003;25:362–6.
- 9 Hari Krishnan K, Leema Pauline C, Kumaresan G, *et al.* Megalencephalic leukoencephalopathy with subcortical cysts. *Indian Pediatr* 2005;42:60–3.
- 10 Sethi PK, Sethi NK. Megalencephalic leukoencephalopathy with Subcortical cysts. *Indian J Pediatr* 2004;71:473–5.
- 11 Masuda T, Ueda M, Ueyama H, *et al.* Megalencephalic leukoencephalopathy with subcortical cysts caused by compound heterozygous mutations in *MLC1*, in patients with and without subcortical cysts in the brain. *J Neurol Sci* 2015;351:211–13.
- 12 Marks HG, Caro PA, Wang ZY, *et al.* Use of computed tomography, magnetic resonance imaging, and localized 1H magnetic resonance spectroscopy in Canavan's disease: a case report. *Ann Neurol* 1991;30:106–10.
- 13 Van der Knaap MS, Naidu S, Breiter SN, *et al.* Alexander disease: diagnosis with MR imaging. *AJNR Am J Neuroradiol* 2001;22:541–52.
- 14 Chen CY, Zimmerman RA, Lee CC, *et al.* Neuroimaging finding in late infantile GM1 gangliosidosis. *AJNR Am J Neuroradiol* 1998;19:1628–30.

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