hormone analog and growth hormone in central precocious puberty. J Clin Endocrinol Metab. 1996, 81: 948-951.

3. Walvoord EC, Pescovitz OH. Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: theoretic and practical considerations. Pediatrics. 1999, 104: 1010-1014.
4. Agarwal DK, Agarwal KN, Upadhyay SK, Mittal R, Prakash R, Rai S. Physical and sexual growth pattern of affluent Indian children from 5-18 years of age. Indian Pediatr. 1992, 29: 1203-1282.
5. Tanner JM, Healy MJ, Goldstein H, Cameron N. Prediction of Adult Height TW3 equations. *In:* Tanner JM, Healy MJ, Goldstein H, Cameron N, Editors. Assessment of Skeletal Maturity and Prediction of adult height by TE3 method, 3rd edn. London, W.B. Saunders, 2001; p 26-43.
6. Root AW. Precocious Puberty. Pediatr Rev 2000, 21: 10-19.
7. Kaplowitz PB. If Gonadotropin-Releasing Hormone Plus Growth Hormone (GH) Really Improves Growth Outcomes in Short Non-GH-Deficient Children, Then What? Clini Endocrin and Metab 2001, 86: 2965-2968.
8. Pucarelli I, Segni M, Ortore M, Arcadi E, Pasquino AM. Effects of combined gonadotropin-releasing hormone agonist and growth hormone therapy on adult height in precocious puberty: A further contribution. J Pediatr Endocrinol Metab 2003, 16: 1005-1010.
9. Pucarelli I, Segni M, Ortore M, Iannaccone R, Pasquino AM. Combined therapy with GnRH analog plus growth hormone in central precocious puberty. J Pediatr Endocrinol Metab 2000,13: 811-820.

Megalencephalic Leukoencephalopathy with Subcortical Cysts

K. Hari Krishnan
C. Leema Pauline
G. Kumaresan
T.K. Vasantha Mallika

Megalencephalic leukoencephalopathy with subcortical cysts is a rare disease first described in 1995. It is characterized by macrocephaly and early onset white matter degeneration. We report two siblings who were diagnosed to have this disease. This disease must be included in differential diagnosis of macrocephaly with early onset leukoencephalopathy.

Key words: *Macrocephaly, Megalencephalic leukoencephalopathy, Subcortical cysts, White matter degeneration.*

Megalencephalic leukoencephalopathy with subcortical cysts (MLC), also known as van der Knaap's disease, is characterized by early-onset macrocephaly, with mild motor developmental delay and seizures; gradual onset of ataxia, spasticity, and sometimes extrapyramidal findings; and usually late onset of mild mental deterioration.

Macrocephaly is present at birth or develops during the first year of life. The degree of macrocephaly is variable and can be as much as 4-6 SD above the mean. Almost all patients have epilepsy from an early age. Some patients have died in their teens or twenties but others are alive in their forties.

From the Department of Pediatrics and Department of Pediatric Neurology, Institute of Child Health and Hospital for Children, Chennai, India.

Correspondence to: Prof. G. Kumaresan, B-9, 26, Desika Road, Mylapore, Chennai 600 004, India.

Manuscript received: December 10, 2003;
Initial review completed: January 29, 2004;
Revision accepted: July 26, 2004.

Case Reports

Case 1: A 4-year-old boy, born of second degree consanguineous marriage in a Muslim community, with uneventful birth history, presented with progressively increasing head size noticed from 1 year of age, and left sided simple focal seizures from 2 years of age. He attained social smile by 4 months and head control by 6 months of age. He could walk with support and was able to speak a few words by 2½ years, which is his current status too. He had not attained bladder or bowel control.

On examination, he had a head circumference of 54.5 cm (>95th percentile). He was able to comprehend, obey commands and could speak a few words only. He had bipyramidal signs. Sensory system was normal and there were no cerebellar signs. His optic fundi were normal, there was no cherry-red spot and did not have organomegaly. MRI brain (*Figs.1 & 2*) revealed bilaterally symmetrical white matter changes with extensive sub-cortical cysts in frontal, anterior temporal and parietal regions, consistent with a diagnosis of MLC.

Case 2: A 2-year-old younger sibling of the patient mentioned above had similar complaints. She had increasing head circumference from 1 year of age and generalized seizures since 1 year of age. She had motor and mental developmental delay. She had a head circumference of 52 cm (>95th percentile) and spasticity in both lower limbs. Her MRI brain revealed identical findings.

Urine metabolic screening was done, for both the patients, which was negative. EEG showed bilateral generalized epileptiform activity in both cases. No other family members were affected with any such neurological illness even in the 3 past generations. Both the patients were treated symptomatically with use of anti-convulsants and physiotherapy.

Discussion

Megalencephalic leukoencephalopathy with subcortical cysts was first described by van der Knaap, *et al.* in 1995(1). MLC is a rare disease with a low carrier rate. The disease has a high incidence in populations in which consanguinity is common(2-4).

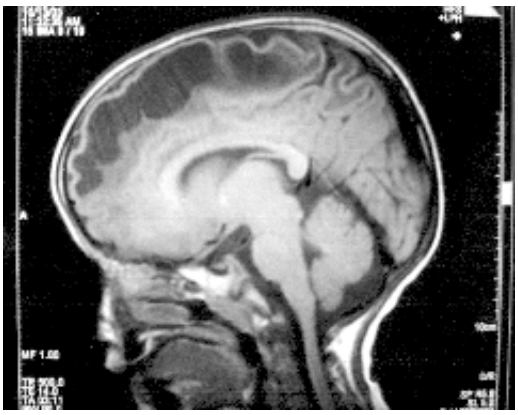

Fig. 1. MRI brain sagittal view showing extensive subcortical cystic changes and sparing of central white matter structures.

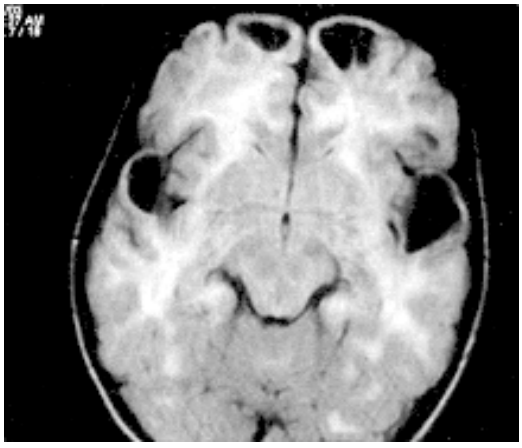

Fig. 2. MRI brain showing bilaterally symmetrical white matter changes and cysts in frontal and anterior temporal region.

MLC is an autosomal recessive disorder due to mutations in MLCI gene(5,6) which has its locus in chr22qter. The physiological function of the protein is at present unknown. It is probably an integral membrane protein.

The diagnosis of MLC can be made with confidence in patients with typical clinical findings and characteristic abnormalities on cranial MRI. 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 cerebellar 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. Mental decline occurs later and is much milder than motor decline. Most patients have epileptic seizures.

The MRI is diagnostic. MRI of the brain shows diffusely abnormal, mildly swollen cerebral hemispheric white matter. Central white matter structures, including the corpus callosum, internal capsule, and brain stem are better preserved, although they are not usually entirely normal. Subcortical cysts are invariably present in the anterior-temporal region and often in the frontoparietal region. Over time, the white matter swelling decreases and cerebral atrophy ensues. The subcortical cysts may increase in size and number.

The differential diagnosis of MLC includes Canavan's disease, Alexander disease, infantile-onset GM2 and GM1 gangliosidosis and merosin-deficient congenital muscular dystrophy.

In Canavan's disease, MRI shows involvement of the thalamus and globus pallidus, which are spared in MLC(7). The white matter may be cystic, but the typical subcortical cysts are lacking. Alexander disease leads to a megalencephaly and leukoencephalopathy with frontal predominance of MRI abnormalities and contrast enhancement of particular brain structures, which is not a feature of MLC(8). Cystic degeneration may occur in Alexander's disease, but deep frontal white matter is mainly affected. MLC characteristically has an early onset and slow progression, whereas Canavan's and Alexander's 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 ganglio-sidosis(9) are very similar to those of GM2 gangliosidosis. Demonstration of deficiency of beta-galactosidase activity in leukocytes confirms the diagnosis.

So far, all attempts to treat MLC have failed. Patients have been treated with acetazolamide, but neither the clinical symptoms nor the white matter swelling improved. Supportive therapy includes the prescription of anticonvulsants if the patient has seizures. Physical therapy is important to improve motor dysfunction. Special education is required for many patients.

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.

Contributors: HK and LP were involved in conception and design, acquisition of data, analysis and interpretation of data and in drafting of the manuscript. GK and TKVM were involved in critical revision of the manuscript for important intellectual content. GK gave final approval of the version to be published and will act as guarantor for the article.

Funding: None.

Competing interests: None declared.

REFERENCES

1. van der Knaap MS, Barth PG, Stroink H, van Nieuwenhuizen O, Arts WF, Hoogenraad F, *et al.* Leukoencephalopathy with swelling and a discrepantly mild clinical course in eight children. Ann Neurol, 1995; 37: 324-334.
2. Ben-Zeev B, Gross V, Kushnir T, Shalev R, Hoffman C, Shinar Y, *et al*. (2001) Vacuolating megalencephalic leukoencephalopathy in 12 Israeli patients. J Child Neurol 2001; 16: 93-99.
3. Topcu M, Saatci I, Topcuoglu MA, Kose G, Kunak B. Megalencephaly and leukodystrophy with mild clinical course: a report on 12 new cases. Brain Dev 1998; 20: 142-153.
4. Singhal BS, Gursahani RD, Udani VP, Biniwale AA. Megalencephalic leukodystrophy in an Asian Indian ethnic group. Pediatr Neurol 1996; 14: 291-296.
5. Leegwater FA, Boor PK, Yuan BQ, van der Steen J, Visser A, Konst AA, *et al*. Identification of novel mutations in MLC1 responsible for megalencephalic leukoencephalopathy with subcortical cysts. Hum Genet 2002; 110: 279-283.
6. Leegwater FA, Yuan BQ, van der Steen J, Mulders J, Konst AA, Boor PK, *et al*. Mutations of MLCl (KIAAOO27), encoding a mutative membrane protein, cause megalencephalic leukoencephalopathy with subcortical cysts. Am J Hum Genet 2001; 68:831-838.
7. Marks HG, Caro PA, Wang ZY, Detre JA, Bogdan AR, Gusnard DA, *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: 106-110.
8. van der Knaap MS, Naidu S, Breiter SN, Blaser S, Stroink H, Springer S, *et. al*. Alexander disease: diagnosis with MR imaging. AJNR Am J Neuroradiol 2001; 22: 541-552.
9. Chen CY, Zimmerman RA, Lee CC, Chen FH, Yuh YS, Hsiao HS. Neuroimaging findings in late infantile GM1 gangliosidosis. AJNR Am J Neuroradiol 1998; 1628-1630.