

Megalencephalic-cystic leukodystrophy

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Abstract

Vacuolating megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare form of leukodystrophy. The phenotype consists of early onset ataxia followed by progressive signs of pyramidal tract involvement and mental deterioration. Megalencephaly, appearing in the first year of life, is a characteristic feature of this syndrome. Magnetic resonance imaging (MRI) of MLC patients shows early and severe cerebral white matter involvement, despite relatively mild neurological findings during the early stages of the disease. In addition to a widespread T2 hyperintensity of the white matter, MRI shows T1 weighted and fluid attenuated inversion recovery (FLAIR) hypointense subcortical cysts in the temporal lobes and in the fronto-parietal subcortical areas. Overall, these severe neuroradiological abnormalities are concomitant with the clinical features, which are milder than those of other childhood leukodystrophie's forms. In the later stages of this disorder, cognitive impairment appears slowly, contributing significantly to the overall disability. Some patients show early onset learning disability starting during the first years of scholarship. MLC is an autosomal recessive inherited disease. Mutations in the MLC1 gene (22q13.33), coding for a protein whose function is unknown, were identified in MLC families of different ethnic background. Some patients do not harbor mutations in MLC1 and there is evidence of genetic heterogeneity in some sibships. No specific therapy is available for MLC. Management is based on physiotherapy procedures, psychomotor stimulation and treatment of seizures.

Keywords

Leukodystrophy, megalencephaly, ataxia, subcortical cysts, MLC1 gene

Disease name and synonyms

- Vacuolating megalencephalic leukoencephalopathy with subcortical cysts (MLC)
- LVM (leukoencephalopathy with vacuolating megalencephaly)

- VL (vacuolating megalencephalic leukoencephalopathy)

Diagnostic criteria/definition

MLC syndrome was first described in 1995 (van der Knaap *et al.*, 1995) and is defined as leukoencephalopathy with swelling and cysts.

Diagnosis is based on established clinical and neuroradiological criteria (van der Knaap *et al.* 1995). Magnetic resonance imaging (MRI) characteristics include severe cerebral white matter abnormalities, which contrast with the relatively mild neurological findings, and typical cysts localized in the tips of the temporal lobes and in the frontoparietal subcortical area. Cerebral hemispheric white matter is diffusely abnormal with increased signal intensity in T2 weighted MRI images, and with considerable swelling, while the white matter of the cerebellum is mildly involved and not swollen. Central white matter structures, including the corpus callosum, internal capsule, and brainstem, are relatively spared. There is no gray matter involvement in early stages, however cortical atrophy with deepened sulci is observed in the late stages of the disease.

Differential diagnosis

A screening may be performed in order to exclude inborn errors, especially those responsible for megalencephaly and/or white matter disease. MRI is useful to rule out [Alexander leukodystrophy](#), [Canavan disease](#), and [glutaric aciduria type I](#). Canavan disease can be confirmed by the evidence of high level of NAA (N-acetyl aspartate) in urines and cerebrospinal fluid (CSF). Alexander leukodystrophy can be confirmed by screening for *GFAP* gene mutations. Glutaric aciduria type I can be ruled out by measuring the activity of glutaryl-CoA dehydrogenase (GCDH) in fibroblasts and then by analysis of *GCDH* gene mutations.

Etiology

A brain biopsy performed in a MLC patient revealed a spongiform leukoencephalopathy without cortical involvement (van der Knaap *et al.*, 1996). Histopathologic findings placed the disease among the vacuolating myelinopathies, although it is distinct from the other forms. Electron microscopy of the white substance showed splitting of the outermost myelin lamellae at the intraperiod line or a disturbance of compaction of the outermost myelin lamellae at the intraperiod line. Recently, expression studies of the transcript of the mouse gene *Mlc1*, which is highly homologous to the human *MLC1* gene (see Genetics), have shed light on the function of MLC1. At the cellular level, highest *Mlc1* expression was found during the pre- and perinatal period in multipotential neural precursor cells, especially in the subventricular zone of the lateral ventricle, whereas in adulthood highest *Mlc1* mRNA concentrations were revealed in Bergmann glia cells and astrocytes. Oligodendrocytes are devoid of *Mlc1* expression.

White matter tract abnormalities observed in MLC may result from a primary astrocytic defect (Schmitt *et al.*, 2003).

Genetics

MLC locus was mapped to the telomeric region of 22q (Topcu *et al.*, 2000) and the *MLC1* gene was localized to 22q13.33 (Leegwater *et al.*, 2001). *MLC1* encodes a putative membrane protein of 377 amino acids with still unknown function. Until today, a broad spectrum of *MLC1* mutations were identified in MLC patients, without a straightforward genotype-phenotype correlation (Leegwater *et al.*, 2001; Leegwater *et al.*, 2002; Ben-Zeev *et al.*, 2002; Patrono *et al.*, 2003). The absence of linkage to any marker on 22qtel or *MLC1* mutations in MLC patients strongly corroborate the existence of other causative gene(s) (Leegwater *et al.*, 2001; Patrono *et al.*, 2003; Blattner *et al.*, 2003). Common mutations have not been found in European populations (Leegwater *et al.*, 2001; Leegwater *et al.*, 2002; Patrono *et al.*, 2003; Rubie *et al.*, 2003), whereas some ethnic communities share some mutations, which suggest a founder effect (Ben-Zeev *et al.*, 2002; Tsujino *et al.*, 2003; Singhal *et al.*, 2003).

Clinical description

Macrocephaly appears in the first year of life and is observed in all MLC patients. Characteristically, motor and mental deterioration do not progress simultaneously. Most patients have a delay in reaching autonomous walking, showing early-onset ataxia, and suffer from recurrent seizures (Patrono *et al.*, 2003). Some patients experience acute motor disability after falling to the ground without a severe or direct head trauma, because of an epileptic drop attack or gait instability. About 50% of patients lose the ability to walk by the first decade of life.

As far as intellectual development is concerned, MLC patients may be divided in two groups: i) patients with normal speech development but with learning difficulties starting in the first years of school; ii) patients without any learning disability in the first decade of life.

Marked intrafamilial variability in the severity of neurological and cognitive development has been found and confirmed in sibs belonging to inbred kindred.

Diagnostic methods

- MRI (see Diagnostic criteria/definition)
- Screening for *MLC1* mutations represents the ultimate step of MLC diagnosis.

Epidemiology

MLC is a rare inherited disorder described in several ethnic groups (Topcu *et al.*, 2000; Leegwater *et al.*, 2001; Leegwater *et al.*, 2002; Ben-Zeev *et al.*, 2002; Patrono *et al.*, 2003; Tsujino *et al.*, 2003; Singhal *et al.*, 2003). The frequency of the disease is still unknown.

Genetic counseling

MLC is inherited as an autosomal recessive condition. Consanguinity is often observed.

Prenatal diagnosis

Identification of *MLC1* mutations is the only tool for prenatal diagnosis.

Management

No specific therapy is available for MLC1. Traumatic falls, sometimes provoked by epileptic fits, can worsen neurological symptoms. No antiepileptic drug is particularly effective in MLC1, however seizures do not reoccur frequently. For mental retardation management is based on psychomotor stimulation.

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