

Childhood ataxia with central hypomyelination (CACH) syndrome

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Abstract

Childhood ataxia with central hypomyelination (CACH) syndrome is a recently described leukodystrophy. The existence of several cases in certain kindreds supports an autosomal recessive inheritance. The diagnosis is made based on a group of clinoradiological arguments, as no biochemical marker has been identified. The disease starts in a child, after an interval of variable duration, with sudden onset of a cerebellospastic syndrome. Progression is rapid, with severe sudden deteriorations, with death frequently occurring during childhood. Magnetic resonance imaging (MRI) shows extensive involvement of the white matter with the presence of so-called 'cavitated' zones, which resemble the cerebrospinal fluid (CSF) signal on all the MRI (T1, T2 and especially fluid-attenuated inversion recovery (FLAIR) sequences). In these cavitated zones, the proton spectrum (NMR spectroscopy) is close to that of the CSF (disappearance of normal peaks and presence of glucose and lactates). In addition to these typical forms, other forms start later (adolescence and adulthood) and have a slower evolution. The specific neurohistological appearance confirms the existence of this entity: orthochromatic cavitory leukodystrophy with increased oligodendrocyte density. CACH syndrome may be caused by mutations in any of the 5 subunits of the translation initiation factor eIF2B. The incidence is unknown. CACH syndrome may represent 30% of leukodystrophies of unknown etiology. At present, treatment is purely symptomatic.

Keywords

Childhood ataxia with central hypomyelination (CACH) syndrome, leukoencephalopathy, cavitated zones, eIF2B

Name of the disease and its synonyms

- Infantile ataxia with diffuse hypomyelination of the central nervous system
- Leukoencephalopathy with loss of white substance
- Central diffuse myelinolysis
- Childhood ataxia with central hypomyelination (CACH) syndrome
- Myelinosis centralis diffusa
- Leukoencephalopathy with vanishing white matter

Diagnostic criteria/definition

Diagnosis is based on a group of clinical and radiological signs [1-4]. In addition to the typical forms of the child, other forms with later onset (adolescence and adulthood) and slower evolution have been described [5, personal observation]. They share the same radiological [1, 2, 4] and neurohistological signs [6-8].

Magnetic resonance imaging (MRI) shows precocious, symmetrical and massive involvement of the white matter, seen as a hypersignal on the T2-weighted sequences; within the diseased white matter, one sees the so-called 'cavitated' zones, *i.e.*, resembling the cerebrospinal fluid (CSF) signal on all the MRI (T1, T2 and especially FLAIR (fluid-attenuated inversion recovery)) sequences. The proton spectrum of this cavitated white matter is also similar to that of the CSF (NMR spectroscopy), with the disappearance of most normal peaks and presence of glucose and lactates.

Elevated glycine levels in the CSF have been reported but the specificity of this anomaly remains to be demonstrated [9]. The novel neurohistological appearance of this entity confirms its existence: orthochromatic cavitory leukodystrophy with increased oligodendrocyte density.

Differential diagnosis/names of excluded diseases

The diagnosis, in the absence of a marker, requires the elimination of acquired anomalies of the white matter (postinfectious, anoxic-ischemic, toxic or inflammatory) and the other known leukodystrophies with metabolic ([Krabbe's disease](#) or globoid cell leukodystrophy, [metachromatic leukodystrophy](#), adrenoleukodystrophy, [Canavan's disease](#) or spongy degeneration, mitochondrial encephalopathy...), neurohistological ([Alexander's disease](#)) and/or genetic markers ([Pelizaeus-Merzbacher disease](#) or progressive familial leukodystrophy). A new clinicoradiological entity - [leukodystrophy with megalencephaly and cysts](#) - must also be excluded.

Incidence

At present, this information is unknown. In our experience, the CACH syndrome represents 30% of leukodystrophies of unknown etiology.

Clinical description

This new entity was first described in children [2]. The onset is marked, after initially normal or only moderately retarded development, by the rapid appearance of a cerebellospastic syndrome before the age of 6 years. The

occurrence of severe episodes of deterioration, after minor head trauma or banal infections, often lead to unexplained coma or episodes of lethargy with vomiting. Cognitive functions are preserved for a relatively long time. During the course of disease evolution, epileptic seizures, optic nerve atrophy and signs indicating involvement of the cerebral trunk (difficulty swallowing or breathing...) can occur. Death frequently occurs during the first decade of life.

More recently, cases of later onset and slower progression have been reported, with a disease starting after 10 years, during adolescence or even in the young adult [5, personal observation]. The symptoms can, in these patients, start with moodiness and motor signs can appear later.

Genetics

A locus was identified for this entity on chromosome 3q27 [10]. CACH is the first human disease related to mutations in any of the five genes encoding subunits of eukaryotic initiation factor eIF2B. eIF2B is essential in all cells of the body for protein synthesis and the regulation of this protein synthesis under different stress conditions [11, 12, 13].

Management and treatment

At present, treatment is purely symptomatic.

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