CACH (childhood ataxia with central hypomyelination): Molecular defect of a severe form

CACH, also termed vanishing white matter (VWM) leukoencephalopathy, is caused by mutations in the eukaryotic translation factor. There are five different subunits in this factor (which play an important role in cellular protein synthesis). Here, Fogli et al. describe an acute, fatal infantile form and report the molecular defect in the ϵ subunit.

see page 1966

Lumping or splitting the childhood leukodystrophies

Commentary by Michael J. Noetzel, MD

Clinicians have approached neurologic disorders using the conceptual framework of lumping and splitting for decades. In the current age of molecular genetics, these old constructs have new meaning. Nowhere is this better illustrated than in childhood leukodystrophies. Despite the advances of biochemistry, neuroradiology, and histopathology, a large number of these leukodystrophies remain “undiagnosed.” Relying on the concept of splitting, clinicians and researchers defined relatively homogeneous groups of these undiagnosed leukodystrophy patients. As a result, new disorders have been described, including CACH/VWM leukoencephalopathy. Although the hybrid name would suggest otherwise, this disorder appears to have a uniform clinical course with late infantile onset and slow progression of disease into adolescence, often punctuated by intermittent acute deterioration. Molecular genetics has demonstrated an autosomal recessive inheritance related to mutations in five genes encoding the eukaryotic translation initiation factor (eIF2B),¹ whose regulation represents a major

Activation of eIF2 by eIF2B. The translation initiation factor eIF2 is activated by exchange of GDP for GTP by the activated factor eIF2B-GTP (composed of five different subunits). The ϵ -subunit of eIF2B permits the GDP/GTP exchange (GEF activity: Guanine Exchange Factor); the β -subunit binds the GTP.

protective mechanism of cells in response to heat-shock stress.²

In this setting come the lumpers (perhaps better designated as genetic expanders) in the form of Fogli et al., who previously had reported two patients with a rapidly fatal infantile leukodystrophy, classified by them as a severe variant of CACH/VWM.³ Their work demonstrates that the DNA of both their affected infants contained a novel homozygous missense mutation in eIF2B. They postulate that mutations in the various subunits of eIF2B account for a clinical

continuum in the severity of the CACH/VMW leukoencephalopathy, ranging from the acute fatal infantile form to the slowly progressive juvenile conditions. The approach presented in this paper extends beyond its intrinsic value; it illuminates a mechanism by which our understanding of brain injury (and thus conceivably treatment) can be expanded by harnessing genomic technology. Taken to its extreme, one could speculate that continued advances in genetics will one day establish an orderly genotype/phenotype relationship for all neurologic disorders and thus render moot the concept of lumping and splitting.

References

1. van der Knaap MS, Leegwater PA, Konst AA et al. Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter. *Ann Neurol* 2002;51:264–270.
2. Proud CG. Regulation of eukaryotic translation initiation factor eIF2B. *Prog Mol Subcell Biol* 2001;26:95–114.
3. Francalanci P, Eymard-Pierre E, Dionisi-Vici C, et al. Fatal infantile leukodystrophy: a severe variant of CACH/VWM syndrome, allelic to chromosome 3q27. *Neurology* 2001;57:265–270.

continued on page 1826

Holoprosencephaly

Lewis et al. studied 15 children with middle interhemispheric variant, a subtype of holoprosencephaly in which the posterior frontal and parietal regions fail to separate during development. Similar to the lobar holoprosencephaly in development function, middle interhemispheric variant differs from classic holoprosencephaly by the absence of endocrinopathies and choreoathetosis.

see page 1860

Barkovich et al. report a high incidence of myelination delay in children with classical holoprosencephaly, but not in the middle interhemispheric variant, possibly suggesting different causes of these two forms of the malformation.

see page 1968

The accompanying editorial by Marc Patterson reviews holoprosencephaly—the most common human brain malformation, its pathogenesis, and clinical classification. The Lewis et al. and Barkovich et al. papers begin to characterize the varying phenotypes of holoprosencephaly using standard MRI and clinical assessment and including patients at three centers. In general, the degree of separation and integrity of deep brain structures correlated well with clinical findings.

see page 1833

Modafinil reduces somnolence in myotonic dystrophy

MacDonald et al. found that modafinil reduced the subjective perception of sleepiness and enhanced selected quality of life measures in patients with myotonic dystrophy (DM1). A 100 mg (morning and noon) dose was similar in efficacy to the 200 mg dose.

see page 1876

Elevation of blood β -carboline alkaloids in essential tremor (ET)

Louis et al. examined blood concentrations of two β -carboline alkaloids, harmaline and harmine, in 100 ET cases and 100 controls. β -carboline alkaloids, tremor-producing chemicals, are normal body constituents and naturally present in the food chain. The mean harmaline concentration was higher in ET cases.

see page 1940

Botulinum toxin in diabetic autonomic gustatory sweating

Restivo et al. studied botulinum toxin type A as initial treatment of gustatory sweating in 14 diabetic subjects. In all subjects sweating ceased within 4 days, the maximal follow-up time lasting 24 weeks.

see page 1971

continued on page 1827

Sleep and hallucinations in PD

The Manni et al. study of 20 patients with PD documented occurrence of visual hallucinations in relation to nocturnal REM sleep or to daytime drowsiness. Neural mechanisms of dream imagery are hypothesized to play a role in the occurrence of visual hallucinations in these patients.

see page 1979

The Frucht (neurologist) and Bernsohn (patient/artist) NeurolImage vividly illustrates hallucinations in PD.

see page 1965

Autoantibodies to glutamate receptor in epilepsy

Bernasconi et al. found that antibodies from Rasmussen's encephalitis and partial epileptic patients bound to specific regions in histoblotted rat brain. This assay adds new insights to anti-GluR3 antibody ELISA and provides a comprehensive overview of antibody immunoreactivity in CNS. GluR3 antibodies were not specific for Rasmussen's encephalitis occurring in 7 of 11 sera from patients with partial epilepsy.

see page 1998

CNS involvement in CMTIX?

Schelhaas et al. report a 14-year-old boy from a family with X-linked dominant Charcot-Marie-Tooth disease caused by a mutation in the gap junction protein connexin 32. He developed confluent cerebral white matter lesions in association with fever. The process resolved spontaneously.

see page 2007

Neuropathy with liability to pressure palsies in a 2-year-old

Hardon et al. report a toddler with rigid wrist drop from radial nerve lesion. EMG also documented disease in the left arm. Genetic evaluation showed the HNPP deletion in 17p11.2 in the patient as well as his mother.

see page 2008

Neurology®

December 24 Highlights
Neurology 2002;59;1825-1827
DOI 10.1212/WNL.59.12.1825

This information is current as of December 24, 2002

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/59/12/1825.full>

References

This article cites 3 articles, 1 of which you can access for free at:
<http://n.neurology.org/content/59/12/1825.full#ref-list-1>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright . All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.