Mutations in a Thiamine-Transporter Gene and Wernicke’s-like Encephalopathy

TO THE EDITOR: We report on two previously healthy Japanese brothers with a newly discovered recessively inherited syndrome similar to Wernicke’s encephalopathy that developed in the second decade of life; this syndrome was manifested clinically as thiamine-responsive diplopia and ptosis without serum thiamine deficiency. The patients had complex partial seizures resulting in status epilepticus. The administration of high-dose thiamine (up to 600 mg) improved the seizures within 24 hours, although the ophthalmoplegia, nystagmus, and ataxia continued for several weeks. There were no extrapyramidal features. Magnetic resonance imaging (MRI) of the brain showed high-intensity signals in the bilateral medial thalamus and periaqueductal region on fluid-attenuated inversion recovery images (Fig. 1A); these signals were characteristic of findings in Wernicke’s encephalopathy and became normal within 1 month after treatment. Interviews of the patients’ relatives confirmed that there was no consanguinity in their parents. Subacute ophthalmoplegia with nystagmus and ataxia occurred repeatedly within several months after the discontinuation of 100 mg of thiamine per day. There was no history of chronic alcoholism in either patient. Korsakoff’s psychosis did not occur even after long periods of Wernicke’s encephalopathy in these patients suggesting that dysfunction of hTHTR2 may induce the expression of another human thiamine transporter 2–encoded gene called SLC19A2, thereby increasing intracellular thiamine transport in enterocytes and neuronal cells. The identification of this syndrome provides insight into the thiamine metabolism associated with Wernicke’s encephalopathy in humans and suggests that the mechanism of Korsakoff’s psychosis may be independent of these thiamine pathways.

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Figure 1. Analyses of Data from Two Brothers with a Wernicke’s-like Encephalopathy.
Panel A shows the brain MRI scans in the older brother on hospitalization for status epilepticus with external ophthalmoplegia at 36 years of age. The scan on the left shows high-intensity signals in the periaqueductal region, and the scan on the right shows high-intensity signals in the bilateral medial thalamus. Panel B shows the results of electrophoresis of directly sequenced SLC19A3 polymerase-chain-reaction products amplified from the leukocyte DNA of an older brother of the two patients. The sequence analyses showed an A→G substitution at nucleotide position 218 in exon 2 resulting in a substitution of lysine at codon 44 with glutamic acid and a G→C substitution at nucleotide position 1047 in exon 3 resulting in a substitution of glutamic acid at codon 320 with glutamine. Sequence analyses of genes associated with thiamine metabolism, including TKT, PDHA2, OGDH, DLD, and SLC19A2, showed no genetic variation involving newly discovered benign polymorphisms. Panel C shows the results of the analysis of the restriction-fragment–length polymorphisms of the family. In the pedigree portion of the figure, solid symbols denote affected family members and half-solid symbols indicate carriers of the mutation. Digestion of a mutant sequence for the K44E or E320Q mutation resulted in 300-bp and 207-bp fragments, respectively. The patients (lanes 3 and 4) had two fragments that indicated compound heterozygosity for K44E and E320Q. The father was heterozygous for E320Q (lane 1), whereas the mother was heterozygous for K44E (lane 2). Panel D shows cellular localizations of wild-type protein and K44E and E320Q mutants by means of immunofluorescence assay. SLC19A3 complementary DNA (cDNA) was subcloned into PcDNA6.2/GW/D-TOPO (Invitrogen) with a C-terminal V5 epitope tag. Chinese hamster ovary (CHO) cells were transiently transfected with wild-type, K44E, or E320Q SLC19A3 cDNA and were processed for immunofluorescence. The cells were labeled with the use of antibodies against V5 or resident protein disulfide isomerase (PDI) in the endoplasmic reticulum. Images in the Merge column are composite overlays of the V5 and PDI images. Panel E shows intracellular [3H]-thiamine uptake by CHO cell lines stably expressing wild-type protein or K44E or E320Q mutants. The results are expressed in counts per minute as the means of uptake values obtained from three independent experiments. 1 bars represent standard errors. P<0.01 for the comparisons of wild-type protein with K44E and E320Q. Panel F shows the SLC19A3 RNA levels in different areas of the human brain calculated with the use of a control messenger RNA–plasmid standard curve, then normalized to glyceraldehyde-3-phosphate dehydrogenase. The results are expressed as the means from three independent experiments. 1 bars represent standard errors.


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