Mutations in a thiaminetransporter gene and Wernicke's-like encephalopathy

1. McAdams M, Staffa J, Dal Pan G. Estimating the extent of reporting to FDA: a case study of statin-associated rhabdomyolysis. Pharmacoepidemiol Drug Saf 2008;17:229-39.
2. Abraham SC, Cruz-Correa M, Lee LA, Yardley JH, Wu T-T. Alendronate-associated esophageal injury: pathologic and endoscopic features. Mod Pathol 1999;12:1152-7.
3. Ribeiro A, DeVault KR, Wolfe JT III, Stark ME. Alendronate-associated esophagitis: endoscopic and pathologic features. Gastrointest Endosc 1998;47:525-8.
4. Singh SP, Odze RD. Multinucleated epithelial giant cell changes in esophagitis: a clinicopathologic study of 14 cases. Am J Surg Pathol 1998;22:93-9.
5. Inderjeeth CA, Foo AC, Lui MM, Glendenning P. Efficacy and safety of pharmacological agents in managing osteoporosis in the old old: review of the evidence. Bone 2008 December 16 (Epub ahead of print).

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-like symptoms.

The clinical and imaging features resembling Wernicke's encephalopathy in these patients suggested that the syndrome was caused by a genetic disorder of thiamine metabolism.[1] Genomic analysis of *SLC19A3* encoding human thiamine transporter 2 (hTHTR2)[2,3] revealed that the patients were compound heterozygotes for the K44E and E320Q mutations; these mutations were not present among 192 ethnically matched control subjects (Fig. 1B and 1C). Gene-expression analyses of mammalian culture cells showed the majority of the K44E mutant to be impaired in intracellular transport while remaining normal in the endoplasmic reticulum. The E320Q mutant was identical in cell-surface localization to the wild-type protein (Fig. 1D), whereas intracellular thiamine uptake activity was decreased significantly (Fig. 1E). High expression of *SLC19A3* RNA in the thalamus (Fig. 1F) may explain the selective thalamic lesions on MRI.

Mutation of *SLC19A3* causes a biotin-responsive basal-ganglia disease characterized by subacute encephalopathy with rigidity and dystonia. Biotin is effective and thiamine is ineffective in treating this childhood-onset disease.[4,5] The features of this process on MRI are bilateral necrotic lesions in the caudate heads; this is markedly different from the locus of lesions in the disease we describe.[4] The absence of serum thiamine deficiency and the efficacy of high-dose thiamine in our patients suggest that dysfunction of hTHTR2 may induce the expression of another human thiamine transporter 1–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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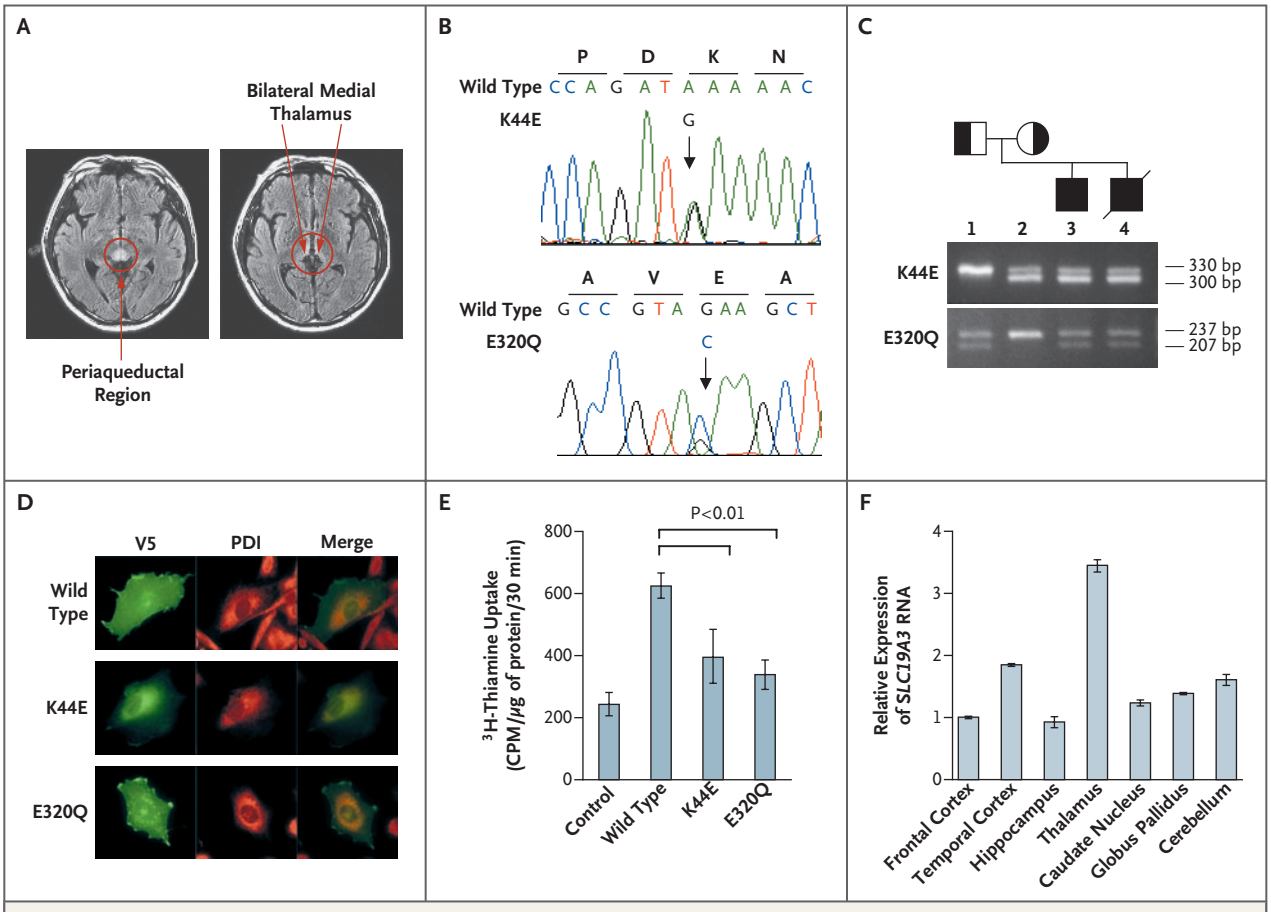

Figure 1. Analyses of Data from Two Brothers with a Wernicke's-like Encephalopathy.

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 [^{3}H]-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. I 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. I bars represent standard errors.

1. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol 2007;6:442-55.
2. Eudy JD, Spiegelstein O, Barber RC, Wlodarczyk BJ, Talbot J, Finnell RH. Identification and characterization of the human and mouse SLC19A3 gene: a novel member of the reduced folate family of micronutrient transporter genes. Mol Genet Metab 2000;71:581-90.
3. Rajgopal A, Edmondson A, Goldman ID, Zhao R. SLC19A3 encodes a second thiamine transporter ThTr2. Biochim Biophys Acta 2001;1537:175-8.
4. Ozand PT, Gascon GG, Al Essa M, et al. Biotin-responsive basal ganglia disease: a novel entity. Brain 1998;121:1267-79.
5. Zeng WQ, Al-Yamani E, Acierno JS Jr, et al. Biotin-responsive basal ganglia disease maps to 2q36.3 and is due to mutations in SLC19A3. Am J Hum Genet 2005;77:16-26.

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