A DE NOVO LGI1 MUTATION CAUSING IDIOPATHIC PARTIAL EPILEPSY WITH TELEPHONE-INDUCED SEIZURES

Telephone-induced seizures have recently been described as a distinct form of idiopathic reflex epilepsy in which seizures are repeatedly and exclusively triggered by answering the telephone. Typical auras consist of auditory or vertiginous symptoms and the inability to speak or understand spoken voices. These features, along with specific EEG ictal findings in one patient, suggest that this condition involves the lateral temporal area.

Autosomal dominant partial epilepsy with auditory features (ADPEAF; OMIM 600512), or autosomal dominant lateral temporal epilepsy (ADLTE), is a rare familial partial epilepsy syndrome with onset in childhood/adolescence and benign evolution. The hallmark of the syndrome consists of the presence of typical auditory auras or ictal aphasia in most affected family members, sometimes triggered by environmental sounds and noises. ADPEAF is associated in about half of the families with mutations of the leucine-rich, glioma-inactivated 1 (LGI1)/Epitempin gene, the function of which is still unclear.

Earlier we described a series of sporadic patients with idiopathic partial epilepsy with auditory features (IPEAF) who were clinically indistinguishable from ADPEAF cases and found an IPEAF patient with a de novo LGI1/Epitempin mutation resulting in protein truncation. We now report another de novo LGI1/Epitempin mutation identified in an Italian woman with telephone-induced seizures.

Clinical case. This 36-year-old, left-handed woman had an 11-year history of recurrent complex partial and secondarily generalized seizures evoked almost exclusively by answering the telephone. Seizures were characterized by a subjective feeling of distortion or attenuation of environmental sounds, inability to understand the language and to speak appropriately, loss of contact, and inconstant secondary generalization. Sometimes the patient reported complex auditory hallucinations (such as music or radio announcers’ voices) at the onset of seizures.

The attacks usually occurred when she answered the telephone, including her mobile phone. Other auditory stimuli, such as hearing the answering machine and the noise of a helicopter, could elicit the seizures. These seizures occurred rarely, however, on a yearly basis. After early withdrawal of carbamazepine (400 mg/day) for a skin reaction, the patient received phenobarbital (100 mg/day) with incomplete control of seizures. Her general history was uneventful, with no family history of epilepsy. Neurologic examination, MRI of the head, and routine and sleep EEG were normal.

Results. A de novo heterozygous c.406C→T mutation in exon 4 of the LGI1/Epitempin gene, resulting in an arginine to tryptophan substitution at position 136 (Arg136Trp), was detected by denaturing high-performance liquid chromatography analysis and confirmed by direct sequencing. This mutation eliminates an MspI restriction site. Digestion of the PCR-amplified wild-type allele with the MspI restriction enzyme yields two fragments of 356 and 109 bp, whereas the undigested mutant allele, found in the proband but not in her parents, yields a fragment of 465 bp (figure 1). Segregation of 30 highly polymorphic microsatellite markers scattered over the human genome was in concordance with paternity (data not shown). Thus, the c.406C→T transition found in the proband must be a de novo mutation. This nucleotide change was not found in 105 Italian unrelated healthy individuals. The Arg136 residue is conserved in many species, including mouse, rat, chicken, zebrafish, and Xenopus tropicalis. Replacement of this charged amino acid with the hydrophobic tryptophan likely hampers the function of the mutated protein, ultimately resulting in the epilepsy phenotype.

Discussion. To our knowledge, this is the second case reported to date of idiopathic nonfamilial partial epilepsy carrying a de novo mutation of the LGI1/Epitempin gene. Interestingly, in our patient, the clinical picture met the criteria for the diagnosis of telephone-induced seizures. In this condition, the seizure features (auditory symptoms, difficulty to speak and understand spoken language) are com-
The de novo mutation eliminated an MspI restriction site, giving rise to an undigested mutant allele. LGI1 exon 4 was PCR amplified as described and extensively digested with the MspI restriction endonuclease. Restriction digests were separated by electrophoresis on a 1.5% agarose gel and stained with ethidium bromide. M = 100-bp ladder molecular weight marker; C = undigested control; bp, base pairs.

patible with a lateral temporal origin and are almost exclusively triggered by answering the telephone—a complex and elaborate auditory stimulus involving the lateral temporal areas. This reflex epilepsy, therefore, is likely related to IPEAF, a notion that is further supported by the de novo LGII/Epitempin mutation found in our patient. We recently screened a series of 53 sporadic IPEAF cases and detected no mutations in LGII/Epitempin. Subsequently, we found a de novo LGII/Epitempin mutation in a patient initially suspected to be a familial case. The affected woman reported here carries the second de novo mutation identified in a total of 77 IPEAF patients screened, suggesting that the frequency of new LGII/Epitempin mutations in sporadic IPEAF could be around 2.5%

Identification and screening of additional IPEAF patients is needed to determine the precise proportion of cases caused by de novo LGII/Epitempin mutations and for genetic counseling purposes.

Figure

Restriction analysis of LGI1 exon 4 PCR products from the sporadic case and her parents (pedigree symbols shown on top)

NEUROLOGICAL FINDINGS IN AMINOACYLASE 1 DEFICIENCY

Recessive ACY1 mutations are responsible for a novel inborn error of metabolism. Consistent with ACY1 deficiency (MIM 609924), all affected individuals exhibited markedly increased urinary excretion of several N-acetylated amino acids. Aminoacylase 1 (ACY1) catalyzes the release of free amino acids from a variety of N-acetylated precursors, but not from N-acetylaspartate. The latter is hydrolyzed by aminoacylase 2 (ACY2, aspartoacylase), a deficiency of which is the cause of the neurodegenerative Canavan disease (MIM 271900).

Patients. Here, we report three additional unrelated children with ACY1 deficiency detected by routine urine screening for organic acidurias by gas chromatography–mass spectrometry. One individual (OS-1381I-1) is the only child of Asian consanguineous parents. She presented with febrile seizures at 11 months of age followed by further seizure episodes 3 months later associated with a viral infection. At the age of 4 years, she displays delayed speech and language development. Another patient (OS-1461I-1) is the second son of healthy Romani cousins. Two cousins and a niece of the mother have epilepsy.

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**Table Clinical findings in patients with biallelic mutations in the ACY1 gene**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Current age</th>
<th>Sex</th>
<th>Ethnic background</th>
<th>Clinical findings</th>
<th>Mutations</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS-104II-1</td>
<td>1.8 y</td>
<td>F</td>
<td>Italian/ German</td>
<td>R197W [589C]</td>
<td>IVSS-1G&gt;A/IVSS-1G&gt;A</td>
<td>Current study</td>
</tr>
<tr>
<td>OS-104II-1</td>
<td>1.8 y</td>
<td>M</td>
<td>Romani</td>
<td>Multifocal, drug-resistant epilepsy; moderate mental retardation</td>
<td>R353C [1057C&gt;T]/R353C [1057C&gt;T]</td>
<td>Current study</td>
</tr>
<tr>
<td>OS-104II-1</td>
<td>1.8 y</td>
<td>M</td>
<td>German</td>
<td>Biotinidase deficiency; normal cognitive function</td>
<td>R353C [1057C&gt;T]/R353C [1057C&gt;T]</td>
<td>Current study</td>
</tr>
<tr>
<td>OS-104II-1</td>
<td>1.8 y</td>
<td>F</td>
<td>Asian</td>
<td>Febrile seizures</td>
<td>R353C [1057C&gt;T]/R353C [1057C&gt;T]</td>
<td>Current study</td>
</tr>
<tr>
<td>OS-104II-1</td>
<td>1.8 y</td>
<td>M</td>
<td>Romani</td>
<td>Multifocal, drug-resistant epilepsy; moderate mental retardation</td>
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<td>Current study</td>
</tr>
<tr>
<td>OS-104II-1</td>
<td>1.8 y</td>
<td>M</td>
<td>German</td>
<td>Prolonged afebrile seizure followed by transient right-sided hemiplegia and facial palsy</td>
<td>R353C [1057C&gt;T]/R393H [1178G&gt;T]</td>
<td>Current study</td>
</tr>
</tbody>
</table>

"Highest age mentioned in the reference.

Results and Discussion. Enzyme activity, assessed according to Sass et al.,' was greatly reduced in Epstein–Barr virus–transformed lymphoblasts of OS-138II-1 (0.15 nmol mg⁻¹ min⁻¹) and OS-152II-1 (0.13 nmol mg⁻¹ min⁻¹). Reference ACY1 activity based on 48 controls was 1.47 ± 0.73 nmol mg⁻¹ min⁻¹ (mean ± SD). Patient OS-146II-1 is the first individual for whom fibroblast homogenate could be used for confirmation of ACY1 deficiency; activity was only 0.09 nmol mg⁻¹ min⁻¹, whereas the mean value for seven controls was 0.95 nmol mg⁻¹ min⁻¹ (SD = 0.22 nmol mg⁻¹ min⁻¹).

Mutational analysis, as described previously, was detected in all three individuals recessive (biallelic) ACY1 mutations supporting autosomal recessive inheritance (table). In addition, we report two novel ACY1 missense mutations that were absent from a large control cohort. Consistent with parental consanguinity, we identified the novel missense variant 589C>T (R197W) in the homozygous state in OS-138II-1. In OS-152II-1, we found a more complex genetic situation with evidence of compound heterozygous mutations. The novel missense mutation 1178G>A (R393H) probably occurred in this child as a de novo mutation because this variant was not found in either parent, whereas the R353C variant was inherited through the father. The novel R393H mutation (OS-152II-1) probably either occurred as a de novo event in the child or was transmitted via a de novo germ line mutation. Two patients (OS-152II-1 and OS-146II-1) carried the already reported R353C variant, which is consistent with previous findings. Interestingly, so far, mutations could be identified in all eight individuals with highly elevated concentrations of several N-acetylamino acids. Thus, there is no indication for another gene involved in ACY1 deficiency.

Most individuals with ACY1 deficiency present with neurologic symptoms (table). In addition to the known clinical presentation with reduced psychomotor function, we now show that epileptic seizures are frequently found in patients with ACY1 deficiency. Consistent with a metabolic disorder,
seizures occurred during episodes of illness (OS-138II-1 and OS-152II-1) or developed later in childhood (OS-146II-1). Due to young age of most ACY1-deficient individuals, the clinical course cannot be fully predicted.

The strong expression of ACY1 in the human brain is compatible with a role of the enzyme in the CNS.1,5 In addition, ACY1 can contribute to the inhibition of apoptosis.6 Interestingly, ACY1 is one of few proteins that exhibits altered expression in mouse models for Huntington disease and fragile X syndrome.7 Thus, ACY1 is a potential modifier affecting severity or manifestation of different neurologic disorders. This could explain the phenotypic variability observed in ACY1-deficient individuals.

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CORRECTION

Genetic diagnosis in Lafora disease: Genotype–phenotype correlations and diagnostic pitfalls

There are several errors in the Views & Reviews “Genetic diagnosis in Lafora disease: Genotype–phenotype correlations and diagnostic pitfalls” by H. Lohi et al. (Neurology 2007;68:996–1001):

1. Niall P. Quinn, MD, should have been listed as the eighth author.
2. In the table, for Family F7, the entry for nucleotide change should be listed as “Homozygous 887T→A”.
3. In the Results section, page 998, subsection headed Intrafamilial heterogeneity in age at onset in LD, the gene name in that paragraph should be EPM2B (not EPM2A). In the Discussion section discussing this result, page 1000, last paragraph of paper, EPM2A (occurring twice) should be changed to EPM2B.

These errors were corrected in the online version at www.neurology.org on May 31, 2007.
Genetic diagnosis in Lafora disease: Genotype–phenotype correlations and diagnostic pitfalls

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