Dysfunction of the brain calcium channel CaV2.1 in absence epilepsy and episodic ataxia—a comment

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Sir,

We read with great interest the article by Imbrici et al. (2004) recently published in your journal. The authors report on a family in which absence epilepsy segregated in an autosomal dominant fashion through three generations, and five of its members exhibited a combination of absence epilepsy and episodic ataxia type 2 (EA2). DNA sequence analysis identified a novel point mutation that resulted in a radical amino acid substitution (E147K) in the main pore-forming \( \alpha_{1A} \) subunit of the brain calcium channel CaV2.1. In a detailed description of two of the patients (case II:6 and case III:3), the authors point out that the patients exhibited marked cerebellar ataxia or a decreased level of consciousness when antiepileptic drugs were given even in the low or middle therapeutic range. They warned that episodic ataxia might be wrongly ascribed to anticonvulsant medication.

Recently we reported on a patient (female, 26 years old) who had had absence epilepsy from 2 to 9 years of age (Strupp et al., 2004). When she was 14 years old, she developed recurrent attacks of ataxia and blurred vision, which lasted several hours and were regularly induced by exercise, e.g. playing tennis. In 2001, EA2 was diagnosed. Sequencing of the \( \text{CACNA1A} \) gene identified a previously described (Jouvenceau et al., 2001) heterozygous point mutation in exon 36 (C5733T), which resulted in an arginine (CGA) to stop (TGA) change at amino acid position 1820 (R1820stop). This mutation is predicted to lead to a protein product truncated behind the last transmembrane segment (IVS6), with a complete loss of the C-terminal intracellular region; electrophysiological studies postulate that this mutation has a dominant-negative effect (Jouvenceau et al., 2001). As the patient only transiently responded to acetazolamide (up to 750 mg/day), treatment was switched to 5 mg of the potassium channel blocker 4-aminopyridine (4-AP) tid in August 2003. Since then, no further attacks have occurred, and she has even taken part in a tennis tournament. When 4-AP was stopped in November 2003 for 1 week, she developed recurrent attacks 2 days after cessation. Resumption of treatment resulted in no more attacks (last follow-up interview: September 2004). Attacks in two other patients were also prevented by 4-AP (Strupp et al., 2004). Meanwhile, two more patients have been treated; diagnosis was proven in both (a mother and her daughter) by a mutation of the \( \text{CACNA1A} \) gene (a 7 bp deletion in exon 26), and 4-AP caused a cessation of the attacks in all of them. It is of interest that in the tottering mouse (an animal model for EA2) 4-AP was observed to ‘completely prevent attacks of ataxia’ (Ellen J. Hess, Johns Hopkins University, personal communication).

Since the patients described by Imbrici et al. (2004) did not tolerate antiepileptic drugs, it may make sense to treat them with 4-AP (5 mg tid). On the one hand, this might prevent episodic ataxia by increasing the release of GABA in the Purkinje cells, most probably by increasing the excitability of Purkinje cells as was observed in animal experiments (Etzion and Grossman, 2001). On the other, it might also prevent absence seizures in patients with \( \text{CACNA1A} \) mutations by increasing the effect of inhibitory GABAergic interneurons. However, it must be kept in mind that one case of epileptic seizure was reported during high dosages of 3,4-diaminopyridine (>100 mg per day) given for Lambert–Eaton syndrome (see Sanders et al., 2000).

References


