SCN4A-associated hypokalemic periodic paralysis merits a trial of acetazolamide

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Primary hypokalemic periodic paralysis (HypoPP) is characterized by episodes of transient flaccid paralysis in association with reduced serum potassium levels.[1] Onset of transient weakness is typically in the first or second decade, often on awakening. Weakness may be mild and focal or progress to flaccid quadriplegia, and the duration may last hours to days. Interindividual attack frequency varies, from daily episodes to a single lifetime episode, commonly decreasing with age. Predictable triggers are rest after exercise and high carbohydrate meals. Unlike hyperkalemic periodic paralysis, myotonia is absent. A proportion of affected individuals have slowly progressive permanent weakness.

Inheritance is autosomal dominant, although one-third of cases are sporadic, and penetrance is reduced in women. HypoPP is genetically heterogeneous. Three common mutations in *CACN1AS*, the α-subunit of the skeletal muscle L-type calcium channel gene,[2] account for 70% of cases (HypoPP1), whereas 10%[3] of patients have a mutation in *SCN4A*, the α-subunit of the voltage-gated sodium channel gene (HypoPP2),[4,5] and are clinically indistinguishable.

Patients with HypoPP are treated with administration of oral potassium at the time of an attack. The carbonic anhydrase inhibitors acetazolamide (ACZ)[1] and dichlorphenamide, as well as potassium-sparing diuretics, are used for prophylaxis. In some patients, ACZ results in exacerbation of symptoms,[3,6] a trait that runs true in families.[6] Two kindreds carrying mutations in the *SCN4A* gene (HypoPP2)[3,6] led some researchers to postulate that all HypoPP2 patients might react adversely to carbonic anhydrase inhibitors.[3] Here we report a HypoPP2 patient treated with ACZ without exacerbation of his episodic attacks of weakness.

Case report. A 29-year-old man had attacks of transient weakness since age 15 years. His family history was negative. Ictal potassium levels were reduced (2.5 to 2.9 mmol/L). Provocative triggers included rest after exercise, carbohydrate or alcohol intake, diarrheal illness, and poor sleep. Respiratory muscles were not involved, and there was no interictal weakness. Interictal neurologic examination was normal, and he had no clinical or electrical myotonia. An exercise test (of abductor digiti minimi) conducted off-treatment showed an increment in amplitude (17%) and area (89%) at 2 minutes postexercise and a maximal decrement in amplitude (38%) and area (59%) at 30 minutes postexercise. DNA testing revealed an R672S mutation in the *SCN4A* gene (Ulm, Germany).

He successfully managed his periodic paralysis with potassium supplementation at the beginning of attacks and before engaging in vigorous physical activity and took ACZ (250 mg/d) for prophylaxis. Episodes of weakness were initially characterized as mild (not interfering with activity, occurring daily, and lasting minutes), moderate (interfering with but not preventing activity, occurring three times a week, with duration of 1 hour), and severe (unable to function, occurring once a month, with duration up to 6 hours). Although never attack free for >1 week, episodes are less frequent with his present treatment regimen (mild, daily; moderate, once weekly; and severe, quarterly).

Discussion. ACZ is used for prevention of attacks in periodic paralysis.[1] However, recent reports of ACZ-induced worsening of symptoms in patients with HypoPP2 led to suggestions that ACZ should be avoided in such patients. The patient with HypoPP2 described here, with an R672S *SCN4A* mutation, was successfully treated with ACZ without aggravation of attacks. Similarly, the proband in a kindred with the R672S mutation in *SCN4A* had decreased attack frequency when treated with ACZ 250 mg twice daily and spironolactone 100 mg daily.[7]

Table *Patients with* SCN4A *mutations: Response to acetazolamide (ACE) treatment*

Reference	No. of patients	Sex	Mutation	ACZ treatment
Bulman et al., 1999	2 (1 family)	M	R669H	Better
Bendahhou et al., 2001	3 (1 family)	M	R672S	Worsened
Davies et al., 2001	1 (sporadic)	M	R672S	Better
Sternberg et al., 2001	3 (1 family)	M	R672G	Worsened
Venance et al., 2004	1 (sporadic)	M	R672S	Better

The variability in responsiveness apparent with ACZ treatment in individuals with missense mutations in the sodium channel (table) suggests the modifying influence of other unidentified genetic and environmental factors. ACZ and other carbonic anhydrase inhibitors should continue to be considered for patients with HypoPP2 as a treatment option along with other potassium-sparing diuretics.

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