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Reply

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Drs Berciano and Ferrer [1] have made important observations by reexamining autopsy material from patients with a pathological diagnosis of olivopontocerebellar atrophy (OPCA). They found glial cytoplasmic inclusions (GCIs) in 5 cases of sporadic OPCA but did not find GCIs in any of the neuropathological material from 3 cases of OPCA with the spinocerebellar ataxia type 1 (SCA-1) genotype. They found that 1 patient with a genetically determined cerebellar degeneration affecting 10 family members in four generations did have both neuronal and oligodendroglial argyrophilic inclusions in the pons and cerebellum. They did not have information concerning the genotype of this patient. Their observations are interesting but leave a number of questions unanswered.

It is unclear whether the neuropathological material from 5 sporadic OPCA cases with GCIs had been examined carefully to determine whether the pathological features of multiple system atrophy (MSA) were detected, including degenerative changes within the basal ganglia, intermediolateral columns of the spinal cord, and autonomic nuclei of the brainstem. It is also unclear where in the nervous system they found GCIs. In their studies of the material from the cases with the SCA-1 genotype, it appears that they did not use tau stains in their search for GCIs, and thus they could have overlooked some glial and neuronal inclusions. In the patient with the SCA-1 genotype described in our article, GCIs were found in the external and internal capsule, midbrain, pons, medulla, cerebellum, and spinal cord and were most numerous in the internal capsule, brainstem, and cerebellum [2]. It is unclear whether Drs Berciano and Ferrer [1] examined these structures in their cases. In addition, we found in our material smaller numbers of GCIs than occur in sporadic OPCA patients, suggesting that a more careful search may be needed in hereditary cases than in sporadic cases. In the 1 case with a hereditary form of OPCA in which Drs Berciano and Ferrer found inclusions, they reported finding them in the pons and cerebellum, but they did not describe where else they looked for these inclusions.

Despite our questions about their observations, we agree with the conclusions that Berciano and Ferrer [1] reached, which are that GCIs are a constant feature of sporadic OPCA, but they can also occur in hereditary OPCA. It is clear that GCIs are not seen exclusively in sporadic MSA.

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Acetazolamide Responsiveness in Familial Hemiplegic Migraine

B. S. Athwal and G. G. Lennox

We read with interest the recent article in *Annals* by Elliot and co-workers [1], describing patients with the syndrome of familial hemiplegic migraine (FHM). They and other authors [2] have called to attention the striking clinical and genetic similarities of this illness to episodic ataxia type 2 (EA-2) and, in a wider context, to other episodic neurological disorders such as periodic paralysis, myotonia fluctuans, and episodic ataxia type 1 (EA-1) [3]. Some of these disorders, in particular EA-2, characteristically respond to acetazolamide [4]. Acetazolamide has not, however, been evaluated in the treatment of FHM.

We describe a mother and son who gave a 15-year history of recurrent hemiparesis and migraine fulfilling the International Headache Society criteria for FHM [5]. A 32-year-old man had between 3 and 12 attacks each month in the past 2 years, and his 60-year-old mother approximately one attack every 2 weeks, despite conventional migraine prophylaxis in each case. Four siblings were unaffected. Both the mother and son had jerky ocular pursuit, gaze-evoked horizontal nystagmus, impaired vestibulo-ocular reflex suppression, and mild limb and gait ataxia. Magnetic resonance imaging of the son revealed mild cerebellar atrophy, and polymerase chain reaction and restriction enzyme analysis for mitochondrial DNA mutations mt 3243 and mt 3271 proved negative. He commenced acetazolamide 250 mg twice a day with resolution of his symptoms. After 3 months he reduced the dose to 250 mg once a day, and for 2 months the attacks returned with much reduced frequency. The mother reports freedom from symptoms over a 5-week period while taking acetazolamide at the same dose.

In recent years, the molecular basis of a number of episodic neurological disorders has been shown to be dysfunction of ion channels in cellular membranes [4]. Although there is no direct evidence to implicate such a deficit in EA-2, its fluctuating nature and response to acetazolamide suggests a similar pathogenesis. The response of this family suggests that FHM too may be a channelopathy. Formal trials

of acetazolamide in FHM, and in nonhemiplegic migraine, are now required.

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Reply

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The apparent prophylactic effect of acetazolamide in a patient with familial hemiplegic migraine (FHM) as described by Drs Athwal and Lennox is provocative. Given the demonstrated response of hereditary paroxysmal cerebellar ataxia to acetazolamide, our group and others [1] have speculated on its potential usefulness in FHM. It has been our uncontrolled observation that verapamil has been an effective prophylactic therapy for our patients with FHM. We have not had the opportunity to observe the effects of acetazolamide on our own patients with this disorder. However, we agree that there is compelling evidence warranting formal trials of acetazolamide in FHM.

It remains unclear whether FHM is a channelopathy. Although FHM may respond to acetazolamide, there are other mechanisms worth considering. In a series of patients with migraine who were given acetazolamide, Schlake and colleagues [2] demonstrated resolution of interictal regional hypoperfusion on single-photon emission computed tomographic studies. Such a vascular mechanism may underlie the prophylactic effect that Drs Athwal and Lennox observed in their patient with FHM. This also suggests that acetazolamide may be useful in the treatment of nonhemiplegic migraine. If proven effective for FHM, further studies will be needed to delineate acetazolamide's exact mechanism of action in this disorder.

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