Familial Periodic Ataxia Responsive to Acetazolamide

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ABSTRACT: Two cases, a father and son, of recurrent cerebellar ataxia in the same family are reported, suggesting a familial trait for the dysfunction. In the older male the onset of each episode (30-90 min.) was signalled by dysarthria which then progressed towards gait ataxia; the son presented closely similar clinical symptoms. Physical examination and blood chemistry revealed no obvious neurological deficit or biochemical abnormalities, with the exception of I-III and III-IV evoked auditory wave interpeak latencies, which were found markedly abnormal on the left side in the father but not in the son; the EEG of both individuals showed some diffuse, slow wave abnormalities. A low dose of acetazolamide, 250 mg daily, has successfully repressed recurrence of the attacks over the past six months. Temporary withdrawal for 14 days of the carbonic anhydrase inhibitor in the father coincided with two observed ataxic episodes.


This paper describes a new family where both the father and son exhibit periodic ataxia. It also confirms the efficacy of acetazolamide in suppressing the clinical incidents; the drug has previously been reported to be beneficial in four other families (Griggs et al., 1978; Donat and Auger, 1979; Zasorin et al., 1983; Aimard et al., 1983). Finally, we discuss the possible mechanisms by which the carbonic anhydrase (CA) inhibitor, acetazolamide, acts to reduce or prevent the appearance of ataxic episodes.

CASE REPORTS

Case I was born in September 1935 and started to seek help at age 32 (in 1967) for incapacitating episodes of ataxia and dysarthria. These occurred initially once a week and lasted 30 to 90 minutes. On careful inquiry the patient acknowledged that in his teens, he frequently had to stop running because of dizziness and unsteadiness of gait which vanished after a few minutes. These episodes were not accompanied by dysarthria, nausea or other subjective symptoms.

In 1969, he underwent an investigation which showed a decreased labyrinthine response on the right side; the neurological examination was however normal. Attention was then drawn to the possibility of hypoglycemia. Fasting glucose was found to be 69, 67, 65, 55 mg %.

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There was no significant variation during a 24 hour period of fasting. The glucose tolerance test demonstrated a normal elevation (30 min.: 185 mg %; 60 min.: 212 mg %; 120 min.: 126 mg %), but a relative hypoglycemia of 39 mg % at 3 hours was observed without, however, being accompanied by atactic manifestations. A tolbutamide test was normal.

The subject was admitted to another hospital in April 1981 because the spells had increased in severity and frequency. These spells started with 5-10 minutes of sweating and progressive dysarthria. By that time, he was unable to walk unassisted because of staggering, or to handle objects, and the speech had become incomprehensible. The severe deficits would persist for 30 to 60 minutes, after which a smooth recovery took place over a period of 10 to 15 minutes. There was no relationship between the episodes and fasting, types of meals, stress or exertion. However, the patient reported never to have had an attack when lying down, either at night or during the day. The frequency of the episodes varied from 1 to 3 per week and he claimed to feel "very good" at the end of each episode. He nevertheless lost his job as a truck driver because of these incidents. This social problem was the reason he was re-investigated in April 1982 when he was seen by one of us (JPB).

The patient denied any neurological problem among his parents, grand-parents, uncles, brother (1) and sisters (2) and their offspring. He is the father of non-identical male twins, one of whom proved to suffer similar episodic ataxia (Case II, see below).

Routine blood and cerebrospinal fluid. Brain computerized tomography and cerebral angiography revealed no abnormalities.

Electronystagmographic studies disclosed a severe peripheral deficit on the right side, as revealed by caloric tests. Calibration, smooth pursuit, gaze tests and position tests were nevertheless normal. The patient admitted to a direct trauma to the right ear when he was a child, but denied having experienced hypoacusia, tinnitus or vertigo.

Brainstem auditory evoked responses (BAER) were normal on the right side, with a delay in wave I of 1.7 msec and, both normal I - III and III - V interval latencies of 2.0 msec. There were marked abnormal values on the left side for both I - III (2.4 msec) and III - V (2.5 msec) interpeak latencies.

In June 1982, the patient was placed on acetazolamide, 250 mg once a day for one week, and then twice a day. He was relieved of any atactic spells, but the dose of acetazolamide then had to be reduced to 250 mg daily because of paresthesia in all four limbs. The patient was placebo under observation to witness possible episodes. The only noticeable finding was a slightly elevated total protein level (57 mg %) in the cerebrospinal fluid. Brain computed tomography and cerebral angiography revealed no abnormalities.

Our cases are quite similar to those reported by Griggs et al. (1978) and Zasorin et al. (1983), both with reference to their episodic manifestations and to their favorable response to acetazolamide. Donat and Auger (1979) successfully treated a mother and her son with acetazolamide, although a somewhat different clinical picture was manifested. They then reviewed the literature to find records of seven other families with periodic ataxia. As early as 1946, Parker coined the expression "periodic ataxia" to described episodic symptoms in multiple sclerosis among four families. He has also underlined the relationship between periodic ataxia in two offsprings of a parent with progressive spino-cerebellar degeneration. The three other families encompassed a large number of individuals over several generations (White, 1962; Farmer and Mustian, 1963; Hill and Sherman, 1968). Persistant mild ataxia and nystagmus were present in more than half of the cases. The duration of the episodes varied from minutes (Parker, 1946) to weeks (Hill and Sherman, 1968), but the overall clinical expression (age at onset of attacks, rapid progression to gait ataxia, dysarthria, variable
upper limbs dysmetria, with or without nystagmus) is quite stereotyped in a given family. An interesting association of ataxic episodes in association with myokymia has been reported by van Duke (1975) in a large kinship.

Hill and Dysart (1975) have discussed the susceptibility of cerebellum in young children to various infections or toxic influences. In the same book, Salam (1975) in a chapter on metabolic ataxias, reviewed the amino acidopathies that are essentially diseases of childhood and which account for most recurrent attacks of episodic ataxia seen at this age. A number of specific enzyme deficiencies have been described in these cases. Often the disorder is so severe that mental retardation becomes the prominent feature.

This is not the case in the syndrome reported as “familial periodic ataxia”. Although the ataxic episodes start in infancy or childhood in some of the large kinships (White, 1962; Hill and Sherman, 1968; Griggs et al., 1978), in these cases no abnormalities were found in the amino acid content of blood or urine, nor in cases beginning in the teens or later in life. In all investigated cases including our own, no biochemical leads have been found.

Electrophysiological studies have also yielded little information on the nature and localisation of the process. Electromyography and nerve conduction studies were normal in all reported instances. EEGs were normal in most cases, and showed only mild generalized slowing (Hill and Sherman, 1968) with dysrhythmia (Donat and Auger, 1979) in some. Bursts of slow and sharp activity were demonstrated in two cases by Zasorin et al. (1983). Although less marked, the bursts of slow activity seen in three different recordings of the father are likely of the same nature. These are reminiscent of the bursts encountered in more than 50 % of the patients with autosomal recessive spastic ataxia of Charlevoix-Saguenay (Bouchard et al., 1979) or much less often, in Friedreich’s ataxia (Rémillard et al., 1976; Bouchard et al., 1979). These episodic EEG manifestations are believed to originate from involvement of diencephalic or brain stem structures in spastic and Friedreich’s ataxia. In our patient, the bursts were not changed in quantity and quality when recording was done during the last minutes of an ataxic spell. Although certainly not specific, these abnormalities point to some similarity between progressive and periodic ataxias.

Of more interest are the brain stem auditory evoked responses (BAER) in the few reported cases with familial periodic ataxia. They were normal in one case (Donat and Auger, 1979) while Asymmetric changes of the BAER have seldom been noted in progressive ataxias. In Zasorin’s case (Zasorin et al., 1983) asymmetric and temporary abnormalities were found. In our older patient, unilateral delay of both I-III and I-V interpeak latencies were present during a non ataxic period, indicating a diffuse brain stem dysfunction even when the subject was asymptomatic. The role of acetazolamide in returning the BAER to normal is unknown.

It is now believed that periodic ataxia is likely caused by a partial defect in enzymes of the pyruvate dehydrogenase (PDH) complex, which leads to the accumulation of pyruvate, lactate and alanine (Zasorin et al., 1983). Other enzymatic defects, as reviewed by Salam (1975), might represent cofactor deficiencies that could influence the rate of pyruvate oxidation and produce this syndrome-complex.

Reynold and Blass (1976) suggested that pyruvate oxidation was lower in the anterior cerebellar vermis, compared to other parts of the brain. They postulated that a defect in PDH, too mild to impair carbohydrate metabolism elsewhere, could selectively cause dysfunction at this level. Furthermore it is known that decreased PDH activity reduces the synthesis of acetylcholine (Gibson et al., 1975). On this basis, physostigmine (Kark et al., 1977) and lecithin (Barbeau, 1978) were given to chronically ataxic patients, with some success. To our knowledge such a therapy has not been evaluated in periodic ataxia.

Acetazolamide in periodic ataxia was first used because the syndrome had been misdiagnosed as periodic paralysis. This carbonic anhydrase inhibitor was first used in familial hyperkalemic periodic paralysis (MacArdle, 1962) because of its kaliuretic effect. Acetazolamide was found efficient as well in the prophylaxis of hypokalemic periodic paralysis (Resnick et al., 1968). One still wonders about its exact role in periodic paralysis. An unexpected dissociation of glucose and potassium arterial-venous differences by acetazolamide has just been reported (Riggs et al., 1984). Acetazolamide is well known for its anticonvulsive action (Woodbury, 1980) but it is also effective on myotonia (Griggs et al., 1978), as are other anticonvulsive agents such as taurine (Durelli et al., 1983) and phenytoin.

The fundamental role of CA in glial cell metabolism has been known for many years (Maren, 1967; Woodbury, 1980). By reversibly catalyzing the hydration of CO to carbonic acid which then spontaneously dissociates into HCO 3⁻ + H⁺, the enzyme closely regulates glial pH and the intracellular ionized bicarbonate concentration. The bicarbonate ion undergoes exchange with extracellular Cl⁻, a process which is accompanied by influx of Na and water. Under circumstances where glia have a problem in ejecting water, carbonic anhydrase activity may therefore promote glial swelling, with pathological consequences. Glutamine synthesis within the CNS is considered to be the exclusive domain of glia and release of glutamine has been proposed to represent the primary mechanism by which glia redress the water balance following CA mediated water influx (van Gelder, 1983). A familial trait or an acquired insufficiency in the complex metabolic cycle leading to glutamine synthesis and release, during stimulated CA activity, may cause periodic swelling of the satellite cells. In at least one form of familial cerebellar ataxia, an abnormality in glutamic acid metabolism has been reported: the amino acid represents the principal substrate for glutamine synthesis.
by inhibition of CA or by some effect on the enzymes concerned with pyruvate metabolism (Evans et al., 1978). That metabolism is however very sensitive to cellular pH changes. The same point can be made about acetazolamide in the treatment of periodic ataxia.

Although generally well tolerated, acetazolamide may cause a number of side-effects. Paresthesias and renal calculi are common in the first few weeks of treatment as in case one in the present report. Paresthesias faded out with reduction of dosage and crystalluria disappeared with better water intake. If more serious side effects would arise, we would like to suggest that a substance with some analogous effects such as taurine could be tried. Whether or not physostigmine might be efficient in stopping or preventing the spells in periodic ataxia has not been evaluated and we plan to answer this question in the future.

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REFERENCES


