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Acetazolamide-responsive Hereditary Paroxysmal Ataxia : Report of a Family

Hereditary paroxysmal ataxia is a rare dominantly inherited disorder characterized by recurrent attacks of cerebellar ataxia, dysarthria, and nystagmus. Each attack lasts from several minutes to few hours or days. Usually there are no motor difficulties between attacks. We report a patient who had had recurrent ataxic episodes since early childhood. Four members of the family over two generations had similar attacks. There were no abnormalities in the laboratory studies including plasma amino acid, lactate, pyruvate, and EEG. Treatment with acetazolamide resulted in complete abolition of the attacks. Because of its dramatic response to acetazolamide, the recognition of this rare disorder is important.

Key Words : *Paroxysmal ataxia, Nystagmus, Acetazolamide*

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INTRODUCTION

Hereditary paroxysmal ataxia was first described by Parker in 1946 (1). It is inherited as an autosomal dominant trait. This disorder is characterized by recurrent episodes of disabling cerebellar dysfunction with gait and limb ataxia, dysarthria, and nystagmus. The episodes occasionally include nausea, vomiting, oscillopsia, and rarely tinnitus and blurred vision. The attacks last several minutes to few hours or days. Onset is usually in early childhood, but few cases have started after age 40 (2-4). The recurrent ataxic episodes do not lead to progressive permanent neurological deficit, although exceptions have been reported (3, 5). Precipitating factors are often present, which include fatigue, physical exercise, emotional stress, coffee, and alcohol. This disorder is very rare, and there have been only few reports since its original description by Parker (1). Only one family has been reported in an abstract form in Korea (6). However, unfamiliarity with this entity often leads to misdiagnosis as in our case, and this disorder may be more common than is currently appreciated. This becomes a very important issue as there is a specific treatment.

CASE REPORT

A 55-year-old man had been suffered from recurrent episodes of severe ataxia and dysarthria since age 15. The episodic symptoms lasted from 1 to 3 hours and recurred once a month. The attacks would start with severe incoordination of the legs and difficulty in walking. Then his speech became dysarthric, and his hand movement clumsy. There was neither alteration of consciousness, strength, and sensation nor convulsive movement. Sometimes he experienced blurred vision or an unpleasant feeling in his legs as prodromal symptoms. The attacks were often precipitated by emotional stress or exertion, and were relieved by rest. As full recovery would follow without specific treatment, he did not seek medical help until recently. As he had had more frequent, prolonged, and severe attacks since age 50, he then visited a hospital, and was started on phenytoin under the diagnosis of epilepsy. The attacks became much more frequent and severe on phenytoin, and he was referred to us.

When examined between attacks, his general physical and neurological examinations were normal including cerebellar function except a subtle horizontal nystagmus on extreme lateral gaze. Blood cell counts, serum sodium, potassium, chloride, total CO_2, calcium, magnesium, urinalysis, thyroid function test, parathyroid hormone, lactic acid, peripheral blood smear, electrocardiogram, chest X-ray, electroencephalography (waking, sleep & during attack), electromyography and nerve conduction studies were all normal. He had mild hypercholesterolemia. Brain MRI showed a small lacune in the left basal ganglia, and mild diffuse cortical atrophy. There was no atrophy of cerebellar vermis. 99 m-Tc-HMPAO brain perfusion SPECT during a symptom-free interval showed nonspecific relative hyperperfusion in the bifrontal area.

Two attacks were observed. He complained of vague unsteadiness, and then gradually developed full blown cerebellar dysfunction over 10-30 mins. The attacks plateaued for about 30 mins, then abated. On examination during the attacks, he was fully alert with intact cognitive function. His speech was severely dysarthric, and difficult to understand. There was marked nystagmus in all directions of gaze, including the primary position. Severe ataxia was present in both arms and legs, and rapid alternating movements were impossible. Gait was severely ataxic, and he was not able to stand without support. There were no clonic or dystonic movements in the limbs. Although muscle tone diminished, strength, sensation, and reflexes remained unchanged. Blood tests during the attack, including lactate, glucose, blood gas, and electrolytes were all normal. Acetazolamide was started at 250 mg/day and gradually increased to 750 mg/day. He noted a decreased frequency and severity of the attacks even on the small dose but felt that the full dose was better. While on medication, he had vague unsteadiness which only rarely interfere with his physical activity. When medication was withdrawn, the attacks returned to the previous state.

Family history revealed that there were four other members with similar clinical features (See Fig. 1 for the pedigree). His 29 year old son (II-3) was interviewed and examined. He had begun to have recurrent episodes of unsteadiness in his early teens. The attacks were unpredictable in occurrence with an usual frequency of once or twice a month. He generally had prodromal symptoms of vague discomfort in the morning, and then had very severe attacks of unsteadiness. During the attacks, he reported that he was not even able to sit unassisted. He described the severe dysarthria as that of a drunken man. More severe spells lasted longer up to several hours. We were not able to observe him during the attacks. His eldest daughter (II-2, age 31) reportedly had the same spells of inability to stand and walk and dysarthria. This individual was not able to be contacted. The elder brother (I-1) and niece (II-1) of the proband reported had exactly the same clinical features, but were not able to be contacted. The younger daughter of the proband (II-4, age 24) had other paroxysmal disorder, migraine. She had intermittent episodes of severe headache and nausea. There were no visual symptoms. She was tried on acetazolamide without benefit. Propranolol improved her headache markedly.

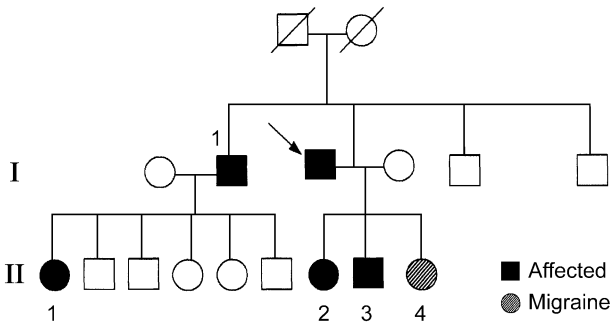

Fig. 1. Pedigree of the family. The proband is indicated by an arrow.

DISCUSSION

When a patient presents with recurrent and paroxysmal neurological symptoms and signs, seizure is the main differential diagnosis. However, prolonged generalized motor disability with preserved consciousness, and no clonic movements make seizure unlikely. Onset age, frequency, and no residual deficit after repeated spells exclude vertebrobasilar insufficiency. Absence of headache makes basilar migraine unlikely. Vestibular disorders are not likely in view of dysarthria. The clinical features and family history in our patient are most consistent with autosomal dominant paroxysmal ataxia. The favorable response to acetazolamide further supports the diagnosis. Paroxysmal ataxia may be a manifestation of autosomal recessive or X-linked inborn errors of metabolism such as Hartnup disease (7), pyruvate decarboxylase deficiency (8), pyruvate dehydrogenase deficiency (9), maple syrup urine disease (10), and defect of ammonia metabolism (11). There is one report of acetazolamide-response periodic sensory ataxia which was caused by pyruvate dehydrogenase deficiency (12). However, all these diseases can be easily distinguished from the dominantly inherited paroxysmal ataxia, by their inheritance pattern and obvious differences in their clinical and biochemical profiles. Griggs et al. reported that plasma pyruvate, lactate, glucose, electrolytes, and arterial pH, oxygen, carbon dioxide and bicarbonate were normal during attacks in familial paroxysmal ataxia responsive to acetazolamide as in our case (13). In autosomal dominant paroxysmal ataxia, clinical heterogeneity has been recognized (5). Classification based on the duration of attacks, and the nature of the ictal and interictal signs has been proposed and is gaining support from genetic studies. Type I is paroxysmal ataxia associated with myokymia or myotonia (14, 15). Ataxic episodes last a few seconds to minutes, and are provoked by startle and exercise. In general, treatment with acetazolamide is of no therapeutic value. Anticonvulsants may reduce the myokymia and attacks in some patients (5, 16). Point mutations in the potassium channel gene, KCNA1, on chromosome 12 p have been found in this type (17). Type II is paroxysmal ataxia asso-

ciated with nystagmus as in our case (2, 4, 10, 13, 18-22). Attacks are more prolonged and can last hours and even days. The most important feature is a favorable response to acetazolamide. Linkage analysis of type II excluded the 12 p locus, and established that type II is not allelic to type I (23). The gene responsible for type II has been mapped to chromosome 19 p (24, 25). Type III is kinesigenic paroxysmal ataxia with choreoathetosis (26, 27). In this type, the attacks consist of ataxia as well as dystonic posturing of the limbs, and usually are not responsive to acetazolamide. Many patients in kindreds with familial hemiplegic migraine have had progressive ataxia and nystagmus similar to that in paroxysmal ataxia, though the migraine patients have not had ataxic attacks (28). Linkage analysis showed that paroxysmal ataxia associated with nystagmus was linked to the same region of chromosome 19 raising the possibility that paroxysmal ataxia is allelic to familial hemiplegic migraine. There are marked clinical differences between familial hemiplegic migraine and paroxysmal ataxia, however, there is a precedent for such marked differing phenotypes being allelic disorders in ion channel diseases (29). However, migraine in the daughter of the proband is not believed to be a manifestation of paroxysmal ataxia gene. The nature of the migraine was a common migraine, not a hemiplegic variant, and did not improve with acetazolamide. Cerebral computed tomography (CT) scans are generally unremarkable (3-5, 19, 20). A selective atrophy of the cerebellar vermis, mostly of the anterosuperior part has been demonstrated by MRI in a few patients (30). There was no cerebellar atrophy on MRI in our patient. The lacune in the left basal ganglia was thought to be an asymptomatic stroke and not related to his neurological problem. Bifrontal hyperperfusion on SPECT during interictal period was seen in our patient, but the significance is not known. We failed to obtain ictal SPECT. The molecular basis of type II autosomal dominant paroxysmal ataxia is not known. It is known that there may be a selective dysfunction of the cerebellar vermis in partial defect in pyruvate dehydrogenase enzyme complex as anterior cerebellar vermis has the lowest pyruvate oxidation rate (31). Such a proposal of a biochemically vulnerable region is topographically consistent with the area of major atrophy demonstrated in some patients. There is one report of metabolic and anatomic abnormalities in familial intermittent ataxia (9). However, pyruvate and lactate levels were normal during the attack (12) as were in our patient, making pyruvate metabolism unlikely candidate. Another possible candidate is channelopathy. Four types of inherited ion-channel disorders have been described: sodium channel disorders producing hyperkalemic periodic paralysis, paramyotonia, myotonia fluctuans (29); calcium channel disorder producing hypokalemic periodic paralysis (32); chloride channel disorders producing myotonia congenita (29); and potassium channel disorder producing paroxysmal ataxia with myokymia (17). There are some clinical differences between these channelopathies, and different phenotypes are possible in same channel disorders. However, all these channelopathies have two common features; all produce paroxysmal symptoms, and respond well to acetazolamide. Therefore, it is tempting to suspect that paroxysmal ataxia with nystagmus is an ion channel disorder even though direct evidence is lacking (33). Bain et al. (34) reported that paroxysmal ataxia might be due to a defect in cerebellar intracellular pH homeostasis. Using phosphorus 31 (^{31}P) nuclear MR spectroscopy, they showed abnormally high intracellular pH levels in the cerebellum of six patients with paroxysmal ataxia when they were not treated. The pH returned to normal by treatment with acetazolamide. Cerebral pH was normal before and after treatment. It is not clear how pH is altered in the cerebellum. The mechanism of acetazolamide is not known. The correction of abnormal intracellular cerebellar pH homeostasis by acetazolamide has been suggested (34). Another suggestion is an intracellular effect on enzyme systems. Acetazolamide inhibits carbonic anhydrase, which catalyzes the interconversion of CO_2 and H_2CO_3. So it reduces arterial pH, Pco_2 and also reduces the amount of brain lactate and pyruvate, resulting in brain acidosis. Therefore the beneficial effect of acetazolamide may result from an effect on brain pyruvate and lactate metabolism. However there is no evidence of abnormal lactate and pyruvate metabolism. Although there are many unsolved questions, recognition of this disorder is important because of its dramatic response to acetazolamide. Identification of more families will facilitate identification of the gene locus and gene itself, and help solve the questions pertaining to this disorder.

ADDENDUM

We suggested that paroxysmal ataxia with nystagmus (episodic ataxia type 2, EA-2) is allelic to familial hemiplegic migraine and an ion channel disorder. After submission of the paper, significant new findings concerning our suggestion have emerged. Ophoff et al. identified that familial hemiplegic migraine and EA-2 are caused by point mutations in the brain-specific P/Q type voltage-dependent calcium channel alpha 1A subunit gene (35). Recently many reports demonstrated that SCA6 is allelic to EA-2 but that SCA6 is caused by a CAG expansion rather than a point mutation (36, 37, 38, 39, 40). However, the two disorders differ clinically because of the presence of progressive rather than episodic ataxia in SCA6.

REFERENCES

1. Parker HL. *Periodic Ataxia. Mayo Clinic Proc 1946; 38: 642-5.*
2. Farmer TW, Mustian VM. *Vestibulocerebellar ataxia. Arch Neurol 1963; 3: 471-80.*
3. Donat JR, Auger R. *Familial periodic ataxia. Arch Neurol 1979; 36: 568-9.*
4. Friedman JH, Hollman PA. *Acetazolamide responsive hereditary paroxysmal ataxia. Movement Disorders 1987; 2: 67-82.*
5. Gancher ST, Nutt JG. *Autosomal dominant episodic ataxia: a heterogeneous syndrome. Movement Disorders 1986; 1: 239-53.*
6. Oh HJ , Kwak KH, Do JK, Lee DK, Lee TH, Kim MS, Kim DW. *A family of familial periodic vertigo and ataxia (abstract). At the 9th Asian Oceanean Congress of Neurology, 1996.*
7. Baron DN, Dent CE, Harris H. *Hereditary pellagra-like skin rash with temporal cerebellar ataxia, constant renal aminoaciduria and other bizarre biochemical features. Lancet 1956; 2: 421-8.*
8. Blass JP, Avigan J, Uhlendorf BW. *A defect in pyruvate decarboxylase in a child with intermittent movement disorder. J Clin Invest 1970; 49: 423-32.*
9. Nespeca M, Evans OB, Rose J. *Metabolic and anatomic abnormalities in familial intermittent ataxia. Neurology 1987; 37 (suppl 1): 107.*
10. Dancis J, Hutztler J, Rokkones T. *Intermittent branched chain ketonuria: Variant of maple-syrup-urine disease. N Engl J Med 1967; 276: 84-9.*
11. Salam M. *Metabolic ataxias. In Vinken PJ, Bruyn GW, eds. Handbook of clinical neurology, Vol 21. Amsterdam: North-Holland, 1975: 573-85.*
12. Evans OB, Kilroy AW, Fenichel GM. *Acetazolamide in the treatment of pyruvate dysmetabolism syndromes. Arch Neurol 1978; 35: 302-5.*
13. Griggs RC, Moxley RT, Lafrance RA, McQuillen J. *Hereditary paroxysmal ataxia: response to acetazolamide. Neurology 1978; 28: 1259-64.*
14. Van Dyke DH, Griggs RC, Murphy MJ, Goldstein MN. *Hereditary myokymia and paroxysmal ataxia. J Neurol Sci 1975; 25: 109-18.*
15. Vaamonde J, Artieda J, Obeso JA. *Hereditary paroxysmal ataxia with neuromyotonia. Movement Disorders 1991; 6: 180-2.*
16. Brunt ERP, Van Weerden TW. *Familial paroxysmal kinesigenic ataxia and continuous myokymia. Brain 1990; 113: 1161- 382.*
17. Browne DL, Gancher ST, Nutt JG, Brunt ERP, Smith EA, Kramer PL. *Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA 1. Nature Genetics 1994; 8: 136-40.*
18. White JC. *Familial periodic nystagmus, vertigo, and ataxia. Arch Neurol 1969; 20: 276-80.*
19. Margolin DJ, Nutt JG, Lorrien E. *Familial periodic ataxia: clinical and genetic studies. Ann Neurol 1981; 10: 75.*
20. Zasorin NL, Baloh RW, Myers LB. *Acetazolamide-response episodic ataxia syndrome. Neurology 1983; 33: 1212-4.*
21. Baloch RW, Winder A. *Acetazolamide-responsive vestibulocerebellar syndrome: clinical and oculographic features. Neurology 1991; 41: 429-33.*
22. Hawkes CH. *Familial paroxysmal ataxia: report of a family. J Neurol Neurosurg Psychiatry 1992; 55: 212-3.*
23. Kramer PL, Litt M, Browne D, Promchotikul T, Brunt EP, Dubay CJ, Gancher S, Nutt J. *Autosomal dominant episodic ataxia represents at least two genetic disorders. Ann Neurol 1994; 36: 279.*
24. Kramer PL, Yue Q, Gancher ST, Nutt JG, Baloh R, Smith E, Browne D, Bussey K, Lovrien E, Nelson S. *A locus for the nystagmus-associated form of episodic ataxia maps to an 11-cM region on chromosome 19 p [letter]. Am J Hum Genet 1995; 57: 182-5.*
25. Vahedi K, Joutel A, Van Bogaert P, Ducros A, Maciazeck J, Bach JF, Bousser MG, Tournier-Lasserve E. *A gene for hereditary paroxysmal cerebellar ataxia maps to chromosome 19 p. Ann Neurol 1995; 37: 289-93.*
26. Mayeux R, Fahn S. *Paroxysmal dystonic choreoathetosis in a patient with familial ataxia. Neurology 1982; 32: 1184-6.*
27. Graff-Radford NR. *A recessively inherited ataxia with episodes of dystonia. J Neurol Neurosurg Psychiatry 1986; 49: 591-4.*
28. Joutel A, Bousser MG, Biousse V, Labauge P, Chabriat H, Nibbio A, Maciazek J, Meyer B, Bach MA, Weissenbach J. *A gene for familial hemiplegic migraine maps to chromosome 19. Nature Genetics 1993; 5: 40-5.*
29. Ptacek LJ, Johnson KJ, Griggs RC. *Mechanisms of disease: genetics and physiology of the myotonic muscle disorders. N Engl J Med 1993; 328: 482-9.*
30. Vighetto A, Froment JC, Trillet M, Aimard G. *Magnetic resonance imaging in familial paroxysmal ataxia. Arch Neurol 1988; 45: 547-9.*
31. Reynolds SF, Blass JP. *A possible mechanism for selective cerebellar damage in partial pyruvate dehydrogenase deficiency. Neurology 1976; 26: 625-8.*
32. Ptacek LJ, Tawil R, Griggs RC, Engel AG, Layzer RB, Kwiencinski H, McManis PG, Stentingo L, Moore M. *Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. Cell 1994; 77: 863-8.*
33. Griggs RC, Nutt JC. *Episodic ataxias as channelopathies. Ann Neurol 1995; 37: 285-7.*
34. Bain PG, O'Brien MD, Keevil SF, Porter DA. *Familial periodic cerebellar ataxia; a problem of cerebellar intracellular pH homeostasis. Ann Neurol 1992; 31: 147-54.*
35. Ophoff RA, Terwindt GM, Vergouwe MN, Frants RR, Ferrari MD. *Involvement of a calcium channel gene in familial hemiplegic migraine and migraine with and without aura. Dutch Migraine Genetics Research Group. Headache 1997; 37: 479-85.*
36. Zhuchenko O, Bailey J, Bonnen P, Ashizawa T, Stockton DW, Amos C, Dobyns WB, Subramony SH, Zoghbi HY, Lee CC. *Autosomal dominant cerebellar ataxia (SCA6) associated with the small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel. Nature Genet 1997; 15: 62-9.*
37. Krebsova A, Macek M Sen, Klockgether T, Zuhlke C, Laccone

FA. *SCA6 is caused by moderate CAG expansion in the alpha1A-voltage-dependent calcium channel gene. Hum Mol Genet 1997; 6: 1289-93.*

38. Jodice C, Mantuano E, Veneziano L, Trettel F, Sabbadini G, Calandriello L, Francia A, Spadaro M, Pierelli F, Salvi F, Ophoff RA, Frants RR, Frontali M. *Episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) due to CAG repeat expansion in the CACNA1A gene on chromosome 19p. Hum Mol Genet 1997; 6: 1973-8.*
39. Stevanin G, Durr A, David G, Didierjean O, Cancel G, Rivaud S, Tourbah A, Warter JM, Agid Y, Brice A. *Clinical and molecular features of spinocerebellar ataxia type 6. Neurology 1997; 49: 1243-6.*
40. Geschwind DH, Perlman S, Figueroa KP, Karrim J, Baloh RW, Pulst SM. *Spinocerebellar ataxia type 6. Frequency of the mutation and genotype-phenotype correlations. Neurology 1997; 49: 1247-51.*