Hereditary myokymia and paroxysmal ataxia linked to chromosome 12 is responsive to acetazolamide

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Abstract
A sixth family with autosomal dominantly inherited myokymia and paroxysmal ataxia is described. The syndrome in this family is linked to the recently discovered locus for inherited myokymia and paroxysmal ataxia on the human chromosome 12p, and a missense mutation is shown in the KCNA1 gene. The attacks of ataxia in this family compare well with those of previously described families and similarly are precipitated by kinesigenic stimuli, exertion, and startle. Responsiveness of these attacks to low dose acetazolamide is confirmed, but some loss of efficacy occurs with prolonged treatment, and side effects are notable. Although not all affected family members showed myokymia on clinical examination, electromyography invariably showed myokymic discharges, in one patient only after a short provocation with regional ischaemia. One affected family member also had attacks of paroxysmal kinesigenic choreoathetosis, responsive to carbamazepine.

Autosomal dominantly inherited episodic ataxias can be classified in two main categories according to the presence or absence of myokymia.[1] Since the first paper by Parker, familial periodic ataxia, without myokymia, has been described in about 25 families.[2 3]

Patients with familial periodic ataxia experience episodes of limb and gait ataxia, vertigo, nausea, and sometimes headache, usually lasting for hours. The attacks are brought on by emotional stress, fatigue, exercise, alcohol, carbohydrate intake, and menstrual periods. Kinesigenic provocation is uncommon, and attacks do not follow a sensory aura. As a rule, nystagmus is present both during and between the attacks. Progressive ataxia, a disorder of pyruvate metabolism, or localised atrophy of the vermis has been found in a few cases. Carbonic anhydrase inhibiting drugs such as acetazolamide and sulthiame, but also phenytoin and various other drugs are effective in the prevention of attacks.[1 3–5]

Hereditary myokymia and paroxysmal ataxia or episodic ataxia and myokymia was first described in 1975 by Van Dyke *et al* with

additional reports of four other families.[1 6–9] In hereditary myokymia and paroxysmal ataxia, patients experience short attacks, lasting up to 15 minutes, which consist of generalised ataxia, slowing of movements, and variably pronounced trembling or shaking. Kinesigenic provocation, often by an axial movement after a period of rest, and a short sensory warning are common. True vertigo and nystagmus are absent, both during and between attacks.

The myokymia or neuromyotonia ranges from minute movements found in relaxed unsupported fingers to obvious stiffening of the hands and feet. Sometimes EMG is needed for its detection.[8] In hereditary myokymia and paroxysmal ataxia, myokymia has been shown to be of multifocal peripheral nerve origin, possibly caused by spontaneous and prolonged axonal depolarisation.[8 10] Phenytoin is variably effective in the prevention of ataxia.[1 6–8] A favourable response to carbonic anhydrase inhibiting drugs has not yet been confirmed, and is refuted in a recent review.[8 11] Although phenytoin and carbonic anhydrase inhibiting drugs act similarly in the prevention of ataxia, their effect on myokymia seems to be different, as phenytoin reduced myokymia in pronounced disease, but acetazolamide and sulthiame caused an increase of stiffness in patients with less pronounced myokymia.[6–8]

After localisation of the trait for episodic ataxia and myokymia, or hereditary myokymia and paroxysmal ataxia, to chromosome 12p, different point mutations in the gene coding for the voltage dependent potassium channel KCNA1 in four unrelated families have recently been reported.[12 13]

We present the clinical, genetic, and EMG findings of an additional family with hereditary myokymia and paroxysmal ataxia.

Methods
All affected family members were neurologically examined. Attacks were brought on by repeated knee bends or sudden rising from a chair. For EEG we used silver-silver chloride scalp electrodes placed according to the international 10–20 system. Serum lactate and pyruvate concentrations were measured during standardised exercise.[14] We used Medelec SE20 surface electrodes to scan for the presence of myokymic discharges before concentric needle EMG. Local ischaemia was applied by inflation of a blood pressure cuff around the upper arm to 220 mm Hg for

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Received 9 February 1995
and in revised form
16 May 1995
Accepted 1 June 1995

three minutes. After informed consent, DNA of affected and non-affected family members was isolated from peripheral blood and typed with the markers D12S100, D12S372, D12S1088, KCNA5, and D12S99.[12 13] The effect of medication was evaluated by comparison of the number and severity of attacks in ensuing periods with and without open label treatment.

DESCRIPTION OF PATIENTS
Patient 1 (IV-7)
The proband, a 20 year old woman, had attacks of "swinging legs" and dizziness during which she experienced involuntary jerky limb movements, dysarthria, and gait ataxia. Sometimes, a sudden sensation in her neck, which within seconds spread over her body, marked the onset of an attack. First noticed at the age of 6, the attacks occurred often three or four times daily, lasting from 10 seconds to five minutes, with varied intensity. On one occasion a prolonged attack with considerable leg jerks during a period of fever had prompted admission to hospital. Attacks happened at rest but more often occurred during exercise or when the patient was startled, standing up, running, slipping, or carrying a heavy bag. The attacks had resulted in a phobic avoidance of public appearances for which she had been treated with clomipramine by a psychiatrist. She also experienced episodes of stiffening of her right hand with her thumb forced inward. These episodes lasted from minutes to hours and occurred mainly during sustained use of her arm.

Examination—Neurological examination showed normal eye movements without nystagmus, and normal coordination, muscle strength, sensation, and reflexes. Rippling of the skin was present in the first interosseous space of both hands, and pendent fingers showed small semirhythmical, lateral movements.

Witnessed attack—During an attack (provoked by five knee bends) that lasted about three minutes, she had rhythmic involuntary shaking of arms and legs that put her off balance. A finger-to-nose test showed a kinetic tremor and dysmetria. A spontaneous or gaze evoked nystagmus was absent. Half an hour later another attack occurred after 20 knee bends, and showed a gradual build up with continued provocation. Rising quickly after a hand clap failed to provoke an attack.

Treatment and follow up—During treatment with acetazolamide no attacks occurred for three days, but then reappeared once or twice a day, at about half the original frequency. This partial effect remained for over three months. When on acetazolamide treatment, performance of knee bends did not provoke an attack and she was able to engage in new activities. After an interruption of the acetazolamide medication she had many long attacks, again easily provoked by exercise. Prevention of attacks and paraesthesiae were obviously both dose related, with an optimal dose of 187

mg/day. Paraesthesiae could be reduced by supplementation with 2 g potassium daily.

Patient 2 (IV-6)
The 22 year old brother of the proband had experienced attacks of dizziness since the age of 6 years, manifesting limb and gait incoordination and dysarthria. The attacks were brought on by sudden movements, lasted for about two minutes, and happened about once daily. At the age of 15, after a mild head injury, he also developed attacks of stereotyped dystonic movements that lasted about 10 seconds, and occurred up to 20 times a day. Usually, these dystonic movements involved the right arm with variable inclusion of the face and leg, but they also happened in the left arm, or involved both sides. As with the dizziness, these attacks were provoked by sudden rising, limping, and other quick movements, but could also be provoked by voluntary contraction of his right thigh muscles. The dystonic attacks started with paraesthesiae in the ulnar side of the right hand. A vague awareness, lasting many hours, indicated proneness for these dystonic attacks. At times, attacks of dystonia and of ataxia coincided, brought on by the same kinesigenic stimulus. Treatment with 400 mg carbamazepine a day effectively reduced the dystonic attacks to less than one a day, but did not obviously reduce the occurrence of ataxia. The patient had a history of finger trembling that diminished during treatment with fluvoxamine for anxiety.

Examination—Neurological examination with special attention to eye movements and coordination was normal. Myokymia was not detected clinically.

Treatment and follow up—Medication with only 62·5 mg acetazolamide once daily caused pronounced paraesthesiae and was discontinued before its effect could be assessed.

Results
Figure 1 shows the relevant data on pedigree and genotype. Table 1 shows characteristics of the affected family members. The attacks were first noticed in childhood, showed a maximum in the second decade, and declined with increasing age. Ataxia was often preceded by a sensory warning and usually built up within 10 seconds followed by a more gradual decline. The shaking that accompanied the ataxia could be slight or pronounced. Several circumstances influenced the occurrence of attacks, and people could often sense a certain proneness. Attempts to provoke an attack by repeated knee bends or sudden rising were uncomfortable and often not successful.

EXAMINATION AND WITNESSED ATTACKS
Apart from the presence of myokymia, neurological examination between attacks was normal in all affected members. Rippling of

Figure 1 Relevant part of the pedigree. Affected people are represented with black symbols. The genotypic data of chromosome 12p markers are shown below each symbol. The following markers are represented:
A = D12S100,
B = D12S372,
C = D12S1088,
D = KCNA5, and
E = D12S99.
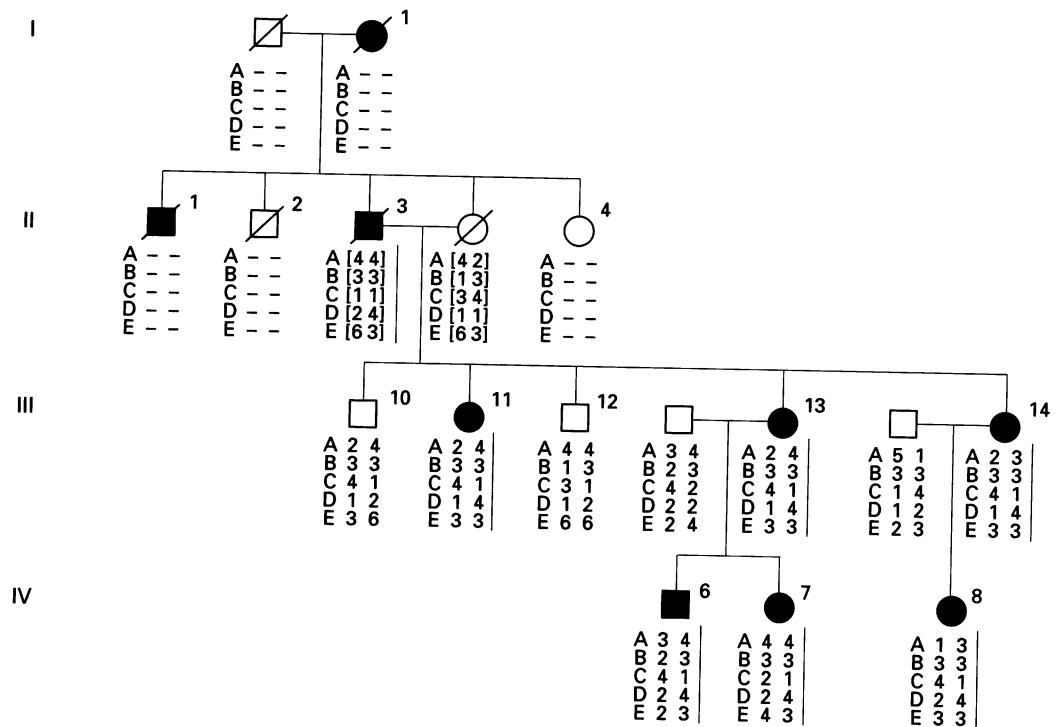
the skin and lateral finger movements indicated myokymia in three of the six patients. In one patient (III-14) the finger movements were semirhythmic in a lateral direction, similar to the appearance of myokymia in the family previously described by us.[8] In two other patients (IV-7 and IV-8) involuntary activity was different, with intermittent, unpredictable small jerky finger movements that we did not at first recognise as a myokymic manifestation. A minor attack witnessed in patient III-13, consisted of an uncomfortable feeling and inability to move freely but without visible ataxia or tremor.

LACTATE AND PYRUVATE TEST
Serum lactate and pyruvate concentrations in cases III-13, IV-6, and IV-7 were within the normal range.

ELECTROENCEPHALOGRAPHY
An EEG of patient IV-7 before and during a provoked attack was normal. An EEG registration of patient IV-6 in 1989 showed lateralised left temporal slowing, unchanged during provoked attacks of dystonia.

Table 1 Data of affected family members

	Patient					
	III-11	*III-13*	*III-14*	*IV-6**	*IV-7*	*IV-8*
Age (y)	52	42	37	22	20	18
Ataxia:						
Age of onset (y)	6	6	5	6	6	4
Attenuation (y)	>20	>16	?	—	>18	>17
Frequency	2–3/week	4–10/day	2/day	2–3/week	3–4/day	2–3/week
Duration	1–5 min	1–5 min	1–5 min	2 min–3 h	10 s–5–min	2–3 min
Sensory aura	+	+	+	+	+	+
Subjective sensations	Diplopia Weakness	Nausea Diplopia Stiffness	Sweating "Dizziness"	Oscillopsia "Dizziness"	Nausea "Dizziness" Carpal spasm	"Dizziness"
Movement coordination	Gait and limb ataxia	Gait and limb ataxia	Gait and limb ataxia shaking limbs	Gait and limb ataxia jerky movements	Gait and limb ataxia	Gait and limb ataxia trembling
Provocation:						
"Spontaneous"	+	+	+	+	+	+
Sudden movements	+	+	+	+	+	+
Exertion	+	+	+	—	+	+
Additional influences	Menses startle	Menses illness,	Emotional stress Smell of food	Emotional stress	Startle	Startle
Examination:						
Nystagmus	—	—	—	—	—	—
Ataxia	—	—	—	—	—	—
Myokymia	—	—	+ (rhythmic)	—	+ (jerky and rhythmic)	+ (jerky and rhythmic)
Myokymia on EMG	+	+	+	+	+	+
Treatment with acetazolamide:						
Dose (mg)	63	125	63	63	188	31
Effect†	?	+	+	?	+	?

*IV-6 also paroxysmal kinesigenic choreoathetosis.
†? = effect could not be evaluated, as treatent was not tolerated; + = attacks reduced by more than half.
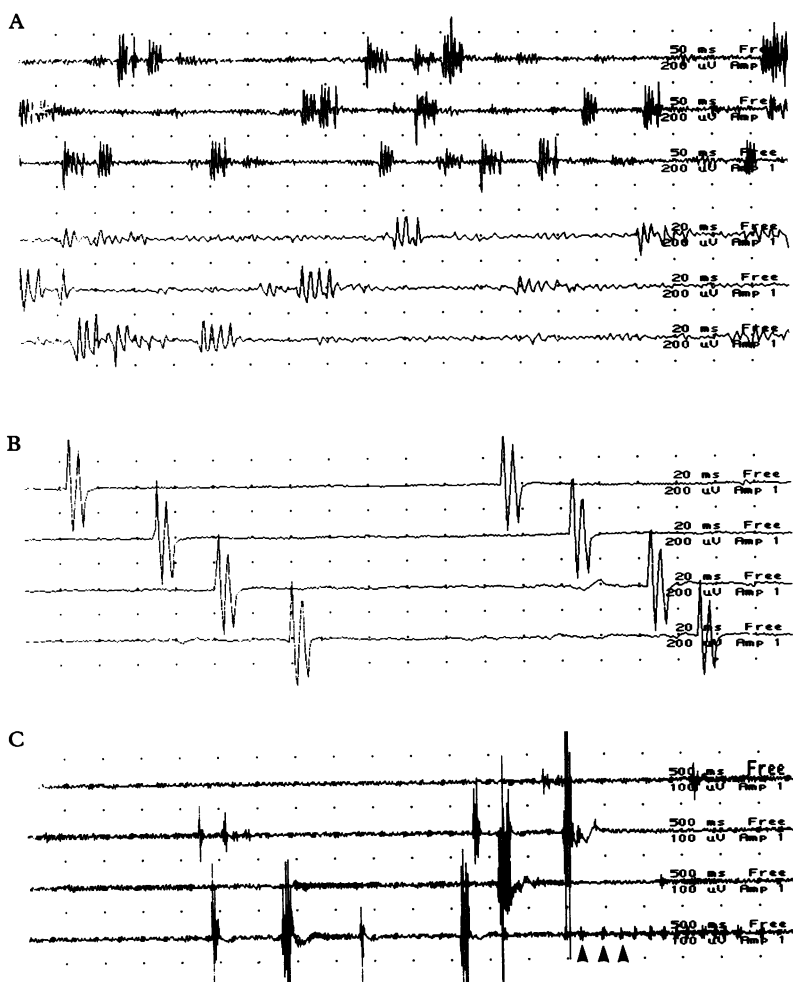
A

B

C

Figure 2   EMG recording of spontaneous muscle activity. (A) Different independently occurring multiplets. Surface recording from muscle abductor pollicis brevis, patient IV-7. (B) Single rhythmically occurring duplet, brought on by three minutes of local ischaemia. Concentric needle recording from muscle abductor digiti quinti, patient IV-6. (C) Irregularly occurring bursts causing small jerky finger movements. Spontaneous myokymic activity marked by ▲ *Surface recording from first dorsal interosseous muscle, patient IV-8.*

ELECTROMYOGRAPHY

All but one (IV-6) of the affected members showed resting EMG activity in the hand and lower arm muscles. In three patients (III-11, III-13, III-14) myokymic activity consisted of rhythmically repeated, independently occurring singlets and multiplets of relatively low amplitude (up to 600 μV), with a frequency of 2–5/s and a spike interval of 5–10 ms (fig 2A). During three minutes of ischaemia, some myokymic discharges showed a gradual two to threefold rise in frequency, which returned to baseline after deflation. After ischaemia additional myokymic discharges were recruited, and myokymic discharges, in which the fre-

quency had risen, increased in length. Volitional contraction during 10–15 seconds interrupted the myokymic activity for one or two seconds, but a short, jerk-like contraction could start myokymic activity that had not been previously present. In patient IV-6, in whom we were unable to detect myokymia by EMG, three minutes of regional ischaemia brought on typical repetitive myokymic activity (fig 2B). In patients IV-7 and IV-8, with more jerky involuntary finger movements, electromyography showed irregularly repeated complex bursts of about 50–100 ms with varying shape as well as the repetitive myokymic activity (fig 2C).

LINKAGE STUDIES

With markers closely linked to the hereditary myokymia and paroxysmal ataxia locus, we show linkage in this family to chromosome 12p (fig 1). No crossover was identified, and in patient III-14, a mutation apparently resulted in a new allele for marker D12S100. Table 2 shows the calculated pairwise lod scores for linkage.

Sequencing of the KCNA1 gene identified a Glu325Asp missense mutation, detailed findings of which will be presented elsewhere.[15]

TREATMENT AND FOLLOW UP

Treatment with acetazolamide was initiated in all affected family members. Paraesthesiae occurred in all patients, even at a low dose, and caused the medication to be stopped in three patients with relatively few attacks. The paraesthesiae appeared about 15 minutes after the ingestion of acetazolamide and lasted for several hours. They could be diminished by oral potassium. Parallel to the occurrence of paraesthesiae, two patients noticed increased muscle stiffness. Relatively low doses of 63–188 mg acetazolamide a day were accepted by three patients (IV-7, III-13, and III-14), reducing both the number and the severity of attacks. This effect was obvious from the first day and lasted for about one day after the treatment ended. After one or two weeks of treatment about half of its initial efficacy was gradually lost. Stabilisation followed thereafter.

Discussion

The syndrome of hereditary myokymia and paroxysmal ataxia in this family compares well with the five families described previously.[1 6–9] Table 3 summarises the data. Obviously, the attacks in childhood may initially pass unrecognised. A kinesigenic provocation, occurring in five out of six families with hereditary myokymia and paroxysmal ataxia, may serve to differentiate within the episodic ataxias, although this is not mentioned in recent reviews.[3 11] Diminished physical activity and kinesigenic provocation may well play a part in the reduced occurrence of attacks after the teenage years. The presence of a sensory warning, mentioned in two other families with hereditary myokymia and paroxysmal ataxia,

Table 2   Lod scores for the 12p markers

	θ value						
	0·001	0·01	0·05	0·10	0·20	0·30	0·40
D12S1088	0·60	0·59	0·56	0·51	0·41	0·29	0·16
KCNA5	2·10	2·07	1·93	1·74	1·33	0·87	0·39
D12S99	0·90	0·86	0·81	0·72	0·51	0·30	0·09

No Lod score was calculated for D12S100 due to the occurrence of a new allele in patient III-14. Marker D12S372 was not informative. The map distances for the markers used are D12S100-4cM-D12S372-3cM-D12S1088-1cM-KCNA5-1cM-D12S99.[12]

Table 3 *Familial paroxysmal ataxia with continuous myokymia*

	Authors					
	Van Dyke et al[6] (1975)	Hanson et al[7] (1977)	Gancher and Nutt[1] (1986)	Brunt and Van Weerden[8] (1990)	Vaamonde et al[9] (1991)	Lubbers et al (1995)
Inheritance	AD	AD	AD	AD	AD	AD
Number:						
Reported	3	3	3	22	3	6
Examined	7	3	7	22	1	6
Affected	11	4	15	28	3	9
Ataxia:						
Age of onset (y)	2–12	4–8	6–15	2–15	6	4–6
Attenuation (y)	?	?	>20	20–50	?	>20
Frequency	0–10/day	0–1/day	0–2/day	0–15/day	0–3/week	0–10/day
Duration	±3 min	10–15 min	±2 min	10 s–10 min (up to 6 h)	few min	10 s–5 min (up to 3 h)
Sensory aura	+	?	?	+	?	+
Subjective sensations	Vertigo, diplopia, blurred vision	Eyes drawn backward, weakness legs	Weightlessness, sensation of falling	Limb stiffness, heavy feeling, ±blurred vision	Blurred vision	Dizziness weakness, stiffness
Movements, coordination	Generalised ataxia, jerking, nodding of head and arms	Generalised ataxia, shaking, staggering	Generalised ataxia, tremor?	Generalised ataxia, postural tremor of head and arms	Generalised ataxia?, jerking	Generalised ataxia, shaking trembling
Stiffening	Generalised myokymia, carpal spasm	Stiffening, cramp in body, arms and hands	Limb muscles twitching, puckering mouth	Few: stiffening hands	Spasm hand and foot	Stiffening hands, carpal spasm
Provocation	Kinesigenic + caloric stimulation +	Kinesigenic + caloric stimulation −	Kinesigenic ? exercise	Kinesigenic +	Kinesigenic +	Kinesigenic + exercise
Additional influences	Hunger, fatigue excitement, anxiety	Perimenstrual illness	Stress, fatigue, excitement	Startle, anxiousness, illness	Stress, fatigue, hyperventilation, illness	Startle, perimenstrual illness
Interval examination:						
Nystagmus	−	−	−	−	−	−
Ataxia	?	?	?	±: few, >50y	−	−
Myokymia	Face, hands, moving fingers, carpal spasm, calf hypertrophy	Resting tremor in body, hands (contractures)	Face distal limbs, moving fingers	Face, hands, pending finger movements (thumb adduction)	Skin rippling face, hands	Face, fingers, regular/jerky movements
EMG	CMUA	CMUA, Neuromyotonia	Neuromyotonia repetitive grouped discharges	Irregular/regular repetitive singlets multiplets	High frequency irregular singlets multiplets	irregular/regular repetitive singlets, multiplets (postischaemic)
Treatment:						
Phenytoin	Ataxia↓ Myokymia→	Ataxia↓ Myokymia→	Ataxia→ Myokymia↓	Ataxia→ Myokymia?	Ataxia ? Myokymia?	?
Acetazolamide	? ?	? ?	Ataxia→ Myokymia?	Ataxia↓ Myokymia↑	Ataxia→ Myokymia?	Ataxia↓ Myokymia↑

AD = autosomal dominant; CMUA = continuous motor unit activity; − = absent; ? = unknown; → = no change; ↑ = increase; ↓ = decrease.

and at times experienced by all members of the present family seems to be another feature that differentiates attacks in hereditary myokymia and paroxysmal ataxia from those in familial periodic ataxia.

The shaking of legs and trunk during an attack shown by one of the members of the present family was more pronounced than previously found by us, but has also been described in two other families with hereditary myokymia and paroxysmal ataxia.[6–8] The normal, unaltered EEG during one of the provoked attacks and the normal pyruvate and lactate are in line with previous findings.[6] The clinical and EMG manifestation and the reactivity of myokymia in this family compare well with our previously described family, with the exception of the irregular, choreiform jerky finger movements and non-repetitive long bursts on EMG in two affected members.[8] The provocation of myokymia by local ischaemia during three minutes extends the reported enhancement of myokymia after ischaemia, and seems to be a simple test to support the diagnosis in patients suspected to have hereditary myokymia and paroxysmal ataxia who have no spontaneous myokymic activity. In the EMG examination with surface electrodes on more than 25 affected people we have not previously encountered

absence of myokymic activity, although we found a wide variation between patients and over time. Myokymic activity brought about by ischaemia also widens this range. Obviously the amount of myokymic activity also varies between families.

Genetic linkage of episodic ataxia and myokymia (hereditary myokymia and paroxysmal ataxia) to loci D12S91, D12S100, CACNL1A1, D12S372, pY21–1 (=D12S1088), KCNA5, D12S93, and D12S99 on chromosome 12p was shown previously.[12] The linkage to the episodic ataxia and myokymia locus and the finding of another missense mutation in the KCNA1 gene groups this family with those previously described.[12–13]

The prevention of attacks of ataxia by acetazolamide in this family confirms our previous findings in hereditary myokymia and paroxysmal ataxia.[8] A reduced efficacy after some weeks has also been found in some patients of the first family that we studied. The early decline followed by a prolonged remaining efficacy suggests a metabolic adaptation rather than a placebo effect, but we have not found changes in laboratory values. The suppressive effect of acetazolamide may not occur in all families with hereditary myokymia and paroxysmal ataxia, but clearly

prevents its use to differentiate hereditary myokymia and paroxysmal ataxia from familial periodic ataxia as recently suggested.[1 9 11] Although not separating episodic ataxias with and without myokymia, Ptáček, commenting on the discovery of the KCNA1 channel mutation in hereditary myokymia and paroxysmal ataxia, drew attention to the shared favourable reaction to acetazolamide of diseases caused by mutations in cation channels.[16] The early occurrence of paraesthesiae and increase in muscle stiffness after the use of acetazolamide confirm earlier findings, and suggest an abnormal sensitivity to acetazolamide as part of the hereditary myokymia and paroxysmal ataxia syndrome.[8] We did not use phenytoin, which proved effective in two of the other families with hereditary myokymia and paroxysmal ataxia, in the present family.[6 7] The occurrence of attacks of paroxysmal kinesigenic choreoathetosis in one affected member (IV-6) is remarkable. The rarity of both conditions and the shared provocation suggest a relation, but the occurrence after a head trauma and different reaction to carbamazepine may argue for a different aetiology.[17 18 19] Gancher and Nutt have described one family (kindred V) in whom attacks of kinesigenic episodic ataxias and of paroxysmal kinesigenic choreoathetosis occurred separately in some members, and jointly in one[1]: in this person, the early manifestation of attacks of episodic ataxia at the age of 6 years, followed by the occurrence of attacks of paroxysmal kinesigenic choreoathetosis at the age of 15 years, closely parallel the temporal sequence in our case IV-7. The presence of myokymia in this family was not obvious at the time of this report, but was found later in some affected members (J Nutt, personal communication).

The observation of a second patient who had combined attacks of hereditary myokymia and paroxysmal ataxia and of paroxysmal kinesigenic choreoathetosis strengthens the suggestion that occurrence of these two types of attacks is not mere coincidence. Also, previous reports on episodic dystonia occurring in two families with progressive ataxia suggest a possible relation.[20 21]

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