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Autosomal dominant paroxysmal kinesigenic choreoathetosis: a clinical  
and genetic study of two families

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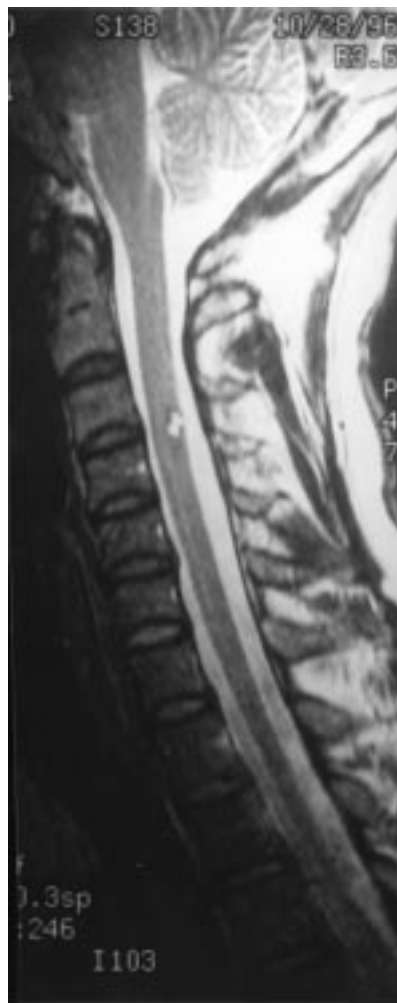
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thy, such as cervical spondylosis and epidural, subdural, and intraparenchymatous tumours. It has also been reported infrequently in radiation myelitis, pernicious anaemia (subacute combined degeneration), pyridoxine toxicity, nitrous oxide misuse, cisplatin and docetaxel neuropathies, cervical herpes zoster myelitis, paroxetine withdrawal, Behçet's disease, and systemic lupus erythematosus. Vascular disease of the cervical spine or intraspinal cord has never been noted to produce Lhermitte's sign.

A 48 year old left handed man presented with a history of a "burst, very brief electrical tingling" in the left forearm, hand, and lower leg for almost 2 years. The symptom occurred only on flexion of the neck and abated even when the neck was kept flexed. No other neck movements caused this symptom. A year later, the patient noted mild dysaesthesia in the left arm and leg. A sagittal heavily T2 weighted fast spin echo MR image of the cervical spine showed a small ovoid area of T2 hyperintensity within the posterior cervical spinal cord at the cervical 3-4 level with minimal mass effect. Subtle low signal intensity about its rim suggested hemosiderin deposition (figure). A few weeks later, after raking his yard, the patient experienced acute



Sagittal T2 weighted MRI (TR 3800/TE 96 ms) of the cervical spine shows a small ovoid area of T2 hyperintensity within the posterior cervical spinal cord at the cervical 3-4 level with minimal mass effect. Subtle low signal intensity about its rim suggests hemosiderin deposition.

neck pain. A day later, he noticed diminished coordination of the left arm and leg. A sagittal T2 weighted fast spin echo MRI of the cervical spine obtained a few days later showed an extensive intramedullary low signal intensity area in the midposterior spinal cord compatible with interval haemorrhage, spinal cord expansion, and oedema. Results of spinal angiography were normal. The pain resolved in 10 days, and only mild numbness in the left hand and to lesser degree in the foot persisted. At operation, the lesion was found to be a cavernous angioma. After resection of the malformation, sensory deficits in the left hand and foot worsened, and discomfort with an unpleasant sensation of swelling developed in the hand. For 1 month after the operation, the patient also complained of spontaneous "electrical bursts" in the right arm and both legs. Neurological examination 6 months after the operation disclosed mild weakness of the left arm and hand with diminished stretch reflexes and equivocal plantar response in the left foot. Abnormalities elicited in the sensory examination were decreased pain sensation in the left hand, mild attenuation of two point discrimination, and dysgraphaesthesia in the left fingertips. Mild sensory ataxia on finger to nose testing and mild pseudoathetotic movements of the left hand were also noted.

Lhermitte's sign is a common symptom in neurological practice. However, the pathophysiology of the sign is not well known. Because flexion of the neck causes the dysaesthetic symptoms, it has been suggested that an increased mechanical sensitivity of these damaged myelinated axons causes an abnormal origin or transmission of sensory information. In the cat model, deformation of experimentally demyelinated dorsal columns by <1 mm increased the frequency of action potentials in both spontaneously active and previously silent fibres.<sup>1</sup> Routine flexion of the neck can lengthen and deform the cervical cord slightly and provide synchronisation of a volley of aberrant activity in damaged dorsal column myelinated axons. Nordin *et al*<sup>2</sup> reported activation of multiple units in the neurogram of the median nerve, presumably arising from activated sensory fibres in the dorsal columns of a patient with Lhermitte's sign on flexion of the neck. As expected, multiple sclerosis is the most common cause of Lhermitte's sign, occurring in about one third of patients.<sup>3</sup> The sign, however, is not specific and may be present in other clinical conditions that compress or damage myelinated sensory axons of the dorsal columns of the cervical cord. Occasionally, Lhermitte's sign is the presenting complaint of the underlying medical cause.

To our knowledge, this is the first reported case of Lhermitte's sign caused by a vascular disease in the cervical spinal cord. It was, in fact, the presenting symptom in our patient. The pathological findings confirmed the MRI diagnosis as a cavernous angioma. It is probable that the underlying lesion acted by producing compression or ischaemia on the dorsal columns of the cervical spinal cord.

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#### Autosomal dominant paroxysmal kinesigenic choreoathetosis: a clinical and genetic study of two families

Paroxysmal kinesigenic choreoathetosis (PKC), characterised by brief attacks of abnormal involuntary movements induced by sudden voluntary movements, is either idiopathic (familial or sporadic) or symptomatic. A total of about 20 families with PKC have been reported, with autosomal dominant inheritance in most of them. No genetic study has been reported in familial PKC up to now.

We report two unrelated families with autosomal dominant PKC, in which we performed linkage analyses with loci involved in other paroxysmal movement disorders: (1) the locus for paroxysmal dystonic choreoathetosis (PDC), also known as paroxysmal nonkinesigenic dyskinesia, on chromosome 2q33-35,<sup>1</sup> (2) the locus for AD paroxysmal choreoathetosis/spasticity (CSE), classified as "complicated" PDC, on chromosome 1p,<sup>2</sup> and (3) the locus for episodic ataxia/myokymia (EA-1) on chromosome 12p13.<sup>3</sup>

Family A was Portuguese and family B was French. They contained a total of 10 affected and nine unaffected family members, who were all interviewed and examined by the same physician. There was no family history of epilepsy. In one family, three of the five affected members also had migraine with visual aura. Except for one patient, who had had a parkinsonian resting tremor since the age of 52, neurological examination was normal. The phenotypes of the 10 patients were very homogeneous. Age at onset of PKC attacks ranged from 1.5 to 13 years (median 6.5 years). Attacks occurred five to 20 times daily in nine patients and once a year in the other. Attacks were always triggered by a sudden movement of a lower limb (rising from a sitting position, running) that often occurred in response to an unexpected stimulus after sustained immobility. Embarrassment and stress were precipitating factors. In a few patients, fatigue, cold, or menstruation also favoured attacks. The latency between the triggering factor and dyskinesia was 0-2 seconds. Dyskinesias were usually preceded by a short aura (paraesthesias, n=4; muscular tension, n=5) in the affected hemibody. Duration of attacks was 3 to 40 seconds. Involuntary movements involved one side of the body, but sometimes extended rapidly to the whole body, with preservation of consciousness. During attacks, the intensity of the dyskinesias increased and decreased progressively. In addition to frequent dysarthria (n=7) related to orofacial dyskinesia, breathing problems (n=1) and falls (n=5) sometimes occurred during violent

Pairwise linkage analyses with markers from candidate regions on chromosomes 1p, 2q33-35, and 12p13 in two PKC families

Marker	Family	Lod score at $\theta =$						
		0.00	0.01	0.05	0.10	0.20	0.30	0.40
D1S197	A	-∞	-2.51	-1.16	-0.63	-0.18	-0.01	0.04
	B	-∞	-6.50	-3.72	-2.54	-1.39	-0.74	-0.31
D2S173	A	-∞	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	-∞	-0.81	-0.18	0.03	0.14	0.13	0.08
D2S163	A	-∞	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	-∞	-1.11	-0.44	-0.19	0.01	0.07	0.06
D2S377	A	-∞	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	0.30	0.29	0.26	0.21	0.13	0.06	0.02
D2S126	A	-∞	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	-∞	-2.81	-1.46	-0.93	-0.46	-0.23	-0.1
D12S77	A	-∞	-4.50	-2.44	-1.59	-0.79	-0.37	-0.13
	B	-∞	-4.80	-2.72	-1.84	-0.99	-0.52	-0.21
D12S99	A	-∞	-2.51	-1.16	-0.63	-0.18	-0.01	0.04
	B	-∞	-6.50	-3.72	-2.54	-1.39	-0.74	-0.31

attacks. One patient wore a helmet during early childhood because of frequent falls. Four out of 10 patients were treated with very low doses of carbamazepine (50–200 mg/day), which completely suppressed the attacks. In six patients who were not treated, however, the frequency of the attacks decreased progressively with age, usually between the ages of 18 and 30, and completely disappeared in five of them between the ages of 11 and 37. Three attacks (lasting 5–20 seconds) were recorded by video-EEG in one patient after carbamazepine withdrawal. No EEG abnormalities were found. Neuroimaging, performed in only four patients (two brain CT and two MRI), was normal.

Because of clinical similarities between PKC and some other paroxysmal movement disorders, we hypothesised that PKC may be allelic to them. Indeed, PDC is also characterised by attacks of mixed involuntary movements (dystonic, and often choreoathetotic), that typically begin as hemidystonia but progressively affect all limbs, trunk, and neck muscles, as well as speech, with preservation of consciousness. Attacks are often preceded by an aura and their frequency decreases with age. However, by contrast with PKC, PDC attacks occur at rest, are precipitated by caffeine and alcohol, not by sudden movements, and last for minutes to hours. In CSE, attacks are similar to those in PDC, except that physical exercise is a precipitating factor, and that some patients exhibit constant spastic paraplegia.<sup>2</sup> Finally, although EA-1 consists of continuous myokymia and attacks of generalised ataxia, often prevented by acetazolamide, some features are shared with PKC—namely, the frequent kinesigenic origin of the attacks, the presence of a sensory aura, the short duration of the attacks (several seconds to 5 minutes), and the early onset.<sup>4</sup> Moreover, an EA-1 family in which attacks of kinesigenic episodic ataxia and PKC occurred separately in some members, and jointly in one, has been reported.<sup>4</sup>

After isolation of DNA from peripheral blood, a series of microsatellite markers were typed on: (1) chromosome 2q (D2S164)-2cM-D2S173-2cM-D2S163-2cM-D2S377-1cM-D2S126 (the PDC locus is contained in a 7 cM region flanked by D2S164 and D2S126)<sup>1</sup>; (2) chromosome 1p, with D1S197 (the CSE locus is situated in the 2 cM interval between D1S443 and D1S197)<sup>2</sup>; (3) chromosome 12p, with the 2 markers (D12S372)-4cM-D12S99-1cM-(D12S93)-7cM-D12S77 (the EA-1 locus maps to the 5 cM interval between D12S372 and D12S93).<sup>3</sup> Inheritance of PKC was dominant in both families, with two male to male transmissions in one family,

excluding X linked and mitochondrial transmission. There were no asymptomatic obligate gene carriers, suggesting complete penetrance. We assumed autosomal dominant inheritance with a gene frequency of 0.0002 and complete clinical penetrance by the age of 17 years. Allele frequencies for a white population were determined according to the genome database. Two point and multipoint lod scores were calculated using the MLINK program of the Fastlink package.<sup>5</sup>

Results of the two point linkage analysis in both families are shown in the table. All markers tested generated negative lod scores at  $\theta=0.00$  except for marker D2S377 in family B. Lod scores below the threshold of  $-2$  were obtained for all candidate regions except for the PDC locus in family B. Multipoint linkage analyses excluded the following intervals including candidate loci in families A and B respectively: 26.5 and 25 cM on chromosome 2q including the PDC locus; 26.5 and 30 cM on chromosome 12p, including the interval containing the voltage dependent potassium channel (KCNA1) gene responsible for EA-1. In conclusion, despite some clinical similarities, AD PKC is genetically distinct from both forms of PDC and from EA-1.

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### Granulomatous angiitis of the CNS causing spontaneous intracerebral haemorrhage: the importance of leptomeningeal biopsy

Granulomatous angiitis (GANS) of the CNS is a rare, idiopathic vasculitis confined largely to the small blood vessels of the CNS. It has also been referred to as “isolated”,<sup>1</sup> “primary”, and “idiopathic”<sup>2</sup> angiitis of the nervous system. Clinical manifestations are usually the result of multifocal ischaemia and infarction and patients with GANS typically present with a chronic and relapsing but ultimately progressive encephalopathy, characterised by cognitive impairment and multifocal deficits. Less commonly, haemorrhage can occur as a result of infarction, focal necrosis of a vessel wall, or aneurysm rupture and the presentation may therefore be primarily neurosurgical.<sup>3,4</sup> It is important to recognise this condition because long term clinical remission is possible with immunotherapy. In this letter we present a case which serves as a reminder to neurosurgeons to include GANS in the differential diagnosis of spontaneous intracerebral haemorrhage and emphasises the importance of leptomeningeal biopsy.

A forty six year old woman was admitted to our unit with a 24 hour history of confusion, vomiting, dysphasia, and a generalised seizure. The patient also had a 30 month history of deteriorating work performance and had had episodes of nausea, vertigo, and headache lasting 1 to 2 days. After one of these episodes she was investigated by one of us (SM). Neurological examination and a CT were normal. Diagnoses of migraine and Ménière's disease were considered. Four months before admission, she had experienced transient mild dysphasia and left hemianaesthesia.

On admission to our unit, she was drowsy but opened her eyes to voice and obeyed simple commands. She had a left retinal haemorrhage and an expressive dysphasia. She was afebrile, there was no meningism, and general examination was normal. Brain CT showed an extensive area of low density involving both grey and white matter of the left frontal lobe, with three separate areas of intraparenchymal haemorrhage and mild mass effect. She was started on dexamethasone, phenytoin, and acyclovir and arrangements were made for MRI and MR angiography to be performed the following day.

An improvement was noted overnight, but the next day her clinical condition deteriorated. Urgent CT was performed and this showed further haemorrhage into the left frontal lobe with appreciable midline shift (figure). Immediately after the scan her left pupil became fixed and dilated. An urgent left frontal lobectomy was performed.