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

		Lod score at θ =						
Marker	*Family*	*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.[2] 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.[4] 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.[4]

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)[1]; (2) chromosome 1p, with D1S197 (the CSE locus is situated in the 2 cM interval between D1S443 and D1S197)[2]; (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).[3] 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.[5]

Results of the two point linkage analysis in both families are shown in the table. All markers tested generated negative lod scores at θ=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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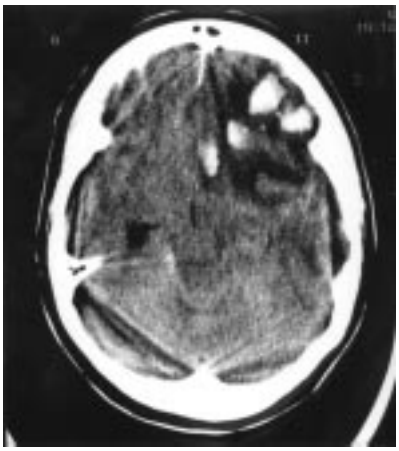
Granulomatous angiitis of the CNS causing spontaneous intracerebral haemorrhage: the importance of leptomeningeal biopsy

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",[1] "primary", and "idiopathic"[2] 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.[3 4] 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.



Brain CT after clinical deterioration. There is extensive patchy haemorrhage into the left frontal lobe with marked mass effect.

Macroscopically the left frontal lobe was swollen, with multiple small areas of haemorrhage in the cortex and white matter, and thrombosis of superficial cortical veins. Histological examination disclosed a coexistant pattern of granulomatous and necrotising non-granulomatous vasculitis affecting the small leptomeningeal and intracerebral blood vessels. Occasional leptomeningeal vessels were occluded by thrombus.The granulomatous lesions featured an infiltrate of lymphocytes and histocytes within blood vessel walls. The vascular intima was variably thickened by a fibrocellular proliferation and small numbers of Langhans and foreign body type giant cells were scattered individually within the media of some vessels.The leptomeninges contained a dense infiltrate of mononuclear inflammatory cells. The cerebral tissues were oedematous with extensive extravasation of erythrocytes and diffuse hypoxic neuronal changes but there was no evidence of a discrete area of infarction. Special stains for organisms (zinc, gram, PAS, PAS-D, Giemsa and GMS) were negative. Viral inclusions were not seen.

Haematological investigation disclosed a mild neutrophil leucocytosis, but haemoglobin, platelet count, and erythrocyte sedimentation rate were all in the normal range as were serological investigations including C reactive protein, complement assays, antinuclear antibodies, double and single stranded DNA antibodies, and rheumatoid antibodies.

The patient was treated intensively with a combination of oral cyclophosphamide and intravenous methyl prednisolone for one week followed by oral cyclophosphamide and prednisone. Treatment was complicated by haemorrhagic cystitis (for which oral cyclophosphamide was changed to pulsed intravenous cyclophosphamide), and organic psychosis. At 2 years the patient is clinically stable. Immunotherapy is being gradually reduced. She has a fixed frontal lobe deficit consisting of impulsivity, a loss of control of emotions, reduced verbal fluency, and impaired insight. Serial CT and MRI show only postsurgical change in the left frontal lobe.

The importance of this case is firstly that it draws attention to the protean manifestations of this rare but treatable condition. Other reported presentations include recurrent intracerebral haemorrhage, radiculomyelopathy, cerebral and spinal aneurysms, subarachnoid haemorrhage, seizures, and mass lesions.[1 2 5]

Secondly, this case emphasises the fact that the disease mostly affects small vessels of the leptomeninges. Neurosurgeons are most likely to encounter this disease in the setting of a request by their neurology colleagues for a diagnostic brain biopsy. Moore suggested that the ideal biopsy in these patients is a 1 cm wedge of cortex including leptomeninges and preferably containing a cortical vessel.[1]

Our patient ultimately required urgent decompressive frontal lobectomy. The diagnosis of GANS was not suspected preoperatively and the inclusion of leptomeninges in the surgical specimen was fortuitous. We would advise others undertaking the evacuation of an intracerebral haematoma of uncertain aetiology to obtain a leptomeningeal biopsy at the same time, particularly when there is a background of neurological symptoms.

Other investigations may not be helpful. Brain CT and MRI are abnormal in 30%-65% and 75%-100% of cases respectively and may show a wide variety of lesions. Angiographic abnormalities are present in 50%-90% of cases but are not specific for GANS. The CSF may be normal.[1 2] It is essential to differentiate GANS, from the many secondary causes of cerebral vasculitis such as giant cell arteritis. The presence of markers of systemic, inflammatory, or autoimmune disease should suggest an alternative diagnosis.

Because GANS is rare, our knowledge of its natural history and optimum management is incomplete. Early reported cases of GANS were invariably fatal[5] but immunotherapy has now been shown to improve symptoms and result in sustained remission in some cases. The results with corticosteroids alone have been disappointing and the combination of prednisone with cyclophosphamide is the mainstay of treatment.[1 3 5]

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Intravesical atropine suppression of detrusor hyperreflexia in multiple sclerosis

Multiple sclerosis commonly causes urinary frequency, urgency, and urge incontinence resulting from detrusor hyperreflexia. This might be associated with voiding difficulties due to detrusor sphincter dyssynergia. These symptoms can be treated effectively with antimuscarinic drugs (principally oxybutynin) and clean intermittent catheterisation, but the antimuscarinic side effects limit clinical usefulness. Typically these are dry mouth and blurred vision, but include constipation, reflux oesophagitis, and flushing.

Oxybutynin, formulated for intravesical administration, has been reported to be effective for suppressing detrusor hyperreflexia with low incidence of side effects in various neuropathic disorders.[1 2] However, this preparation is not widely available.

Atropine is a cheaper, easily obtainable, antimuscarinic drug. Administered intravesically it has been shown to be effective in increasing bladder capacities without side effects in patients with spinal cord injury.[3] However, the only study was small and uncontrolled. Whereas the pathologies of multiple sclerosis and spinal cord injury are different, the bladder impairments are similar. This study was designed to investigate the efficacy of intravesical atropine in increasing bladder capacities in patients with multiple sclerosis with detrusor hyperreflexia.

The study received ethics committee approval. Written informed consent was obtained from each patient.

Patients with a definite diagnoses of multiple sclerosis and urodynamically demonstrated detrusor hyperreflexia were recruited into the study. Each was taking oral antimuscarinic medication and using clean intermittent catheterisation. A sample size calculation based on previous data[3] identified a target recruitment of 15 patients to achieve a significance level of 0.05 with a power of 0.80 using a crossover study design. Eighteen patients were contacted, of whom 16 consented and 15 completed the study.

Antimuscarinic drugs were stopped 2 days before cystometric testing. Patients attended on two occasions. They were allocated 30 ml of either atropine (6 mg) in normal saline or normal saline only (as placebo). This was done according to random code with both patient and investigator blinded. An independent nurse prepared the solutions.

Standard static saline fill cystometry with a filling rate of 50 ml/min was performed before and 2 hours after intravesical instillation of the test preparations. As this was a first randomised study of a single dose of intravesical drug the outcome measure used was cystometric bladder capacity and not urgency or episodes of urge incontinence. A single prophylactic dose of ciprofloxacin (250 mg) was administered orally on each occasion. At the beginning and end of each cystometric study the patient's heart rate and blood pressure were measured. All patients were questioned about known antimuscarinic side effects. Blood samples were collected for atropine assays 2 hours after instillation of the test solutions.

Urodynamic data were not normally distributed, therefore non-parametric analysis techniques were used. When comparisons between the difference in change in cystometric bladder capacities were made a Wilcoxon sign ranked test was used quoting the 95% Wilcoxon confidence interval.

The study group consisted of 15 patients (six men and nine women) with a median age of 51 years (range 39–73 years). All patients retained their test solutions after each instillation. The results are shown in table 1. After atropine the bladder volumes increased by a