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A preliminary investigation of laterality in Parkinson's disease and susceptibility to psychosis

Cerebral disease with more prominent left sided cerebral involvement may be more closely associated with psychotic phenomena; a comprehensive review of cerebral laterality in relation to psychosis has suggested that a special, although unclear, pathophysiology may be at work.[1]

A review of patients with treated Parkinson's disease found an overall incidence of psychiatric side effects of 20% (range 10–50) in 908 patients treated in major studies.[2] Psychoses—that is, hallucinations and delusions—occurred with a frequency of 4% and were more likely to occur with concurrent dementia, increasing age and use of higher dose of levodopa. It is assumed that the main precipitant of psychotic phenomena in Parkinson's disease is dopaminergic excess secondary to treatment. Cognitive impairment, which has been reported to occur in as many as 29% of patients with Parkinson's disease, associated with increased age and older age at onset, may also increase vulnerability to psychosis.

Asymmetry in Parkinson's disease is said to remain unchanged over time,[3] and patients with unilateral onset of Parkinson's disease manifestations have greater degeneration of the contralateral substantia nigra at postmortem examination.[4] If predominantly left sided pathology increases the vulnerability to psychotic phenomena then initial right sided predominance of parkinsonian symptoms and signs might be a predictor of increased vulnerability. If initial right sided symptom predominance did indeed predict the subsequent development of psychotic phenomena (independent of cognitive decline, age, and medication) this might be clinically useful in identifying a patient subgroup in whom particular care is required in titrating medication.

A retrospective review of all case notes of patients with Parkinson's disease, identified by their presence on the specialist Parkinson's disease nurse register in a district general hospital, was carried out (*a*) to evaluate the presence of psychotic symptoms using a checklist, (*b*) to record asymmetry of parkinsonism both currently and at onset, and (*c*) to record handedness. Psychotic symptoms (delusions and hallucinations) were only noted when they occurred outside an acute confusional state. All patients had been diagnosed by one of two consultant neurologists. The level of medication, both current and while having psychotic symptoms, cognitive assessment, number of years of illness, and demographic variables were also recorded. Patients who had had a psychotic episode were compared with the remainder with respect to asymmetry of symptoms at onset of illness, age, duration of illness, medication levels and demographic variables. This was repeated with a subgroup of patients with no cognitive deficit. Logistic regression analysis (forward stepwise) was carried out with psychosis as the dependent variable.

The case notes of 100 patients were reviewed. There were 51 men and 49 women in the sample. Fifty one patients were right handed, four were left handed, and in 45 handedness was unknown. Dementia was noted in 30 patients, with "memory difficulties" recorded in a further eight. Hallucinations were recorded in 28 patients and delusions in six. The patients with hallucinations or delusions were classified as the psychosis group (n=30), and those with dementia and memory difficulties as the cognitively impaired group (n=38), for analysis. Details of illness, for the whole sample and separated into psychotic and non-psychotic subgroup, side of onset, and the demographic data, are shown in the table.

Patients' characteristics and the presence of psychosis

	Total sample	*Psychosis*		*p Value*
		Yes	*No*	
Patients (n)	100	30	70	
Age (y):				
Mean	71	71.8	71	NS
SD	6.8	4.5	7.5	
Age at onset:				
Mean	64	61.6	64.7	NS
SD	8.9	8.2	9.1	
Duration of illness (y):				
Mean	7	10	6.3	<0.02
SD	5.7	7.1	4.6	
Dose of levodopa (mg/day):				
Mean	455	506	433	NS
SD	353	320	367	
Dose of selegeline (mg/day):				
Mean	3.8	2.8	4.1	NS
SD	5.7	4.3	6.1	
Side of onset total (n=100):				
Right	43	16	27	NS
Left	45	9	36	
Side of onset cognitively unimpaired (n=62):				
Right	25	7	18	<0.03
Left	32	2	30	
EPS at onset (n=95):				
Tremor	55	13	42	NS
Rigidity	19	4	15	
Akinesia	21	10	11	

Comparison of side of onset with presence of psychosis disclosed more patients with right sided onset of parkinsonian symptoms having psychotic symptoms, although this was not significant (χ^2=3.0, df=1 p<0.09; table). Presence of psychosis was significantly associated with presence of cognitive decline. Eighteen out of 38 in the cognitively impaired group were psychotic by comparison with 12 out of 62 in the cognitively intact group (χ^2=13.5, df=1, p<0.003). Presence of psychosis was also associated with duration of illness (*t* test=2.69, df=36, p<0.02). There were no significant differences between the psychotic symptom group and the other patient groups in age, age at onset of symptoms, and dosage of current medication. Comparative dosage of levodopa and selegiline are shown in the table. Benzhexol, bromocriptine, pergolide, and orphenadrine were taken by 10, 14, 13, and seven patients respectively, and showed no differences between the groups. Furthermore there were no significant differences in the dose of current medication and the dose noted when undergoing a psychotic episode.

Cognitive decline was associated with increasing age but was not related to age of onset or dosage of medication. When patients with cognitive decline (n=38) were removed from the analysis, right sided onset of symptoms was significantly related to the presence of psychosis (χ^2=5.0, df=1, p<0.03) in the remainder. In this subsample there were no significant differences between left and right side onset for age, duration of illness, or dosage of different medication.

Logistic regression analysis of the total sample, with psychosis as the dependent variable, confirmed the association between psychosis and cognitive decline (*t*=3.89, p<0.003) and increased duration of illness (*t*=2.64, p<0.02). There were no other significant contributing variables, although side of onset was the strongest associated variable remaining (*t*=1.69, p<0.09). However, when the logistic regression was repeated with the subsample without cognitive decline, right sided onset was the only variable significantly associated with psychotic symptoms (*t*=2.30, p<0.03).

Our results show only a trend, in the sample as a whole, linking right sided symptoms at onset and the subsequent development of psychosis; perhaps unsurprising in view of the confounding effect of cognitive impairment. In the cognitively intact subsample there was a significant association with right sided onset of symptoms of Parkinson's disease. This suggests that damage to left hemispheric structures involved in Parkinson's disease is associated with a predisposition to psychosis. Our results do not support an iatrogenic dopaminergic excess as a cause of psychosis; this may be because of subsequent dosage adjustment, or the explanation may lie in asymmetric upregulation of dopaminergic receptors and supersensitivity to dopaminergic therapy at equivalent doses of medication.

The limitations of using retrospective data are well recognised and the possibility of mild cognitive dysfunction not being detected in the cognitively intact group needs to be recognised. However, this preliminary study provides support for our a priori hypothesis that right sided predominance of neurological deficit at the onset of Parkinson's disease predicts the subsequent development of psychosis.

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Cerebral venous sinus thrombosis associated with 20210A mutation of the prothrombin gene

Predisposing factors can be identified in up to 80% of patients who develop cerebral venous thombosis (CVT).[1] In many patients risk factors are acquired but 10 to 15% of patients may have inherited tendencies to thrombosis. Deficiencies of protein C, protein S, or antithrombin are reported in large series. The recently identified factor V Leiden mutation (FVR506Q) giving rise to activated protein C resistance is one of the most prevalent genetic mutations currently identified (10% to 15% of the white population),[2] and it is now known to be an important risk factor for cerebral venous thrombosis.[3–6] All of these thrombophilic tendencies, and particularly the factor V Leiden mutation, are compounded by other factors such as the oral contraceptive pill, pregnancy, pueperium, or immobility.

Prothrombin is a precursor of the serine protease thrombin and is a key enzyme in the process of haemostasis. Recently, a single nucleotide substitution (G to A) at position 20210 in the 3' untranslated region of the gene encoding prothrombin has been identified.[7] Its heterozygous state, 20210A, is a risk factor for the development of deep vein thromboses,[7 8] and it has recently been implicated in the development of superior sagittal sinus thrombosis in a woman taking the oral contraceptive pill.[9] We report the development of extensive cerebral venous thrombosis in a patient, without other risk factors, who was found to be heterozygous for this newly identified genetic mutation.

A 46 year old man had headaches for 2 weeks which became acutely worse and were associated with vomiting and dizziness. His conscious level fluctuated but was progressively deteriorating. He had a generalised tonic-clonic seizure and a history of a spontaneous deep vein thrombosis. There was no family history of thromboses.

He was obtunded with bilateral papilloedema. There were no focal signs except for a right extensor plantar. Unenhanced brain CT was normal but a lumbar puncture disclosed a pressure of 34 cm of CSF with 28 000 red blood cells, 40 white blood cells/mm^3 and a protein concentration of 1.5 g/l with normal glucose. A repeat brain CT with contrast showed diffuse swelling in the posterior fossa, with supratentorial and infratentorial haemorrhages and high attenuation around many of the venous sinuses. Brain MRI disclosed extensive thrombosis of the superior sagittal sinus, the straight sinus, and both transverse and sigmoid sinuses. There was haemorrhage in the left cerebellar hemisphere and haemorrhagic infarcts in the left parietal and both cerebellar hemispheres.

Results of thrombophilia screening

Test	*Result*	*Laboratory normal range*
Prothrombin gene (20210A) mutation	Heterozygous	
Factor V Leiden mutation	Negative	
Antithrombin III activity (%)	70	80–155
Antithrombin III (4 months later) (%)	85	80–155
Protein C activity (%)	66	65–165
Protein S free antigen (%)	79	70–115
Protein S total antigen (%)	87	65–115
Activated protein C resistance ratio	3.05	>2.3
IgG anticardiolipin antibodies (GPL U/ml)	4.1	0.0–14.1
IgM anticardiolipin antibodies (MPL U/ml)	1.3	0.0–1.6 MPL U/ml
Russell's viper venom test ratio	1.16	0.9–1.1
50/50 Russell's viper venom ratio	1.01	0.9–1.1
Platelet neutralisation ratio	1.16	
Correction (%)	0.0	0.0–12

Full blood count and biochemistry were normal. The erythrocyte sedimentation rate was 24 mm in the first hour and C reactive protein was 24.1 mg/l (normal<8). Autoantibodies including antinuclear antibodies were negative. Treponemal pallidum haemagglutination test and rapid plasmin reagin tests were negative. The prothrombin time and activated partial thromboplastin time were normal. A thrombophilia screen was performed 24 hours after starting heparin (table). Initial antithrombin activity was reduced at 70% but was normal when repeated 4 months after the initial presentation; however, the patient was found to be heterozygous for the 20210A prothrombin gene mutation. This was identified using the polymerase chain reaction (PCR) of exon 14 and the 3'-untranslated region of the prothrombin gene, followed by restriction digestion by Hind III. The mutant allele then appeared as an extra DNA fragment on agarose gel electrophoresis. The presence of the 20210A allele was subsequently confirmed by DNA sequencing.

He was treated with intravenous heparin (APTT ratio 2 to 3) with the gradual introduction of warfarin which he will continue for life. His condition gradually improved; he had mild residual pyramidal signs, but no significant disability, and no further seizures.

The substitution of G to A at position 20210 of the prothrombin gene is a recently recognised risk factor for venous thrombosis. It has been found in 18% of selected patients with a family history of venous thrombosis, 6% to 7% of unselected patients with deep vein thrombosis, but only 1% to 2% of controls,[7 8] making it the second most common hereditary thrombophilia after the factor V Leiden mutation.[2] Prothrombin is encoded by a 21 kb gene located on chromosome 11p11 to q12. Patients with the mutation (20210A) have higher plasma prothrombin concentrations than controls with the normal genotype (20210G), suggesting that hypercoaguability is due to hyperactivity of the common coagulation pathway resulting in increased thrombin production.[7]

Our patient had reduced antithrombin concentrations at 70% on initial testing. Thrombotic tendencies arise when concentrations are less than 60% of normal. The initial concentration was probably secondary to the acute thrombosis or treatment with heparin. Repeat testing after 4 months showed normal concentrations, hence we think that antithrombin deficiency is unlikely to be implicated in this patient's CVT. There were no other risk factors for venous thrombosis in our patient, unlike the recently reported patient with sagittal sinus thrombosis, who was taking the oral contraceptive pill.[9]

Activated protein C resistance due to the factor V Leiden mutation is the most common hereditary thrombophilia associated with CVT,[3–6] although in most cases it is also associated with an acquired prothrombotic tendency,[3] such as the oral contraceptive pill. In a recent study of 40 patients with CVT, Activated protein C resistance with the Leiden mutation was found in four patients, protein C deficiency in one, and protein S deficiency in another.[3] Isolated hereditary thrombophilias as a cause of CVT seem to be rare in the absence of other factors, with only the patient with protein S deficiency in the series of Deschiens *et al*[3] and other occasional cases[4 5] having no other predisposing factor.

The identification of an inherited thrombophilia in a patient with CVT should not, therefore, preclude a search for other provoking factors. To the list of inherited thrombophilias should now be added the newly identified 20210A prothrombin gene mutation.

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