

Demographical and laboratory findings of patients with OpS-MS

Patient	Sex	Age	AAO	Duration	p-ANCA	c-ANCA	ANA	aCL
1	F	79	76	2y 8m	-	-	1:80	-
2	F	57	48	8y 6m	-	-	-	-
3	F	61	58	3y 5m	+	-	1:320	+
4	F	27	20	6y 8m	-	-	-	+
5	F	56	56	5m	-	-	1:80	-
6	F	34	27	7y	-	-	-	-
7	M	36	30	6y	+	-	-	-
8	F	66	46	24y	-	-	-	-
9	F	56	52	4y 8m	+	-	-	-
10	M	21	19	2y 4m	-	-	-	-
11	F	58	46	11y 9m	+	-	1:320	-
12	M	58	55	3y 2m	+	-	1:640	-
13	F	54	52	2y	+	-	1:160	-

OpS-MS = the optic-spinal form of multiple sclerosis; AAO = age at onset; duration = duration of the illness; ANA = antinuclear antibody; aCL = anticardiolipin antibody.

the active phase, served as controls. Any patient taking an immunosuppressive drug or steroids during the month before the time of blood sampling was excluded. Serological testing for autoantibodies (rheumatoid factor (RF), anti-nuclear antibody (ANA), anti-double stranded DNA antibody, anti-Ro antibody (SS-A), anti-La antibody (SS-B), anticentromere antibody, antiribonucleoprotein antibody, and anticardiolipin antibody (aCL)) was performed in all patients. We considered an ANA titre of 1:80 or more by indirect immunofluorescence on Hep-2 cells as positive. Patients who were serologically positive for ANA without any other evidence of collagen diseases were enrolled in this study. Tests for anti-HTLV-1 antibodies were negative in all patients. The 13 patients with a diagnosis of OpS-MS comprised three men and 10 women aged between 21 and 79 (mean 51.0 (SD 16.7)) years. The age at onset of disease ranged from 19 to 76 (mean 45.0 (SD 16.7)) years and the duration of the illness ranged from 0.5 to 24 (mean 6.3 (SD 6.1)) years. The 26 patients with conventional multiple sclerosis comprised eight men and 18 women aged between 23 and 66 (mean 42.2 (SD 13.8)) years. The age at onset of disease ranged from 16 to 59 (mean 31.9 (SD 14.5)), and the duration of the illness ranged from 0.3 to 43 (mean 10.2 (SD 9.1)) years. In nine patients with acute transverse myelopathy, there were four men and five women aged between 21 and 59 (mean 40.2 (SD 13.3)) years. ANCA were detected by standardised indirect immunofluorescence,³ and were examined by the same experienced investigator (SM) without the knowledge of the clinical profiles. Two different staining patterns of ANCA were investigated: a cytoplasmic pattern (c-ANCA), and a perinuclear pattern (p-ANCA).¹

The table summarises the immunological laboratory findings of the 13 patients with a diagnosis of OpS-MS. Six of the 13 (46.2%) were positive for p-ANCA and no patients were positive for c-ANCA. Six patients were ANA positive, four among the p-ANCA positive patients and two among the p-ANCA negative patients ($p = 0.29$). Four patients were both p-ANCA positive and ANA positive and two patients were p-ANCA positive but ANA negative. Age at onset, age at the time of blood sampling, and duration of illness were similar between p-ANCA positive and p-ANCA negative patients. Titres of ANCA were not detectable in serum samples from the 26 patients with conventional multiple sclerosis and the nine patients with acute transverse myelopathy. Samples were positive for ANAs in three (11.5%) of the 26 patients with conventional multiple sclerosis and in none of the nine patients with acute trans-

verse myelopathy. Among the 39 patients in this study, the p-ANCA positive rate was similar between men and women. The mean age at blood sampling for p-ANCA positive patients was 53.8 (SD 9.0) years, and for negative patients, 43.5 (SD 15.6) ($P = 0.13$). The mean duration of illness of p-ANCA positive patients was 5.2 (SD 3.5) years and for negative patients, 9.6 (SD 8.8) years ($P = 0.23$). The p-ANCA positive patients were older at onset of disease (mean 48.8 SD (10.0) years) than p-ANCA negative patients (mean 33.9 (SD 16.2) years) ($P = 0.038$). The ANA positive rate was significantly higher in p-ANCA positive patients (4 of 6; 66.7%) than in p-ANCA negative patients (3 of 33; 9.1%) ($P = 0.018$). The p-ANCA positive rate was significantly higher (46.2%) in the 13 patients with OpS-MS than in the 26 patients with conventional multiple sclerosis ($P = 0.0005$). The ANA positive rate was significantly higher in patients with OpS-MS (46.2%) than in patients with conventional multiple sclerosis (11.5%) ($P = 0.04$). Other tests for autoantibodies were negative in all 48 patients.

We found a significantly higher p-ANCA positive rate (46.2%) among patients with a diagnosis of OpS-MS, compared with that (0%) among the 26 patients with conventional multiple sclerosis ($p = 0.0005$), and p-ANCA was not detectable in serum samples from the nine patients with acute transverse myelopathy of unknown aetiology, suggesting that the positivity for p-ANCA was not an epiphenomenon. As p-ANCA may be involved in the pathogenesis, at least of vasculitis,¹ a possible pathogenetic role of ANCA associated vasculopathy in patients with p-ANCA positivity should be considered. Six of the 13 patients with OpS-MS, were ANA positive, among whom four were p-ANCA positive and two were p-ANCA negative. Other collagen screening studies were negative. Although ANAs can produce a staining pattern in indirect immunofluorescence that is difficult to distinguish from that of p-ANCA⁴ and the frequency of positive ANAs was significantly higher in patients with positive p-ANCA than in patients with negative p-ANCA, two patients were p-ANCA positive without being ANA positive. This indicated that being ANA positive could not explain the p-ANCA positivity. The ANA positive rate among patients with OpS-MS was also significantly higher (46.2%) than that among patients with conventional multiple sclerosis (11.5%) in our series. Therefore, vasculopathy may play an important part in patients who are positive for p-ANCA, ANAs, or both. Further investigations on the antigenic specificities of p-ANCA which were positive in this study are also important.^{4,5}

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- Gross WL, Schmitt WH, Csernok E. ANCA and associated diseases: immunodiagnostic and pathogenic aspects. *Clin Exp Immunol* 1993;91:1-12.
- Fukazawa T, Hamada T, Moriwa F, Tashiro K. Acute transverse myelopathy in MS: clinical consideration. *International MS Journal* 1994;1:27-33.
- Maguchi S, Takizawa M, Ryu T, et al. Clinical significance of antineutrophil antibody (ANCA) for the diagnosis of Wegener's granulomatosis in the early stage. *American Journal of Rhinology* 1994;9(suppl):369.
- Hagen EC, Andrassy K, Chernok E, et al. The value of indirect immunofluorescence and solid phase techniques for ANCA detection. A report on the first phase of an international cooperative study on the standardization of ANCA assays. *J Immunol Methods* 1993;159:1-16.
- Wiik A, Stummann L, Kjeldsen L, et al. The diversity of perinuclear antineutrophil cytoplasmic antibodies (pANCA) antigens. *Clin Exp Immunol* 1995;101(suppl 1):15-7.

Cerebral venous sinus thrombosis associated with factor V gene mutation

Activated protein C resistance, caused by a mutation in the gene coding for protein C cofactor (factor V), has recently been found to be a major cause of familial thrombophilia.¹ One previous case of cerebral venous thrombosis, occurring in a woman taking the oral contraceptive pill who was a heterozygous carrier of the factor V mutation, has been described.² We present a case of cerebral venous thrombosis in a patient homozygous for the factor V mutation who was taking hormone replacement therapy.

A 45 year old woman was admitted with a two day history of headache. On the morning of admission she awoke with vomiting and an unsteady gait. Later that morning she became drowsy. She was premenopausal, had a history of migraine, and was a non-smoker. She had started hormone replacement therapy (oestradiol and oestradiol with norethisterone acetate) three months earlier for premenstrual exacerbations of migraine. There was no history of deep vein thrombosis, but a paternal grandmother had had a deep venous thrombosis, and her mother had had two episodes of thrombophlebitis. A brother (later found to be homozygous for the factor V mutation) had recently had a thrombosis of a superficial short saphenous vein. Neither her father nor her two other brothers had a history of venous thrombosis. On examination she was conscious but verbal responses were limited to "yes". She had roving eye movements with intact reflex ocular movements. There was a left hemiplegia. Both plantar responses were extensor.

Brain CT showed hypodensity within both thalami, the right internal capsule, and the left parietal region consistent with infarction. Lateral and third ventricles were

enlarged. Brain MRI showed haemorrhagic infarction in both thalami, extending to the internal capsule on the right and in the peripheral posterior left parietal lobe. Carotid angiography showed occlusion of the vein of Galen, inferior sagittal sinus, and straight sinus consistent with thrombosis.

Routine biochemical and haematological screens were normal. Lupus anticoagulant and cardiolipin antibodies were not detected. The international normalised ratio was 1.0 (normal range < 1.2) and the activated partial thromboplastin time (APTT) was 30 seconds (normal range 20–34 seconds). Antithrombin III and protein C and S concentrations were normal. The activated protein C resistance ratio (a ratio of the APTT measured in the presence of added activated protein C to the APTT measured in its absence) was 1.27 (normal > 2.5). Genetic testing disclosed homozygosity for the factor V mutation (using the method described by Bertina *et al.*,³ after amplification of the factor V cDNA by the polymerase chain reaction, the cDNA fragment was enzymatically digested and hybridised with the biotinylated oligonucleotide specific for the allele of interest). Anticoagulation was started with intravenous heparin and dexamethasone was given. Her conscious level deteriorated over the next 24 hours despite continued therapeutic anticoagulation. She developed fixed dilated pupils, impaired reflex ocular movements, and exhibited extensor posturing in response to painful stimuli. Anticoagulation was continued throughout, and two weeks after admission further MRI showed progression of thrombus into the lateral sinus and left jugular bulb. Over the next four weeks her conscious state improved. She began to follow commands appropriately; ocular movements returned to normal, but she remained mute with an asymmetric spastic tetraparesis, left worse than right. Over the subsequent seven months, speech returned to near normal with corresponding improvement in upper and lower limb function. She is now independent in all daily activities despite bilateral upper motor neuron signs and a mild trunk ataxia. Progress of the cerebral venous thrombosis will be followed up by MRI and it is intended to continue anticoagulation indefinitely.

Activated protein C is a natural inhibitor of blood coagulation which acts by inactivating plasma cofactors Va and VIIIa. Activated protein C resistance is known to occur in up to 50% of people with a personal and family history of deep venous thrombosis⁴ compared with a prevalence of about 5% in the general population. The genetic defect responsible for most cases of activated protein C resistance is now known to be a single point mutation in the factor V gene on chromosome 1.³ This codes for a defective factor V molecule which is not properly inactivated by activated protein C.

Women taking the oral contraceptive pill who also have activated protein C resistance are considered to have a higher risk of venous thrombosis than women with activated protein C resistance alone.⁵ Oestrogens in replacement doses have not been shown to increase the risk of thrombosis but were stopped in the present case. There are no clear guidelines to the duration of anticoagulation after cerebral venous thrombosis, with or without activated protein C resistance. The decision to continue lifelong anticoagulation in this patient was

based on the catastrophic nature of the venous thrombosis and on the increased risk of future thrombosis as a result of homozygosity for the factor V mutation.

Of the patient's family, her mother and one brother are heterozygous for the factor V mutation and another brother is homozygous. They have been advised that they should receive standard prophylaxis against venous thrombosis for procedures with thrombotic risk but that full anticoagulation would only be indicated for a proved thrombosis.

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- 1 Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. *Lancet* 1994;330:517–22.
- 2 Bridey F, Wolff M, Laissy JP, Morin V, Lefebvre M, de Prost D. Fatal cerebral venous sinus thrombosis associated with the Factor V Leiden Mutation and the use of oral contraceptives. *Thrombostasis and Haemostasis* 1995;74:1382.
- 3 Bertina R, Koelman B, Koster T, *et al.* Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994;369:64–7.
- 4 Griffin JH, Evatt B, Wideman C, Fernandez JA. Anticoagulant C pathway defective in majority of thrombophilic patients. *Blood* 1993;82:1989–93.
- 5 Vandenbroucke J, Koster T, Briet E, Reitsma P, Bertina R, Rosendaal F. Increased risk of venous thrombosis in oral contraceptive users who are carriers of factor V Leiden mutation. *Lancet* 1994;344:1453–6.

Isolated dysarthria caused by a right paravermal infarction

Information on the topography of speech disorders in cerebellar disease is lacking.¹

The few reports agree that the paravermal zone of the rostral cerebellum is the most frequent site of damage in patients with dysarthria and focal cerebellar disorders.^{1–3} However, it is not clear if there is a cerebellar hemispheric dominance. In fact, topographical study of the cerebellar speech centre is difficult because most speech disorders in cerebellar lesions result from involvement of brain stem or occipitotemporal structures.

We report details of a patient with a single infarct in the right paravermal zone who presented with an isolated dysarthria.

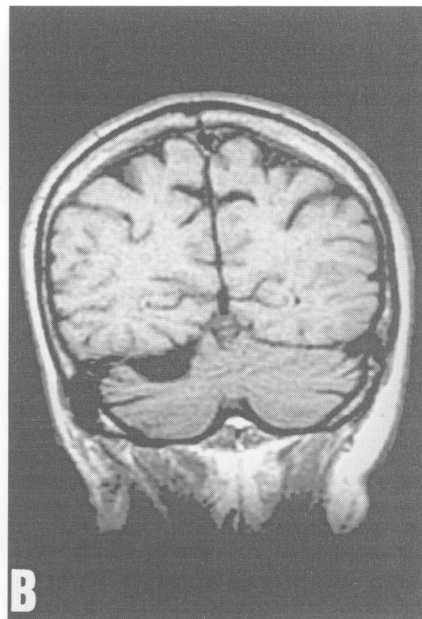
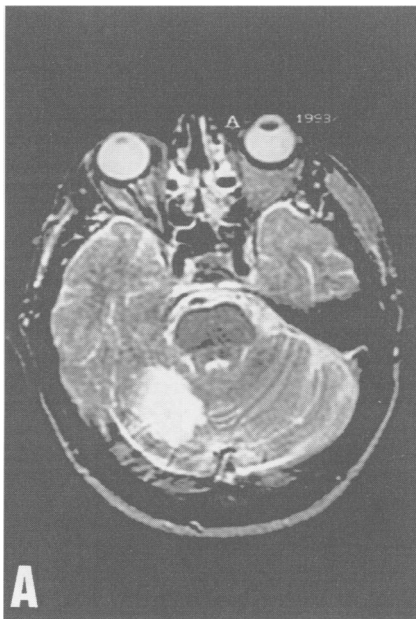
The patient was a 78 year old right handed man (Edinburgh handedness inventory: 16) with an abrupt onset of dysarthria without other symptoms.

On admission he was alert and oriented. There was severe dysarthria, consisting of slurred articulation and exaggerated consonants. The rest of the neurological examination was normal, without gait disturbance, disequilibrium or limb ataxia, or dysphagia. His gag reflex was normal. Initial CT was normal. Brain MRI showed an ischaemic lesion located in the paravermal zone of the right rostral cerebellar hemisphere, in the territory of the medial branch of the superior cerebellar artery (figure).

The patient had a good clinical outcome, and recovered completely from the speech disorder within 10 days.

The patient presented with a pure cerebellar dysarthria after a right superior cerebellar artery infarction involving the right rostral cerebellar hemisphere. This area corresponds with that delineated by previous studies^{1,2} but in the opposite cerebellar hemisphere. Thus the present case is the first report of isolated dysarthria caused by a right paravermal infarct in a right handed patient.

Dysarthria is common in superior cerebellar artery infarcts, being a characteristic sign of involvement of the medial branch of the superior cerebellar artery.^{1,3,4} In fact, dysarthria may be the only distinguishing clinical feature between lateral posterior inferior cerebellar artery infarcts and superior cerebellar artery infarcts.⁴ However,



(A) Axial MRI T2 weighted scan and (B) Coronal MRI T1 weighted scan showing an infarct in the superior portion of the right paravermal zone (medial branch of the superior cerebellar artery).