

# PostScript

## LETTERS

### Remission of progressive multifocal leucoencephalopathy in SLE after treatment with cidofovir: a 4 year follow up

Progressive multifocal leucoencephalopathy (PML) is an opportunistic infection caused by human polyomaviruses such as the JC virus. It usually occurs as a severe complication of immunosuppression in patients with primary disorders of the immune system or secondary impairment of immune function, for example, after iatrogenic states of immunosuppression. PML usually takes a rapidly progressive course and advances to death within 1 to 18 months. Today, PML is mainly seen in AIDS, while previously it was typically found in patients with granulomatous, neoplastic, or infectious diseases. In granulomatous diseases particularly, PML is thought to occur as a result of iatrogenic states of immunosuppression, but it is also seen in patients aggressively treated with immunosuppressive agents for systemic lupus erythematosus (SLE).<sup>1,2</sup> PML progresses to death in most of these patients even after withdrawing immunosuppressive therapy.<sup>2</sup> Therefore additional therapy, aimed at supporting a more rapid restoration of immune function his warranted.

#### Case report

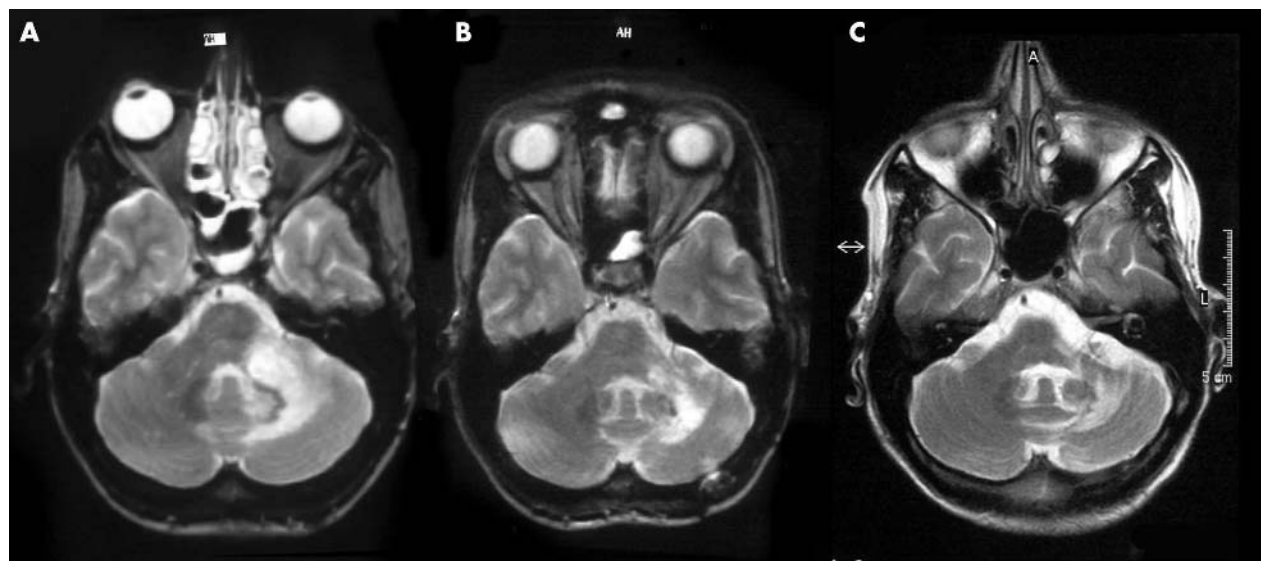
We report a 40 year old woman diagnosed with SLE at the age of 20 years, based on four American College of Rheumatology criteria (erythema, arthritis, elevated antinuclear antibodies, and anti-dsDNA antibodies). Owing to neuropsychiatric lupus (the patient had experienced several psychotic episodes

with suspected vasculitic changes on cerebral magnetic resonance imaging (MRI), the patient had undergone 12 cycles of cyclophosphamide pulse therapy in 1995/96 followed by immunosuppressive treatment with mycophenolate mofetil in 1998, and azathioprine in 1999. Follow up cerebral MRI scans at that time were normal.

In January 2001, she again developed psychotic episodes and an initially mild ataxia. She had repeatedly been put on low doses of corticoids but on no other immunosuppressive therapy during the previous 2 years. MRI revealed a lesion in the left cerebellum, which was hyperintense on T<sub>2</sub> and hypointense on T<sub>1</sub> weighted images. No lesions were seen in the cerebral hemispheres. Central nervous system manifestation of SLE was suspected, although the patient revealed only moderate signs of SLE activity (elevated anti-dsDNA antibodies, slightly decreased complement levels C3c and C4, increased erythrocyte sedimentation rate, but normal C reactive protein). There were no signs of severe immunosuppression; laboratory data showed normal levels of immunoglobulins and only slightly decreased lymphocytes, especially CD8+ T lymphocytes. The patient received two pulses of cyclophosphamide and high doses of corticosteroids to reduce the presumed cerebral SLE activity. In addition, she received antipsychotic medication.

While the psychosis was readily controlled by this treatment, the patient deteriorated neurologically. She developed a severe, disabling, rapidly progressive, left sided hemiataxia, and was unable to walk. A control MRI of the brain in February 2001 revealed a progression of the lesion in the left cerebellum and a new lesion in the middle cerebellar peduncle. The lesions again presented as hyperintense on T<sub>2</sub> and hypointense on T<sub>1</sub>-weighted images (fig 1A). Owing to the

neurological deterioration after initiation of immunosuppression and the presentation of the lesions on MRI, PML was considered as a differential diagnosis. PCR revealed JC virus DNA in the cerebrospinal fluid (CSF). As cerebral SLE and PML require an intense but divergent therapy, a brain biopsy was obtained from the cerebellar lesion. Histopathology confirmed the diagnosis of PML. HIV tests were negative, T cell counts were normal, and signs of malignancy were lacking. Immunosuppression was discontinued. Because PML is usually lethal in patients with SLE even after omission of immunosuppression,<sup>1,2</sup> we considered options for an active antiviral therapy. There was evidence from several reports in AIDS patients that cidofovir, an inhibitor of viral DNA polymerase, may reduce the size of PML lesions and thus prolong survival.<sup>3,4</sup> Lacking therapeutic alternatives we therefore administered intravenous cidofovir (5 mg/kg body weight) at initially bi-weekly intervals, after obtaining informed consent. After the third and fourth cycle, the patient improved dramatically. She was able to walk again and only showed a mild residual ataxia. MRI revealed reduction of the lesions in the cerebellum and middle cerebellar peduncle with no new sites of active disease (fig 1B). PCR for JC virus DNA in the CSF was now negative. The treatment with cidofovir was continued with longer intervals (8-12 weeks). The therapy was generally well tolerated. After the fifth cycle, mildly increased creatinine levels were found. After one cycle with 4 mg cidofovir/kg body weight, kidney function was quickly normalised and the following cycles could be administered at the initial dosage. Fourteen months after initiation of the treatment, the patient had completed the 10th cycle of therapy with no signs of disease activity. MRI scans of the brain showed further regression of the lesion with no signs of



**Figure 1** T2 weighted MRIs showed (A) extended white matter lesions in the middle cerebellar peduncle and left cerebellum, February 2001; (B) regression of the lesions after four cycles of cidofovir, July 2001; and (C) further regression with residual gliotic lesions, July 2004.

active inflammation (not shown), and cidofovir treatment was discontinued. At present, (4 years follow up after the first treatment and 2.5 years after the last cycle of cidofovir), the patient still shows no signs of disease activity. CSF PCR for JC virus DNA remains negative, and a recent MRI scan of the brain was unchanged (fig 1C). As of March 2005, the patient lives at home, is able to walk, and is independent.

## Discussion

We report a patient with SLE who survived PML after treatment with cidofovir and discontinuation of immunosuppression. First evidence for possible efficacy of cidofovir in the treatment of PML in a patient with SLE was presented in a case report.<sup>3</sup> Discontinuation of immunosuppression and treatment with cidofovir resulted in reversal of JC virus positivity and stabilisation of MRI lesions. However, the patient died due to serious kidney failure.

It remains unclear whether the improvement in both patients was induced or supported by cidofovir or whether it could have been acquired by discontinuation of immunosuppression alone. However, patients with PML in SLE usually die after discontinuation of immunosuppression alone.<sup>1,2</sup> Interestingly, our patient did not show signs of severe immunosuppression at the point of manifestation of PML. These observations may suggest a predisposition of patients with SLE to PML that may not be explained by their immunosuppression alone.

We conclude that cidofovir should be offered to SLE patients developing PML due to immunosuppression in addition to withdrawal of immunosuppressive therapy, as death is likely without antiviral therapy. Cidofovir may be effective against PML caused by non-AIDS related states of immunosuppression.

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## Dramatic improvement in non-AIDS related progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare disorder occurring when a strain of papovavirus (JC virus) infects the central nervous system. It results in a generally quick and fatal outcome. It is associated with cell mediated immune deficient diseases but some few cases were reported in immunocompetent hosts. Since 1981, it has been commonly associated with AIDS. In AIDS related PML, long term survival without real neurological improvement has been reported in patients treated with highly active antiretroviral therapy (HAART).<sup>1</sup> Few cases of improvement with cidofovir or cytosine arabinoside have been described in AIDS related or non-AIDS-related PML,<sup>2,3</sup> but in larger trials in AIDS related PML, no clinical benefit was found.<sup>4</sup> As a whole, the treatment of this progressive demyelinating disease remains controversial, in particular in the rare cases of non-AIDS-related PML. We describe a patient with an underlying haematological disease, without clear cut immune cell deficiency, who developed rapidly progressive PML. The patient showed clinical, virological, and imaging improvement when treated with an association of intravenous and intrathecal cytosine arabinoside combined with intravenous cidofovir.

A 48 year old man presented with progressive multiple lymphadenopathies, hepatosplenomegaly, weight loss, and blood cell count abnormalities. Fine needle aspiration cytology of lymphadenopathy diagnosed marginal zone B cell lymphoma. There was also bone marrow and blood proliferation. A few weeks after the diagnosis, the patient noticed rotatory vertigo and visual problems suggestive of a right homonymous hemianopia. Because of dissemination and the large tumour mass, chemotherapy (CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone) was started one month after the onset of neurological symptoms. Following the first course of chemotherapy, his neurological symptoms worsened, and language disorders appeared. No real immunodeficiency was shown—the absolute CD4+ count was 549/mm<sup>3</sup> (normal 858±260), and there was discrete hypogammaglobulinaemia (4.6 g/l; normal 5–12). The patient was HIV and HTLV1 seronegative. Cerebral magnetic resonance imaging showed a non-contrast-enhancing lesion in the left occipital white matter (fig 1A).

Cerebrospinal fluid (CSF) analysis was normal apart from a moderate increase in

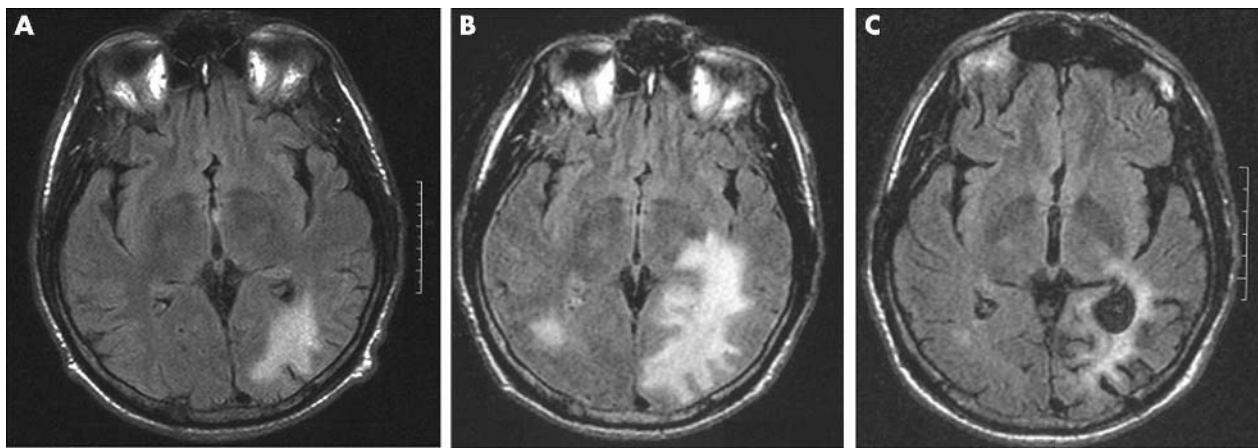
CSF protein (0.7 g/l). Suspicion of PML was confirmed by a positive polymerase chain reaction (PCR) for JC virus DNA. Chemotherapy was discontinued (after one cycle) but neurological symptoms worsened rapidly and the patient developed a right hemiplegia, global aphasia, alexia and agraphia, apraxia, and cortical blindness concurrently with MRI deterioration (fig 1B).

Three months after his first symptoms, treatment was started with intravenous aracytine 2 mg/kg/d for five days every three weeks, combined with intrathecal aracytine (30 mg) weekly and intravenous cidofovir 5 mg/kg/d once every two weeks. The main adverse effect of this treatment was grade IV bone marrow toxicity, inducing spacing in the rhythm of treatment administration. One week after treatment onset, the patient stabilised and after one month began improving. After three months, he had recovered completely from his hemiplegia, and had significant improvement in his aphasia and cortical blindness. Right hemianopia and minor alexia without agraphia persisted. This dramatic improvement was confirmed by cerebral imaging, by the absence of JC virus DNA detection in CSF, and by a specific response of CD4+ T cells against JC virus. We decided to continue subcutaneous aracytine 2 mg/kg/d for five days monthly and intravenous cidofovir twice weekly. Fifteen months after treatment onset, the patient was ambulatory and cerebral MRI continued to improve (fig 1C). Lymphoma tumour burden did not clearly change during the treatment.

## Comment

We report the favourable outcome of a patient with non-AIDS-related PML treated with a combination of intravenous and intrathecal aracytine and cidofovir. As the patient was not immunocompromised and had not received immunosuppressive treatment at PML onset, risk factors for the occurrence of PML are unclear. Treatment led to a rapid clinical and radiological improvement which was long lasting despite treatment delay and the patient's worrying clinical condition at treatment onset. Dose and administration schedules of cytarabine and cidofovir were derived from reports suggesting individual beneficial effects of these drugs.<sup>2,3</sup> To our knowledge, these drugs have not been used in combination before. In comparison with previous reports, the present case suggests a more rapid and prolonged effect of this therapeutic combination than with either aracytine or cidofovir treatment alone. This efficacy may be explained by a synergy between the drugs and by their different routes of administration. We thought that the improvement in our patient was related to the treatment because there was a temporal link with treatment onset and because of the radiological features (the rare cases of PML stabilising without specific treatment have usually been associated with an inflammatory response to the virus, indicated by contrast enhancement on imaging).

The main limiting factor of this treatment was bone marrow toxicity. During the periods of immune deficiency, the patient's neurological condition did not deteriorate, suggesting that PML occurrence in this patient was linked to a qualitative defect of CD4 cells rather than to their absolute count. Immunological studies have shown that JCV specific CD4-T cell responses play a



**Figure 1** evolution of cerebral magnetic resonance imaging (MRI) before and during treatment. (A) The first cerebral MRI, two months after the first neurological symptoms. Flair weighted axial images (TR 9000 ms; TE 114 ms) showing high signal intensity lesion in the left occipital white matter with respect to cortical grey matter. (B) Brain MRI one week after treatment onset. Flair weighted axial images (TR 10 002 ms; TE 160 ms) showing extension of the lesions. At that time, extension of the lesions was greater, with bilateralisation of the lesions in both occipital white matter and extension through temporal white matter. (C) Brain MRI three months after treatment onset. Flair weighted axial images (TR 10 002 ms; TE 160 ms) showing dramatic improvement under treatment. Hyperintense signal has diminished in both occipital lobes, but cerebral atrophy had appeared in the left occipital and temporal cortex. TE, time of echo; TR, time of repetition.

major role in the control of PML development; for example, in one study<sup>7</sup> no specific T cell response was demonstrated in a series of 14 patients before treatment, whereas nine of 10 survivors recovered specific immunity. Our patient thus probably had no specific T cell response against JCV before treatment, but recovered a moderate but significant response while on treatment, possibly explaining PML regression. Such a restoration of T cell response can be achieved by HAART in AIDS. This observation suggests that the combination of aracytine and cidofovir could have had a similar action in restoring a specific T cell response against JCV in our patient. A direct effect of these nucleosidic analogues against JC virus DNA may also explain the rapid clinical and radiological improvement in our patient.

Despite its substantial bone marrow toxicity, this observation suggests that the new association of intrathecal and intravenous aracytine with intravenous cidofovir could be useful in patients with PML, particularly those with an underlying haematological disease. It is worth noting that bone marrow toxicity did not lead to deterioration of the neurological status of the patient, supporting the view that a specific defect in CD4 function is more important than the absolute CD4 count. The dramatic improvement observed in our patient warrants further prospective studies testing this drug combination.

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### Diaphragmatic paralysis and respiratory failure as a complication of Lyme disease

There have been five recorded cases of diaphragmatic paralysis as a complication of neuroborreliosis.<sup>1-5</sup> Here we report another case of Lyme meningoradiculitis, caused by an identified tick, leading to bilateral diaphragmatic paralysis with an abbreviated course on treatment.

### Case report

A 59 year old female presented with a recent history of abdominal pain and falls because of a weakness in her right leg. She had been complaining of flu-like symptoms with twitches in her back and pain in her right side for a month. She gave a history of

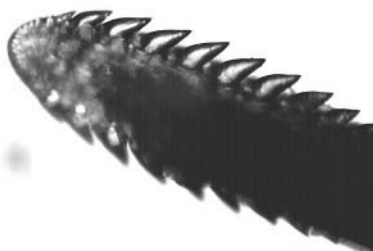
recently having been bitten by ticks whilst gardening. There was no history of any recent rash. On the day of presentation, she complained of a mild cough, reduced appetite, abdominal distension, constipation, and dysuria. She was a lifelong smoker but was generally healthy.

At presentation her blood pressure was 206/107 mm Hg. There was some epigastric tenderness. She had bruising on her right leg that she associated with the falls.

The chest radiograph on admission was unremarkable. Abdominal x ray showed dilated loops of small bowel and a loaded colon. Her only blood abnormality was hyponatraemia at 121 mmol/l. She was admitted for further investigations.

On day 3 of admission she became increasingly short of breath and on examination had decreased bibasal air entry. On day 4 her respiratory rate was 25/min and arterial blood gases (ABG) demonstrated hypoxaemia but adequate ventilation with pH 7.51, Po<sub>2</sub> 6.7 kPa, and Pco<sub>2</sub> 4.7 kPa. Her chest radiograph showed left basal changes. On day 5 her Pco<sub>2</sub> had risen to 6.8; she was admitted to the intensive care unit and non-invasive ventilatory support was commenced. She had a decreased inspiratory pressure and a decreased vital capacity. She was noted to have absent gag reflex and poor swallow and on day 6 was intubated to protect against aspiration pneumonia. The patient remained fully conscious and co-operative, easily triggering the ventilator but requiring significant inspiratory pressure support of 20 cm H<sub>2</sub>O.

Neurological examination demonstrated right hip and knee extensor weakness (2/5), absent right knee jerk, and a loss of sensation on her left lateral thigh. Because she lived in a known endemic area we thought about Lyme disease, but we also considered differential diagnoses such as Guillain-Barre syndrome, listeriosis, and acute poliomyelitis. We commenced treatment with doxycycline whilst awaiting the results of further investigations. Around this time the patient indicated a small black lesion on her upper abdomen that was removed and on closer examination was identified as tick mouthparts (fig 1).



**Figure 1** Photomicrograph of tick recovered from patient, showing tick mouthparts.

Given her smoking history and persistent hyponatraemia, a chest computerised tomography was performed which showed only left lower lobe collapse and a small left pleural effusion. Bronchoscopy was unremarkable. Chest ultrasound screening showed only minimal movement of both diaphragms.

Cerebrospinal fluid analysis (CSF) demonstrated a white cell count 181 cells/mm<sup>3</sup> (100% mononuclear), red cell count 22 cells/mm<sup>3</sup>, glucose 2.3 mmol/l (serum glucose 6.8 mmol/l), and protein 0.96 g/l. Immunological analysis of the CSF was not done because an insufficient sample was obtained. Brain magnetic resonance imaging (MRI) was normal. Spinal MRI and electromyography were not carried out. Immunoglobulin M and immunoglobulin G antibodies to *Borrelia burgdorferi* were detected in serum, and at this point intravenous ceftriaxone (2 g for 30 days) was commenced.

Over the next 7 days her strength increased and a repeat ultrasound of the diaphragm on day 16 of admission showed marked improvement with the right dome moving normally and some residual left sided weakness associated with overlying lung consolidation.

The patient was weaned from the ventilator and extubated following a total of 22 days of respiratory support. She underwent intensive physiotherapy and has made an uneventful recovery. One year later she complained of mild shortness of breath on lying flat with an exercise tolerance of 1 mile on the flat. On examination she had hyperaesthesia in her right leg with slightly brisk knee reflexes (previously absent right knee jerk). She had persistent bilateral diaphragmatic paralysis demonstrated on chest ultrasound screening. Pulmonary function tests showed a 40% reduction between erect and supine vital capacity measurements.

**Discussion**

The first case of diaphragmatic paralysis as a complication of Lyme disease was reported in 1986: a 73 year old male, treated with ampicillin and netilmicin, who required ventilation for 3 months and then died after receiving treatment for a pulmonary embolism.<sup>1</sup> Another four cases have been reported in patients between the ages of 39 and 68, all of whom were treated with either doxycycline or ceftriaxone and two of whom required ventilation due to respiratory failure.<sup>1-5</sup> All patients were well at follow up, although one patient had persistent phrenic paralysis 6 months after treatment.<sup>5</sup>

In all previous cases of diaphragmatic palsy as a complication of Lyme disease, either the patient reported dyspnoea or hypoxia was noted on ABG. The diagnosis of phrenic nerve palsy was made by the following methods: hemidiaphragm elevation, fluoroscopic screening of diaphragmatic movements, or electrical stimulation of phrenic nerves.<sup>1-5</sup> Our patient had a lymphocytic meningitis with sensory and motor neuropathies including bilateral phrenic nerve palsies. Diaphragmatic paralysis due to Lyme disease was diagnosed on the basis of clinical features, chest ultrasonography, the presence of the tick head, and serology indicating a recent infection with *B burgdorferi* as well as a rapid response to antibiotic therapy.

The clinical diagnosis of Lyme disease may be supported by serologic testing. *B burgdorferi* antibody tests may be negative in early infection, but patients are usually seropositive at or shortly after presenting with neurological symptoms. In some patients, antibodies against *B burgdorferi* may be detectable in CSF slightly earlier than serum. Culture and *B burgdorferi* deoxyribonucleic acid detection using polymerase chain reaction may also be used but were not in our case.

The three patients reported in the literature with respiratory failure caused by neuroborreliosis were ventilated for 3 months, 1 month, and 13 months, respectively, whilst our patient required ventilation for only 22 days.<sup>1-4</sup> We speculate that early recognition of the possibility of Lyme disease and appropriate treatment shortened our patient's acute illness.

In conclusion, it is important to consider Lyme disease in the differential diagnosis of acute respiratory failure – with or without erythema migrans.

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**Benign paroxysmal positional vertigo (BPPV) predominantly affects the right labyrinth**

We read with great interest the article "Benign paroxysmal positional vertigo predominantly affects the right labyrinth", by M von Brevern et al,<sup>1</sup> which prompted us to review our data of the last 10 years (1995-2004).

A total of 661 patients, referred to the ear, nose, and throat department or to the neurology department, were diagnosed as having benign paroxysmal positional vertigo (BPPV) in its various forms. The pathology was located in the posterior canal in 477 patients, in the horizontal canal in 142, and in the anterior canal in 22. Multiple canals were affected in 20 patients (table 1).

The right ear was 1.50 times more frequently involved than the left. The predominance of the right ear was seen in all types of BPPV (table 1).

Hence, our data confirm the preponderance of right sided BPPV. The predilection of right sided BPPV was seen in all variants. Horizontal canal BPPV was observed in 22%, confirming our previous data.<sup>2</sup> This number is higher than in other series.<sup>3,4</sup> The apogeotropic form should not be considered as a rarity as it contributes to 23% of horizontal canal BPPV in our series and 38% in the series of Casani et al.<sup>3</sup>

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**Table 1** Laterality of the affected ear in different forms of BPPV

No. of patients	Posterior canal	Horizontal canal			Multiple canals	Totals
		Geotropic	Apogeotropic	Anterior canal		
Right n=379	266	61	23	15	14	57%
Left n=253	185	48	10	7	3	38%
Bilateral n=29	26	0	0	0	3	5%
	72%	22%	3%	3%		100%
		77% geotropic	23% apogeotropic			

Total n = 661.

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## Aciclovir induced posterior leucoencephalopathy

Aciclovir is an extremely effective agent for the treatment of herpes simplex encephalitis and varicella-zoster infections in immunocompromised individuals.<sup>1</sup> Encephalopathy induced by aciclovir is an infrequent but well recognised adverse effect of aciclovir.<sup>2</sup> The predisposing factors to aciclovir induced encephalopathy (AIE) include age, acute or chronic renal failure, and other neurotoxic drugs.<sup>2</sup> Tremors (40–58%), disorientation (40–50%), agitation (22–38%), hallucinations (25%), and delirium (25%) are common presentations of AIE, whereas seizures (10%), cerebellar ataxia (11%), sensory symptoms (9%), speech disorders (9%), fever (3%), and cranial nerve palsies (0%) are much less frequent.<sup>2</sup> The supportive diagnostic criteria for AIE include a temporal association between the symptoms and aciclovir use, as well as acellular cerebrospinal fluid (CSF) in cases without herpes simplex or varicella-zoster encephalitis. In the majority of cases symptoms develop within 72 hours of starting aciclovir treatment, although up to 120 days has been reported.<sup>2</sup> The clinical recovery may take several days (five days in 57% of cases) following discontinuation of aciclovir.<sup>2</sup> The EEG typically shows diffuse slow wave activity rather than focal abnormalities.<sup>2</sup>

The radiological features are not well described in AIE. Case reports have identified multifocal white matter signal abnormalities involving the cerebellum, pons, and periventricular region as well as evidence of vascular encephalopathy on MRI.<sup>2,3</sup> We report a case of AIE with MRI features consistent with posterior leucoencephalopathy with clinical and radiological improvement following the discontinuation of aciclovir, along with raised serum and CSF concentrations of aciclovir and 9-carboxymethoxymethylguanine (CMMG), the main metabolite of aciclovir.

## Case report

A 47 year old woman with a 15 month history of cANCA<sup>+</sup> glomerulonephritis and chronic end stage renal failure (serum creatinine 957 µmol/l), managed on continuous ambulatory peritoneal dialysis, azathioprine (100 mg/day), and prednisolone (10 mg/day), developed a mid-thoracic varicella-zoster rash. She was given a reduced dose of intravenous aciclovir (250 mg three times daily). Within 48 hours she became agitated, developed visual hallucinations and drowsiness (Glasgow coma scale (GCS): overall 6; eye 1, motor 4, verbal 1). On admission to the intensive care unit she was apyrexial, the highest blood pressure recorded was 180/104 while agitated, and fundoscopy was unremarkable. The tendon reflexes were exaggerated, with extensor plantar responses. Oculocephalic and corneal reflexes as well as spontaneous respiration were present.

Laboratory investigations showed a haemoglobin of 9.7 g/l, white cell count  $5.8 \times 10^9/l$ , urea 22 mmol/l, ESR 90 mm/h, C reactive protein 27 mg/l, albumin 22 g/l, ammonia 10 mmol/l, and cANCA negative. Computed tomography of the head, done immediately after she became obtunded, showed posterior white matter hypodensities. The lumbar CSF contained no white cells and four red blood cells per mm<sup>3</sup>, with a protein of 0.63 g/l and a CSF/serum glucose ratio of 3.9/6.4. The opening pressure was 41 cm. CSF cultures, including culture for acid fast bacilli, were negative. CSF testing by polymerase chain reaction was negative for herpes simplex virus I and II, varicella-zoster virus, cryptococcal antigen, and JC virus. An EEG showed excessive slow wave activity. Magnetic resonance imaging (MRI) of the brain and an MR venogram (done after five days on aciclovir) showed

symmetrical posterior white matter changes predominantly in the occipital and parietal lobes (fig 1A and 1B) without evidence of venous sinus thrombosis, gadolinium enhancement, or matched defects in diffusion weighted images.

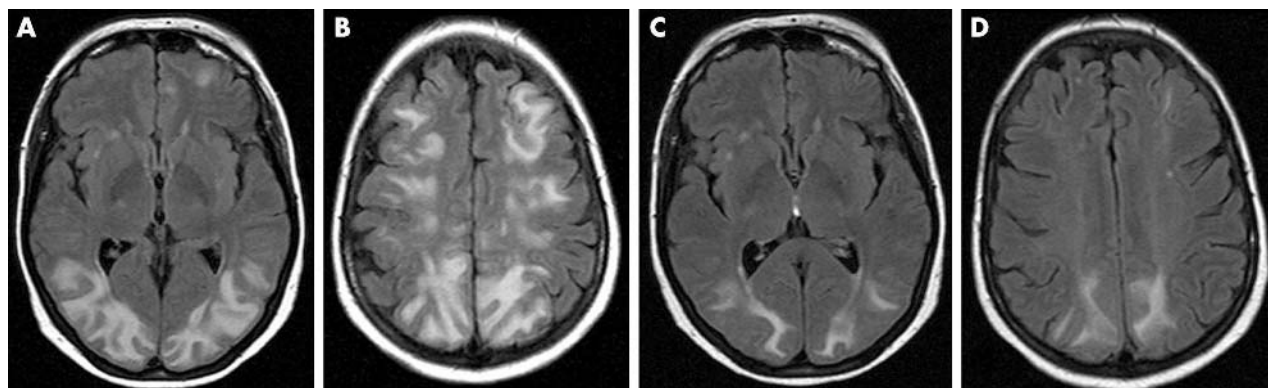
On admission, azathioprine was stopped and intravenous methylprednisolone (500 mg/day for three days) was started for presumed CNS vasculitis. There was no improvement 72 hours after this treatment and after eight days of aciclovir. Aciclovir was discontinued when AIE was suspected, and peritoneal dialysis was maintained. Within 48 hours of discontinuation of aciclovir, the GCS improved (eye score 3, motor score 6, verbal score 3) and neurological examination showed bilateral upper limb postural tremor, which resolved over 24 hours. The Addenbrooke's score was 77/100. Repeat MRI (fig 1C, 1D) showed a significant improvement. Analysis of aciclovir and CMMG levels in the serum and CSF showed high values, at levels generally associated with neurotoxicity.<sup>4</sup> The serum aciclovir and CMMG concentrations were, respectively, as follows:

- 5 days post-aciclovir initiation: 34.9 µmol/l and 91.7 µmol/l;
- 6 days post-aciclovir: 35.4 µmol/l and 148.5 µmol/l;
- 7 days post-aciclovir: 17.2 µmol/l and 141 µmol/l.

The CSF aciclovir and CMMG concentrations four days post-aciclovir initiation were, respectively, 5.99 µmol/l and 2.25 µmol/l (CMMG levels are not detectable in CSF unless there is neurotoxicity (Helldén A, submitted for publication)), supporting a diagnosis of AIE.<sup>4</sup>

## Comment

The clinical presentation of our patient, her rapid recovery, and the CSF and EEG findings are characteristic of AIE in cases without herpes simplex or varicella-zoster encephalitis.<sup>2,5</sup> The lack of significantly raised blood pressure or papilloedema excludes hypertensive posterior leucoencephalopathy. ANCA<sup>+</sup> vasculitis causing posterior leucoencephalopathy has been reported but only in the presence of severe hypertension. AIE, an infrequent but well recognised adverse effect of aciclovir, has until now been diagnosed



**Figure 1** Fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of the brain done five days after initiation of aciclovir treatment, showing features consistent with posterior leucoencephalopathy (panels A and B). Repeat MRI five days after discontinuation of aciclovir showed a marked improvement (panels C and D).

mainly on clinical features.<sup>2-5</sup> Factors predisposing to AIE include age, acute or chronic renal failure, and other neurotoxic drugs.<sup>5</sup> The diagnosis is facilitated by analysis of aciclovir and CMMG in serum and CSF. In cases with renal failure, the half life of aciclovir extends from 3 to 20 hours and as a result aciclovir is metabolised to CMMG by alcohol and aldehyde dehydrogenases.<sup>4</sup> At present, reliable dose recommendations are not available for patients with renal failure.

In a case study of 93 patients, mainly with renal failure,<sup>4</sup> we found mean (SD) serum aciclovir concentrations of 21.0 (30.7)  $\mu\text{mol/l}$  (in 49 patients with neurotoxicity) and 7.2 (6.7)  $\mu\text{mol/l}$  (in 44 asymptomatic patients receiving aciclovir), while CMMG concentrations were 34.1 (39.4)  $\mu\text{mol/l}$  in patients with neurotoxicity and 4.7 (4.7)  $\mu\text{mol/l}$  in asymptomatic patients. CMMG levels of  $>10$   $\mu\text{mol/l}$  seemed to be associated with neurotoxicity. A high CMMG level is a strong predictor of AIE in patients with renal failure.<sup>4</sup> Haemodialysis is effective in clearing aciclovir and CMMG, and to a lesser extent so is peritoneal dialysis.<sup>4</sup>

This case highlights the difficulties in diagnosing AIE and the value of measuring aciclovir and CMMG levels in making the diagnosis.<sup>4</sup> In cases with renal failure and herpes simplex or varicella-zoster encephalitis, aciclovir should not be discontinued prematurely, but a total daily dose exceeding 400 mg is not generally recommended in patients with renal impairment. Pharmacokinetic studies of aciclovir and CMMG are being undertaken at Karolinska University Hospital, Sweden, with the aim of achieving dose recommendations for patient with renal failure.

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## Normal memory and no confabulation after extensive damage to the orbitofrontal cortex

Subarachnoid haemorrhage caused by the rupture of an anterior communicating artery (ACoA) aneurysm is often followed by amnesia, confabulation, and personality change including social decision making.<sup>1-3</sup> However, the regions responsible for each symptom have not been determined conclusively. We describe a patient who showed personality change, but neither memory impairment nor confabulation, after extensive damage to the bilateral orbitofrontal cortex demonstrated by magnetic resonance imaging, providing evidence that the destruction of the medial orbitofrontal cortex alone cannot cause amnesia and confabulation.

### Case report

The patient was a 45 year old, right handed man with a 16th grade education. He was not an apathetic person and worked hard as a manager before the onset. His past medical history was unremarkable and he had no medication. He had sudden onset of headache, became unconscious, and was admitted to an emergency hospital. Brain computed tomography showed a subarachnoid haemorrhage in the cisterns around the brainstem, longitudinal cerebral fissure, and bilateral Sylvian fissure caused by a ruptured aneurysm of the ACoA. On the same day, he underwent an operation to repair the ruptured aneurysm. There were slight brain oedema and vasospasm (four to 10 days). He did not become delirious, agitated, or suspicious. He had 200 mg of phenitoin each day to prevent secondary seizures. His family noted that he showed mild anterograde amnesia, which improved over two months, but no retrograde amnesia.

The patient was discharged home after three months. He began working again as a manager at his company, but could not do his job as well as before the onset. Twenty months after the onset, he was admitted to our hospital for assessment of his problems.

On admission, the patient was fully alert and oriented. General physical and neurological examinations were unremarkable. During his stay in hospital, he had no problems communicating with others, kept his appointments and could find his way around the hospital. His family and his superior at his company reported that his personality had changed since the onset of his illness (in terms of lack of concern for others including his family, his appearance, and his future; the loss of spontaneity, initiative, and self motivation; disinhibition; and rigidity of thought).

General neuropsychological assessments were performed between the second and 12th hospital days. He was attentive, cooperative, and showed no confabulatory response. His intelligence level was normal on the Wechsler Adult Intelligence Scale-Revised (full IQ, 113; verbal IQ, 114; performance IQ, 109), Mini Mental State

Examination (30 of 30), and Raven Progressive Colored Matrices (35 of 36). He showed no linguistic deficit on the Western Aphasia Battery. The results of the Wisconsin Card Sorting Test (six categories achieved) and Verbal Fluency Test (animals, initial syllables "A", "Fu", and "Ni": 15, 10, 10, and 15/minute, respectively) were normal. His immediate memory spans were normal (forward: verbal, 7; spatial, 6; and backward: verbal, 6; spatial, 6). The indices on the Wechsler Memory Scale-Revised were above average, except for a somewhat low score for delayed index (general, 112; verbal, 110; visual, 108; attention/concentration, 112; delayed, 85). He showed no retrograde amnesia in a structured interview, on the Autobiographical Memory Interview (incidents 9, 9, 8 and personal semantic 21, 20, 21 for childhood, early adult life, and recent, respectively), and on the Public Events test (14, 15, 14, and 16/16 for 60th, 70th, 80th, and 90<sup>th</sup>, respectively).

Brain magnetic resonance imaging performed 20 months after the onset (fig 1) showed bilateral lesions in the ventromedial prefrontal lobe extending to the frontal pole and subcortical regions under the middle and superior frontal gyri. Additional lesions were seen in the left insula and the right ventral anterior nucleus of the thalamus.

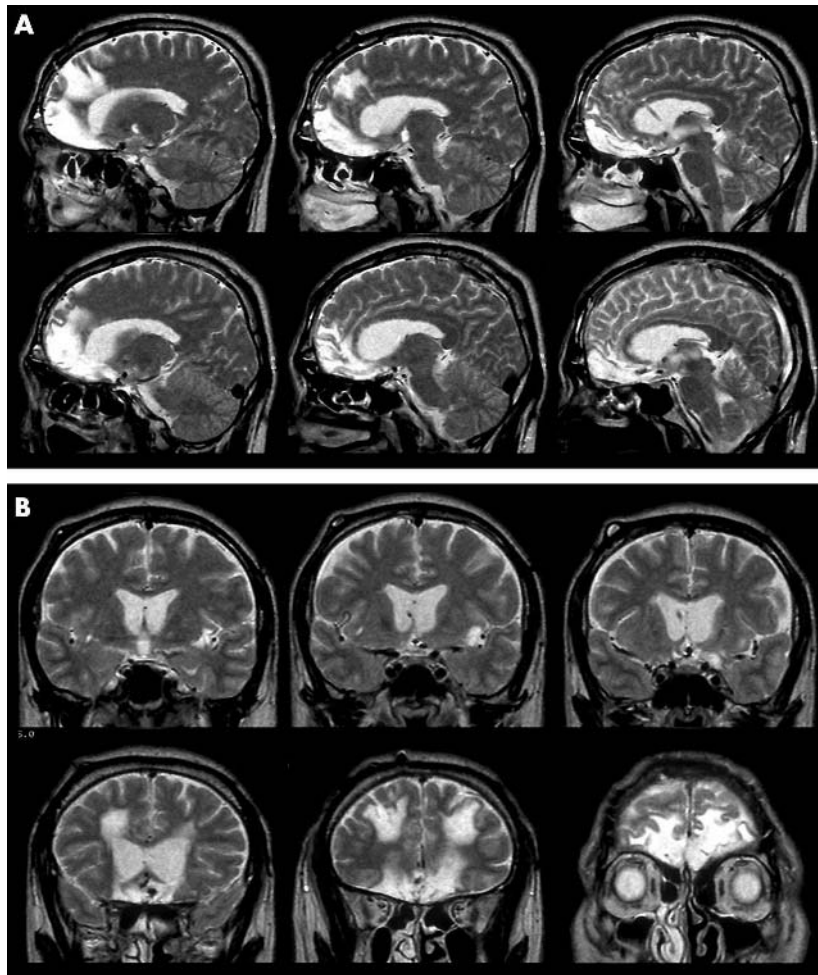
### Discussion

After extensive damage to the bilateral orbitofrontal cortex, with no concomitant lesion in the basal forebrain, the patient showed personality change as a result of a subarachnoid haemorrhage, but neither memory deficits on comprehensive neuropsychological assessment nor confabulation. His personality change could be classified as a combined type (apathetic and disinhibited) and was consistent with those (lack of concern, loss of spontaneity, disinhibition, impaired decision making, and rigidity of thought) generally agreed in the literature to be the result of dysfunction of the frontal lobe, particularly the orbitofrontal cortex.<sup>1-3</sup>

Importantly, the patient showed no memory deficit. Damage to the basal forebrain without damage to the frontal lobe causes amnesia.<sup>4</sup> With regard to the orbitofrontal cortex, it has been argued that destruction of this region is not necessary for the development of amnesia or basic cognitive function.<sup>1,3</sup> However, there has so far been no conclusive evidence as to whether or not damage to the orbitofrontal cortex alone (especially the medial caudal part of it) gives rise to amnesia.<sup>1</sup> Our present study provides evidence that damage to the orbitofrontal cortex alone does not result in amnesia and therefore strengthens the notion that the basal forebrain is one of the crucial sites for human memory.

It should be noted that the assessment of memory in our present study is based on standardised tests. This means that memory that is not measurable using these standardised tests (for example, temporal context memory) may be related to the function of the orbitofrontal cortex. In addition, we cannot draw a strong conclusion regarding frontal lobe function, because we did not use tests sensitive to damage to the ventromedial prefrontal cortex (for example, the Iowa Gambling Task<sup>5</sup>).

The patient showed no confabulation. Damage to the orbitofrontal lobe alone might not be sufficient for confabulation to be



**Figure 1** (A) Sagittal and (B) coronal T2 weighted magnetic resonance images showing extensive lesions in the bilateral orbitofrontal cortex. The core structures of the basal forebrain (medial septal nucleus, vertical and horizontal limb nuclei of Broca's diagonal band, and nucleus basalis of Meynert) were not damaged. In the sagittal sections, the images in the upper row show the right hemisphere and those in the lower row show the left hemisphere. In each row, the first, second, and third images are 15 mm, 10 mm, and 5 mm away from the longitudinal cerebral fissure, respectively. In the coronal sections, the left side of the image corresponds to the right side of the brain. In the upper row, the first, second, and third images are 0 mm, 5 mm, and 10 mm rostral from the anterior commissure. In the lower row, the first, second, and third images are 20 mm, 30 mm, and 50 mm rostral from the anterior commissure.

manifest. In one study, confabulation was seen in amnesic but not in non-amnesic patients with rupture of the ACoA and frontal lobe lesions,<sup>1</sup> and in another study of amnesic patients with rupture of the ACoA, only those with frontal lobe lesions showed confabulation,<sup>3</sup> suggesting that both frontal lobe lesions and amnesia are necessary for the development of confabulation. In contrast, a patient with confabulation and amnesia after damage to the basal forebrain but without frontal lobe damage has been reported.<sup>4</sup> Further studies involving comprehensive neuropsychological and magnetic resonance imaging examination are needed to determine whether both frontal and basal forebrain involvement or basal forebrain involvement alone is required for the manifestation of confabulation.

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The patient gave informed consent for this letter to be published.

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## Adult onset SSPE: experiences in West Yorkshire over a 12 month period

Subacute sclerosing panencephalitis (SSPE) is a rare delayed complication of measles virus infection in infancy. It is characterised by behavioural changes, myoclonus, cognitive impairment, visual disturbance, pyramidal and extrapyramidal signs, and ultimately coma leading to death.<sup>1</sup> Typically, SSPE presents in childhood or early adolescence, but adult onset cases are recognised. Widespread measles immunisation in the UK has led to a dramatic fall in the incidence of SSPE in children, leading to the disease almost becoming extinct.<sup>2</sup> However, a latent disease pool remains and cases may still come to the attention of adult neurologists, as borne out by our recent experience in West Yorkshire.

## Case histories

An 18 year old man gave a three week history of blinking episodes lasting approximately one second, associated with a brief head jerk. These were not present in sleep. Examination revealed myoclonic jerks involving the neck associated with blinking. Initial electroencephalograms (EEGs), blood tests, and a magnetic resonance imaging scan were normal. Several anticonvulsant medications failed to suppress the jerks, which by four weeks had spread to the legs, causing unsteadiness. The mini mental test examination score at this stage was 26 of 30. He began to deteriorate rapidly, with disorientation, blunted affect, dystonic posturing of the left arm, bradykinesia, and rigidity. Cerebrospinal fluid (CSF) was sent for analysis of 14-3-3 and S-100 proteins, which were negative. A further EEG, nine weeks after onset, demonstrated high voltage periodic complexes occurring every 10 seconds, consistent with SSPE. CSF and serum measles titres were raised at 35110 mIU/ml and 152930 mIU/ml, respectively. The CSF to serum albumen ratio was 1:300, consistent with intrathecal antibody synthesis. There was no past history of measles, although he had received MMR (measles mumps rubella) immunisation at age 9. Oral inosiplex (isoprinosine) and subcutaneous interferon  $\alpha 2b$  were started and an Ommaya reservoir was inserted to administer intraventricular interferon  $\alpha 2b$ . By this stage, the myoclonus had subsided but he had gaze paresis, mutism, widespread spasticity, and required gastrostomy feeding. He received intraventricular treatment for six weeks before reservoir infection necessitated its removal. His condition plateaued and he was maintained on inosiplex alone. Eventually, he was discharged home in a dependent state.

A 25 year old woman presented to her general practitioner complaining of impaired concentration, mood swings, disturbed sleep, and memory loss. One month later, she had noticed a fine tremor in both hands and occasional spasms affecting her right foot. Her concentration was worse and she mentioned word finding difficulties. She also had a tendency to stagger and fall. She was seen by a psychiatrist and somatisation was initially suspected. Later, she was referred to a neurologist. He noted that she had been acting oddly—for example, being found by her mother in a bath of cold water. Neurological examination was normal except for a mini mental test examination score of 20 of 30 with a child-like effect and stilted speech. A magnetic resonance imaging scan was unremarkable. She continued to deteriorate, developing right sided myoclonus. By this stage, she was unable to perform simple tasks, such as washing, and was aware of crawling sensations all over her body. Six months after her first presentation she had an EEG. This revealed repetitive complexes occurring every four to six seconds, often associated with a myoclonic jerk and consistent with SSPE. CSF analysis confirmed oligoclonal bands not present in the serum, which were positive for measles antibody antigen by immunoblotting. She had contracted measles at age 11 months. She was started on oral piracetam and inosiplex, along with subcutaneous interferon  $\beta$ 1a, but she became bed bound with quadriplegia, dysarthria, and diffuse hyperalgesia. Her treatment was changed to intraventricular interferon  $\alpha$ 2a administered via an Ommaya reservoir. She required subcutaneous infusions of midazolam and diamorphine for symptom control, and nasogastric feeding was started. Her condition subsequently stabilised and she was discharged to a children's hospice.

## Discussion

The estimated incidence of SSPE each year in developed nations is < 1/10 million of the population under the age of 20. The occurrence of two adult cases in the small region of West Yorkshire (population two million) within a few months of one another is remarkable. Although probably a chance finding, our experience emphasises the need for continued surveillance in populations where measles is no longer endemic. In theory more adult onset SSPE cases could present to neurologists in the future. This is because slow central nervous system spread of the virus over many years leaves open the potential for SSPE to present in later life, decades after population eradication of measles. In addition, routine immunisation has led to a shift in the incidence of measles towards unprotected children age < 1, who are at a higher relative risk of developing SSPE in later life after a longer incubation period.<sup>2</sup> Recently, there has been an increase in the number of measles outbreaks after a decline in the uptake of the combined MMR immunisation because of safety fears.<sup>3</sup>

In our patients, SSPE was not initially suspected, leading to diagnostic delay. Enquiring about measles in childhood may have been helpful in case 2, but not case 1, because infection in infancy was probably subclinical. In this patient the lack of typical findings on initial EEGs led to further delay, and instead we considered variant Creutzfeldt Jakob disease as a possibility. Patient 2 presented with early cognitive and

behavioural changes. Initially, patients may come to the attention of other specialties with non-specific or psychiatric symptoms.<sup>4</sup> It was only subsequent worsening of the patient's mental state associated with the development of unilateral myoclonic jerks that prompted further investigation, including EEG.

There is no curative treatment for SSPE. Trials have been complicated by variable natural history and spontaneous long remissions of the disease, although it is eventually fatal (median survival, three years). One study demonstrated similar response rates among patients randomised to inosiplex, with or without intraventricular interferon  $\alpha$ 2b treatment for six months (35% v 34%).<sup>5</sup> However, these figures were substantially higher than historical remission rates of between 5% and 10%. In our hands, intraventricular interferon was associated with initial worsening of encephalopathy and pronounced hyperpyrexia, possibly the result of chemically induced meningitis, and reservoir infection was a further complication. In both patients, disease appeared eventually to stabilise after antiviral treatment, particularly in patient 1, in whom rapid progression at onset was suggestive of fulminant SSPE, usually fatal within three months.

Prevention seems to be the best approach, with mass immunisation leading to a drastic reduction in reported cases of measles and associated complications. However, our experience suggests that SSPE in adults should not be forgotten. Clinicians should remain vigilant for this devastating disease.

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## Laterality of symptoms in patients admitted to a stroke unit who had a discharge diagnosis of a psychiatric condition

Some psychiatric conditions produce symptoms that can mimic an acute neurological disease, including stroke.<sup>1–3</sup> In several studies, such symptoms seemed to be more common on the left side of the body.<sup>1–3</sup> The

predominant processing of emotional information by the right hemisphere offers a hypothetical explanation for this finding.

We reviewed the discharge summaries of patients who were admitted to a stroke unit during the period May 1996 to December 2003 with a diagnosis of acute stroke and who had a discharge diagnosis of somatoform disorder and/or anxiety disorder according to the DSM-IV, revised<sup>4</sup> criteria, and no recent stroke, according to the World Health Organisation definition.<sup>5</sup>

Two investigators (CS and LC) reviewed the discharge summaries independently and collected the following data in a standardised form: (a) age; (b) sex; (c) discharge psychiatric diagnosis (somatoform disorders: somatisation disorder and conversion disorder; anxiety disorders: generalised anxiety disorder and panic disorder); (d) type (motor paresis and/or involuntary movements, sensory, visual, other) and side (right, left, bilateral) of the symptoms; (e) vascular risk factors; (f) neuroimaging data; and (g) length of stay. Disagreements were solved by consensus.

## RESULTS

From 2279 consecutively admitted patients to our stroke unit, we included 35 (1.5%) discharge summaries for review. Of these, 25 patients had received a diagnosis of somatoform disorder (14 with somatisation disorder and 11 with conversion disorder), and 7 patients had a diagnosis of anxiety disorder (4 with generalised anxiety disorder and 3 with panic disorder). Three patients had other psychiatric diagnoses. Symptoms were presented on the left side of the body in 11 patients, on the right side of the body in 14, and 10 presented bilateral symptoms (table 1). There were 21 patients (60%) with vascular risk factors, of whom 11 (31.4%) had more than one risk factor. Median hospitalisation stay was 3 days.

There were no statistical differences in demographic variables, discharge psychiatric diagnosis, type of the symptoms, vascular risk factors, neuroimaging data, or length of stay between patients with left sided symptoms and those with right sided symptoms concerning (table 1). Patients with somatoform disorders had motor symptoms more frequently than did patients with anxiety disorders ( $\chi^2 = 6.84$ ;  $p = 0.02$ ).

## DISCUSSION

In this study, 1.5% of the patients admitted to a stroke unit presented symptoms unexplained by stroke or other neurological disease and fulfilling the criteria for psychiatric diagnosis. Contrary to most of published studies, our results did not show a preponderance of left sided symptoms. In a meta-analysis of all studies describing patients with medically unexplained symptoms, Stone *et al* concluded that is not certain that the functional symptoms are more common on the left side than on the right side of the body. They found a preponderance of the left symptoms only in the studies in which the investigators were aware of the laterality hypothesis before performing the study.<sup>1</sup> As in that meta-analysis, we did not find a preponderance of left sided symptoms.

The younger median age and the female preponderance of patients with psychiatric conditions mimicking a stroke reflects the demographic characteristics of somatoform



**Table 1** Differences between patients with a psychiatric diagnosis and with left and right sided symptoms

Variables	n (%)	Left group	Right group	p value
<b>Demographics</b>				
Age (median)	41.0	41.0	38.0	0.94*
Sex (F/M)	28 (80.0)/ 7 (20.0)	9 (81.8)/ 2 (18.2)	10 (71.4)/ 4 (28.6)	0.66†
<b>Diagnosis</b>				
Somatoform disorders	25 (71.4)	9 (81.8)	10 (90.9)	–
Somatisation disorder	14 (40.0)	4 (36.4)	7 (63.6)	1.00†
Conversion disorder	11 (31.4)	5 (45.5)	3 (27.3)	–
Anxiety disorders	7 (20.0)	2 (18.2)	1 (9.1)	–
GAD	4 (11.4)	1 (9.1)	1 (9.1)	–
Panic disorder	3 (8.6)	1 (9.1)	0	–
Other	3 (8.6)	–	3	–
<b>Symptoms</b>				
<b>Paresis</b>				
Total	26 (74.3)	9 (81.9)	12 (85.7)	1.00†
Left	10 (38.5)	–	–	–
Right	12 (46.2)	–	–	–
Bilateral	4 (15.4)	–	–	–
<b>Involuntary movements</b>				
Total	1 (2.9)	0	1 (7.1)	1.00†
Right	1	–	–	–
<b>Sensory</b>				
Total	17 (48.6)	4 (36.4)	7 (50.0)	0.69†
Left	4 (23.5)	–	–	–
Right	7 (41.2)	–	–	–
Bilateral	6 (35.3)	–	–	–
<b>Visual</b>				
Total	5 (14.3)	1 (9.1)	2 (14.3)	1.00†
Bilateral	5	–	–	–
<b>Other</b>				
Total	19 (54.3)	3 (27.3)	9 (64.3)	0.15†
Left	11 (31.4)	11	–	–
Right	14 (40.0)	–	14	–
Bilateral	10 (28.6)	–	–	–

\*p value for Mann-Whitney *U* test (left group/right group); †p value for  $\chi^2$  test (left group/right group). GAD, generalised anxiety disorder.

and anxiety disorders. One interesting finding was the high frequency of vascular risk factors, which increases diagnostic uncertainty and could explain the admission to the stroke unit. A major limitation of our study is the lack of use diffusion magnetic resonance imaging to exclude definitively the unlikely possibility of a concomitant ischaemic lesion.

We conclude that left sided laterality of symptoms cannot be used as a tool to establish a psychiatric diagnosis in patients with acute lateralised neurological symptoms.

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## BOOK REVIEW

### Atlas of neuromuscular diseases

Edited by Eva L Feldmand, Wolfgang Grisold, James W Russell, Udo Zifko. Published by Springer Verlag, 2005, €198 (hardcover), pp 474. ISBN 3-211-83819-8

This book is titled an “atlas” and subtitled “a practical guideline”. I had the expectation of a heavily illustrated book of neuromuscular conditions with annotations. The book has been designed as a comprehensive coverage

of disorders of peripheral nerve (including cranial nerves), muscle, neuromuscular junction, and motor neurone. Each condition is outlined in note form, with particular emphasis on causation—which can be lengthy and repetitive. The style of the text is abbreviated and can be difficult to read. The précis can be misleading or inaccurate at times. A useful list of references is given.

It is not clear to me to whom this book would appeal. The text is probably too comprehensive and potentially misleading or confusing for students, and does not add much to those already informed. The number and quantity of the illustrations is disappointing. I had expected more clinical illustrations of the conditions described. As a practical guideline it is not helpful and in particular the therapeutic suggestions are too abbreviated, incomplete, and uncritical for clinical application. Problems to be addressed in the next edition include the use of the same nerve biopsy illustration for patients with chronic inflammatory demyelinating polyneuropathy and Charcot-Marie-Tooth disease, despite one image being rotated by 90 degrees; the illustration of text relating to genetically defined young onset spinal muscular atrophy with an elderly man who appears to have progressive muscular atrophy; and the spelling of fascioscapulothoracic (sic) dystrophy.

The authors point out that “no other book provides a complete overview in a structured and easily comprehensible pattern supported by figures and pictures”. There are, however, a number of excellent books related to diseases of muscle and nerve, some providing a wider range of clinical and pathological illustrations and a more critical review of clinical presentation, diagnosis, and treatment. At the present time the role claimed by this book remains unfilled.

R W Orrell

## CORRECTION

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M S Welgampola, S M Rosengren, G M Halmagyi, *et al*. Vestibular activation by bone conducted sound (*J Neurol Neurosurg Psychiatry* 2003;**74**:771–8). This relates to calibration of the output of the bone conductor that was used. The audiometric calibrator was not fully aware of the specific units in which bone conductors are generally calibrated but rather was influenced by the units of the sound level meter (suitable for air conducted sound). The calibration procedure is normally performed purely for testing hearing, in which case the precise units used are not strictly relevant (and under conditions which are quite different from those that the authors used). The authors have now purchased the required equipment to allow calibration of the B71, and have provided a guide to the force levels obtained:

Bone conducted stimuli should be measured in units of dB FL (force level) as a ratio to a reference force of 1  $\mu$ N. These levels are 10–20 dB higher, depending upon frequency, than the values given as “SPL”. The standard parameter 500 Hz 7ms “112 dB SPL” tone burst stimulus, obtained with a 10 V peak to peak input, corresponds to an intensity of 127 dB FL (RMS).