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). PML progresses to death in most of these patients even after withdrawing immunosuppressive therapy. 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 T2 and hypointense on T1 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 hemi-ataxia 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 T2 and hypointense on T1 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,1, 2 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.3, 4 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...
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. 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 die after discontinuation of immunosuppression alone. Interestingly, our patient did not show signs of severe immunosuppression at the point of presentation in a case report. 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.

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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References


Dramatic improvement in non-AIDS related progressive multifocal leucoencephalopathy

Progressive multifocal leucoencephalopathy (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, the long term survival without real neurological improvement has been reported in patients treated with highly active antiretroviral therapy (HAART). Few cases of improvement with cidofovir or aracytine have been described in AIDS related or non-AIDS-related PML. In large trials in AIDS related PML, no clinical benefit was found. 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 count abnormalities. Fine needle aspiration cytology of lymphadenopathy with 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+ T cells against JC virus. We detected JC virus DNA detection in CSF, and by a specific PCR for CD4+ T cells against JC virus. We decided to continue subcutaneous aracytine 2 mg/kg/d for five days monthly 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 PCR for 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 imaging remained stable. 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 previous studies suggesting individual beneficial effects of these drugs. To our knowledge, these drugs have not been used in combination before. In comparison to 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 improvement. In 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 T cells rather than to their absolute count. Immunological studies have shown that JCV specific CD4-T cell responses play a
major role in the control of PML development; for example, in one study 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, 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 JCV 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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References


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. 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 206/144 mm Hg. There was no abnormality of the abdomen that was removed and on closer inspection there was a marked loss of tone. 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, Po2 6.7 kPa, and Pco2 4.7 kPa. Her chest radiograph showed left basal changes. On day 5 her Po2 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 H2O.

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).
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.\(^1\)\(^2\)\(^3\)\(^4\) 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* desoxyribonucleic 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.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\) 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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We would like to thank Mr P R Randell of the Microbiology Department, St Richard’s Hospital, Chichester, UK and Dr Susan O’Connell of the Microbiology Department, St Richard’s Hospital, Chichester, UK.

### References


### 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 Brevtern et al.,\(^1\) 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.\(^2\) This number is higher than in other series.\(^3\)\(^4\) 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.\(^5\)

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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 5 months and then died after receiving treatment for a pulmonary embolism.\(^1\) 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.\(^2\)\(^3\)\(^4\)\(^5\) All patients were well at follow up, although one patient had persistent phrenic paralysis 6 months after treatment.\(^5\)

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

<table>
<thead>
<tr>
<th>Horizontal canal</th>
<th>No. of patients</th>
<th>Posterior canal</th>
<th>Geotropic</th>
<th>Apogeotropic</th>
<th>Anterior canal</th>
<th>Multiple canals</th>
<th>Totals</th>
</tr>
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<tbody>
<tr>
<td>Right n = 379</td>
<td>266</td>
<td>61</td>
<td>23</td>
<td>15</td>
<td>14</td>
<td>57%</td>
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<tr>
<td>Left n = 253</td>
<td>185</td>
<td>48</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td>38%</td>
<td></td>
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<tr>
<td>Bilateral n = 29</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>5%</td>
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<tr>
<td></td>
<td>72%</td>
<td>22%</td>
<td>3%</td>
<td>3%</td>
<td>100%</td>
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<td>77% geotrop</td>
<td>23% apogeotropic</td>
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Total n = 661

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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.\textsuperscript{1,3} Factors predisposing to AIE include age, acute or chronic renal failure, and other neurotoxic drugs.\textsuperscript{4} 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.\textsuperscript{5} At present, reliable dose recommendations are not available for patients with renal failure.

In a case study of 93 patients, mainly with renal failure,\textsuperscript{6} we found mean (SD) serum aciclovir concentrations of 21.0 (30.7) \text{\(\mu\text{g/mL}\)} (in 49 patients with neurotoxicity) and 7.2 (6.7) \text{\(\mu\text{g/mL}\)} (in 44 asymptomatic patients receiving aciclovir), while CMMG concentrations were 34.1 (39.4) \text{\(\mu\text{g/mL}\)} in patients with neurotoxicity and 4.7 (4.7) \text{\(\mu\text{g/mL}\)} in asymptomatic patients. CMMG levels of >10 \text{\(\mu\text{g/mL}\)} seemed to be associated with neurotoxicity. A high CMMG level is a strong predictor of AIE and the value of measuring aciclovir and CMMG in serum and CSF. In cases with renal failure, the half life of aciclovir and CMMG in serum and CSF. In a case study of 93 patients, mainly with renal failure,\textsuperscript{6} we found mean (SD) serum aciclovir concentrations of 21.0 (30.7) \text{\(\mu\text{g/mL}\)} (in 49 patients with neurotoxicity) and 7.2 (6.7) \text{\(\mu\text{g/mL}\)} (in 44 asymptomatic patients receiving aciclovir), while CMMG concentrations were 34.1 (39.4) \text{\(\mu\text{g/mL}\)} in patients with neurotoxicity and 4.7 (4.7) \text{\(\mu\text{g/mL}\)} in asymptomatic patients. CMMG levels of >10 \text{\(\mu\text{g/mL}\)} seemed to be associated with neurotoxicity. A high CMMG level is a strong predictor of AIE and the value of measuring aciclovir and CMMG in serum and CSF.

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**References**


**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.\textsuperscript{1,2} However, the regions responsible for each symptom have not been conclusively established. 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 aphatic patient 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 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 his medication and was able to start methylenedopa every day to prevent secondary seizures. His family noted that he showed mild antegrade 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 having worsened 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 result of Wisconsin Card Sorting Test (six categories achieved) and Verbal Fluency Test (animals, initial syllables “A”, “F”, and “N”: 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, 8, and 8, respectively) 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.\textsuperscript{3,4}

Importantly, the patient showed no memory deficit. Damage to the basal forebrain without damage to the frontal lobe causes amnesia.\textsuperscript{5} 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.\textsuperscript{6} 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.\textsuperscript{7} 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 our present study is that is not measurable using these standardised tests (for example, temporal context memory) may be related to the function of the orbitofrontal cortex. 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)\textsuperscript{8}.

The patient showed no confabulation. Damage to the orbitofrontal lobe alone might not be sufficient for confabulation to be
manifest. In one study, confabulation was seen in amnesic but not in non-amnesic patients with rupture of the ACoA and frontal lobe lesions, 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.

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.

References


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. 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. 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 protein. SSPE. CSF and serum measles titres were 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 intraventricular interferon a2b were started and an Ommaya reservoir was inserted to administer intraventricular interferon a2b. 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 daughter 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 was found dead in her bath. Further investigation revealed that 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 oligodendroglia 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 intravenous interferon beta 2a, but she became bed bound with quadriparesis, dysarthria, and diffuse hyperalgesia. Her treatment was changed to intraventricular interferon beta 2a administered via an Ommaya reservoir. She required continuous 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 < 0.1/10 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. 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.

In our patients, SSPE was not initially suspected, but its diagnosis was confirmed by a positive CSF measles IgG index. Occurrence of two adult cases in the small region of West Yorkshire (population two million) was discharged to a children’s hospice. In our patients, SSPE was not initially suspected, but its diagnosis was confirmed by a positive CSF measles IgG index. Occurrence of two adult cases in the small region of West Yorkshire (population two million) was discharged to a children’s hospice. In our patients, SSPE was not initially suspected, but its diagnosis was confirmed by a positive CSF measles IgG index. Occurrence of two adult cases in the small region of West Yorkshire (population two million) was discharged to a children’s hospice.

References


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. In some studies, such symptoms seemed to be more common on the left side of the body. 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 criteria, and no recent stroke, according to the World Health Organisation definition.

Two investigators (CS and LC) reviewed the discharge summaries independently and collected the following data: 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 both 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 (51.4%) 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 more moderate symptoms than 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 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 it 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 side symptoms only in the studies performed after a longer period of time. In our study, investigators were aware of the laterality hypothesis before performing the study. As in that meta-analysis, we did not find a preponderance of left sided symptoms.

The younger median age and female preponderance of patients with psychiatric conditions mimicking a stroke reflects the demographic characteristics of somatiform conditions.
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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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 normalised for testing hearing, in which case the specific 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.

**CORRECTION**

Bone conducted stimuli should be measured in units of dB Fl (force level) as a ratio to a reference force of 1 mμ.

This book it titled an “atlas” and subitled “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 neuron. 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 deemyelinating polynuropathy 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 fascioscapulohumeral (sic) dystrophy.

The authors point out that “no other book provides a complete overview in a structured and easily comprehensive 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 unfulfilled.

R W Orrell

**REFERENCES**


**BOOK REVIEW**

Atlas of neuromuscular diseases

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

This book it titled an “atlas” and subitled “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 neuron. 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 deemyelinating polynuropathy 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 fascioscapulohumeral (sic) dystrophy.

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Bone conducted stimuli should be measured in units of dB Fl (force level) as a ratio to a reference force of 1 μN. 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).

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

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