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).1,2 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, was 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 psychic 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-axia, 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.1-3 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.1 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.3,4 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.2

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.

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 related PML, long term survival without real neurological improvement has been reported in patients treated with highly active antiretroviral therapy (HAART).6 Few cases of improvement with cidofovir or aracytine have been described in AIDS related or non-AIDS related PML.1,7 But in larger trials in AIDS related PML, no clinical benefit was found.8 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 lymph nodes biopsy revealed a 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/mm3 (normal 858–1320/mm3). 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 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 spaicing 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 previous reports, suggesting individual beneficial effects of these drugs.1,2 To our knowledge, these drugs have not been used in combination before. In combination of the drugs, 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 findings. 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 in our 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+ T 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 side. Major role in the control of PML development; for example, in one study5 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 JCV 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.14 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 twitchs 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 260/107 mm Hg. There was marked right upper quadrantal 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, Po2 6.7 kPa, and Pco2 4.7 kPa. Her chest radiograph showed left basal changes. On day 5 her Pco2 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 to cold in the right leg. There have been five recorded cases of diaphragmatic paralysis as a complication of neuroborreliosis.14 Here we report another case of Lyme meningoradiculitis, caused by an identified tick, leading to bilateral diaphragmatic paralysis with an abbreviated course on treatment.
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.1–4 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* 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.1–4 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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References


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

<table>
<thead>
<tr>
<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>
</thead>
<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>
</tr>
<tr>
<td>Left n = 253</td>
<td>185</td>
<td>48</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td>38%</td>
</tr>
<tr>
<td>Bilateral n = 29</td>
<td>26</td>
<td>72%</td>
<td>22%</td>
<td>3%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

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.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 1.5 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.1 This number is higher than in other series.1,4 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.1

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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 immuno-compromised individuals.1 Encephalopathy induced by aciclovir is an infrequent but well recognised adverse effect of aciclovir.2 The predisposing factors to aciclovir induced encephalopathy (AIE) include age, acute or chronic renal failure, and other neurotoxic drugs. Tremors (40–58%), disorientation (40–90%), agitation (22–30%), 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.2 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.3 The clinical recovery may take several days (five days in 57% of cases) following discontinuation of aciclovir.4 The EEG typically shows diffuse slow wave activity rather than focal abnormalities.5

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.6,7 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 women with a 15 month history of cANCA5 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 5.8×10⁹/l, urca 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 mm³, with a protein of 0.63 g/l and a CSF/serum glucose ratio of 3.96:1. 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 1 and 2, 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.3 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 (Heiliden A, submitted for publication)), supporting a diagnosis of AIE.8

Comment

The clinical presentation of our patient, her rapid recovery, and the CSF and EEG findings are characteristic of AIE without herpes simplex or varicella–zoster encephalitis.2,5 The lack of significantly raised blood pressure or papilloedema excludes hypertensive posterior leucoencephalopathy. ANCA 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.
mainly on clinical features.\textsuperscript{3} Factors predisposing to AIE include age, acute or chronic renal failure, and other neurotoxic drugs.\textsuperscript{3} 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{3} 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{1} we found mean (SD) serum aciclovir and CMMG concentrations of 21.0 (30.7) \textmu mol/l (in 49 patients with neurotoxicity) and 7.2 (6.7) \textmu mol/l (in 44 asymptomatic patients receiving aciclovir), while CMMG concentrations were 34.1 (39.4) \textmu mol/l in patients with neurotoxicity and 4.7 (4.7) \textmu mol/l in asymptomatic patients. CMMG levels of >10 \textmu mol/l seemed to be associated with neurotoxicity. A high CMMG level is a strong predictor of AIE in patients with renal failure.\textsuperscript{2} Haemodialysis is effective in clearing aciclovir and CMMG, and to a lesser extent so is peritoneal dialysis.\textsuperscript{2}

This case highlights the difficulties in diagnosing AIE and the value of measuring aciclovir and CMMG levels in making the diagnosis.\textsuperscript{4} 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 patients with renal failure.

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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{5}\textsuperscript{5} However, the regions responsible for each symptom have not been assessed conclusively. We describe a patient who showed personality change, but neither memory impairment nor confabulation, after extensive damage to the bilateral orbitofrontal cortex demonstrating 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 a pathetic 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, lateral ventricular effusion, 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 a good memory and worked hard every 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 the evaluation 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) generally agreed in the literature to be the result of dysfunction of the frontal lobe, particularly the orbitofrontal cortex.\textsuperscript{6,7}

Important, the patient showed no memory deficit. Damage to the basal forebrain without damage to the frontal lobe causes amnesia.\textsuperscript{8} 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{9} 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{1} 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 the assessment is not measurable using these standardised tests (for example, temporal context memory) may be related to the function of the orbitofrontal cortex. However, 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{10}

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,\(^1\) and in another study of amnesic patients with rupture of the ACoA, only those with frontal lobe lesions and amnesia are necessary for the development of confabulation.\(^1\) In contrast, a patient with confabulation and amnesia after damage to the basal forebrain but without frontal lobe damage has been reported.\(^1\) 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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**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.

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**References**


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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.\(^1\) 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.\(^1\) 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 anti-body 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 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 episodes of anger and fall. 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 1b, but she became bed bound with quadriparesis, dysarthria, and diffuse hyperalgesia. Her treatment was changed to intraventricular interferon 1a administered via an Ommaya reservoir. She required parenteral 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 1-2 years, who are at a higher relative risk of developing SSPE in later life after a longer incubation period.7 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.8

In our patients, SSPE was not initially suspected as a diagnostic possibility. 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 subclinical EEG 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.9 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 1b treatment for six months (35% vs 34%).10 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 hyponatraemia, possibly the result of chemically induced meningitis, and reseroir 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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doi: 10.1136/jnnp.2005.062828
Competing interests: none declared

References


L 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.11 In several studies, such symptoms seemed to be more common on the left side of the body.12 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.7

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 one or both psychiatric disorders (4 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 there were bilateral presentations (table 1). There were 21 patients (60%) with vascular risk factors, of whom 11 (52.4%) 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 myoclonus more frequently than 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 other 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 symptoms only in the psychiatric group. The investigators were aware of the laterality hypothesis before performing the study.13 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 somatoform...
Table 1 Differences between patients with a psychiatric diagnosis and with left and right sided symptoms

<table>
<thead>
<tr>
<th>Variables</th>
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<th>Right group</th>
<th>p value</th>
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<td>28 (80.0%)</td>
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<td>Conversion disorder</td>
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<td>5 (15.6%)</td>
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<td>Anxiety disorders</td>
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<td>2 (6.6%)</td>
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<td>GAD</td>
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<td>Panic disorder</td>
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<td>Other</td>
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<td>3 (21.4%)</td>
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<tr>
<td>Symptoms</td>
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<td>Paresis</td>
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<td>12 (36.4%)</td>
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<td>Bilateral</td>
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<td>Involuntary movements</td>
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<td>Total</td>
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<td>4 (12.2%)</td>
<td>13 (92.9%)</td>
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<td>6 (35.3%)</td>
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<td>Visual</td>
<td>5 (14.3%)</td>
<td>1 (9.1%)</td>
<td>4 (28.6%)</td>
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<td>–</td>
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<td></td>
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<tr>
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<td>5 (14.3%)</td>
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<tr>
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<td>–</td>
<td>–</td>
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<tr>
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<td>19 (54.3%)</td>
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<td>10 (71.4%)</td>
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<tr>
<td>Right</td>
<td>14 (40.0%)</td>
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<td>4 (28.6%)</td>
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<tr>
<td>Bilateral</td>
<td>10 (29.4%)</td>
<td>–</td>
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</tbody>
</table>

*p value for Mann-Whitney U test (left group/right group); †p value for χ² 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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doi: 10.1136/jnnp.2005.062893
Competing interests: none declared

REFERENCES


CORRECTION

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

BOOK REVIEW

Atlas of neuromuscular diseases


This book it 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 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 quality 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 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 unfilled.

R W Orrell

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doi: 10.1136/jnnp.2002.003392

M S Welgampola, S M Boas, 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 μl. These levels are 10–20 dB higher, depending upon frequency, than the values given as “SPL”. The standard parameter 500 Hz “112 dB SPL” tone burst stimulus, obtained with a 10 V peak to peak input, corresponds to an intensity of 127 dB FL (RMS).
Aciclovir induced posterior leucoencephalopathy

D Mahad, J Jarvis, P F Chinnery, D Mitra, A Gholkar and A Helldén

J Neurol Neurosurg Psychiatry 2005 76: 1308-1309
doi: 10.1136/jnnp.2004.059824

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"Who came with you?" A diagnostic observation in patients with memory problems?

The importance of obtaining collateral history when assessing patients attending the neurology clinic complaining of memory difficulties is well known. Patients developing amnesia in the context of Alzheimer’s disease may underplay their difficulties because of cognitive anosognosia, whereas those with purely subjective memory complaints (the “worried well”) may overemphasise difficulties. Memory complaint, preferably corroborated by an informant, is one of the suggested diagnostic criteria of mild cognitive impairment (MCI). Misdiagnosis of memory complaints may occur when no collateral history is available.1

For these reasons, all patients referred to my cognitive function clinic are sent, as part of their clinic appointment letter, a request asking them to bring a relative, friend, or carer from whom additional clinical information may be obtained; this is printed in bold type and in a separate paragraph. Despite this, some patients attend the clinic alone. A study was undertaken to measure the diagnostic value of this observation.

As part of an audit of referrals over a 2 year period (September 2002 to August 2004 inclusive), attendance or non-attendance of a relative or friend at each consultation was noted. Diagnosis of dementia was based on DSM-IV criteria, established by clinical interview, neuropsychological assessment and structural neuroimaging. Diagnosis of dementia subtype (Alzheimer’s disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia) and of MCI followed widely accepted diagnostic criteria. All patients had minimum follow up of 6 months.

Of 183 new referrals seen, 150 (82%; 95% confidence interval (CI) 76 to 88%) followed the written instruction in the clinic appointment letter and attended with a relative, friend or carer; the remaining 33 (18%; 95% CI 4 to 31%) attended alone. In this cohort, 90 patients were diagnosed with dementia and 93 were not demented; three had MCI. Of the 150 patients accompanied to the clinic, 90 (60%; 95% CI 52 to 68%) had dementia; of the 60 not demented, one had MCI. None of the 33 patients attending alone had dementia, although two had MCI.

Hence, if attending the clinic with a relative, friend, or carer (that is, following the instructions given in the appointment letter) were considered a diagnostic test for dementia, it would have a sensitivity of 100% (95% CI 96 to 100%, Wilson method), specificity of 35% (95% CI 26 to 46%), and positive and negative predictive values of 60% (95% CI 52 to 67%) and 100% (95% CI 95 to 100%) respectively. Positive likelihood ratio was 1.55 (95% CI 1.33 to 1.80, log method), judged unimportant, but negative likelihood ratio (0) was large.

Although not absolute, as those unaccompanied patients with MCI might yet evolve to dementia, the period of follow up for some patients is brief, and clinically established diagnoses may require revision (for example, when neuropathological data become available), these findings nevertheless support the belief that attending the无所remory clinic alone despite written instructions to the contrary is a robust sign of the absence of dementia.2

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Competing interests: none

References

Laryngeal abductor paralysis can be a solitary manifestation of multiple system atrophy

Laryngeal abductor paralysis (LAP) and stridor are well known features that occur in over one third of patients with multiple system atrophy (MSA). The pathogenesis of LAP is thought to be crico-arytenoid abductor muscle denervation,1 although there is a lack of consistent evidence of motor cell loss in the nucleus ambiguus.2 More recently, dystonia of the laryngeal abductor muscle has also been proposed.3 LAP/stridor usually occurs in the advanced stages of the disease,4 and is considered to be a poor prognostic feature.5 In contrast, some MSA cases have shown LAP initially, with most of these reported by otolaryngologists departments.6,7 However, there are no systematic surveys as to the extent to which MSA patients initially present with LAP. We describe the result of a survey of 200 MSA inpatients conducted in a neurology department.

We reviewed the case records of 200 consecutive “probable” MSA patients who met the inclusion and exclusion criteria. They were 119 men and 81 women, mean age 60 years; 29 had the Parkinsonian form (MSA-P) and 171 the cerebellar form (MSA-C). Among these, eight patients (4%) (four MSA-P, four MSA-C) were shown to have stridor as the initial manifestation (table 1). Stridor was the solitary manifestation in six of the patients, though it was combined with minimal laryngeal signs in two of these six patients (inspiratory gasp in one and REM (rapid eye movement)-sleep related behavioural disorder (“night terror”) in one. In the remaining two patients stridor occurred together with bladder dysfunction or gait ataxia. In the former six patients, stridor was followed by bladder dysfunction in four, constipation in three, tremor/akinesia in one, ataxia in one, and postural hypotension in one. The average interval between the development of stridor and these later symptoms varied from 5.4 years (range 1 to 6). The average interval between stridor and hospital admission was cause by LAP. The grade of LAP at the first admission to our hospital (table 1), according to Isosaki’s laryngoscopy classification, was moderate (abductor paresis during waking; paradoxical adduction during sleep) in three and severe (complete paralysis) in five. Among those patients, continuous positive airway pressure was introduced in three, laser incision of the vocal fold was carried out in one, and subsequent tracheostomy was necessary in five.

In the cases presented, it proved true that LAP/stridor can be a solitary manifestation of MSA. The interval between LAP/stridor and hospital admission was rather long (on average 5.4 years), suggesting that the progression of LAP was not very rapid in those patients. Although the initial presentation of LAP/stridor was not common (it occurred in only 4% of all MSA patients), it is clinically relevant because patients with LAP/stridor but without obvious neurological symptoms may see general physicians or otolaryngologists first. Laryngeal stridor also occurs because of local inflammation or tumours, or from distant causes that affect the vagal nerves, such as upper thoracic or nasopharyngeal carcinoma. If such conditions have been excluded, central neurological causes should be considered. Co-morbid bladder dysfunction (particularly urinary incontinence and post-voiding residual volume of more than 100 ml), postural and postprandial syncope, parkinsonism, and ataxia are all red flags suggestive of MSA.8 In our eight patients, bladder dysfunction was an early sign and was chronologically correlated with LAP/stridor; this finding is in line with a previous report.9 These atypical features for a local laryngeal cause suggest that further studies of the brain are necessary to confirm the diagnosis of MSA.

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Table 1  Patients with multiple system atrophy who initially presented with laryngeal abductor paralysis/stridor

<table>
<thead>
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<th>Patient*</th>
<th>Years from the onset of illness</th>
<th>Laryngoscopy findings†</th>
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<td>1. 62/M</td>
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<td>MSA-P</td>
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<td>2. 74/F</td>
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<td>3. 83/F</td>
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<td>Laryngeal stridor</td>
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<td>6. 57/F</td>
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<td>MSA-P</td>
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<td>7. 53/M</td>
<td>6</td>
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<td>8. 63/F</td>
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<tr>
<td>MSA-C</td>
<td>Laryngeal stridor, atactic gait</td>
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*Age, sex, diagnosis.  
†Laryngeal abductor paralysis: + (mild), ++ (moderate), +++ (severe). Isozaki's classification.

AHI, apnoea hypopnoea index; BD, bladder dysfunction; CPAP, continuous positive airway pressure; F, female; HUT, head up tilt (60° for 10 min); M, male; MSA-C, cerebellar form of multiple system atrophy; MSA-P, parkinsonian form of multiple system atrophy; ODI, oxygen desaturation index (dips per hour); PH, postural hypotension; RBD, REM sleep behavioural disorder; SAS, sleep apnoea syndrome.
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Competing interests: none declared

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Disseminated Pseudallescheria boydii infection successfully treated with voriconazole

A 56 year old, right handed African-American man with past history of left knee osteoarthritis, remote intravenous drug use, remote atrioventricular fibrillation, and seropositivity for hepatitis C was admitted to a local hospital for fatigue, chest pain, 13.6 kg weight loss, night sweats, and vision loss. On examination, a loud systolic murmur was present. An electrocardiogram (ECG) displayed T wave alternans and a transoesophageal echocardiogram revealed severe mitral regurgitation with mitral valve vegetations, ruptured chordae tendineae, and left ventricular ejection fraction of 73%. He was diagnosed as having endocarditis and cytomegalovirus endophthalmitis, and was treated with ceftriaxone, vancomycin, ganciclovir, foscartern, aspirin, metoprolol, lisinopril, nifedipine, and intravenous enoxinol. He developed fever (39.3°C) and his mental status declined. A head computed tomography (CT) scan showed left occipital haemorrhage. His left leg became cold and pale with an ankle:brachial index of 0.4. Blood cultures grew yeast. Amphotericin B was started and he was transferred to our hospital for further care.

Upon arrival his temperature was 36.4°C, pulse was 80 beats per minute and regular, respiratory rate was 25 per minute, and blood pressure was 106/76 mm Hg on the right and 160/83 mm Hg on the left. On auscultation a II/VI holosystolic murmur over the apex and basilar ribs were heard. His left leg was cold with pulses detectable only by Doppler. He was alert and oriented to person and place only, and recalled 1/3 items after short delay. His speech was fluent and well articulated. He had light perception on the right and was only able to count fingers centrally on the left. He displayed mild left leg weakness, normal reflexes and flexor plantar responses, mild right pronator drift, and diminished left sided proprioception. Ophthalmological examination disclosed bilateral vitreous infiltrates, retinal lesions, segmental retinal detachments, and scattered choroidal inflammation worse on the right. Fluocytosine was added.

An ECG revealed a prolonged QT interval, Q waves in II, III, and AVF leads, and signs of left ventricular hypertrophy. The laboratory studies revealed a white blood cell count of 25,600/μl with 69% neutrophils, 23% lymphocytes, 6% monocytes, 1% eosinophils, and 1% bands; haematocrit, 30%; platelets, 207,000/μl; troponin T, negative; aspartate aminotransferase (AST) and alanine aminotransferase (ALT), mildly elevated at 79 U/l and 99 U/l, respectively (a finding attributed to active hepatitis C); alkaline phosphatase 96 U/l and the erythrocyte sedimentation rate (ESR) 26 mm/hr. Serological examination for human immunodeficiency virus (HIV) was negative.

A thoracoabdominal CT scan disclosed a 2 x 2 cm mass in the right subclavian and common carotid arteries and a right renal infarct. The left iliac artery was occluded. Intravenous heparin, in attempt to salvage the left leg, resulted in left parietal subarachnoid, intraparenchymal, and intraventricular haemorrhages. The causative organism was identified as Pseudallescheria boydii resistant to amphotericin, flucytosine, and fluconazole. On day 13 voriconazole was begun. He underwent urgent mitral valve replacement and left superior and profunda femoral, and iliac embolectomy. Heparin was discontinued, and he remained in prolonged coma. A head CT scan displayed new right frontoparietal, right anterior cerebral artery (ACA), right posterior cerebral artery (PCA) and bilateral small cerebellar infarcts (fig 1A). A follow up brain magnetic resonance imaging (MRI) scan revealed several new small left frontoparietal and haemorrhages and ischaemic infarcts of the right thalamus, ACA, and PCA along with the left insula, basal ganglia, and parietal lobe (fig 1B). The right internal carotid artery was occluded (fig 1C). The findings were attributed to infectious emboli and haemorrhaging from myotic aneurysms.

On day 38 of hospitalisation the patient’s coma resolved. He was eventually able to follow simple commands, and sit and stand, although expressive aphasia and left hemiparesis remained. His vision improved to 20/800 on the left. He was subsequently discharged to a long term care facility.

Discussion
Pseudallescheria boydii (anamorph or asexual phase: Scedosporium apiospermum) is a ubiquitous saprophytic fungus commonly found in soil, manure, decaying vegetation, and polluted water. Its commonest clinical presentation in the USA is as mycetoma, a chronic limited subcutaneous infection in immunocompetent individuals engendered by minor trauma, and is characterised by granuloma formation and local tissue destruction.1 However, P. boydii has recently emerged as an agent of invasive fungal disease as well, a phenomenon linked to the increasing prevalence of immunosuppression in the community.2 Although endocarditis and endophthalmitis have been described,1 lung, bone, joint, or central nervous system (CNS) involvement is more typical of this organism.3 Infections are classically acquired through penetrating trauma4 or massive inoculation through inhalation, such as may occur in near drowning in stagnant or polluted water.5 Disease subsequently results from contiguous extension and haemageneric dissemination. It is likely that our patient acquired his infection through prior intravenous drug use, resulting in endocarditis with secondary dissemination to eye, kidney, extremities, and brain.

Among the various types of invasive fungal disease attributable to P. boydii, survival rates
appear to be particularly poor with central nervous system and/or valvular involvement. A relatively recent literature review revealed that of 39 patients with documented CNS disease, only nine were known to have survived; no prior reports exist of survivors of endocarditis. Intrinsic resistance to amphoterin B, a mainstay in the treatment of most invasive fungal diseases including aspergillosis and mucormycosis, has been reported repeatedly, a trait undoubtedly associated with poor survival in patients in whom the diagnosis is delayed. We describe the first immuno-compromised survivor from *P. boydii* native valve endocarditis complicated by multiple ischemic and hemorrhagic strokes and peripheral embolisation.

Successful treatment of invasive disease due to *P. boydii* hinges upon surgical resection with institution of appropriate antifungal therapy. Miconazole, an imidazole derivative used topically for many dermatophyte infections, was previously the treatment of choice in the light of this organism's resistance to many commonly used systemic antifungals, including amphoterin B and fluconazole. However, its poor CNS penetration, toxicity profile, and unavailability in the USA as an intravenous formulation render it less than desirable. Of the azole antifungals, voriconazole and ketoconazole have been used successfully in the treatment of pulmonary pseudallescheriasis, their poor CNS penetration significantly impairs their therapeutic utility in the treatment of brain abscess.

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References


Ocular tilt reaction and anterior inferior cerebellar artery syndrome

The ocular tilt reaction (OTR) is an eye-head postural reaction consisting of ipsilateral head and neck tilt, skew deviation, and ocular torsion. OTR indicates either a unilateral peripheral vestibular deficit (inner ear or vestibular nerve) or a unilateral lesion of brain stem pathways from the vestibular nuclei to the interstitial nucleus of Cajal in the rostral midbrain.

The anterior inferior cerebellar artery (AICA) supplies the lateral inferior pontine tegmentum and middle cerebellar peduncle, vestibulocochlear nerve including the root entry zone, inner ear, and anterior inferior cerebellum. Although there has been one report of skew deviation owing to an AICA infarction, the cardinal features of the OTR have not previously been documented. We describe two patients with AICA infarction, each of whom had ipsiversive OTR—on with complete OTR, the other with skew deviation and tonic ipsiversive ocular torsion.

The first was a 58 year old man with long standing hypertension who presented with sudden vertigo and imbalance. On neurological examination, he had bilateral gaze evoked horizontal nystagmus, left peripheral facial weakness and numbness, dysmetria of the left limbs, and gait ataxia. There was no caloric response on the left side. Pure tone audiometry showed 65 dB sensorineural hearing loss on the left side. The subjective visual vertical with binocular viewing was tilted 17 degrees to the left (that is, counterclockwise from the patient’s point of view). Fundus photography showed 25° extorsion of the left eye and 12° intorsion of the right eye. He had a skew deviation with a right hypertropia of 20 prism dioptries in primary gaze (fig 1). Magnetic resonance imaging (MRI) including diffusion images showed acute infarcts in the left middle cerebellar peduncle and the left lateral inferior pontine tegmentum (fig 1).

The second patient was a 58 year old woman with type 2 diabetes mellitus and hypertension who developed severe vertigo, hearing loss, tinnitus on the left side, dysarthria, and imbalance. She had bilateral gaze evoked nystagmus with a horizontal-rotatory component. There was left peripheral facial weakness and numbness, dysmetria of the left limbs, and gait ataxia. Pure tone audiometry showed a 65 dB sensorineural hearing loss on the left side. Fundus photography showed 14° extorsion of the left eye and 3° extorsion of the right eye. Prism testing showed a skew deviation with a right hypertropia of 6 dioptries in the primary position. Subjective visual vertical with binocular viewing was tilted 13° to the left (that is, counterclockwise from the patient’s point of view). Caloric response was absent on the left side. MRI showed new infarcts in the left middle cerebellar peduncle, left lateral inferior pontine tegmentum, and anterior inferior cerebellum, possibly including the flocculus. Two months later the subjective visual vertical was normal. Fundus photography

![Figure 1](image)

Tonic ocular tilt reaction in patient 1. Note sustained head tilt and concurrent vertical divergence of the eyes (skew deviation). T2 weighted axial magnetic resonance imaging of the brain showed acute infarcts in middle cerebellar peduncle and lateral inferior pontine tegmentum. There is conjugate leftward torsion of the eyes (that is, counterclockwise from the patient’s point of view): a 25° extorsion of the left eye and a 12° intorsion of the right eye. HT, hypertropia; LT, left; RE, right eye; RT, right. Patient consent was obtained for publication of this figure.

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now showed 1° of extorsion of the left eye, indicating that the left eye had been extorted by 13° at the first examination (that is, by 14° minus 1°) and 9° of extorsion of the right eye, indicating that at the first examination the right eye had in fact been intorted by 6° (that is, by 3° minus 9°).

Comment

Most earlier reports of AICA infarction have focused on the brain stem or cerebellar findings. Recently, there have been several reports describing the clinical importance of inner ear symptoms, vertigo and/or sudden deafness. However, a detailed description of OTR as a sign of AICA infarction has not been reported previously.

OTR, a sign of vestibular dysfunction in the roll plane, is characterised by a triad of conjugate ocular torsion, skew deviation, and head tilt. It results from destructive or irritative lesions of central or peripheral graviceptive vestibular pathways. Although head tilt is a common component of OTR, skew deviation with conjugate ocular torsion often occurs without head tilt in our patient. Thus the pathophysiology of a partial OTR (that is, skew deviation and conjugate ocular torsion without head tilt) is similar to that of a complete OTR, and skew deviation with conjugate ocular torsion is sufficient for the diagnosis of OTR.

In addition to lesions of the central and peripheral vestibular pathways conveying graviceptive signals, lesions of the cerebellum may also result in OTR. Skew deviation is commonly seen with cerebellar infarction. Mossman and Halmagyi described two patients with cerebellar stroke, presumably in the territory of the posterior inferior cerebellar artery, who had tonic conjugate ocular torsion without associated head tilt.5 These investigators speculated that interruption of nodular inhibitory projections to graviceptive neurones in the ipsilesional vestibular nuclei may have accounted for the contraversive conjugate ocular torsion.5 Sensorineural hearing loss and canal paresis to caloric stimulation on the left side clearly indicated involvement of the peripheral auditory-vestibular system. Ipsiversive OTR without peripheral vestibular lesions was described in a previous report.2 Considering the direction of OTR and known vascular anatomy of the AICA, damage to the inner ear or the root entry zone of the eighth nerve probably accounts for the ipsilesional OTR with AICA infarction.

In conclusion, this is the first report of well-documented OTR with AICA infarction. The ipsiversive OTR in these patients probably resulted from infarction of the inner ear or the root entry zone of the eighth nerve.

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Table 1: Mean differences (before and after rTMS) and confidence intervals of clinical scores

<table>
<thead>
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<th>Premotor rTMS</th>
<th>Sham rTMS</th>
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<tr>
<td>MRVS total score</td>
<td>1.5</td>
<td>1.1</td>
<td>0.4</td>
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<td>Mean difference</td>
<td>0.8 to 3.8</td>
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<td>-1.2 to 2.0</td>
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<tr>
<td>95% CI</td>
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<td>AYVS total score</td>
<td>4</td>
<td>2.1</td>
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<tr>
<td>Mean difference</td>
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<td>0.2 to 4.0</td>
<td>2.6 to 3.1</td>
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<tr>
<td>95% CI</td>
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<tr>
<td>AYVS motor score</td>
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<td>1.4</td>
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<tr>
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<td>0.5 to 0.9</td>
<td>-0.9 to 2.4</td>
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<tr>
<td>95% CI</td>
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<tr>
<td>AYVS vocal score</td>
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<td>0.8</td>
<td>0.5</td>
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<td>Mean difference</td>
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<td>-1.1 to 2.6</td>
<td>-2.4 to 1.4</td>
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<tr>
<td>95% CI</td>
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AYVS, Adapted Yale Video Scale; CI, confidence interval; MRVS, Modified Rush Video Scale.

References


Video assessment of rTMS for Tourette syndrome

In a recent study, subthreshold 1 Hz repetitive transcranial magnetic stimulation (rTMS) over left motor or premotor cortex yielded the total tic impairment score (0–20). As the MRVS does not consistently score the complexity, intensity, and interference of tics, we devised an additional scale using the categories of the Yale Global Tic Severity Scale (YGTSS).7 This new scale, the AYVS, rated the following five domains from 0 to 5 according to severity: number of different tics, frequency of tics, intensity of tics, complexity of tics, and interference of tics. Each domain was rated separately for motor and vocal tics. The sum of the five domains gave a total motor tic score and a total vocal tic score; these scores combined yielded the total tic impairment score (0–50).

In a placebo controlled cross-over study of 16 patients with GTS, subthreshold 1 Hz rTMS did not exceed the effect observed following sham stimulation. rTMS effects in this study were variable and tic scores showed a regression towards the mean, that is patients with high scores at baseline tended to have lower scores after the rTMS intervention, and vice versa (univariate ANOVA with the difference in video score before and after rTMS as dependent factor and baseline scores as covariate). In other words, the changes of tic severity that we observed most likely reflect the waxing and waning course of tics rather than an intrinsic rTMS effect.

The results of this video assessment are in keeping with patients’ self assessment based on the Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey (MOVES),4 a self rating scale that patients completed before and after rTMS. Neither motor nor vocal tic subscales nor obsession and compulsion subscales were changed by rTMS, which indicates that rTMS as used in the present study is not an effective treatment for obsessions or compulsions. However, because ADHD symptoms were not assessed, we cannot exclude the fact that rTMS as used in the present study might have an effect on ADHD.

There was good correlation between the MRVS and the AYVS (r = 0.69; p < 0.01, Spearman’s correlation). The AYVS thus
appears to be a valid and comprehensive tool to assess tic severity in GTS patients, but it needs to be evaluated further.

We conclude that left motor or premotor low intensity 1 Hz rTMS does not improve tics in GTS patient as assessed by blinded video scoring. Further studies, perhaps using higher intensity rTMS, longer rTMS trains, or bilateral stimulation, are needed to delineate the usefulness of rTMS in GTS patients. In these studies, blinded and independent video rating should be used.

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Competing interests: none declared

Figure 1  Video scores before and after each intervention (means and standard error of the mean). (A) Modified Rush Video Scale (MRVS) total score; (B) Adapted Yale Video Scale (AYVS) total score; (C) AYVS motor score; (D) AYVS vocal score.

References

A case of superior cerebellar artery syndrome with contralateral hearing loss at onset

Deafness is rare in ischaemic stroke but sometimes occurs as a result of lower pons infarction. The main cause of such deafness is occlusion of the anterior inferior cerebellar artery (AICA); occlusion of the superior cerebellar artery (SCA), which perfuses the higher pons, causes SCA syndrome and also results in deafness but is extremely rare. In the present report, we describe a patient with SCA syndrome, whose initial complaint was contralateral hearing loss.

Case report

A 64 year old male with untreated hyperglycaemia and hypertension was admitted 4 h after the sudden onset of deafness in his right ear. Hearing loss was the only complaint and other neurological signs were absent. Right sensorineural hearing loss was revealed by a hearing test (fig 1A). After several examinations including stapedial reflexes and speech discrimination, an initial diagnosis of sudden deafness was made. However, 8 h later the patient complained of diplopia, vertigo, and nausea. Impaired abducens function in the right eye and bilateral lateral gaze nystagmus were observed. Finger-nose and heel-knee tests suggested left cerebellar ataxia. Hence, a diagnosis of SCA syndrome was made, and argatroban, an anti-coagulant, was adminis- tered. Diffusion weighted magnetic resonance imaging (MRI) 12 h after onset showed infarctions in the left cerebellum (fig 1B) and lateral superior pons (fig 1C). Magnetic resonance angiography showed loss of blood flow in the lower basilar artery (fig 1D). Respiratory failure developed 4 h later, and the next day the patient also showed right hemiparesis and Horner’s syndrome. Bilateral cortical blindness was also present. A diagnosis of SCA syndrome with hemiparesis and cortical blindness was made.

A fluid attenuated inversion recovery (FLAIR) image 2 weeks later showed an enlarged infarction in the left cerebellum, and a new infarction in the right cerebellum, dorsal pons, and bilateral occipital lobes (fig 1E). The patient’s symptoms remained unchanged 3 months later.

Discussion

SCA syndrome shows ipsilateral cerebellar ataxia and Horner’s syndrome, contralateral superficial sensory disturbance and hearing loss, as well as nystagmus toward the impaired side, vertigo, and nausea. Fibres from the contralateral auditory nucleus join the lateral lemniscus, pass into the brain, and terminate in the hearing centre. Therefore, impairment of the lateral lemniscus on one side causes hearing loss on the other. In SCA infarction, the ischaemic lesion occurs in the area where fibres from the nucleus have already crossed, and therefore sensory hearing loss is observed in the contralateral side.

We describe a rare case of SCA syndrome which began with deafness in one ear. Although deafness sometimes occurs as a result of brainstem infarction, most cases of ipsilateral hearing loss are due to AICA infarction. To our knowledge, the study by Doyle et al is the only previous report of hearing loss due to contralateral SCA infarction. Amarenco et al described a large series of SCA syndrome cases, where no patient showed contralateral deafness. The present report presents an important finding regarding symptoms of ischaemic stroke, and suggests that hearing loss, although rare, can be the first symptom. It is necessary to carefully observe patients with sudden deafness.

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Myology, third edition


This is the third edition of an established two volume text covering all aspects of human muscle disease. Since the second edition in 1994 rapid advances in the molecular genetic understanding of a range of muscle diseases have occurred. Indeed some diseases, such as muscle channelopathies, have only been fully recognised as distinct entities during this period. These huge advances are reflected in a complete and up-to-date revision. Myology contains 70 chapters divided into three parts: Part 1, Scientific basis of muscle disease; Part 2, General approaches to neuromuscular disease; and Part 3, Diseases of muscle. All chapters are well constructed and written by authorities in each field. It is likely to be parts 2 and 3 that are of most interest to the readers of the JNNP. Part 2 is full of practical information. In particular the chapters on clinical examination and electrodiagnosis will be of interest to clinicians frequently encountering patients with neuromuscular symptoms and will also be valuable for trainees. Also in part 2 is an informative chapter on the evolving clinical uses of imaging in the investigation of muscle disease. It seems clear that MRI is going to play an increasing role in the evaluation of muscle diseases in the future. Part 3 contains comprehensive chapters on all of the known human muscle diseases. More genes have been discovered in the area of muscle disease than in virtually any other area within neurology in the past few years. This is reflected in the fact that 21 of the 30 chapters describing individual muscle diseases are given over to genetic disorders, including the muscular dystrophies, congenital myopathies, muscle channelopathies, genetic inclusion body myopathies, and the metabolic myopathies. I found it difficult to fault any of these chapters. The continuing challenges involved in understanding the molecular pathogenesis of and in treating the inflammatory myopathies are well covered. The final seven chapters of part 3 cover disorders of neuromuscular transmission, neuropathies, and neuromyopathies. Myology the third edition must have been a mammoth task to produce and the editors are to be congratulated. I think there is plenty of accessible information, of practical use for clinicians and trainees dealing with muscle disease. I can thoroughly recommend this text.

BOOK REVIEWS

Essential Neurology, 4th edition


Lecture Notes: Neurology, 8th edition


What constitutes the “core knowledge” of neurology that all medical students should reasonably be expected to learn? Is this a question that Lecture Notes: Neurology (LNN) and Essential Neurology (EN)—two stalwarts of the medical student library—continue to grapple with in their latest editions? EN, longer but with fewer chapters than LNN, tackles subjects in greater depth (and hence claims to be a review text for MRCP), whilst LNN has greater breadth, with suggestions for extra reading and key points summarising each chapter. Both texts incorporate case histories, somewhat more successfully in EN if only because the answers are physically separate. I find it encouraging readers to pause and think about each presentation. Illustrations seem more integral to the text in EN, but this volume does have some surprising typographical gaffes—for example, Brown-Séquard, L’Hermitte, Angiell Robertson with a hyphen. I enjoyed reading about “messy breakfast syndrome” and “Kellogg’s epilepsy” which, like “flying saucer syndrome”, are variant names for juvenile myoclonic epilepsy. Considering my experience of general neurological clinics, I would have valued more discussion in EN on “neurologically unexplained symptoms”, which seem so frequent, and a specific section on neurofibromatosis, the commonest monogenic disorder that I see, albeit rarely.

How should the undergraduate neurology text develop, assuming that it is not wholly superseded by internet browsing? Should there be more emphasis on expert consensus diagnostic criteria and management guidelines, rather than succinct qualitative descriptions of neurological conditions, facilitating pattern recognition, and their treatment? Should there be greater reference to the evidence base (and its inadequacies)—for example, citing of systematic reviews? These are issues to be addressed by the authors in future editions, but for now one has no hesitation in recommending either of these volumes to medical students, or both, since it would be invidious to choose one as “better”.

A J Learner

A historical dictionary of psychiatry


Edward Shorter is Professor of History of Medicine at the University of Toronto and this 338 page volume is claimed to be the first “Historical Dictionary of Psychiatry”. As always in alphabetical order, discovery of individual entries is easy and an index takes us to words embodied in the text, more in encyclopaedia fashion.

Neurology without physical signs? The neurologist may still feel this is adequate definition of psychiatry, particularly nowadays with so many publications that bring together works in
The Auditory Cortex, A Synthesis of Human and Animal Research


A spirit who hears me tapping/The five-sensed cane of mind

Amid such unguessed glories/That I am worse than blind.

H Kemp, Blind, 1919

Most clinical neurologists scarcely spare a thought for the auditory brain: it is what takes over where the VIIIth nerve ends, and if they think of it at all, it is probably in connection with such exotic maladies as cortical deafness or curious like musical hallucinations. But by any criterion this is an important area — from pitch-difference limens it is but a few synapses to Mozart and Shakespeare.

I attended the scientific meeting that spawned this book, and so I had the odd experience while reading it of hearing in my mind’s ear the cut and thrust of platform discussion petrified to the more sober exchanges of scientific prose. For the auditory neuroscientist, the book provides a state of the art overview of the field, refreshingly catholic in its scope. There are idiosyncrasies, but they are the quirks of luminaries, and all the more valuable for that. No question, then, that the book will please the crowd for whom it was intended. But is there anything for the neurologist?

Things start reassuringly enough in Part I (‘Auditory cortical fields and their functions’) with auditory cortex anatomy. This is truly a closed book for most clinicians, both figuratively and, because the cortex lies deep within the recesses of the Sylvian fissure, quite literally. A chapter on the neuro-behavioural study of auditory cortex reminds us that Ferrier, no less, used it to make fundamental claims about the organisation of the brain. We move on to voices, and speech: so far, so good. Part II (‘Coding of sounds’), with its heavy-duty electrophysiology, is more of a challenge; and yet the coding of sounds is a problem of the most fundamental scientific and philosophical interest. How on earth is it possible to reconstruct the world we hear from the one-dimensional flutter of two membranes? Part III (‘Plasticity, learning and cognition’) addresses the interface between the brain and experience. Confronted with a chapter about ferrets, perhaps the clinician will master an initial rising sense of alarm by recalling that this is the science that made possible the cochlear implant and may yet explain how cocktail parties work (or fail).

If neurologists should learn something here about bats, barn owls, or ferrets, it can’t hurt. This book is a bracing corrective to the error, too often implicit in clinical practice as in daily life, that the eyes (human eyes, at that) are the sole windows of the brain. To paraphrase that poem of Kemp’s, the unguessed glories of the auditory cortex remind us that the five-sensed cane of mind is, after all, five-sensed.

C Gardner-Thorpe

Mechanism and management of headache, seventh edition


As a general rule, it is safe to assume that any textbook entering a seventh edition does so on its merits and must be worth reading. The latest edition of the classic Mechanism and Management of Headache by Lance and Goadsby does not disappoint. It is occasioned not just by the passage of time but also by advances in the field of headache that make a new edition necessary. Among these, the long-awaited revision of the International Classification of Headache Disorders is the most important, as it has created some entirely new headache entities and significantly altered criteria for others. New information about the structural consequences of seemingly benign headache disorders — iron deposition in the brainstem — has increased our understanding of headache pathophysiology.

Reference


Oxford handbook of psychiatry


Psychiatry, third edition, Oxford core texts


The Oxford Handbook of Psychiatry is a wonderful little book. The “little” applies to its size.
Volume 76 Assessors

The Editor is grateful to the following, who have assisted in the assessment of papers during the past year.

D Aarsland
G Abbruzzese
K Abe
J Acheson
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J Bland
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A Bleasell
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O Blin
B Bloem
C Booke

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doi: 10.1136/jnnp.2004.059824corr1
D J Mahad, A Helldén, J Jarvis, et al. Aciclovir induced posterior leucoencephalopathy (J Neurol Neurosurg Psychiatry 2005;76:1308–9). The authors of this letter were mistakenly grouped according to their affiliations. The correct ordering of the authors is: D J Mahad, A Helldén, J Jarvis, D Mitra, A Ghoklar, P F Chinnery.
Volume 76 Reviewers

The Editor is grateful to the following for reviewing books during the past year.

A Bahra
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