PostScript

LETTERS

Relapsing encephalopathy with headache: an unusual presentation of isolated intracranial neurosarcoidosis

We report a presentation of relapsing and remitting isolated intracranial neurosarcoidosis in a female patient who presented with episodic severe headache and behavioural disturbance initially misdiagnosed as psychosis. Eventually, several episodes were accompanied by visual disturbance secondary to papilloedema, ultimately leading to a diagnosis of neurosarcoidosis on meningeal biopsy.

Sarcoidosis is a multisystem inflammatory disease of unknown aetiology, and is characterised by non-caseating granulomata. Pulmonary disease is the most common manifestation, occurring in 90% of patients. Clinical involvement of the nervous system is said to occur in 5–15% of patients.[1] Isolated intracranial neurosarcoidosis is even rarer, with systemic sarcoidosis being detected in more than 95% of cases of sarcoidosis initially presenting with neurological symptoms.[2]

Case report

A woman presented initially at age 30 years, and then subsequently five times over 3 years with stereotyped episodes of headache, confusion and psychomotor agitation. In each instance, a history was given of a constant, severe bifrontal headache that was associated with nausea, vomiting, photophobia and/or visual field disturbance. As each presentation evolved, she became confused and encephalopathic. Early in the course of her illness these episodes were misinterpreted as acute psychosis because she exhibited pressured unintelligible speech, and was combative and sometimes frankly violent. However, although disoriented and confused, there were no features of a formal thought disorder. The accompanying headache was exacerbated by sneezing, coughing and the Valsalva manoeuvre. Treatment with analgesia and sumatriptan provided only limited relief as did prophylaxis with beta blockers. There was no history of a previous psychiatric disorder or substance abuse. The patient did have a long past history of migrainous headaches that were typically unifrontal, mild and managed adequately with simple analgesics. Systemic review revealed no respiratory or dermatological complaint.

On examination she was consistently afebrile. There was no neck stiffness or rash. Transient visual field loss (bitemporal or subtotal loss of vision) was noted during later episodes; visual acuity was well preserved. Retinal examination showed papilloedema, perivenular inflammation and absence of venous pulsations.

Plain chest *x* rays were unremarkable during each of her five presentations. Cranial MRI with contrast, MR angiography and MR venography were all initially normal. Serial CSF analysis showed lymphocytic pleocytosis, suggestive of an encephalitis, only during her initial admission (57 cells/μl), but consistently elevated protein (0.90, 0.63 and 0.83 g/l) and normal glucose. Lumbar puncture opening pressures were raised (32 cm H_2O) when symptomatic, but normal (16.5 mmH_2O) 5 months later during a period of remission. Viral PCR studies for enterovirus, Murray valley encephalitis, herpes simplex and herpes zoster, and bacterial and fungal microscopy and cultures were negative. Oligoclonal bands were not present in the CSF. Angiotensin converting enzyme was not elevated in the blood or CSF. Results were within normal limits for all remaining laboratory tests, including autoimmune screens.

On her fourth admission, cranial MRI demonstrated subtle meningeal enhancement seen with contrast (fig 1). Subsequent open meningeal biopsy showed abundant non-necrotising epithelioid granulomas localised to the arachnoid, consistent with granulomatous leptomeningitis. There was no evidence of acid-fast bacilli or fungal organisms or the presence of significant fibrotic or vasculitic change. The cerebral cortex and dura were histologically normal. A diagnosis was made of isolated neurosarcoidosis.

The patient was commenced on oral prednisolone 75 mg daily. There was an excellent and sustained response to corticosteriods and, with the addition of hydroxychloroquine, the dose of prednisolone could be tapered to 16 mg on alternate days. Prednisolone doses were episodically increased to control symptoms. During the last 36 months of follow-up she has been headache-free and has had no further episodes of encephalitis or encephalopathy. Her papilloedema has largely resolved and a follow-up CSF sample 10 months after treatment commenced was acellular (neutrophils 0 cells/μl, lymphocytes 0 cells/μl) with normal protein (0.3 g/l) and opening pressure.

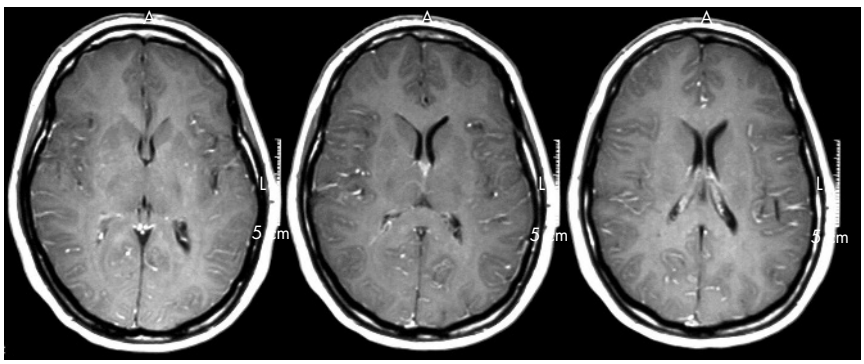

Figure 1 Cranial MRI: T1 sequences with gadolinium contrast showing subtle but widespread cerebral leptomeningeal enhancement without thickening or nodularity.

Discussion

Neurosarcoidosis without pulmonary or other extracranial involvement can be a diagnostic challenge. The clinical features are protean. After cranial neuropathy, headache is the most common manifestation of neurosarcoidosis, affecting an estimated 30% of patients.[2] There is no typical headache although reports suggest leptomeningeal inflammation is often associated with diffuse or bifrontal pain, and may be associated with papilloedema, as noted in this case.[3] CSF analysis can be helpful when a pattern of mild pleocytosis, high protein content and, sometimes, reduced glucose is seen. However, CSF abnormalities are not specific to the disease, may be evanescent and in more than a third of cases patients have a normal CSF.[1] Cranial MRI is the most valuable investigative tool with CNS lesions present in 80–90% of affected patients.[4] In our case the MRI findings suggestive of leptomeningeal inflammation were made 3 years after the first admission, following previously normal cranial magnetic resonance imaging studies. Alternative diagnoses such as hypertrophic pachymeningitis were considered but the meningeal biopsy showing abundant non-caseating epitheliod granulomas in the absence of fibrosis allowed the definitive diagnosis of neurosarcoidosis.

Neurosarcoidosis has been associated with neuropsychiatric dysfunction, including dementia, amnesia, depression, delirium and psychosis.[1] In our patient, however, the episodic relapsing remitting course of headache, meningoencephalitis and papilloedema was unique. Furthermore, over 3 years of follow-up there have been no emerging signs of extracranial sarcoidosis. The presentation is reminiscent of headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL) a disorder of unknown aetiology but with a benign course.[5] It is possible that neurosarcoidosis is the cause of some cases of HaNDL.

Isolated neurosarcoidosis is a differential diagnosis that requires consideration in a patient presenting with otherwise unexplained headache and encephalopathy, even if it is relapsing. Our case has demonstrated that this diagnosis may require considerable persistence with repetition of previous normal diagnostic and imaging investigations.

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Complete remission induced by rituximab in refractory, seronegative, muscle-specific, kinase-positive myasthenia gravis

Rituximab is a chimeric IgG1 κ monoclonal antibody that targets CD20, a transmembrane phosphoprotein on most B cells. Rituximab depletes B cells by binding to the CD20 molecule and initiating complement-dependent cytolysis or antibody-dependent cell-mediated cytotoxicity.[1]

Recently, there was a case of muscle-specific kinase (MuSK)-positive myasthenia gravis (MG) successfully treated with rituximab.[2]

We report a patient with MuSK-positive generalised MG who achieved complete remission with rituximab, after being refractory to steroids, intravenous immunoglobulin, immunosuppressants, thymectomy and less responsive to plasmapheresis.

A 32-year-old man was referred for refractory MG. He gave a 2.5-year history of mild bulbar and generalised weakness, mostly in proximal extremities, without sensory symptoms. He denied ptosis and diplopia but reported mild dysphagia and dysarthria. Family history was negative for neuromuscular disorders. He was receiving no medications. He denied any history of smoking and drank socially.

The general physical examination was unremarkable. Neurological examination demonstrated diplopia on extreme lateral gaze without fatigable ptosis or Cogan's lid twitch sign. There was moderate weakness of facial muscles bilaterally and of the tongue, without atrophy. He had mild dysarthria without voice fatigue and mild proximal limb weakness with sustained shoulder abduction for 10 s. No neck weakness was detected. He could perform 10 squats without difficulty. Sensation, gait, coordination and deep tendon reflexes were all normal except for mild hyporeflexia at the ankles. Plantar responses were flexor.

Initial investigations elsewhere included baseline 2 Hz repetitive nerve stimulation with decremental responses of 17% at the right median and 66% at the right musculocutaneous nerves without post-exercise facilitation, a negative Tensilon test with simultaneous measurement of forearm and grip strength, and repetitive nerve stimulation of the median nerve 2 h before and 2 days after 120 mg of Mestinon, and a negative acetylcholine-receptor antibody panel. A muscle biopsy did not show any myopathic features.

His symptoms had not responded to a 1-month trial of pyridostigmine at maximal doses of 240 mg/day. Prednisone at 60–80 mg/day for 2 years had been ineffective. A thymectomy had been performed 2 years before, which revealed thymic hyperplasia, but he had failed to improve. Azathioprine caused hepatotoxicity with jaundice. His condition deteriorated and he developed profound, mainly proximal upper and lower limb weakness. The only beneficial treatment was plasmapheresis, and he eventually obtained good control with three exchanges per week, alternating with two exchanges per week. Plasmapheresis was suspended briefly to try intravenous immunoglobulin 2 g/kg, but his condition worsened dramatically, and plasmapheresis was re-started.

Ciclosporin (150–200 mg twice daily) was added to stabilise his condition and to reduce his dependence on plasmapheresis, with some success. At times he had no limb weakness, but the moderate to severe facial and tongue weakness did not change. After 5 years, his condition began to deteriorate slowly, becoming less responsive to plasmapheresis, and he became continuously weak. Mycophenolate mofetil (1000 mg twice daily) was added for 3 months, but without success. A 6-month trial of cyclophosphamide IV, 1 g/m^2 surface area every month, also provided no benefit.

When the assay became commercially available, MuSK antibodies were found; titres were not measured. A repeat CT showed no residual thymic tissue. His condition continued to decline despite plasmapheresis three times a week, and so treatment with rituximab was started 3 months after his last dose of cyclophosphamide. He received four doses of rituximab 375 mg/m^2 every week for two cycles and noted improvement of his symptoms after the first cycle. After that, he received one infusion every 10 weeks. After several months, he was able to discontinue plasmapheresis, and has remained off all other medications for 1.5 years. Rituximab infusions were stopped 6 months ago after 1 year of treatment and he remains in complete remission. MuSK antibodies have not been checked for again because of insurance restrictions.

A chimeric murine/human IgG1 κ monoclonal antibody against CD20, rituximab depletes B cells by binding to the CD20 molecule and initiating complement-dependent cytolysis or antibody-dependent cell-mediated cytotoxicity,[1] hence providing therapeutic benefit for many B cell-mediated diseases. Rituximab is a Food and Drug Administration-approved drug for the treatment of relapsing/refractory CD20-positive low-grade non-Hodgkin's lymphoma. Rituximab has been used successfully with other autoimmune neuromuscular diseases. Side effects include severe or fatal infusion reactions, infections, hypersensitivity, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

Previous reports have described refractory generalised seropositive MG responding serendipitously to rituximab when MG arose in association with bone marrow transplantation or with lymphoma.[3–5] Recently, there was a report of a 56-year-old woman with bulbar MuSK-positive MG refractory to prednisone, azathioprine and mycophenolate mofetil, but less responsive to plasmapheresis, who had improved with 2 months of rituximab treatment. She has been stable for 12 months, but needed to be re-treated with Mestinon and mycophenolate mofetil 1000 mg/day, 3 months after the first rituximab course.[2] Ours is the second case of isolated refractory seronegative, MuSK-positive MG achieving complete remission after receiving rituximab, and the first case to achieve and maintain this for over 1.5 years. Rituximab provides more selectivity in targeting B cells compared with immunosuppressants such as ciclosporin, azathioprine and mycophenolate mofetil, which makes this an attractive treatment choice for MG. Rituximab should be considered as a treatment option in MuSK-positive MG refractory to other immunomodulatory agents.

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Aggravation of ataxia due to acetazolamide induced hyperammonaemia in episodic ataxia

Acetazolamide has been used to reduce the number of attacks in patients with episodic ataxia type 2 (EA 2), presumably by inhibiting