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Idiopathic hypertrophic pachymeningitis responsive to mycophenolate

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Abstract

Idiopathic hypertrophic pachymeningitis (IHP) represents a rare inflammatory condition that affects the central nervous system, often difficult to treat. We report the case of a patient who presented with difficulty in swallowing, slurred speech and ataxia associated with headache, vomiting and weight loss. He was diagnosed with IHP. He deteriorated despite treatment with high dose steroids and other immunosuppressants, including pulsed cyclophosphamide. Mycophenolate mofetil was therefore administered resulting in improvement and stabilization. This is the first report in English literature of the use of mycophenolate mofetil in the treatment of IHP and could stimulate further research in its efficacy in managing this condition.

Key words: Mycophenolate; idiopathic hypertrophic pachymeningitis.

Case report

A 47-year-old gentleman presented with a four month history of progressive difficulty in swallowing, slurred speech, ataxia, headache and vomiting. Past medical history included epilepsy since childhood, depression and traumatic enucleation of the right eye.

Clinical examination demonstrated slurred speech, left sided facial weakness, poor palatal elevation and difficulty in swallowing. He had left-sided papilloedema, nystagmus on lateral gaze and gait ataxia.

Routine blood tests including C-reactive protein and a CT head were normal. A brain MRI scan demonstrated dural enhancement, mainly in the posterior fossa (Fig. 1). Differential diagnosis included idiopathic hypertrophic pachymeningitis (IHP), limited Wegener's granulomatosis, sarcoidosis and granulomatous tuberculous meningitis. Serum angiotensin converting enzyme, a chest X-ray and a whole body scan including high resolution chest CT were all normal. Erythrocyte segmentation rate was 47. Cerebro-spinal fluid (CSF) examination showed an opening pressure of 8 cm, protein of 650 mg/l, glucose of 4.8 mmol/l (serum glucose was 7 mmol/l), 8 white cells with cytology demonstrating lymphocytes and a few larger cells with irregular nuclei. No malignant cells were seen. Oligoclonal bands were present. Immunological screen (including ANCA and rheumatoid factor), a Ziehl-Neelsen film and tuberculosis (TB) cultures were negative. The patient was reluctant to undergo biopsy.

He received a short course of anti-TB treatment until all cultures were negative. A clinical diagnosis of IHP was made.

He was initially treated with steroids and azathioprine without clinical benefit. A repeat MRI scan at 3 months demonstrated progressive basal meningeal enhancement with encasing of the cerebellum. Intensive treatment was therefore instituted with intravenous methylprednisolone and pulsed cyclophosphamide. Three months later he returned with more frequent headaches and vomiting, a severely constricted left visual field and an oedematous left optic disc. A brain CT scan demonstrated ventricular prominence, in keeping with developing hydrocephalus. He was therefore treated with the insertion of a ventriculoperitoneal shunt. His headaches persisted over the following four years, during which he had several episodes of intermittent shunt dysfunction, attributed to the extremely high CSF protein concentration (greater than 3 g/L). Immunosuppressive therapy was escalated with a progressive increase of prednisolone to 50 mg and two weekly cyclophosphamide pulses of 500 mg.

As there was no evidence of any benefit from cyclophosphamide, and as the cumulative dose reached potentially bone marrow suppression levels, cyclophosphamide was stopped and mycophenolate mofetil was added. Over the next weeks the

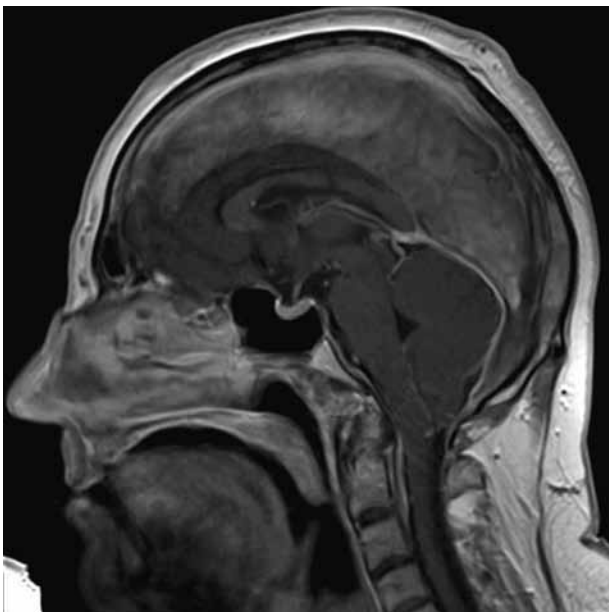

FIG. 1. — Sagittal T1-weighed contrast enhanced magnetic resonance imaging of the brain, demonstrating thickened meninges. Pathology (hazy white appearance between the cerebral hemispheres) is particularly prominent anterior to the brainstem and over the cerebellum (tentorium). This section was taken through the falx cerebri.

mycophenolate was increased to1.5 g twice daily. The patient reported less headaches and that his olfaction had returned. There was resolution of the papilloedema but the reduced visual acuity and restricted visual field persisted. Over the next 5 years and until this day, his condition has remained stable, requiring no further shunt revisions and with his CSF protein currently at 570 mg/l. Two further lumbar punctures that were performed during this period were negative for malignant cells and cells with irregular nuclei.

Discussion

IHP represents an uncommon inflammatory condition that causes diffuse fibrosis, thickening and dural radiological enhancement, initially described by Charcot and Joffroy, as a process affecting the spinal meninges, in 1869 (1). Many conditions have been described as potential causes of pachymeningitis, including treponemal infections, TB, rheumatoid arthritis, fungal infections, neurosarcoidosis and Wegener's granulomatosis. In a substantial proportion of patients no cause is found and the term idiopathic hypertrophic pachymeningitis was introduced, often a diagnosis of exclusion (2).

Common presenting symptoms include chronic headache, multiple cranial nerve palsies and ataxia (3). The course of IHP is variable, but it usually presents with a chronic relapsing and remitting pattern (2). In our case no biopsy was obtained as the patient refused to have one. However, we confidently excluded TB on the basis of negative cultures and the eventual response to immunosupression. Neurosarcoidosis is usually extremely responsive to steroids and this was not the case here, despite high dose steroids. Wegener's granulomatosis is another possibility but the negative ANCA and the absence of lung and/or renal involvement argues against it. Although we cannot exclude a spontaneous remission of the disease, the long period of follow up (10 years) with an aggressive disease over the initial 5 years which necessitated shunt insertion, followed by a dramatic improvement soon after the introduction of mycophenolate argues in favor of this being related to mycophenolate rather than being spontaneous.

Recently, several immunosuppressive drugs have been introduced in addition to steroids, such as azathioprine, cyclophosphamide and methotrexate (4), on the basis that an immune-mediated process would possibly respond to such agents. These drugs facilitate reduction of the dose of steroids and have a place in steroid resistant cases. To our knowledge, the use of mycophenolate in the treatment of IHP has never been previously reported.

Mycophenolate is derived from the fungus *Penicillium stoloniferum* (5). It inhibits inosine monophosphate dehydrogenase, the enzyme controlling the synthesis of guanine monophosphate in the *de novo* pathway of purine synthesis in the proliferation of lymphocytes (6). Although widely used in organ transplantation, it has a growing role in autoimmune conditions and more specifically in neuroimmunological diseases such as myasthenia gravis, neurosarcoidosis and central nervous system vasculitis, with results suggesting that it can be effective and well tolerated on a long-term basis (7).

We present a patient with IHP refractory to steroids and other commonly used immunosuppressants. The introduction of mycophenolate mofetil proved to be beneficial, with a rapid and sustained improvement, as the patient has been regularly followed-up for the past five years. Mycophenolate could therefore be considered in patients with IHP unresponsive to other immunosuppressive medication. The very rare occurrence of IHP makes it an unlikely entity to be studied in a systematic trial set up, hence why such case reports may be valuable in increasing future therapeutic options.

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