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Case Report

Idiopathic hypertrophic cranial pachymeningitis successfully treated with weekly subcutaneous methotrexate

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Summary

Idiopathic hypertrophic cranial pachymeningitis is a very infrequent disorder. Adequate management is still a matter of debate. We describe the use of low-dose pulse methotrexate in treating a 63-year-old woman with idiopathic hypertrophic cranial pachymeningitis. A weekly scheme with subcutaneous methotrexate was tried. Clinical improvement occurred in one week. Total remission of the clinical and neuro-imaging abnormalities was evident 6 months later, with minimal side effects. The patient is in complete remission after one year of follow-up without treatment. Hence, low-dose weekly subcutaneous methotrexate may be safe and effective in inducing complete and sustained remission of this condition. The experience with subcutaneous methotrexate to treat this entity has never been reported.

Keywords: Dura mater; headache; inflammation; methotrexate; pachymeningitis.

Introduction

Hypertrophic pachymeningitis is characterised by diffuse thickening of the dura mater, mostly associated with inflammation [10]. It is subdivided into cranial, spinal and craniospinal types, the latter being the less common [9]. The main clinical manifestations are headache, cranial nerve palsies and ataxia [7, 9, 10]. Hypertrophic pachymeningitis can be caused by a variety of diseases, including systemic auto-immune disorders, malignancies, tuberculosis, fungal and HTLV-1 infections [1, 7–10, 13]. However, most cases are of unknown aetiology. Several therapeutic strategies have been used, including steroids and other immunosuppressive agents, as well as radiotherapy and surgical removal of the affected tissue, with rather limited success [9, 10]. Here we report on a patient with idiopathic hypertrophic cranial pachymeningitis (IHCP) successfully treated with weekly subcutaneous methotrexate. To the best of our knowledge, this is the first report on the use of subcutaneous methotrexate in the treatment of IHCP.

Case report

A 63-year-old woman was referred to our hospital in November 2002 for exacerbation of her neurological deficits and atypical CT and MRI findings. Her complaints began 4 years before (in 1998) with episodic headaches. In 1999 the headaches increased in severity and frequency, being daily associated with dizziness, otalgia and tinnitus, as well as hearing and visual impairment. She had two generalised tonic-clonic seizures, but no anti-epileptic drugs were prescribed. In 2000 she was admitted to another hospital with diplopia, ataxic gait and mental disturbances. She was initiated on steroid therapy with an acceptable response for a short time, but with remissions and exacerbations of her clinical complaints in the following months. No history of trauma, intrathecal drug administration or contrasted spinal studies was declared.

At presentation to our hospital, neurological examination revealed slow mental processing, bilateral papilloedema, multiple bilateral cranial nerve palsies (nerves affected: II, IV, V, VI, VII, VIII) and ataxic gait. CT scans performed 2 years before arrival to our centre showed diffuse thickening of the dura at the posterior and middle cranial fossa, as well as the pontocerebellar cistern. In our hospital, a gadolinium-enhanced MRI showed an 8 to 10 mm thickening of the dura in the same locations with oedematous changes in anteromedial temporal and temporo-occipital gyri (Fig. 1). There was no evidence of active or inactive forms of neurocysticercosis.

Blood analyses of C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, complement components C3 and C4, P/C-antineu-

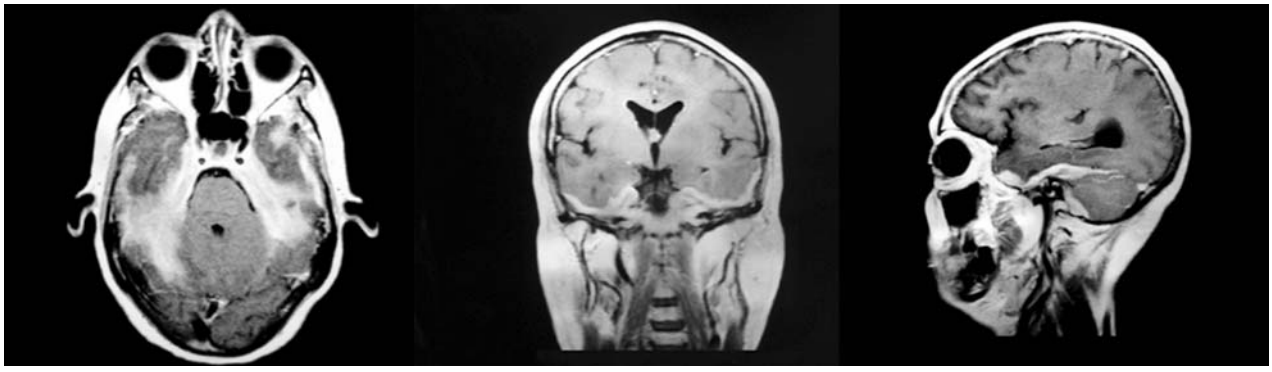

Fig. 1. Pretreatment axial, coronal and sagital views of a T1-weighted MRI after gadolinium enhancement. Diffuse thickening of the dura with oedematous changes in both anteromedial temporal and temporo-occipital lobes is evident

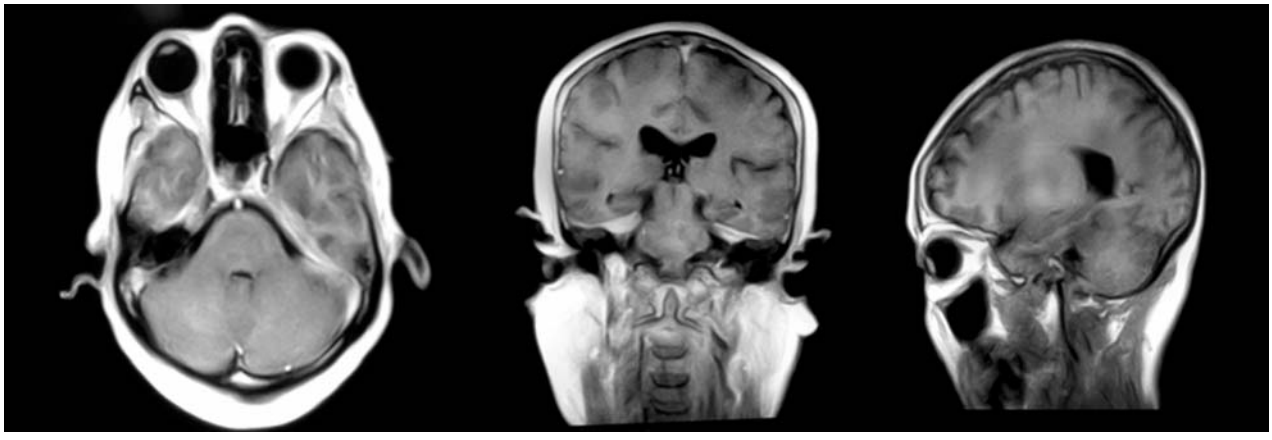

Fig. 2. Axial, coronal and sagital views of a gadolinium-enhanced T1-weighted MRI performed 6 months after having initiated the weekly subcutaneous methotrexate scheme. Important improvement of the dura and brain parenchyma, with respect to basal MRI is evident

trophilic cytoplasmatic antibodies (ANCA), antinuclear antibodies, tumoral markers, thyroid and hepatic functions, anti-HIV-1 and anti-HIV-2 antibodies, VDRL test and fluorescent treponemal antibody test; yielded all normal results. Chest and cranial X-ray films had also normal findings. Lumbar puncture revealed an opening pressure of 200 mm H_2O. Laboratory CFS analysis showed pleocytosis with 169/mm^3 cells (90% mononuclear), protein 74 mg/dL and a CSF/plasma glucose ratio of 0.5 (50%). Gram and Ziehl-Neelsen stains were negative for pathogenic micro-organisms. PCR assay for detection of Mycobacterium tuberculosis DNA was negative. Three CSF samples were also negative for malignancies in cytological examinations. A CSF enzyme-linked immunosorbent assay (ELISA) was positive for cysticercosis, at low titres.

The patient refused brain surgery and biopsy. Hence, based on the experience in other entities of auto-immune origin, we decided to initiate treatment trying with a low-dose scheme of weekly subcutaneous methotrexate at a dose of 12.5 mg. The patient showed improvement of her neurological deficits as early as 1 week after the first dose of methotrexate. One week later the patient was discharged with a final diagnosis of IHCP, given the lack of evidence of a particular causative factor. At the 6 months follow up, and still under methotrexate treatment, the patient was in complete remission of her neurological disturbances and a new gadolinium-enhanced MRI showed a very important improvement of the previous abnormalities (Fig. 2). Based on two normal CSF analyses at 8 and 12 months of treatment, and since the clinical manifestations of the disease were in sustained remission, we decided to taper subcutaneous methotrexate (in November 2003) within a 6-month period as follows: 4 months with subcutaneous methotrexate 6.25 mg weekly, and 2 months with oral methotrexate 2.5 mg weekly (completely discontinued in May 2004). During the course of the treatment the patient reported minimal side effects, limited to a subtle pain at the sites of injection. The patient completed 12 months of follow up after discontinuation of methotrexate, completely asymptomatic (by May 2005).

Discussion

Hypertrophic pachymeningitis has been increasingly reported since the introduction of CT and MRI. The spine and cranio-cervical junction are the zones of preponderance for this affection, followed by the skull base and less frequently by cortical regions [12, 15]. Clinical manifestations are related to the topography of the lesions and rarely are cause-specific. Chronic headache and signs of cranial neuropathies are the main clinical presentations [7, 9, 10]. Headache is almost invariably present, but does not show any specific pattern, except when there is an associated hydrocephalus [10, 12].

Ophthalmoplegia and optic nerve dysfunction are probably the most important cranial nerve affections [9, 10, 12]. Eventually the clinical picture may be that of Tolosa-Hunt or Garcin syndrome [8]. Differential diagnosis is wide. In immunocompromised patients, syphillis and tuberculosis could be frequent. Neoplasms such as lymphoma, a variety of adenocarcinomas, melanoma and meningeal carcinomatosis can also cause pachymeningitis [10]. Brain and meninges are affected in approximately 10% of patients with Wegener's granulomatosis, being the presence of cANCA highly suggestive of this disease [8].

In our patient, an exhaustive clinical and serological approach was inconclusive regarding a rheumatological diagnosis. Indeed, the positive CSF ELISA test for neurocysticercosis needs comment. In this case no past or present evidence on neuroimaging exists for active or inactive forms of neurocysticercosis to be considered [3]. Hence, this test result could be a false-positive, or could indicate a past exposure without current clinical significance [4]. Moreover, biological or methodological false-positive results can be yielded by CSF ELISA test for neurocysticercosis, as those observed in the context of CNS infections (e.g., syphilis), subarachnoid haemorrhage, neoplasms, degenerative diseases and other inflammatory processes [3].

MRI is the most useful method of evaluating a patient with suspected thickening of the meninges [10]. Peripheral enhancement and T2 hyperintensity are common in the early stages, corresponding to inflammation, while hypo-intensity is attributed to fibrosis. Biopsy of the thickened dura mater is useful for confirmation of the inflammatory process and for orientation of the aetiological diagnosis [10]. Since our patient refused any invasive procedure, we did not obtain a biopsy. Nonetheless, to our knowledge, the clinical course of this case, the results of laboratory examinations, as well as the basal and post-treatment MRI findings support the diagnosis of IHCP. Furthermore, it has been demonstrated that histological findings closely correlate to those in the gadolinium-enhanced MRI, as much before as during the treatment [10].

Medical treatment of IHCP remains, controversial. Very interesting and imaginative approaches have been proposed. However, steroid therapy is the most widely used pharmacological treatment; nevertheless, usually there is an inevitable progression of the disease and many cases may eventually become steroid-dependent for relapse to be avoided [7]. Pulse therapy with methylprednisolone has been advocated in order to increase efficacy [10]. Immunosuppressive agents as azathioprine, cyclophosphamide and cytarabine have been tried with limited success [2, 9]. Hidden tuberculosis as the elusive aetiology of IHCP has been suggested, and empirical treatment with antituberculous medications has been used [14]. Radiation therapy has also been given [11].

Methotrexate is an antifolate with immunosuppressive and anti-inflammatory properties, which inhibits the proliferation of lymphocytes (notably the CD3 and CD4 subtypes) [5, 6]. It also reduces pro-inflammatory Th-1 cytokines and enhances Th-2 cytokines with anti-inflammatory properties [5, 6]. Methotrexate has been used as high-dose pulse therapy for treatment of malignancies since 1947. On the other hand, low-dose pulse methotrexate (given weekly as 7.5 to 30 mg orally or subcutaneously) was introduced in the 1950s for the treatment of patients with psoriasis and psoriatic arthritis [5]. This low-dose weekly scheme has also been used to treat other inflammatory conditions with encouraging results [6]. Low-dose methotrexate is given parenterally to ensure effective compliance and uniform availability, as compared with the oral route [5, 6]. Also, subcutaneous methotrexate is better tolerated [5]. The rationale of this low-dose scheme is quite simple. Methotrexate is stored as polyglutamates in the intracellular space of monocytes, erythrocytes and hepatocytes (among other cells); this intracellular accumulation allows drug administration once weekly as a bolus or divided into three equal subdoses [5]. Based on these assumptions, and given that IHCP may have a similar pathophysiological mechanism to other conditions in which low-dose methotrexate has been proven effective in inducing remissions, we decided to give the patient a trial with low-dose pulse methotrexate. In our experience with this case, this scheme is effective and well tolerated, and may induce complete remission of the disease. Also, the subcutaneous route could require less drug monitoring than the oral route, an issue that, however, deserves more study. Nevertheless, the uncommon frequency of IHCP precludes the design of large randomised controlled trials aimed to prove the tolerability and efficacy of methotrexate at different doses and routes of administration. The best treatment could prove efficacy with time, unfortunately based mostly on reports of isolated cases or small case series.

In conclusion, weekly subcutaneous methotrexate may be safe and effective in treating IHCP. However, as the first report on this issue, this communication should be considered only a hypothesis-generating work

waiting for systematic confirmation, or for the test of time.

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Comments

The problem with ''hypertrophic pachymeningitis'' is whether this term should be regarded as a phenomenon or disease entity. Hypertrophic pachymeningitis is a localized or diffuse thickening of the dura mater associated with rheumatoid arthritis, syphilis, Wegener's granulomatosis, tuberculosis, cancer. The term ''idiopathic hypertrophic pachymeningitis'' is used when these other causes are ruled out. Also in the present case the diagnosis was made *per exclusionem*; diseases causing the meningeal thickening were ruled out by lab testing for various infectious diseases, auto-immune diseases and cancer. No biopsy was taken, however, the value of a biopsy may be disputable. Perhaps the ELISA for cysticercosis could have been repeated. So the message of the paper is that in this case of IHPM low-dosage of MTX reduced the symptoms.

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The two main points of this manuscript which make it a valuable contribution are

– the description of a new case of a rare disorder
– a variation in the therapeutical management by subcutaneous application of methotrexate which in the present case led to complete remission of the symptoms and neuroradiological alterations.

The only shortcoming of the report appears to be the lack of confirmation of the diagnosis by biopsy because the patient refused surgery. However, the observation that the disorder may be successfully treated by subcutaneous methotrexate by far outweighs this disadvantage. The authors rightly state that subcutaneous application of methotrexate is better tolerated and ensures effective compliance and uniform availability of the drug.

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