

Mycophenolate mofetil as a novel immunosuppressant in the treatment of neuro-Behçet's disease with parenchymal involvement: presentation of four cases

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ABSTRACT

Background. Behçet's disease is a multisystemic, relapsing, inflammatory disorder of unknown origin. Among Turkish cohorts, 5–15% of patients show involvement of the central nervous system (CNS) at some time during their disease. There are mainly two types of clinical presentation: parenchymal CNS inflammation manifesting mainly as meningoencephalitis of the brainstem, or dural sinus thrombosis. Several drugs like high-dose steroids or immunosuppressive agents, mainly azathioprine, are used in the treatment. For patients who do not respond sufficiently to these agents or are not able to tolerate them, other options are needed.

Patients. We are presenting 4 cases with parenchymal neuro-Behçet's disease, where commonly used immunosuppressive drugs could not be continued due to intolerance or inefficacy. However, the patients benefited well from mycophenolate mofetil. The benefit was sustained during 3–7 years of follow-up (median 6.5 years).

Conclusion. Mycophenolate mofetil seems to be an alternative drug in parenchymal neuro-Behçet's disease; however, large controlled studies should be performed for verification of our results.

Introduction

Behçet's disease is a multisystemic, relapsing, autoinflammatory disorder of unknown origin, characterised with recurrent oral aphtae, genital ulcers, erythema nodosum, pseudofolliculitis, and uveitis (1–4). While the expected age of onset in Behçet's disease is between 20 and 30 years, neurologic involvement is, on average, seen 5 years after initial onset. Males are more prone to the disease (3). Neurologic involvement,

which mostly affects the CNS, has been reported in 5–15% Behçet's disease patients among large Turkish cohorts (1, 3). Most of these patients develop brainstem meningoencephalitis, and in 15–20% dural sinus thrombosis occurs (1, 3). The most prominent feature of parenchymal neuro-Behçet is a spacious lesion expanding from the brainstem towards the basal ganglia. Evaluation of clinical and radiologic signs is needed to establish the diagnosis, and presence of inflammation in the cerebrospinal fluid (CSF) is supportive.

Parenchymal neuro-Behçet has an unfavourable prognosis and might result in severe disability or death (1). Treatment should be initiated immediately to prevent morbidity and mortality. However there are no randomised controlled trials in neuro-Behçet due to the relatively low number of cases. Relapses are treated with high-dose intravenous steroids. Intravenous cyclophosphamide (CTX) is an alternative drug in cases where steroids fail; however it can be highly toxic and prolonged use might lead to secondary malignancies. Long-term prophylactic therapy with immunosuppressive drugs is generally required and azathioprine (AZA) is widely used for this purpose (5). However, patients who are homozygous for thiopurine methyl transferase (TPMT) allele mutation will have a defective metabolism of AZA, which can lead to serious bone marrow toxicity and to gastrointestinal side effects (6). In these cases alternative treatment options should be considered.

Mycophenolate mofetil (MMF) is a relatively new immunosuppressive drug, which, in the last two decades, has been widely used in transplantation, systemic lupus erythematosus and myasthenia gravis patients. MMF is a selective, strong but reversible in-

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hibitor of the enzyme inosine-5-mono-phosphate dehydrogenase. It blocks de novo synthesis of the nucleotide guanosine and thus prevents proliferation of B and T lymphocytes (7).

In our clinical practice, we have used MMF in 4 patients with neuro-Behçet's disease in whom we could not use alternative drugs for various reasons. In this paper we are presenting the observational data and clinical follow-up of these four patients that were treated with MMF.

Patients

Case 1: A 29-year-old man was seen in our outpatient clinic due to right hemiplegia in 2003. He reported to have developed oral aphtae, uveitis and genital ulcers by the age of 21 and was using AZA and cyclosporine-A (CSA) since 1996. Neurologic examination revealed right-sided hemiparesis and impaired coordination on the same side. Cranial magnetic resonance imaging (MRI) revealed a gadolinium-enhanced lesion in the brainstem (Fig. 1a). CSF analysis resulted in 22 lymphocytes/mm³, protein and glucose levels were within normal limits and there were no oligoclonal bands (OCB). He was diagnosed with parenchymal neuro-Behçet's disease, received high-dose steroid treatment and almost fully recovered. Since he was taking AZA and CSA in sufficient doses for a sufficient time, the prophylactic treatment was considered ineffective. MMF (2x1000 mg per day) was started instead, and he remained relapse-free from 2003 until 2007.

In 2007 treatment with MMF was terminated at another hospital while he was doing his military service. Two months later he suffered from weakness and loss of coordination on the left side and was again seen in our outpatient clinic. Neurologic examination showed left hemiparesis (muscle strength in the range 3/5 of the MRC scale) and left sided ataxia, he was not able to walk without aid. Cranial MRI revealed a new expansive lesion in the brainstem (Fig. 1b). He received high-dose intravenous steroid treatment again, but recovered incompletely this time. Treatment with MMF (2x1000 mg per day) was initiated once more. The patient

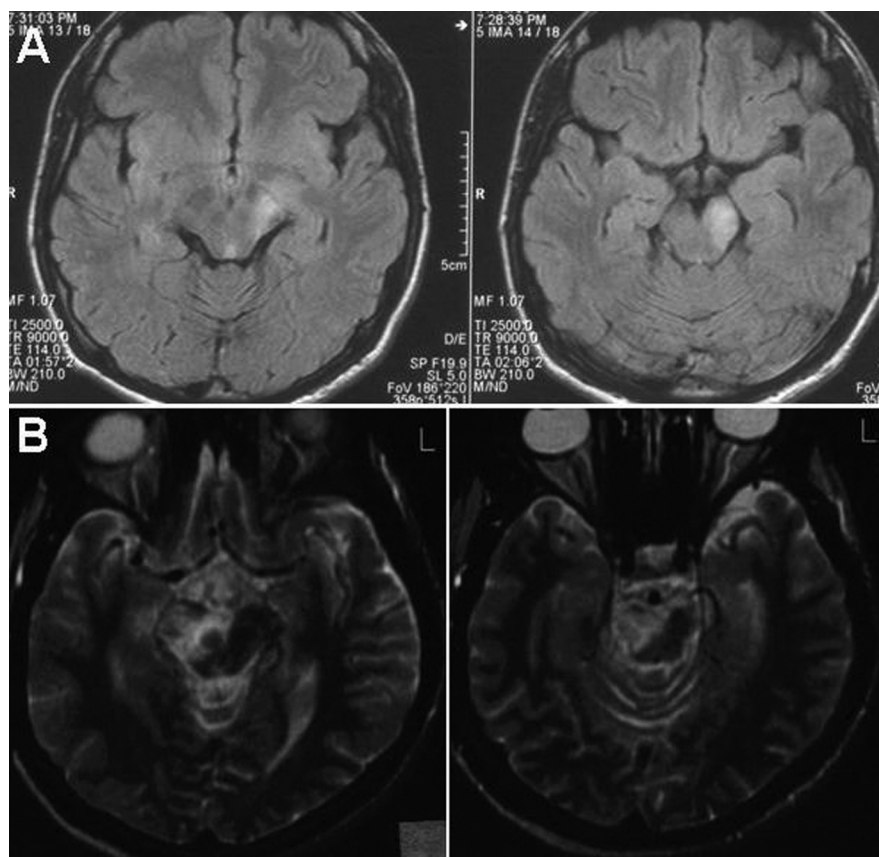


Fig. 1a. Cranial MRIs of Case 1 at initial presentation (2003). Axial FLAIR sections are showing an extensive lesion in left midbrain.
b. Cranial MRIs of Case 1 at second attack (2007). Axial T2 sections are showing an extensive lesion in right midbrain extending to pons.

was last seen in 2010, his neurologic status showed residual left-sided hemiparesis (muscle strength in the range 4/5 of the MRC scale) and slight truncal ataxia, he was able to walk without aid; he has had no further relapse.

Case 2: This 28-year-old woman was seen in another clinic due to vertigo, ataxia and double vision in 2003. Her cranial MRI showed a lesion in the brainstem, the analysis of CSF resulted in 18 lymphocytes/mm³ and a mildly elevated protein level. Combined with her history of recurrent oral aphtae and genital ulcers, she was diagnosed with neuro-Behçet's disease, and was treated with high-dose intravenous steroids for 10 days and recovered. A year later she had another relapse involving the brainstem, received high-dose steroid therapy again and recovered completely. AZA was added for prophylaxis, but she could not tolerate AZA due to gastrointestinal side effects (severe nausea and vomiting after the first dose on),

therefore oral CTX (2 mg/kg/d) was initiated, which was also terminated after 1 year to prevent long-term toxicity. AZA was retried as a prophylactic agent, but the patient did not tolerate the drug even in very low doses due to nausea and vomiting, therefore MMF (2x1000 mg per day) was started. Under this treatment she remained relapse-free for 3 years. Then, a short time after cessation due to difficulties in providing the drug, she experienced sudden loss of balance. Neurological examination showed impairment of coordination on the left side and truncal ataxia and cranial MRI revealed a new hyperintense lesion on T2 images in the brainstem. CSF analysis showed 6 lymphocytes/mm³ and protein levels were normal without OCBs. Clinical and radiological findings were interpreted as a new relapse, and after high dose steroid treatment MMF was restarted. After that, the patient remained relapse-free for the last 2 years. She

was seen at her follow-up appointment in 2010 and her neurological status revealed only slight ataxia and a mild paresis in the left leg.

Case 3: A 38-year-old man, who reported to have oral aphtae, genital ulcerations, erythema nodosum, pseudofolliculitis and uveitis since the age of 26 was diagnosed with Behçet's disease in another clinic and was using colchicine and cyclosporine (CSA) since then. He was seen in our outpatient clinic in 2004. His complaint was impaired vision and neurologic examination revealed left homonymous hemianopia. His cranial MRI revealed a large hyperintense lesion on T2 weighted images, reaching from the midbrain up to the right corpus geniculatum, involving also some temporal white matter, and appearing hyperintense on T2 images. CSF analysis was normal. The patient was treated with high-dose steroids. For prophylaxis CSA was stopped and AZA was initiated, but he could not tolerate this regimen due to gastrointestinal side effects (nausea and vomiting). MMF (2x1000 mg per day) was initiated instead and he remained relapse-free until 2007. In April 2007 he experienced double vision, slurred speech and hypoesthesia in the left arm and it turned out that he was not using MMF for the last 6 months. Neurological evaluation resulted in dysarthria, horizontal nystagmus and limb ataxia on the left side. Cranial MRI revealed a new lesion on the right pontomesencephalic junction. The relapse was again treated with high-dose steroids and MMF treatment was restarted. He was last seen in 2010, had no relapse meanwhile and neurologic examination showed a restriction of lateral gaze in both eyes and a mild hemiparesis of the left arm.

Case 4: In 2008, a 34-year-old woman was seen in another clinic for weakness of the left arm which was preceded by weakness of the complete right side a month before that. Back then, the neurological evaluation revealed left hemiparesis, and cranial MRI showed multiple millimetric hyperintense lesions in T2 images. The symptoms regressed spontaneously without treatment. She was seen in our clinic in

April 2009 when she had a left-sided weakness following a dental infection. Neurological evaluation showed left hemiparesis and loss of vibration, the patient could not walk without aid. Her cranial MRI showed a large brainstem lesion in the pons, extending up to the midbrain. Analysis of the CSF revealed 19 lymphocytes/mm³, the protein level was normal and no OCB was detected. From her history we learned that she had recurrent oral aphtae, genital ulcerations and erythema nodosum since the age of 9. A diagnosis of Behçet's disease with parenchymal neurological involvement was established, her recent complaints were considered as a new relapse and she was treated with high-dose steroids. AZA was administered for prophylaxis but she could not tolerate the treatment, due to nausea and vomiting; her liver enzymes were also elevated. As a result, treatment was switched to MMF (2x1000 mg per day). She was last seen in August 2010 during her follow-up appointment and it was noted that she did not have further relapses.

Discussion

Here we report 4 cases of parenchymal neuro-Behçet's disease who could not tolerate AZA, but responded well to MMF. Three of our cases could not use azathioprine due to nausea and vomiting probably due to TPMT mutation; however in none of the cases this could be checked.

Cyclosporine is known to be very effective in treating exacerbations of uveitis in Behçet's disease, but is suspected to trigger relapses in parenchymal neuro-Behçet, and is therefore an inappropriate choice (8). Cyclophosphamide has been effectively used especially in vascular Behçet's disease and some cases of refractory neuro-Behçet's disease. However, due to its high cumulative toxicity, the treatment interval must not exceed 2 years, which is a drawback for a chronic disease like neuro-Behçet's disease (5). Interferon-alpha and tumour necrosis factor (TNF) antagonists could be efficient alternatives, but both may have serious side effects and are very expensive.

There are only a few publications de-

scribing the use of MMF for systemic involvement in Behçet's disease. In a retrospective study, Piernegro *et al.* reported that MMF is a successful treatment in patients with exacerbations of uveitis and who failed to respond to other immunosuppressive drugs in Behçet's disease (9). Santana *et al.* published 9 cases of Behçet's disease with pulmonary involvement, which were treated with chlorambucil (CHB), CTX, or MMF, and showed good clinical improvement and high survival rates (10). However, in an earlier prospective study, MMF was unable to control the signs of mucocutaneous Behçet's disease and the study was interrupted due to inefficacy of MMF (11). Behçet's disease is a peculiar disorder where some of its manifestations may respond to a certain agent while some other manifestations may not benefit from the same treatment, as in the example with cyclosporine and ophthalmological *versus* neurological involvement (5, 8). This might also be the case for MMF and neurological involvement *versus* mucocutaneous disease. MMF has also been used in other inflammatory CNS diseases like multiple sclerosis and results of pilot studies have been published. Remington *et al.* evaluated 24 relapsing remitting multiple sclerosis (RRMS) cases receiving interferon beta-1a and MMF, and their results suggested that MMF might be useful in MS (12).

Considering the above-mentioned results of experience with MMF in the literature, we started 4 patients with parenchymal neuro-Behçet on MMF 2x1000 mg per day. These patients either could not tolerate other conventional immunosuppressive agents, or their prior regimen was ineffective. In two of the four cases, neurological involvement developed while under other immunosuppressive therapy, and one of those and the remaining 2 patients could not tolerate AZA due to gastrointestinal side effects manifesting as intractable nausea and vomiting. While treated with MMF our patients were stable over years showing no systemic or neurological exacerbations. Interestingly, 3 of the cases developed relapses after cessation of MMF. After

having initiated the drug again they remained relapse-free for another 1–3 years. Adverse effects like elevated liver function tests, development of opportunistic infections, development of lymphoma and skin malignancies are reported with long term MMF treatment, but none of the above were seen in our patients in a relatively long follow-up period.

Since parenchymal neuro-Behçet is a serious life-threatening disease, with possible serious morbidity, and even mortality, patients who experience frequent relapses and do not respond to conventional immunosuppressive agents, or show marked intolerance could be treated with MMF. Further studies are needed to establish its use in neuro-Behçet, maybe even as a prophylactic drug of first choice.

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