Behçet Disease Presenting with Neurological Complications Immediately after Conversion from Conventional Cyclosporin A to Microemulsion Formulation

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Abstract

A 53-year-old man with Behçet disease was treated with conventional cyclosporin A (CyA), because of refractory bilateral uveitis. Immediately following the conversion from conventional CyA to a microemulsion formulation, he presented with neurological complications. The neurological findings, pleocytosis of the cerebrospinal fluid (CSF) and brainstem lesions revealed by brain magnetic resonance imaging (MRI) suggested neuro-Behçet disease. After discontinuing CyA and introducing oral prednisolone, the neurological symptoms, pleocytosis of CSF and brainstem lesions on MRI improved. Although the microemulsion formulation, which can maintain a stable level of blood CyA, is a useful agent for the control of ocular lesions in Behçet disease, the resulting abrupt increase in blood CyA level may have induced neuro-Behçet disease.

Key words: Behçet disease, cyclosporin A, microemulsion formulation

Introduction

Cyclosporin A (CyA) is a potent immunosuppressive agent that is widely used not only for the prevention of graft-vs-host disease after organ transplantation, but also for various autoimmune diseases. Refractory uveitis in Behçet disease is one of the main therapeutic targets of CyA, however its neurotoxicity is also a serious problem (1, 2). Intestinal absorption of CyA is also another problem. The intrindividual variations in CyA blood level resulting mainly from the influence of diet may cause an insufficient control of the disease. To resolve this problem, a new microemulsion formulation of CyA (cyclosporin A MEPC, as MEPC hereafter) was developed. MEPC has been demonstrated to maintain a stable level of blood CyA in various diseases because of an improved intestinal absorption. Initially, the efficacy of MEPC was established in transplant patients (3). Furthermore, MEPC has also been introduced for the treatment of refractory uveitis with Behçet disease (4). Here we describe a case of Behçet disease presenting with neurological complications immediately after the conversion from conventional CyA to MEPC.

Case Report

A 53-year-old man was admitted to our hospital presenting with headache, nausea and dysarthria in October 2000. He had manifested four major symptoms (aphtha, genital ulcer, nodular erythema of the skin and uveitis) of Behçet disease since 1995. As the ocular symptom was serious, he was first treated with colchicine. Because the control of ocular symptoms with colchicine was poor, CyA was introduced in 1999. When the trough blood CyA level was maintained within the therapeutic range, the ocular symptoms improved. Although CyA seemed to be more effective than colchicine, the control of the ocular symptoms remained unstable probably because of the fluctuations of blood CyA level. One week before the onset of neurological symptoms, the ophthalmologist in charge of this patient changed the conventional CyA to MEPC to stabilize the blood CyA level.

On admission, a few aphthae were observed in the oral
cavity but no genital ulcers or skin lesions were detected. Bilateral uveitis was also observed, predominantly on the left side. On neurological examination, dysarthria and swallowing difficulty with a weak pharyngeal reflex were detected. Although muscle strength was generally in the full range with normal muscle stretch reflexes, plantar reflex was flexor bilaterally. No sensory deficits were observed. Laboratory tests demonstrated mild leukocytosis and anemia (WBC 8,200/mm$^3$; Hb, 10.5 g/dl) with an increased erythrocyte sedimentation rate (80 mm in 1 hour). The trough blood CyA level was 109 ng/ml. HLA typing showed the presence of A26, A29, B61, B70, Cw3, and Cw7. CSF analysis revealed pleocytosis (113/mm$^3$; poly 18, mono 95) with a slight increase in total protein level. T2-weighted MRI showed high-intensity lesions in the brainstem with marked contrast enhancement by Gd-DTPA on T1-weighted images (Fig. 1). These clinical and laboratory findings supported the diagnosis of neuro-Behçet disease. MEPC was discontinued and oral prednisolone was administered. The initial dose of prednisolone was 60 mg/day, which was tapered with the improvement of clinical symptoms (Fig. 2). Oral prednisolone is maintained at a dose of 15–20 mg/day and he has remained free from a recurrence of neuro-Behçet disease.

Discussion

CyA is a potent immunosuppressive agent which is widely used for patients with graft-vs-host disease and various autoimmune diseases. CyA use is associated with numerous side effects; nephrotoxicity and hypertension are the most common, but neurotoxicity is also known to occur (5). In recognizing its side effects, neurological side effects were reported in up to 40% of patients receiving CyA. The most common neurological complication is postural tremor, which is often mild and does not require dose reduction. In addition to postural tremor, posterior leucoencephalopathy and generalized seizure are occasionally serious and require the immediate cessation of CyA (5). These side effects involving the central nervous system (CNS) are generally called CyA encephalopathy. The mechanism underlying the neurotoxicity of CyA remains unclarified. Endothelial impairment by CyA with the consequent occlusion of small vessels may cause some degree of ischemic damage and subsequent seizure or leucoencephalopathy.

CyA also induces neurological complications in patients with Behçet disease (2). Its neurotoxicity, occurring in 20–30% of patients with Behçet disease receiving CyA, seems different from that causing general CyA encephalopathy. The neurological complications in patients receiving CyA are difficult to distinguish from typical neuro-Behçet disease. That is, CyA seems to induce neuro-Behçet disease. Although many neurological deficits may occur in Behçet disease, brainstem lesions, motor deficit and psychiatric symptoms are the common clinical manifestations (6, 7). Most patients with Behçet disease who suffer from the side effects of CyA present with brainstem lesions or pleocytosis of CSF.

Similar to other reported cases, the present patient developed bulbar palsy associated with severe headache. The marked pleocytosis of CSF and typical brainstem lesions revealed by brain MRI confirmed the diagnosis of neuro-Behçet disease. Although permeability of the CNS to CyA remains controversial (8–10), vasculitis in Behçet disease might enhance CyA penetration to the CNS and induce neurological complications. Whether the permeability of the CNS to CyA increases or not in the presence of vasculitis, the reason for the similarity between neurological complications in patients with CyA induced neuro-Behçet disease and the symptoms of typical neuro-Behçet disease remain unclarified.

Compared with previously reported cases of neuro-Behçet disease, which developed during CyA therapy, the most prominent feature of the present patient is that he developed neurological symptoms immediately after the conversion from conventional CyA to MEPC. Recently, MEPC has been substituted for conventional CyA, because conventional CyA shows limited absorption from the intestinal tract mainly due to the influence of a fat-rich diet (11). This problem results in an unstable blood CyA level and an insufficient clinical control of a disease. To overcome this problem, MEPC was developed. MEPC is pharmacologically designed to become microemulsified when it comes in contact with body fluids.
such as gastric juices. The trough blood CyA level in the present patient did not increase after switching to MEPC. Similar to our patient, Kotake et al pointed out that most patients presenting with symptoms of neuro-Behçet disease while receiving CyA exhibit a normal trough blood CyA level (2). These results suggest that another factor in addition to trough blood CyA level is likely related to neurotoxicity. Takahara et al performed a detailed pharmacokinetic study of MEPC on patients showing a poor absorption of conventional CyA among stable renal transplant recipients (12). Interestingly, while trough blood CyA levels in both CyA-treated and MEPC-treated groups were similar, the peak blood CyA level measured 2 hours after oral administration was very high in the MEPC-treated group. If similar pharmacokinetics occurs in patients with Behçet disease, an abrupt elevation of blood CyA level and a fragile blood-brain barrier due to occult vascular lesions in Behçet disease may enhance the neurotoxicity of CyA, resulting in the onset of neuro-Behçet disease. Presently, this theory remains a speculation; however, further investigations of the peak blood CyA level in Behçet disease may clarify this phenomenon.

Despite the potential for severe adverse effects, CyA remains an indispensable drug for preventing blindness due to refractory uveitis in Behçet disease. From our experience in treating the present patient, the blood CyA level should be monitored not only at the trough but also at the peak. To establish the safety protocol for CyA therapy of patients with Behçet disease, further detailed investigations of the pharmacokinetics of CyA are necessary.

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References