Case Report

Cyclosporine therapy

Does it provoke neurological complications in Behcet's disease

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ABSTRACT

Cyclosporine was suggested recently by Japanese workers to provoke central nervous systems symptoms in Behcet's disease. We report 2 cases supporting this notion. Our aim is to draw the attention of physicians to such phenomenon as cyclosporine being frequently advocated in the treatment of uveitis due to Behcet's disease.

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Behcet's disease (BD) is a multi-system inflammatory disorder of unknown etiology usually manifesting as mucocutaneous ocular syndrome. Its prevalence is higher in Japan and the Mediterranean basin.[1,2] Behcet's disease is not uncommon in the Kingdom of Saudi Arabia (KSA) as many authors reported on its different clinical and neurological presentation, though the exact incidence is unknown.[3-5] The most serious complication of BD is neurological, beside the visual loss. There are regional variations in the incidence of neurological complications in BD, but in a large series most of the figures quoted vary between 3-10%.[1,2,6] In a recent Japanese study of 317 patients with BD with ocular complications, 12 (25.5%) of 47 patients on CSA developed neuro-Behcet's implying that cyclosporine (CSA) may predispose BD sufferers to develop central nervous system (CNS) complications.[7] The purpose of this report is to support this notion by describing 2 more cases with such phenomenon.

Case Report. ***Patient One.*** This is a 27-year-old Saudi male, diagnosed as a case of BD based on the International Study Group criteria,[8] receiving CSA for 10 months to control severe uveitis. He presented with a 3 day history of fever, slurred speech and decreased level of consciousness. On examination he was hypophonic and most of the time mute and had a masked face. He had left VII nerve palsy, left Horner's and bilateral upper and lower limbs weakness with power of 4 (Medical Research Council grading) on right, 3 on the left, and bilateral Babniski sign. The rest of the physical examination was normal apart from evidence of previous uveitis. Complete blood picture and routine biochemistry tests were normal. Cyclosporine level was within therapeutic range. Cerebrospinal fluid examination showed normal composition except for a protein of 0.7gm/L (normal range 0.25-0.45). Magnetic resonance image (MRI) of brain findings revealed hyperintense lesions in the internal capsules, basal ganglia, the thalami, cerebral peduncles and the midbrain which were gadolineum dietylenetriamine pentaacetic acid (Gd-DTPA) enhancing (**Figure 1a**). Methylprednisolone pulse therapy was given intravenously and followed by tapering dose of prednisolone with gradual withdrawal of CSA. He showed a remarkable improvement on MRI (**Figure 1b**). Subsequently, the patient was kept on 30mg prednisolone daily though the neurological deficit

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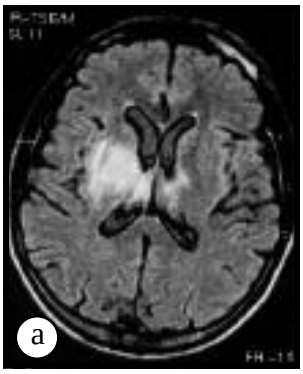


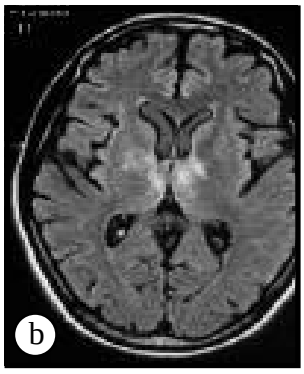
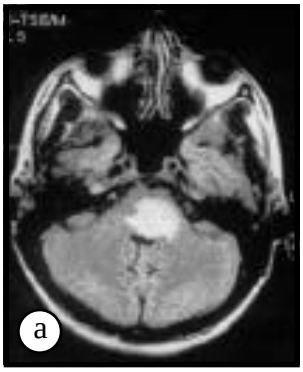


Figure 1 - Fluid attenuated inversion recovery MRI showing **a)** hyperintense signal in the right basal ganglia (internal capsule, both thalami, upper midbrain and both cerebral peduncles. **b)** the hyperintensity signal seen in the former MRI has been significantly reduced in size.



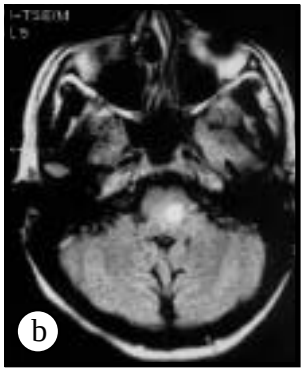


Figure 2 - Fluid attenuated inversion recovery MRI showing **a)** hyperintense signal is seen in the central part of the pons deforming the lateral aspect of the 4th ventricle. **b)** the pontine lesion described above is much reduced in size.

showed a relatively minimal improvement with tendency for exacerbation when discontinuation of prednisolone was attempted.

Patient 2. A 20-year-old Saudi female, a documented case of BD according to the International Study Group Criteria,[8] was receiving 100mg CSA to suppress her uveitis for the preceding 6 months. She presented with a 2 day history of fever, headache and vomiting associated with diplopia and left side weakness. Examination revealed right VI and VII nerve palsies and left-sided weakness with a power of grade 3 in the left upper limb and 4 in the lower. The rest of physical examination was unrevealing. Investigations were as follows: normal blood picture and chemistry. Cyclosporine level was within therapeutic range. Magnetic resonance image of brain findings showed hyperintense lesions in the left pontine medullary junction which enhanced with Gd-DTPA (**Figure 2a**). Cyclosporine was tapered gradually and she was treated with intravenous methylprednisolone pulse therapy, with remarkable improvement in the clinical and MRI findings. The hemiparesis completely resolved, but the VI palsy persisted. The MRI lesions became smaller and finally rudimentary (**Figure 2b**). Azathioprine was later introduced by the ophthalmologists to replace CSA. She is currently on 25mg prednisolone and azathioprine 100mg daily. On attempting discontinuation of prednisolone 8 weeks later, the patient developed a relapse of her weakness, but this was reversed by re-institution of steroids.

Discussion. Cyclosporine is a potent immunosuppressive agent that modulates T cell function. Its use in BD was introduced in Japan in 1984 for treatment of ocular involvement in BD,[7] though its use was limited due to side effects, mainly nephrotoxicity.[9] Recently there are a few reports from Japan incriminating its potentiality to precipitate neurological complications in BD.[7,10,11] Kotake et al[7] in 1999 in a study of 317 patients of BD found that 21 (6.6%) developed neuro-Behcet's. Among those 47 on CSA,12 (25.5%) manifested neurological complications, compared to 9 (3.3%) of those not taking CSA which gives a Fisher exact probability test of P=0.000037.7 It is worth mentioning that CNS involvement settled only after discontinuation of CSA in 3 of 11 patients on CSA. The exact mechanism of CSA causing neurological symptom in BD is not known, though it is suggested that CSA, by causing microangiopathy leads to the breakdown in the blood brain barrier, and hence facilitates CSA neurotoxicity.[12] Another study showed highly active anti-endothelial cell antibodies in patients with BD.[13] Our 2 cases developed neuro-Behcet's supporting the Japanese current finding which suggest that either CSA causes neurotoxicity or accelerates its development. The remarkable response of the MRI lesions to dexamethazone suggests that the shadows are mainly edema due to the blood barrier breakdown. Cyclosporine is known to cause transient MRI shadows in posterior leucoencephalopathy syndrome probably through similar a mechanism.[14] It seems that CSA predisposes the commonly vulnerable areas of BD brains to such changes as demonstrated in our 2 cases in whom the brunt of the lesions were on the brain stem and the basal ganglia regions.

The relapse of the neurological deficit in the 2 patients on discontinuation of steroids in spite of the fact that the patients were off CSA argues against incrimination of CSA as the sole factor causing neuro- Behcet's and it may be possible that CSA might be an innocent bystander.

As CSA is commonly instituted in treatment of uveitis in BD, we recommend that patients on this drug should be observed closely for development of neuro-Behcet's. We also think that methylprednisolone intravenous pulse therapy is an effective way of treatment, and patients should be kept on long term steroids to prevent acute neurological relapses. A further well-designed prospective controlled study is warranted to settle this important issue.

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