Cyclosporine for Behçet's uveitis: is it associated with an increased risk of neurological involvement?

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ABSTRACT

Objective. *The immunosuppressant cyclosporine is widely used to treat Behçet's disease (BD). The aim of this study was to determine whether cyclosporine increases the risk of neurological involvement in BD.*

Methods. *Patient files from the Ophthalmology Department for the period 2000-2005 were screened retrospectively, and the occurrence of neurological involvement and its relationship to ocular severity were evaluated.*

Results. *A total of 454 patients with BD were seen at the Ophthalmology Department in this period, including 24 who had been referred from the Neurology Department. Excluded from the study were 47 patients who did not have uveitis and 114 patients with an inadequate follow-up. The remaining 269 patients had been treated with either cyclosporine (Group I, n=92), other immunosuppressants (Group II, n=132), or no treatment other than colchicine (Group III, n=45).*

Patients with neurological symptoms were sent to the Neurology Department for evaluation: 20 from Group I [10 with primary headache, 1 with depression, 1 with sinus thrombosis, and 8 with parenchymal neurological involvement (pNBD)]; 13 from Group II [10 with primary headache, 1 with premorbid epilepsy, 1 with sinus thrombosis, and 1 with pNBD]; and 5 from Group III with primary headache.

The frequency of pNBD was significantly higher in Group I, and included atypical features such as seizures and MRI lesions as well as the typical symptoms of brainstem involvement and pleocytosis. Eye involvement tended to be more severe in Group I, and the difference remained significant both when milder cases were excluded from the analysis (6 vs. 0; p=0.03) and when severe cases were excluded (p=0.04). pNBD was significantly more frequent in patients on cyclosporine alone than in those receiving cyclosporine plus another agent.

Conclusion. *In patients with Behçet's uveitis, cyclosporine seems to be associated with an increased risk of developing pNBD, although the reason for this is unknown. A prospective trial is needed to shed light on this problem.*

Introduction

Behçet's disease (BD) is a multi-systemic inflammatory disease of unknown etiology. It was first described by the Turkish dermatologist Hulusi Behçet as a triple symptom complex featuring oral aphtae, genital ulcers and uveitis (1). Since then, many other manifestations of BD have been identified, including venous thrombosis, arthritis, pulmonary aneurysm, gastrointestinal ulcers, and neurological involvement (2).

Before the 1980s, the prognosis for vision in BD was believed to be dismal. In a study dated 1970, vision was reported to be lost an average of 3.36 years after the onset of ocular symptoms (3). However, a more recent study found the prognosis to have improved in the 1990s due to the early, more aggressive use of immunosuppressive agents including cyclosporine (4). Cyclosporine is a kinase/phosphatase inhibitor (calcineurin inhibitor) that has been widely used to treat BD since 1983 (5). Its efficacy in slowing ocular involvement has been demonstrated in controlled trials (6, 7).

Lately, however, it has been suggested that cyclosporine may increase the risk of neurological involvement (8-10); one paper reported the development of neurological complications in a patient who had just been switched to a microemulsion form of cyclosporine (11). The aim of this study was to determine whether such a risk exists.

Patients and methods

All patient files from January 2000 to January 2005 at the Uveitis Service of the Ophthalmology Department of Istanbul Medical Faculty were screened retrospectively. Included in this study were patients who fulfilled all of the following criteria: (i) a diagnosis of BD based on the International Study Group's criteria for BD (12); (ii) a diagnosis of uveitis due to BD; (iii) the patient's first admission was to the Ophthalmology Department; (iv) the first admission took place in the period between January 2000 and January 2005, and (v) there was a follow-up of at least 3 months.

All patients were seen by the same ophthalmologist (ITT) at each visit, and underwent routine questioning for other systemic findings of BD, including neurological complaints such as headache. Those reporting neurological complaints were sent to the Neuro-Behçet Outpatient Clinic of the Neurology Department for further evaluation. Demographic features, baseline treatment modalities, and ocular involvement were compared in the patients with and without neurological involvement. Three groups were identified: patients placed on cyclosporine treatment (Group I), patients taking other immunosuppressants (Group II), and patients not on any long-term treatment apart from colchicine (Group III).

For the purposes of this study, we developed an index to evaluate the severity of ocular involvement. One point each was attributed for the presence at any time during the follow-up of: 1) hypopyon; 2) retinitis; 3) severe vitritis (*i.e.*, 3+); 4) branch retinal vein occlusion; and 5) macular edema. The score for these items was added up, and further points were assigned based on the visual acuity for each eye achieved at remission – perfect vision (1.0) received a score of 0 points; vision <1.0 but ≥0.5 was assigned a score of 1 point; vision <0.5 but >0.1 received a score of 2 points; and vision ≤ 0.1 was given a score of 3 points). Using this system, the worst possible ophthalmological score was 11.

All patients being treated with cyclosporine received the drug in microemulsion form, as this was the general practice in our clinic. The patients' records did not include data on blood levels of cyclosporine, as this parameter is not routinely measured at our ophthalmology department.

Statistical analysis

For the parametric comparisons between the three groups, the one-way ANOVA test was applied. For the non-parametric analyses, the Kruskall Wallis test was used to compare all three groups and Fisher's exact test was applied to compare Group I to Groups II and III.

Results

A total of 454 BD patients (138 females and 316 males) were seen at the Ophthalmology Department between January 2000 and January 2005. A total of 185 patients had to be excluded from this study: 24 who had been referred from the Neurology Department, where they were initially seen; 47 referred for a routine ophthalmological evaluation after a diagnosis of BD made elsewhere, who were found not to have any ocular involvement; and 114 whose records showed a single visit or inadequate follow-up (in most cases, patients who were being treated elsewhere and had been referred for a second opinion).

The remaining 269 patients (67 F, 202 M) were enrolled in the study. All had been treated with colchicine or short-term systemic or topical steroids as indicated. We divided the study cohort into 3 groups based on the long-term treatment received (Table I). Group I (n=92; F/M 19/73) consisted of patients being treated with cyclosporine alone (n=17) or a combination of cyclosporine and other immunosuppressants (74 patients on cyclosporine + azathioprine, and 1 patient on cyclosporine + mycophenolate mofetil). In 39 patients, other immunosuppressants were also used after cyclosporine. The patients in Group II were taking medications other than cyclosporine (n=132; F/M 32/100): 126 were on azathioprine (15 switched to other immunosuppressants later) and 6 were taking other immunosuppressants. The patients in Group III were being treated only with colchicine (n=45; F/M 16/29). Group I was characterized by a higher M/F ratio and younger age (although these differences were not statistically significant) and a significantly longer follow-up than Groups II and III. In Group I the median duration of cyclosporine use was 18 months (mean: 21.1+14.3 months; range: 2-60).

Eye involvement was significantly more severe in Group I, and was mildest in Group III (Table II). In Group I significantly more patients had hypopyon, retinitis, severe vitritis, and macular edema ($p<0.05$, Kruskall Wallis test), and there was a (non-significant) tendency to more branch retinal vein occlusion. In Group I, 10% had

Table I. Demographic features of the patients with Behçet's disease seen at the Ophthalmology Department of the Istanbul Faculty of Medicine in the period 2000-2005, grouped by treatment.

Demographic features	Whole group	Group I (cyclosporine)	Group II (other immunosuppressants)	Group III (no immunosuppressive treatment)	*p*
n (F/M)	269 (67/202)	92 (19/73)	132 (32/100)	45 (16/29)	NS*
Mean age (SD); median, years	28.3 ± 8.1; 27	26.7 ± 6.8; 25	29.0 ± 8.1; 28	30.0 ± 10; 28	NS*
Median follow-up; mean (SD), months	28; 32.3 ± 37.7	35; 35.9 ± 20.6	22.5; 30.6 ± 49.7	24; 29,9 ± 22.0	<0.01*

*One-way ANOVA test.

Table II. Characteristics of the ocular involvement in each group.

Eye involvement	Whole group	Group I (cyclosporine)	Group II (other immuno-suppressives)	Group III (no immuno-suppressive treatment)	*p*
Hypopyon; n (%)	34 (12%)	24 (25%)	9 (7%)	1 (2%)	<0.01*
Retinitis; n (%)	141 (52%)	75 (79%)	63 (47%)	3 (7%)	<0.01*
3+ vitritis; n (%)	152 (56%)	64 (67%)	83 (63%)	5 (11%)	<0.05*
Branch retinal vein occlusion; n (%)	43 (16%)	20 (21%)	20 (15%)	3 (7%)	0.055*
Macular edema; n (%)	116 (43%)	68 (74%)	45 (34%)	3 (7%)	<0.01*
Best vision 1.0 in both eyes; n (%)	82 (30%)	8 (9%)	47 (36%)	27 (60%)	<0.01*
Best vision <0.1 in one eye; n (%)	84 (31%)	36 (39%)	47 (35%)	8 (17%)	<0.05*
Best vision <0.1 in both eyes; n (%)	9 (3%)	9 (10%)	0	0	<0.01*
Median total visual acuity score (range)	2 (0-6)	3 (0-6)	1 (0-5)	0 (0-4)	<0.01**
Median total ocular score (range)	4 (0-10)	6 (0-10)	3 (0-9)	0 (0-4)	<0.01**

*Kruskall Wallis test; **one-way ANOVA test.

permanent bilateral vision loss, whereas in Groups II and III none of the patients experienced permanent bilateral vision loss (p<0.01, Kruskall Wallis test). The median severity scores for Group I, Group II and Group III were 6 (range: 0-10), 3 (range: 0-9), and 0 (range: 0-5) (p<0.01, one-way ANOVA test), respectively (Table II). The median visual acuity scores for Groups I, II, and III were 3, 1, and 0 respectively (p<0.01, one-way ANOVA test).

Among the patients in Group I, 20 (22%) were referred to the Neurology Department (Table III). Ten (11%) had primary headache disorders (migraine and tension type headache), one had depression, one had sinus thrombosis, and 8 (9%) had parenchymal neurological involvement. In Group II 13 patients (10%) were sent to the Neurology Department, and among these 10 (7.5%) had primary headache disorders, one had pre-morbid epilepsy, one had sinus thrombosis, and one (0.75%) had parenchymal neurological involvement. In Group III, 5 patients (11%) were sent to the Neurology Department, all with complaints of primary headache disorders. Significantly more patients from Group I required a neurological consultation (p=0.03, Kruskall Wallis test), mainly for parenchymal neuro-BD (pNBD), which was significantly more frequent among patients being treated with cyclosporine (p<0.02, Kruskall Wallis test).

To study the correlation between ocular severity and the development of neurological involvement, mild cases (with scores below the median for the whole group) were excluded and the analyses were repeated. We found 146 patients with an ocular severity score ≥4. Seventy-seven were from Group I, of whom 6 had pNBD, while 69 were from Groups II and III and none had pNBD. The difference between Group I and Groups II and III was statistically significant (p=0.03, Fisher's exact test). To double-check this finding, the analysis was repeated after excluding all severe cases. There were 123 patients with a total score ≤3. Of these, 15 were from Group I and 2 had pNBD, while 108 patients were from Group II or III, and 1 patient (from Group II) had pNBD. The difference was again statistically significant (p=0.04, Fisher's exact test). When the ocular scores of all cases with pNBD were evaluated, one had 0 points, two had 2 points (one each from Groups I and II), one had 5 points, one had 6 points, two had 7 points, and two had 8 points. However, this result did not reach statistical significance.

In Group I, 4 of the patients with pNBD were being treated with cyclosporine alone (out of 17), whereas the remaining 4 were on cyclosporine plus another drug – 3 were taking azathioprine and one mycophenolate mofetil (out of 75). This difference was also statistically significant (p=0.03, Fisher's exact test).

The neurological features of the patients with parenchymal neurological involvement are summarized in Table IV. Such involvement developed after a median of 16.5 months of cyclosporine therapy in patients from Group I (mean: 20.2+13.2 months; range: 8-50). One patient's MRI scan showing atypical features is presented in Figure 1. When pNBD was detected patients were switched from cyclosporine to other medications (azathioprine, cyclophosphamide, mycophenolate mofetil, chlorambucil, or interferon alpha, as indicated) after aggressive treatment with high-dose IV methylprednisolone. All of the patients responded well to steroid treatment; the MRI lesions regressed or disappeared and none experienced further neurological attacks under the new long-term treatment. Only one patient

Table III. Distribution of neurological complaints among the groups.

	Whole group	Group I	Group II	Group III
No neurological complaints	231 (86%)	72 (78%)	119 (90%)	40 (89%)
Primary headache disorders	25 (9.2%)	10 (11%)	10 (7.5%)	5 (11%)
Comorbidity*	2	1	1	0
Sinus thrombosis	2	1	1	0
Parenchymal neurological involvement	9 (3.3%)	8 (8.6%)	1 (0.75%)	0

*Any neurological disorder not related to BD.

Table IV. Clinical characteristics of the parenchymal neurological involvement in Group I and Group II.

Pt. no.	Age, sex	Ocular score	Neurological picture	Cranial MRI	CSF cells (/mm^3); protein (mg/dl)	Atypical features	Treatment at neurological attack	CsA duration (mo.)
1	21, M	7	Brainstem syndrome	Typical: L thalamus-mesencephalon	2Gr, 22Ly; N	No	CsA 300 (4mg/kg/d) AZA 150	12
2	35, F	7	Brainstem syndrome	Typical: bilateral basal ganglia	4Gr, 27Ly; 77	No	CsA 200 (4mg/kg/d) AZA 100	21
3	42, M	6	Brainstem syndrome	Typical: mesencephalon	125Gr, 44Ly; 55	No	CsA 200 (2.5mg/kg/d) MMF 2000	19
4	32, M	0	Epileptic seizure	Typical+atypical: R thalamus-mesencephalon + R occipital cortical	ND	Yes	CsA 200 (3mg/kg/d)	8
5	40, M	7	L hemiparesis, hemianopia	Atypical: cortical	N	Yes	CsA 200 (3mg/kg/d)	50
6	31, M	2	Epileptic seizure + confusion	Typical+atypical: bilateral basal ganglia + R temporal cortical	4Gr, 29Ly; N	Yes	CsA 300 (4mg/kg/d)	24
7	17, M	4	Brainstem syndrome	Typical: bilateral thalamus-mesencephalon	4Gr, 17Ly; 53	No	CsA 200 (3mg/kg/d) AZA 100	14
8	22, F	8	Epileptic seizure	Atypical: bilateral mesial temporal	700Gr, 60Ly; 115	Yes	CsA 200 (4mg/kg/d)	12
9	22, M	2	Brainstem syndrome	Typical: L thalamus-mesencephalon	2Gr, 15Ly; N	No	AZA 100	(-)

MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; M: male; F: female; L: left; R: right; Gr: granulocytes; Ly: lymphocytes; CsA: cyclosporine; AZA: azathioprine; MMF: mycophenolate mofetil, N: normal; ND: not done.

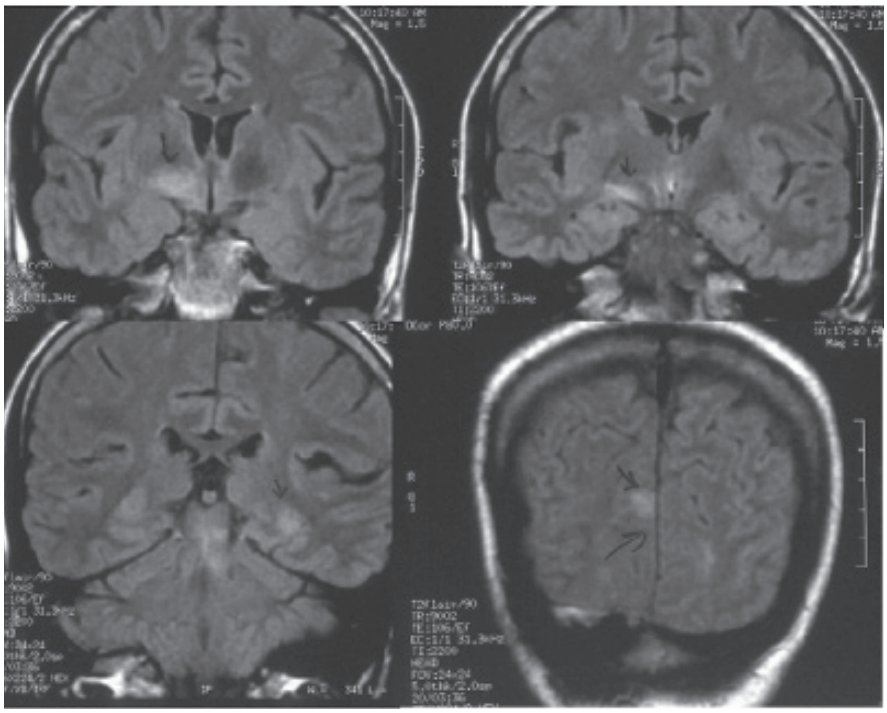

Fig. 1. Cranial MRI sections (FLAIR sequences) for patient no. 4, showing typical neuro-Behçet lesions (located in the right thalamus, mesencephalon, and left upper pons), as well as an atypical cortical lesion involving the right occipital cortex and left mesial temporal cortex.

with brainstem syndrome suffered a relapse one year later, after prematurely stopping mycophenolate. None of these patients ever resumed cyclosporine treatment.

Discussion

Behçet's disease is a multi-system inflammatory disorder of unknown etiology. In large studies from Turkey about 5-10% of patients experienced neurological involvement (13, 14). In the majority of cases there was parenchymal neurological involvement, mainly presenting as brainstem meningoencephalitis; in about one-third of the patients, dural sinus thrombosis was seen (15).

In recent years debate has arisen, prompted by two studies from Japan and one from Germany, concerning the possible association of cyclosporine with an increased risk of neurological involvement in BD (8-10). Although these were retrospective studies and the patient recruitment criteria were

Table V. Case summaries of all published cases of cyclosporine-induced neurological involvement.

Study	Present study (Akman-Demir *et al.*)	[10] (Kötter *et al.*)	[9] (Kotake *et al.*)	[8] (Kato *et al.*)	[11] (Mitsui *et al.*)	[26]* (Igarashi *et al.*)
Number of cases (total)	8 (out of 92)	6 (out of 21)	12 (out of 47)	6 (out of 40)	1	2 (out of 8)
Male:female	3:1	5:1	11:1	6:0	M	1:1
CSF pleocytosis	6/7	6/6	11/12	5/5	Yes	2/2
Typical MRI lesion	6/8	5/6	NA	NA	Yes	2/2
Atypical MRI lesion	4/8	1/6	NA	NA	No	NA
Atypical clinical feature	4/8	2/6	4/12	2/6	No	1/2
Epileptic seizures	3/8	1/6	1/12	None	No	None

*Tacrolimus was used in this study.
CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

not always clear, neurological involvement was observed almost 8 times more frequently among patients treated with cyclosporine in one study (9), and in the other two studies 6 patients with neurological involvement were found in the cyclosporine treatment group versus none in the other groups (8, 10). In all three studies the case descriptions appeared to be compatible with parenchymal neurological involvement.

Our experience in daily practice has been similar, with the additional observation of some atypical features. We therefore designed a retrospective study with strict inclusion criteria, in which we analyzed all new admittances of BD patients to the Ophthalmology Department over a 5-year period, and further evaluated those with neurological complaints. The patients were divided into 3 groups based on the treatment received – Group I: a cyclosporine-based regimen; Group II: other immunosuppressants; and Group III: no immunosuppressant treatment. All patients in Group I received cyclosporine from the outset in microemulsion form and therefore we could not speculate on the issue raised in one study regarding the development of neurological involvement after switching to this form of administration (11).

Group I had significantly more patients with neurological complaints, including a significantly higher number of cases with pNBD. The frequency of parenchymal involvement was about 9%, almost double our previous observation (13), whereas in Groups II and III pNBD was far below (<1%) the expected frequency in our country. The possible reasons for this finding are many. Before attributing the cause to cyclosporine, we evaluated the severity of ocular involvement, which could provide an immediate explanation for the higher rate of neurological involvement. In fact, ocular involvement was more pronounced in Group I as evidenced by the higher scores and higher ratio of clinically blind patients. However, due to the low numbers of neurologically affected patients in our cohort, the statistical significance of our results is limited. We sought to circumvent this limitation by repeating the analysis, first considering only severe cases (ocular severity scores at or above the median for the whole cohort), and then only the mildly affected cases. In both analyses, parenchymal neurological involvement was still significantly higher in patients from Group I compared to Groups II and III. Moreover, there was no correlation between the severity of ocular involvement and pNBD; patients with very mild ocular symptoms could also develop parenchymal neurological involvement. In the German study, which focused on a heterogeneous group of patients with and without ocular involvement, the authors found no difference in severity scores for BD between the patients using cyclosporine and those taking other medications (10). In the present study, the severity score focused on eye disease alone, and all patients had ocular involvement. Therefore, a direct comparison between the two studies is not possible.

There could be many explanations for the increased parenchymal neurological involvement in patients taking cyclosporine for Behçet's uveitis. First of all, cyclosporine may not be sufficient to prevent neurological involvement. It has been observed that a given drug may be quite effective in treating some manifestations of BD but not others. For example, thalidomide is highly efficacious against orogenital ulceration, but has no apparent effect on eye disease or the involvement of other vital organs (16). Furthermore, even its effect on mucocutaneous lesions may be variable; while thalidomide reduces oral and genital ulcers and follicular lesions, it exacerbates erythema nodosum lesions (17). However, cyclosporine is so effective in the treatment of BD uveitis that the hypothesis of its lack of potency seems unlikely, particularly if – as some studies suggest – there is an association between uveitis and neurological involvement (13).

In our cohort, 4 of the 8 patients on cyclosporine alone developed parenchymal neurological involvement, whereas a significantly smaller proportion of the patients on combination therapy developed pNBD. Concomitant treatment with azathioprine could therefore be preventing the development of neurological involvement, although these patients did tend to have more severe eye disease. Moreover, it is impossible to predict what would happen to the Group I cases if they received no cyclosporine at all. Based on our data, it cannot be determined whether the use of cyclosporine reduced the risk of pNBD in these patients.

There are other possible reasons for the higher rate of neurological involvement in the cyclosporine group.

Cyclosporine could induce neurotoxicity, or it may directly contribute to the development of parenchymal CNS involvement in BD. To explore these two points, we should first discuss the neurotoxicity of cyclosporine. It is well known that cyclosporine can produce a clinical picture very similar to the posterior reversible leucoencephalopathy syndrome seen in hypertensive encephalopathy (18-20). Such cases present with epileptic seizures, confusion, and focal neurological manifestions usually associated with the posterior aspects of the cerebral hemispheres (such as hemianopia or cortical blindness). Reversible subcortical white matter abnormalities may be seen on MRI (18-21). However, there is no CSF pleocytosis associated with this syndrome (19), and to date no brainstem lesions have been reported, although rare cases of brainstem-cerebellar involvement have been described (21, 22).

A higher risk of cyclosporine neurotoxicity is to be expected when its presence in the blood exceeds therapeutic levels. In a study of liver transplant recipients, trough levels of cyclosporine suggested neurotoxicity in 61% of patients, but neurologic findings were reported to be reversible when cyclosporine was discontinued and then resumed at a lower dosage (23). On the other hand, Kotake *et al*. reported that the trough levels of cyclosporine were high in only 2/12 patients who developed neurologic complications (9), and Kötter *et al*. observed blood levels of cyclosporine within the therapeutic range in their patients (10). Unfortunately, we had not data on blood levels of cyclosporine as this parameter is not routinely measured in our clinic. However, as shown in Table IV patients were receiving doses ranging between 2.5 and 4 mg/kg/day and at these doses elevated blood levels seem unlikely.

Our patients showed both typical and atypical features of pNBD. In patients on cyclosporine who developed parenchymal neurological involvement, epileptic seizures were far more common than would normally be expected in pNBD (15, 24). Moreover, some patients also exhibited atypical subcortical/cortical MRI findings, which are also uncommon in pNBD (25). However, most of our patients showed typical brainstem findings both clinically and radiologically, in addition to the CSF pleocytosis that is generally present in pNBD (15). Although MRI lesions were not specified, previous studies have found CSF pleocytosis (8, 9). In the German study, one patient had aphasia and one had seizures, both of which are relatively atypical for pNBD; however, all patients exhibited typical MRI findings as well as CSF pleocytosis (10). Table V summarises the data from all previously published cases, as well as our own.

Based on these data, it appears that patients can exhibit both the typical features of pNBD and atypical features more consistent with cyclosporine toxicity. This suggests that cyclosporine may play a role in breaking the blood brain barrier, which could in turn exacerbate the neurological insult caused by the immune system; or else, as Kötter *et al*. (10) have suggested, the "potential neurotoxic effects of cyclosporine could be a predisposing factor for CNS vasculitis". Another calcineurin inhibitor – tacrolimus – has also been reported to cause parenchymal neuro-Behçet-like involvement in 2 cases of BD and uveitis, and a link with increased blood brain barrier permeability was proposed (26). Of course, these hypotheses must be verified in the experimental setting as well as in clinical trials.

This study has some limitations due to its retrospective nature; baseline severity and the duration of follow-up were not the same for the three groups, and not all patients underwent routine neurological screening (although it is unlikely that any case of pNBD would have gone unnoticed). However, it does constitute one of the largest single-center studies published so far and suggests that patients with Behçet's uveitis who are treated with cyclosporine may be at increased risk of developing parenchymal neurological involvement. A large, prospective multi-center study should be conducted to explore the reasons for such an association.

Since cyclosporine is a very efficacious drug for the treatment of Behçet's uveitis, its use should not be abandoned; however, until we have more solid data concerning its risks, caution must be exerted in its administration. Our data suggests that the combination of cyclosporine with azathioprine may lower the risk of pNBD. Nevertheless, any new neurological symptom should be monitored closely in patients taking cyclosporine as monotherapy or in combination with other drugs. If any parenchymal neurological involvement is detected, we would suggest stopping cyclosporine treatment and replacing it with another immunosuppressant medication.

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