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ORIGINAL PAPER

Early isolated optic neuropathy caused by cyclosporine

Karin Mimouni · Moshe Lusky · Michal Kramer · Michael Gdalevich · Dov Weinberger · Michael Mimouni

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Abstract
Purpose To examine, for the first time, whether cyclosporine intake has an early isolated effect on the optic nerve.
Materials and methods This observational case series consisted of 192 eyes of 98 patients treated with cyclosporine. Patient age and duration and dosage of cyclosporine were recorded, and visual acuity, optic nerve function, visual fields, and visual evoked potential (VEP) were tested. Fundus examination was also performed. Patients with glaucoma, vascular retinopathies, and deep amblyopia were excluded.
Results Mean patient age was 46 years, average duration of treatment was 6 years, and median dosage of cyclosporine was 200 mg daily. VEP was tested in 73 patients (142 eyes) and yielded a delayed P100 wave in 9 (12.32%) (14 eyes). Among these 9 patients, abnormal findings were also noted on the Ishihara colour test in 42.86% of the eyes, and on the visual field test in 64.3% of the eyes. Abnormal VEP showed a significant correlation ($p < 0.05$) with older age (> 46 years) and a non-significant correlation with longer duration of treatment. Higher abnormal VEP potential was not correlated with higher cyclosporine dose, and there was no correlation between abnormal VEP and blood level of cyclosporine.
Conclusion Optic neuropathy was significantly associated with older age in cyclosporine-treated patients. A correlation between optic neuropathy with longer duration of cyclosporine treatment was noted but was not statistically significant. We suggest that tests of optic nerve function, including VEP, be a part of the follow-up of patients receiving cyclosporine.

Keywords Systemic · Cyclosporine · Optic neuropathy · VEP

K. Mimouni · M. Lusky · M. Kramer · D. Weinberger
Department of Ophthalmology, Rabin Medical Center, Petah Tiqva, Israel

K. Mimouni · M. Lusky · M. Kramer · D. Weinberger
Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

M. Gdalevich
The District Health Office, Barzilai Medical Center, Ashkelon, Israel

M. Mimouni (✉)
Department of Ophthalmology, Rambam Health Care Campus Affiliated with the Technion-Israel Institute of Technology, Haifa, Israel
e-mail: michael@internname.co.il

Introduction

Cyclosporine immunosuppression has led to a revolution in the use of organ transplantation [1, 2]. However, cyclosporine has been associated with

several complications, one of which is deterioration in visual acuity [3–6]. There are several mechanisms that may underlie this process. The majority of reported cases show occipital white cortex damage, which causes homonymous hemianopsia or bilateral homonymous hemianopsia with secondary cortical blindness [5, 6]. A second mechanism is a cyclosporine-induced increase in intracranial pressure leading to papilledema which, if untreated, later causes concentric constriction of the visual fields and optic nerve atrophy. Third, cyclosporine can be directly toxic to the retina [7, 8]. Although a few studies have implicated cyclosporine in optic neuropathy, most of the affected patients also had papilledema; [9–14] no study has so far succeeded in isolating the injury to the optic nerve alone.

To the best of our knowledge, the effect of cyclosporine on optic nerve functions has not been systematically investigated. The primary purpose of the present study was to determine whether cyclosporine administered in organ transplant patients and to treat inflammatory conditions has a direct toxicity to the optic nerve which is unrelated to cyclosporine-induced intracranial pressure, cortical damage, or retinal toxicity.

In addition, most of cyclosporine's adverse effects have been found to be dose-dependent and reversible after dose reduction or cessation of the drug. The secondary purpose of the present study was to examine, for the first time, whether cyclosporine dose or blood level is correlated with optic nerve toxicity. A positive finding would have important implications for the early detection of this complication.

Patients and methods

All patients who had been treated with cyclosporine for whatever reason and had undergone blood testing at Rabin Medical Center, Beilinson Campus during a period of two consecutive months were included. Patients included in this study were treated with cyclosporine following organ transplantation or to treat autoimmune inflammatory conditions.

The study followed the tenets of the Declaration of Helsinki and approval from the local ethics committee of Rabin Medical Center for the use of medical records was obtained.

Cyclosporine blood levels were retested, and patient age, gender, reason for cyclosporine treatment, dose and duration of treatment, additional medications, and other systemic or ophthalmological problems (specifically, diabetic retinopathy and laser photocoagulation treatment, other vascular retinopathies, and glaucoma) were recorded. All patients underwent visual acuity test with the Snellen chart, Ishihara colour test, pupillary reaction test including afferent pupillary defect, intraocular pressure measurement, and visual field test with 30-2 Humphrey Swedish Interactive Threshold Algorithm (SITA) perimetry. In addition, funduscopy was performed to examine the retina and optic nerve disc appearance, and a visual evoked potential (VEP) test was performed as an objective measure of transport along the optic nerve to the visual cortex. The P100 waveform was compared to the accepted norm for the general healthy population.

Patients with glaucoma, any retinopathy especially diabetic and hypertension retinopathy, vein occlusion, and status post-panretinal photocoagulation (which can cause abnormal results on visual field and Ishihara tests) were excluded from the analysis, as were patients with optic atrophy due to other known problems, patients with known brain damage or neurological deficit (cerebrovascular accidents and transient ischaemic attacks, etc.), with secondary visual field abnormalities. Patients treated with drugs other than cyclosporine that had a potential to cause optic neuropathy and thereby increase the P100 waveform latency on VEP were also excluded.

Statistical analysis

Data were analysed with the Minitab software, version 17 (Minitab Inc, State College, PA). The correlation between independent variables and the outcome was first tested in a univariate approach with Fisher's exact test. All the independent variables that were included in the univariate analysis were also included in a logistic regression model to test their association with the VEP variable, while adjusting for possible confounding factors.

Results

Of the 317 patients tested for cyclosporine blood level, 102 agreed to take part in the study. Four of the 102 study participants were later excluded owing to findings of severe retinopathies: central vein occlusion in their only eye as well as panretinal photocoagulation (PRP) secondary to neovascularisations in 2 of them; and proliferative diabetic retinopathy bilaterally after PRP in the other 2. There were no differences in patient characteristics or indications for cyclosporine treatment between the patients who participated in the study and those who did not. The reasons for cyclosporine treatment included Behcet disease, chronic posterior uveitis (of unknown origin), Crohn's disease, and liver, kidney, heart, or bone marrow transplantation (Table 1).

The final study group consisted of 98 patients (192 eyes), 70 men (71.42%), and 28 women (28.57%) aged 20–71 years (median 46 years). In four patients, only one eye was included in the analysis. Their contralateral (excluded) eye had poor visual acuity and a pathologic VEP test secondary to central vein occlusion (left eye), history of severe foreign body injury (left eye), severe amblyopia for unknown reason (left eye), or optic nerve melanocytoma (right eye), and it was impossible to differentiate between these pathologies and cyclosporine treatment as the reason for a pathologic VEP response.

The duration of cyclosporine treatment ranged from 0.08 to 15 years (average 6 years), and cyclosporine dosage ranged from 50 to 450 mg per day (median 200 mg). Cyclosporine blood level measured 85 to 496 ng/ml, (median 170 ng/ml).

Table 1 Indications for cyclosporine treatment in study participants

Indication	No. patients (%)
Behcet disease (panuveitis)	2 (2/04%)
Chronic posterior uveitis	1 (1.02%)
Crohn's disease	1 (1.02%)
Liver transplantation	14 (14.28%)
Kidney transplantation	70 (71.42%)
Heart transplantation	9 (0.18%)
Bone marrow transplantation	1 (1.02%)

The cyclosporine blood measurements were performed as part of the routine follow-up in the Transplantation Clinic Service or the clinic where the cyclosporine treatment was prescribed. The ophthalmic examinations and ancillary tests were performed on the same day as the blood test.

VEP testing was performed in 73 of the 98 study patients (74.48%), including all 4 patients tested only unilaterally for VEP (total, 142 eyes), and visual field testing was performed in 69 patients (70.4%), including 2 patients whose contralateral eye was excluded from the analysis (total, 136 eyes). The failure to test the remainder was due in all cases to patient noncompliance. Overall, 13 patients failed to do both the VEP and visual field test; 85 patients (86.72%) underwent at least one test and 58 (59.18%) underwent both.

Ophthalmologic tests

Optic nerve functions, visual fields and VEP were analysed by duration of cyclosporine treatment (more or less than 3 years), cyclosporine dose (more or less than the group median of 200 mg/d), and cyclosporine blood level (above or below the group median of 170 ng/ml). The effect of cyclosporine was also analysed by patient age (more or less than the group mean of 46 years).

Visual acuity

Visual acuity with the Snellen chart ranged between 20/20 and 20/200. All patients had normal intraocular pressure.

Ishihara test

The Ishihara test was considered pathological when 14 plates or fewer of the 17 plates were identified correctly. Pathological findings were recorded in 30 eyes (15.62%) of 20/98 patients (20.4%). Three patients (6 eyes) were colour-blind.

No significant statistical correlation was found between a pathological Ishihara test and long duration of cyclosporine treatment, high cyclosporine dose, high cyclosporine blood level, or older patient age.

Pupils

The pupils were round, equal, and reactive to light in all patients, with no afferent pupillary defect in any of the patients.

Optic nerve discs

Fifteen eyes (7.8%) in 10 patients (10.2%) had diffuse (13 eyes) or temporal (2 eyes) pallor of the optic nerve head. Five of these patients had an abnormal optic nerve unilaterally (3 left eyes and 2 right eyes). No oedema of the optic nerve head was noted in any of the study eyes.

The visual field was abnormal in 6 of the 15 eyes and normal in 3; the remainder were not tested (Table 2). The VEP was normal in 11 eyes and not measured in 4. In all cases, failure to test was due to patient refusal.

There was no significant statistical correlation between optic nerve disc abnormality and patient age, duration of cyclosporine treatment, cyclosporine dose, or cyclosporine blood level.

Visual fields

Visual fields were tested in 136 eyes and were abnormal in 55 (28.64%), including 6 (10.9%) with an abnormal optic nerve disc. An abnormal optic disc was also noted in 3 of the 81 eyes (3.7%) with normal visual fields and in 6 of the 56 eyes (10.7%) that did not undergo visual field testing because of patient refusal (Table 3).

The visual field pathologies were variable and included congruent hemianopsia, superior or inferior accurate defects or both, nasal steps, paracentral scotoma, concentric restriction, and enlarged blind spot. None tended to appear more often than the others.

No significant statistical correlation was found between abnormal visual fields and any of the background parameters tested.

Visual evoked potentials

VEP testing was performed in 142 eyes of 73 patients (74.5%). Abnormal values, defined as latencies exceeding 110 ms or reduced amplitudes, were recorded in 14 eyes (8 left, 6 right) of 9 patients

Table 2 Association of abnormal optic nerve discs and pathologic visual field and VEP tests

Patient	Eye	Optic nerve	Visual field	VEP
1	Right	Normal		
	Left	Abnormal	Normal	Normal
2	Right	Abnormal	Abnormal	Normal
	Left	Normal		
3	Right	Normal		
	Left	Abnormal	Abnormal	Not performed
4	Right	Abnormal	Normal	Not performed
	Left	Normal		
5	Right	Abnormal	Not performed	Normal
	Left	Abnormal	Not performed	Normal
6	Right	Abnormal	Not performed	Normal
	Left	Abnormal	Not performed	Normal
7	Right	Abnormal	Abnormal	Not performed
	Left	Abnormal	Abnormal	Not performed
8	Right	Normal		
	Left	Abnormal	Normal	Normal
9	Right	Abnormal	Abnormal	Normal
	Left	Abnormal	Abnormal	Normal
10	Right	Abnormal	Not performed	Normal
	Left	Abnormal	Not performed	Normal

Table 3 Visual field results

Visual field	Right eye	Left eye	Abnormal optic nerve disc	
			Right	Left
Normal	42	39	1	2
Abnormal	27	28	3	3
Not done	28	28	3	3
Total	97	95		

(12.32%), 8 men, and 1 woman. Their P100 latency values ranged from 112 to 136 ms (Table 4). In one of the 4 patients with unilateral findings, VEP was tested only in the right eye because the left eye had central vein occlusion; in the other 3, VEP was pathological in the left eye and within normal limits in the right (albeit upper normal in 2; Table 4).

The patients with abnormal VEP were aged 43–67 years (average 57.45) and had been receiving cyclosporine treatment for 1–9 years (average 6 years) at a dose of 75–300 mg per day (median 187.5 mg/day). Their cyclosporine blood levels ranged from 94 to 538 ng/ml (median 172 ng/ml). Indications for cyclosporine treatment were kidney transplantation in 4 (44.44%), heart transplantation in 2 (22.22%), liver transplantation in 2 (22.22%), and posterior uveitis in 1 (11.11%).

Best corrected visual acuity of these 9 patients ranged between 20/20 and 20/40. All had equal, round, and reactive pupils except one patient who had left eye central vein occlusion with a sluggish pupillary reaction but no afferent pupillary defect. This eye did not undergo VEP testing and was excluded from the analysis.

Table 4 Delayed P100 wave results (in msec)

Patient	Right eye	Left eye
1	112	112
2	132	135
3	132	122
4	120	124
5	130	130
6	102[a]	126
7	107[a]	127
8	106[a]	112
9	136	Not done

[a]Normal values compared with the general population

Six of the 14 eyes (3 left, 3 right; 42.86%) had abnormal findings on the Ishihara test, and 9 (5 left, 4 right; 64.28%) had an abnormal visual field. None of the eyes with an abnormal VEP had an abnormal optic nerve disc.

Ninety-three of the 142 eyes (7 patients) tested for VEP had been treated for > 3 years, including 12 of the 14 eyes with abnormal findings. On statistical analysis, there was a correlation between abnormal VEP and long duration of treatment but it was not statistically significant ($p = 0.14$, Fisher's exact test). Abnormal VEP was significantly correlated with lower cyclosporine dose (< 200 mg/day) ($p < 0.001$, Fisher's exact test). There was no significant statistical correlation between high P100 latency and blood levels of cyclosporine.

The distribution of VEP results according to age groups and gender is shown in Table 5 and Fig. 1, respectively. Eighty-four of the patients tested for VEP were > 46 years old, including 8 patients (12 eyes) with abnormal findings. There was a strong association between age and the findings of abnormal VEP in the univariate analysis. The prevalence of abnormal VEP was 4 times higher in patients older than 46 years old [$p = 0.045$, Fisher's exact test, RR = 4.02 (95% CI 0.94−17.31)]. In a multivariate logistic model that included age, cyclosporine dosage, duration of treatment, and blood level, with VEP as a

Table 5 Distribution of VEP results by gender

VEP	Females		Males	
	Right	Left	Right	Left
Normal	21	20	46	41
Abnormal	1	1	5	7
Not tested	6	7	19	22
Total	28	28	70	70

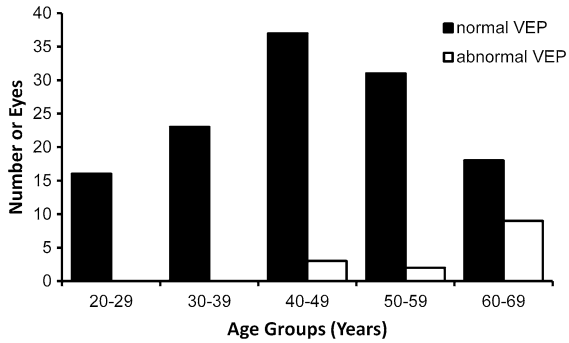

Fig. 1 Distribution of visually evoked potential results by age group

dichotomic outcome variable, age was the only variable that had a statistically significant association ($p = 0.017$) with VEP abnormality.

Discussion

This is the first study to report a correlation between cyclosporine treatment and isolated toxicity of the optic nerve. Although optic neuropathy has often been reported in cyclosporine-treated patients, none of these studies was able to isolate the optic nerve effect of the drug from nerve damage caused by increased intracranial pressure [9–14], primary and secondary cortical cortex damage, or retinal toxicity [7, 8]. In the present study, we tested a variety of optic nerve functions, including VEP, which indicates the latency of information transmission from the retina to the visual occipital cortex via the optic nerve and is considered a good test of optic nerve damage. We also included cyclosporine-treated patients with a variety of pathologies and a wide range in age, cyclosporine dose, cyclosporine blood levels, and treatment duration in order to test the correlation of optic neuropathy to these parameters. To better isolate the drug effect, patients with vascular retinopathies (diabetic or other) as well as patients with glaucoma and suspected brain cortex damage were excluded. We used SITA perimetry to test visual fields because it has been proven sensitive and reliable and has the advantage of short time of performance, which increases patient motivation and credibility, without lessening the quality of the results [15–18].

VEP results were compared with findings in the general population, as reported in the literature. Chu et al. [19], Mitchel et al. [20], Armstrong et al. [21], and Celsia et al. [22] measured the VEP in 123, 68, 86, and 112 healthy subjects, respectively, aged 20–86 years with good visual acuity. None had a P100 wave latency above 105 ms. In other studies in healthy populations, the P100 wave latency tended to increase with age, but in no case did it exceed 105 ms [23–26]. By comparison, in our sample, VEP ranged from 112 to 136 ms in one or both eyes of 9 patients, representing 12.32% of the patients tested and 9.18% of the entire study group. About half these patients also had a pathologic Ishihara colour test and 64.3% an abnormal field test. Optic disc pallor or oedema was not noted in these patients but abnormal VEP results can precede optic nerve head pathology and visual field pathology as previously reported by Kupersmith et al. [27] and Diem et al. [28] in multiple sclerosis patients with 20/20 visual acuity, no history of optic neuritis, and normal ophthalmic examination. Optic nerve toxicity was significantly correlated with older age (> 46 years, the mean group age) ($p = 0.045$); 6 of the 9 affected patients were older than 60 years. A non-significant correlation was found between abnormal VEP and long duration of treatment. Cyclosporine blood level had no effect on VEP. Interestingly a statistically significant correlation was found between abnormal VEP and lower cyclosporine dose ($p < 0.001$). This could be as result of a confounding effect between the different variable tested, or an interaction between them. It could also be due to our small study group or simply a coincidental finding.

A potential limitation of this study was the lack of a control group of patients with a similar background and disease that were not treated with cyclosporine. As such, in the absence of proper controls, it may be that other factors other than the cyclosporine contributed to the described changes in optic nerve function. However, we speculate that it is unlikely that the organic diseases they had and other treatments they received could explain the reduction in optic nerve function described in this study. Nevertheless, further studies may consider comparing optic nerve function between patients treated with cyclosporine and those not treated with cyclosporine.

To the best of our knowledge, this is the first large series presenting various visual functions in patients on systemic cyclosporine. Our findings suggested finding of an isolated and early cyclosporine-induced toxicity of the optic nerve has important heuristic

value and potential clinical implications. We suggest that tests of optic nerve functions and VEP be included in the follow-up of patients receiving cyclosporine and consider replacement of cyclosporine should the findings become abnormal. Further longer-term controlled studies are needed, including repeated VEP testing after cyclosporine is stopped or switched with another agent.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (place name of institute/committee) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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