CASE REPORTS
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Tacrolimus-induced optic neuropathy – a case report

Optička neuropatija izazvana takrolimusom

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Abstract

Introduction. Tacrolimus (fujimycin or FK506) is a potent immunosuppressive drug with growing usage. It is usually used in the prevention of transplanted organ rejection. Its use is highly valuable, but like other immunosuppressants, it has adverse effects. One of them is optic neuropathy. **Case report.** A 47-year-old male patient, who had received tacrolimus therapy for nine years after kidney transplantation, developed a subacute, painless vision loss in both eyes. He was thoroughly examined on different possible optic neuropathies and other causes of vision loss. After exclusion of other possible causes, the diagnosis of toxic optic neuropathy was established. The patient's therapy was converted to cyclosporine by his nephrologist, but his vision had improved only slightly. **Conclusion.** Toxic optic neuropathies are presented in everyday ophthalmological practice, but they are underestimated. Diagnosis can be demanding, especially when it comes to drugs and substances whose possible toxic effect on the optic nerve is not widely known. Unlike other adverse effects of tacrolimus therapy on the nervous system, optic neuropathy can cause great and permanent functional impairment.

Key words:
drug-related side effects and adverse reactions; tacrolimus; toxic optic neuropathy; treatment outcome.

Apstrakt

Uvod. Takrolimus (fujimycin, FK506) je potentan imunosupresivni lek čija upotreba je u porastu. Obično se koristi u prevenciji odbacivanja transplantiranih organa. Njegova primena je dragocena, iako, poput drugih imunosupresivnih lekova, ima i neželjena dejstva. Jedno od takvih dejstava je optička neuropatija. **Prikaz bolesnika.** Bolesnik muškog pola, star 47 godina, koji je zbog transplantiranog bubrega primao takrolimus devet godina, razvio je bezbolni gubitak vida na oba oka, subakutnog toka. On je detaljno ispitan na moguće uzroke optičkih neuropatija i druge moguće uzroke gubitka vida. Nakon isključenja drugih mogućih uzroka, postavljena mu je dijagnoza toksične optičke neuropatije. Nadležni nefrolog je izmenio terapiju i uveo ciklosporin, ali vid se samo diskretno poboljšao. **Zaključak.** Toksične optičke neuropatije se javljaju u svakodnevnoj oftalmološkoj praksi, ali se na njih retko posumnja. Postavljanje dijagnoze može biti zahtevno, posebno u slučaju lekova i suspstanci čije moguće toksično dejstvo na očni nerv nije šire poznato. Za razliku od ostalih neželjenih dejstava takrolimusa na nervni sistem, toksična optička neuropatija može izazvati značajan i trajan gubitak vida.

Ključne reči:
lekovi, neželjeni efekti i neželjene reakcije; takrolimus; neuropatija, optička, toksična; lečenje, ishod.

Introduction

Tacrolimus (fujimycin or FK506) is an immunosuppressant used mainly after allogeneic organ and bone marrow transplantation to prevent transplanted organ rejection and graft versus host disease (GVHD). This macrolide was isolated from a strain of *Streptomyces*. The mechanism of action is similar to cyclosporine, but it is more potent and has less serious adverse effects [1]. Tacrolimus acts by the calcineurin phosphatase inhibition and so intervenes on interleukin (IL)-2 transcription and T lymphocyte signal transduction. In recent years it has been increasingly used, even in ophthalmology, for some unwanted or excessive topical or systemic immune responses inhibition [2].

Immunosuppressive drugs have revolutionized transplant medicine. However, they have numerous adverse effects on almost every organ system [3]. Calcineurin inhibitors are known for their neurotoxicity, both central and peripher-

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al [4]. One of the most frequent toxic effects is posterior reversible encephalopathy syndrome (PRES). Side effects related to a visual deficit in this syndrome occur in nearly 40% of patients [5], but they are usually reversible after the therapy modification. Peripheral toxic neuropathies are also described, and they develop after weeks or months of therapy [4].

Toxic optic neuropathies (TONs) are usually bilateral, more or less symmetric, painless, and progressive, but otherwise they have characteristics similar to some other optic neuropathies (diminution of vision, dyschromatopsia, normal or edematous optic disc, visual field scotomas, a disorder of pupillary response to light, and later, some degree of optic nerve atrophy) [6]. Although they are not uncommon in ophthalmic practice, elucidating TONs demands a serious and demanding approach. The diagnosis is made based on exhaustive anamnesis, the disease features, and course and exclusion of other possible causes. The most widely known causes of TONs are antituberculosis drugs (isoniazid, ethambutol, streptomycin), some antibiotics (chloramphenicol, linezolid, sulfonamides), antimalarials (chloroquine, quinine), antiarrhythmics (amiodarone, digitalis), anticancer agents (vincristine, methotrexate, cyclosporin), alcohols (methanol, ethylene glycol), heavy metals (mercury, lead, thallium), and other (carbon monoxide, tobacco) [7], and inhibitors of phosphodiesterase 5 (sildenafil). If they are caused by drugs, the majority of them recover after the therapy cessation or conversion, but in others, such as optic neuropathy induced by tacrolimus, the favorable outcome may be lacking.

Case report

A 47-year-old male patient was first seen after he received intravenous pulse methylprednisolone therapy with prednisone tapering because his condition was diagnosed as bilateral inflammatory retrobulbar optic neuropathy. As there was no improvement on the subsequent checkups, he was directed to the Ophthalmology Department for further examinations.

The onset of the disease manifested with the patient's vision deterioration bilaterally, gradually, for eight to ten days before visiting an ophthalmologist. At first, the patient had noticed visual disturbances for distance and shortly after for near vision. Visual loss was painless, with slight daily variations and without other neurological symptoms. As his life quality decreased rapidly and seriously, he decided to visit an ophthalmologist.

The patient had a blunt trauma of his right eye some 20 years ago with residual light visual decline and posttraumatic mydriasis. Secondary glaucoma and incipient cataract developed years after that accident and was recorded during this hospitalization. Occupied with other health and family issues, he has not been controlled ophthalmologically for years. He started wearing a hearing aid twelve years ago because of bilateral sensorineural hearing loss. He had kidney transplantation in 2010, and since then, he has been on tacrolimus therapy (3 mg prolonged-release capsules), together with mycophenolic acid 540 mg twice daily, with regular checkups and without any adverse effects. At the time of this hospitalization, his therapy was also enalapril and amlodipine. He had stopped smoking cigarettes and consuming alcohol more than ten years ago.

On admission, visual acuity on his right eye was counting fingers on 30 cm, and on his left eye, on 1m. He had an incipient cataract on both eyes, more prominent on the right but not dense enough to explain vision loss. Both optic nerve heads were somewhat paler, and the right one had shallow excavation (Figure 1). Foveal reflex was absent on the right and decreased on the left eye. Blood vessels were thin. His pupils reacted weakly and sluggishly. Intraocular pressure was 24 on the right and 20 mmHg on the left eye. His visual field showed serious defects, without response on his right eye, and significant scotomas on his left eye (Figure 2).

In order to examine the possible origin of optic neuropathy, a series of analyzes and exams were performed. The serum level of tacrolimus (7.56 ng/mL) was within therapeutic concentration range (target range 5–20 ng/mL). Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, and fibrinogen) were within normal ranges. Antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), and rheumatoid factor (RF) tests were negative.

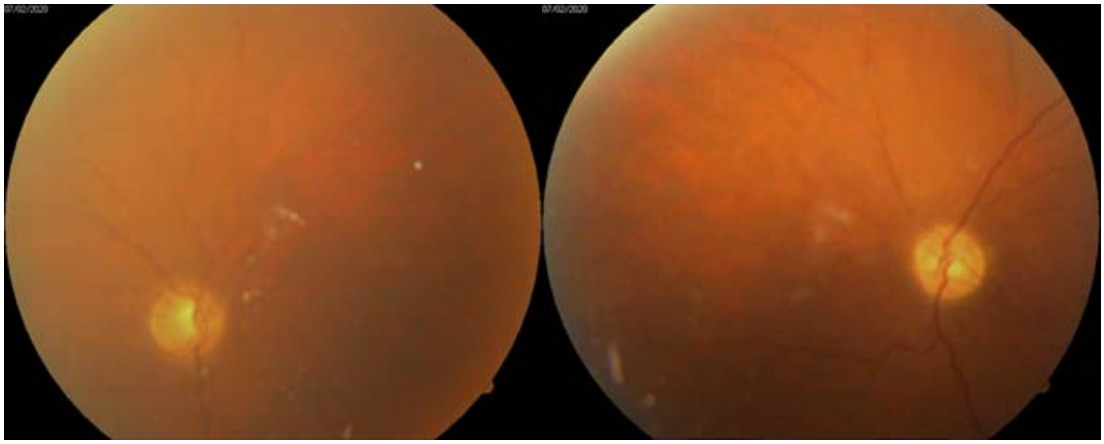


Fig. 1 – Photo fundus of the right and the left fundus: optic nerve heads are paler and arterial blood vessels are thinner; on the right eye is visible excavation (glaucomatous); details are less visible due to incipient cataract.

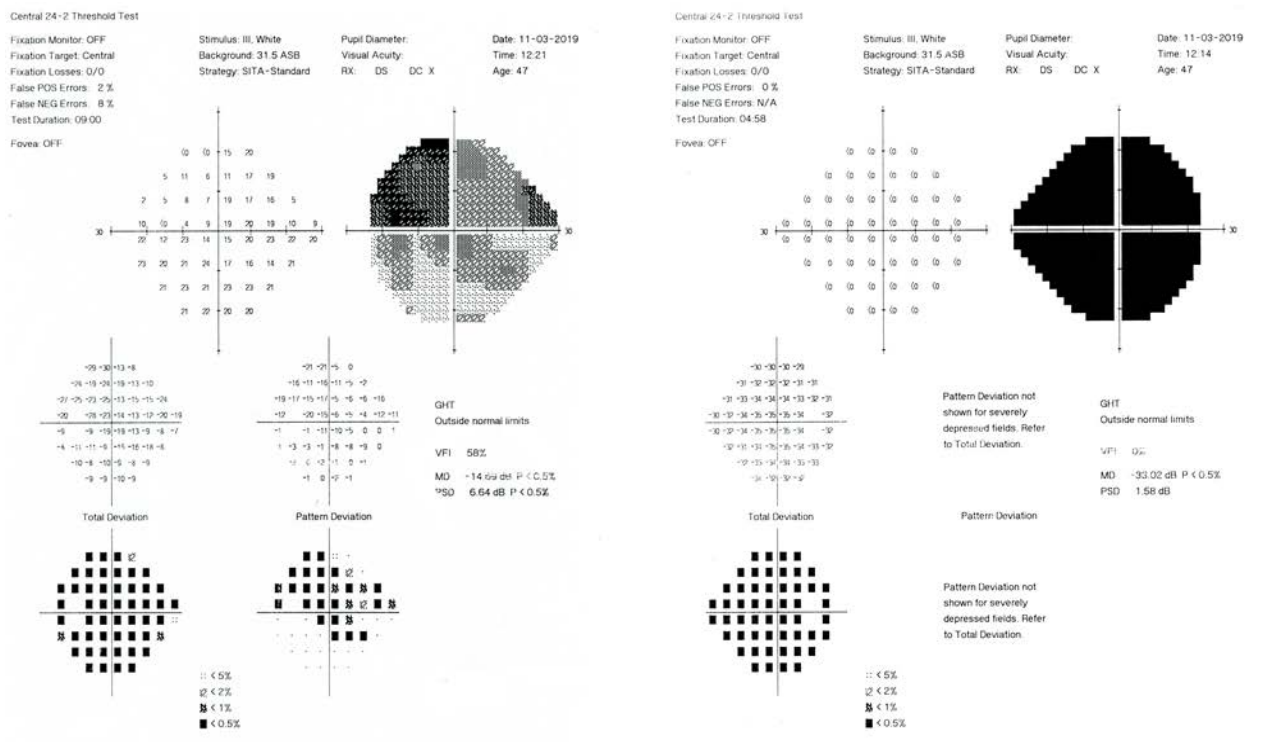


Fig. 2 – On admission, visual field deficits on the left eye of the patient were irregular and covered the central and upper, more temporal region; sensitivity is low; visual field on the right eye shows perimetrically blind field.

Biochemical analyses showed only high triglyceride level (7.07 mmol/L), while antibodies to viruses such as herpes simplex (HSV1), varicella-zoster (VZV), cytomegalovirus (CMV), hepatitis B and C, human immunodeficiency virus (HIV), and *Treponema pallidum* (TPA) were negative. Quantiferon gold tuberculosis (TB) test was also negative, as well as aquaporin 4 antibodies. Angiotensin-converting enzyme (ACE) was within normal limits (23.85 U/L), as well as homocysteine (7 μmol/L) and coagulation factors levels. The laboratory results also did not point to thrombophilia. Vitamin B12 concentration was high (1,131.0 pg mL^{-1}, normal range: 239–931 pg/mL), probably because the patient was taking supplements for weeks since the disease started, and folate (5.50 ng/mL) and vitamin D concentration (26.3 nmo/L) were normal. Arterial pressure was normal all the time.

Lungs, core, and sinuses radiography revealed maxillar sinusitis on his right side. Postcontrast magnetic resonance imaging (MRI) showed infra and supratentorial cortical reductive changes and vasculopathic changes in subcortical frontoparietal regions and a slightly reduced diameter of the left optic nerve at the level of orbital apex.

Although our suspicion was directed to toxic neuropathy from the beginning, as his cousin lost vision in her thirties for no clear reasons, we performed a genetic analysis for Leber hereditary optic neuropathy.

Another reason was that nephrologists were reasonably satisfied with the patient's therapy, and they did not meet such side effects in their numerous patients for almost two decades of usage. However, their first step was a conversion from an extended-release formulation that is to be taken every 24 hours, which he had used in a 3 mg dose, to the immediate-release formulation to be taken every 12 hours, 1.5 mg twice a day. The rest of the therapy remained the same, except that atorvastatin was introduced. However, further decline in visual acuity in the next two weeks (VOD L+ P+/-, VOS L+P+) convinced them to convert therapy to cyclosporine A 125 mg twice daily, while the rest of the therapy remained the same. A few weeks after being dismissed from the hospital, we received results for Leber mitochondrial base-pair mutations G11778A, T14484C, and G3460A, and they were negative.

After a month of cyclosporine therapy, his visual acuity was L+P+ on his right eye and his fingers counting on 50 cm on his left eye. In the further course, it improved a little on his right eye and now is stabile on counting fingers on 50 cm on each eye, with a discrete improvement of the visual field on the right eye.

Pattern visual evoked potentials showed low amplitudes, lower on his right eye, while the latencies were within normal range. Pattern electroretinogram had low values of N95 amplitudes, better on the left side, while P50 were just below normal values. His optic nerves were pale. Optic coherence tomography revealed retinal nerve fiber layer (RNFL) thinning in all sectors of his right eye and partial on his left eye (Figure 3), as well as ganglion cell layer (GCL). All this confirms consequent bilateral atrophy of the optic nerve after neuropathy.

The patient tolerated cyclosporine therapy well, without the appearance of possible side effects for a year and a half.

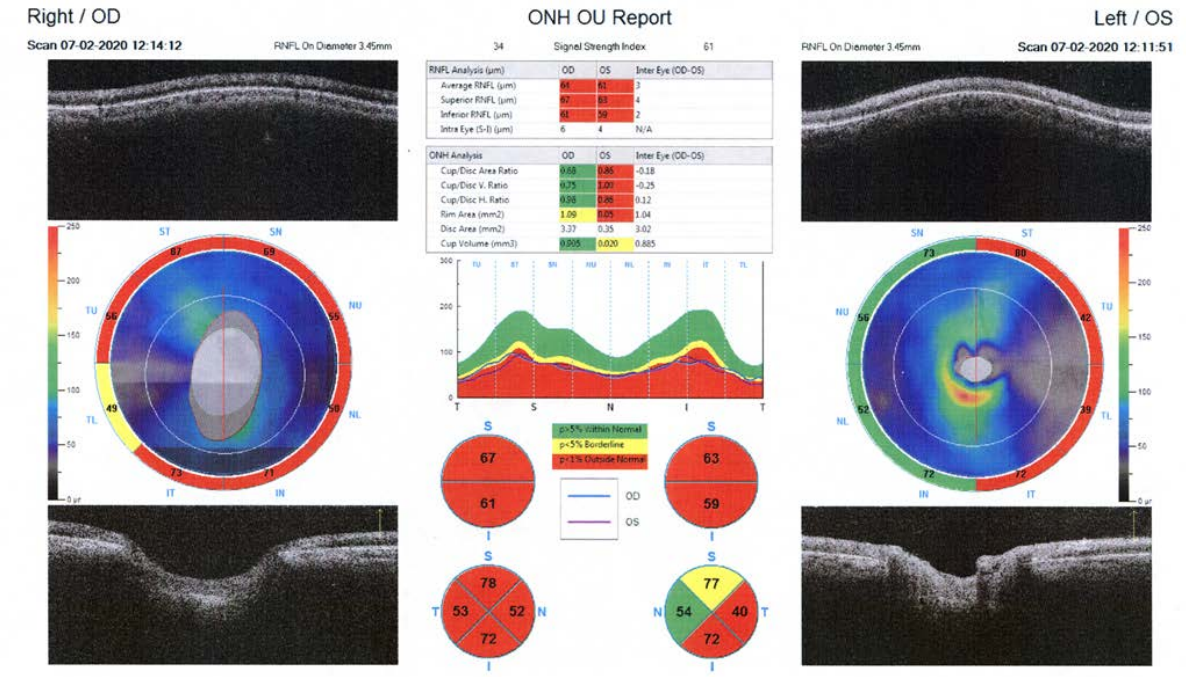


Fig. 3 – Retinal nerve fiber layer (RNFL) analysis shows thinning on both eyes, slightly more prominent on his right eye; poor fixation resulted in optic nerve interpapillar parameters differences, which do not otherwise exist (see Figure 1) (note: a better, control shot was used).

Moreover, he was on latanoprost topical therapy for glaucoma, which was recently converted to dorzolamide/timolol for better control of intraocular pressure.

This presentation was made with the patient's written consent to use the data and photographs describing his case.

Discussion

Tacrolimus is a valuable immunosuppressant, but like other similar drugs, its use is associated with some serious side effects. Almost one-third of patients on this or similar therapies have neurological complications [4]. PRES, which predominantly affects the parietooccipital lobes, is the most common tacrolimus toxic effect of the central nervous system. Besides other significant neurological effects, significant visual loss may occur, but with a favorable outcome after the therapy modifications [5, 6]. Peripheral nerves could be affected as demyelinating or axonal forms. Possible mechanisms of toxicity and risk factors are numerous [7–9].

Since tacrolimus optic neuropathy was recognized some twenty years ago [8], there has been a small but permanent increase of reports of this toxic effect on the optic nerve. It appears sporadically after liver, kidney, multivisceral, or bone marrow transplantation [9]. This complication is rare and usually occurs after several months to a few years of immunosuppressant therapy, rarely after longer usage [10]. However, both PRES and optic neuropathy complications may manifest in the same patient [11]. On the other hand, even unilateral tacrolimus TON was described [12].

It is important that all case reports find appearing of TON independently of tacrolimus blood concentration. Possible mechanisms of toxic tacrolimus influence on the nervous system and optic nerve are not fully understood, and there are few possible explanations. The most cited are direct neurotoxicity on oligodendrocytes, whose damage can lead to demyelination, vascular complications where neurotoxicity may be caused by vasoconstriction in cerebral microvasculature (like probably in PRES) [4], or genetic variations in tacrolimus elimination mechanism from the central nervous system [13]. The male gender and type and duration of the disease which preceded transplantation or TON may play a role [9, 14]. There is a relatively high incidence of neurotoxicity after liver transplantation, which may be due to changes in tacrolimus metabolism, leading to cumulative toxicity. Unusually, tacrolimus optic neuropathy was described even in the patient who was on this drug therapy for nephrotic syndrome and not in GVHD [15].

Recovery of visual acuity is described occasionally, mainly in cases that have been significantly shorter on tacrolimus therapy, after the therapy conversion, and/or in those where an inflammatory component exists that provides a good response to anti-inflammatory therapy [9].

Our patient developed toxic neuropathy after nine years of excellent enduring tacrolimus. The only possible side effects, until then, were high lipid levels and arterial hypertension, which nephrologists expected in such patients [16]. Both conditions were regulated by the listed therapy (amlodipine, enalapril, atorvastatin). They are risk factors for ischemic optic neuropathy, as well.

Visual loss and other findings on his right eye are, without doubt, to some extent connected with previous trauma and consequent glaucoma, but the visual decline and subsequent optic atrophy are bilateral now. Because of the course of his visual loss and optic atrophy, the absence of

pulse corticosteroid therapy answer and the length of tacrolimus therapy, as well as slight improvement after the therapy conversion, the most likely mechanisms of tacrolimus action was a toxic accumulation of the drug. Previous illness and vasculopathic changes on MRI may contribute another assumption to the vascular, ischemic causes. However, posterior ischemic optic neuropathies are very rare, especially as bilateral simultaneous occurrences [17].

According to the clinical aspect, the diagnosis of toxic optic neuropathy is of the exclusion type. Diagnosis of tacrolimus-induced optic neuropathy is even more difficult, as it is described in literature exclusively as case presentations with a great amount of variability of clinical features and, as it appears, independently of the blood drug concentration. For these reasons, it is a reasonable restraint of the other specialists, but from a neuro-ophthalmic aspect, after eliminating demyelinating and non-demyelinating inflammatory, compressive, infiltrative, traumatic, nutritive, to great extent ischemic and paraneoplastic, and even some hereditary neuropathies, our patient's diagnosis is toxic neuropathy. In less than two weeks, from a man who was reading, watching TV, and hanging out with people, the patient became a person who does not recognize faces and moves precariously while touching objects around him. The exclusion of all possible causes is methodologically and temporally very difficult and is neither rational nor necessary. Monitoring a patient who has not taken good care of his eyes until profound bilateral visual acuity loss sets an additional aggravating circumstance in establishing a conclusion.

According to the pharmacovigilance, the likelihood that optic neuropathy was induced by tacrolimus is probable (score 7) as stated by the Naranjo Adverse Drug Reaction Probability Scale (APS) [18]. On the World Health Organization – Upsala Monitoring Center (WHO UMC) scale, our case is somewhere between probable ("reasonable") and certain [19]. In this and similar cases, it is impossible to meet all the requirements set in the scales (therapeutic rechallenge, use of placebo, dose increasing). There is no ideal scaling system or diagnostic procedure.

Conclusion

Vision disorders can be caused by many substances and drugs, and early recognition may be important for treatment and prognosis. A thoughtful approach to all patients with optic neuropathies is essential and, as a first step, a detailed medical history and similar consequent examination are crucial in establishing the diagnosis. TONs are underestimated in ophthalmology practice, and unfortunately, on some occasions, they could be diagnosed when vision has already been severely damaged.

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