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Authors Lepša Žorić*,ǂ,, Aleksandra Ilićǂ,**, Emina Čolakl, Miloš Mirković*, Jelica Pantelićǂ,**, Dijana Miroić†, Bojana Kisić† Vojnosanitetski pregled (2020); Online First January, 2021.

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BILATERALNA OPTIČKA NEUROPATIJA IZAZVANA TAKROLIMUSOM: PRIKAZ SLUČAJA

Authors: Lepša Žorić*,Aleksandra Ilić**, Emina Čolak†, Miloš Mirković*, Jelica Pantelić†**, Dijana Mirić†, Bojana Kisić†

Affiliation:
* - Ophthalmology Department, Faculty of Medicine, University of Priština, Kosovska Mitrovica
† - Institute of Eye Diseases, Clinical Centre of Serbia, Belgrade
**- Faculty of Medicine, University of Belgrade
†- Institute of Medical Biochemistry, Clinical Centre of Serbia, Belgrade
‡- Institute of Medical Biochemistry, Faculty of Medicine, University of Priština, Kosovska Mitrovica

Correspondence author: Lepša Žorić
E address: zoriclepsa@gmail.com
Abstract

Introduction. Tacrolimus (fujimycin or FK506) is a potent immunosuppressive drug with growing usage. It is usually used in 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 white male patients who had received tacrolimus therapy for nine years, after kidney transplantation, developed a subacute, painless vision loss on 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. His 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 nervous system, optic neuropathy can causes great and permanent functional impairment.

Key words: tacrolimus, toxicity, optic neuropathy.

Apstrakt

Uvod. Takrolimus (fujimycin, FK506) je potentan imunosupresivan lek čija upotreba stalno raste. Obično se koristi u prevenciji odbacivanja transplantiranih organa. Njegova primena je dragocena, iako, poput drugih imunosupresivnih lekova, takrolimus ima i neželjena dejstva. Prikaz slučaja. Pacijent muškog pola, star 47 godina, koji je primao tacrolimus devet godina zbog transplantiranog bubrega, razvio je gubitak vida na oba oka, bezbolan, subakutnog toka. Detaljno je ispitan na moguće uzrake optičkih neuropatija i druge moguće uzroke gubitka vida. Nakon isključenja drugih mogućih uzroka, postavljena je dijagnoza toksične optičke neuropatije. Terapija je konvertovana na ciklosporin, uz diskretno poboljšanje vida. Zaključak. Toksične optičke neuropatije se javljaju u svakodnevnoj oftalmološkoj praksi, ali se na njih reče posumnja. Postavljanje dijagnoze
može biti zahtevno, posebno kada se radi o lekovima i suspstancama 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: takrolimus, toksičnost, optička neuropatija.**

**Introduction**

Tacrolimus (fujimycin or FK506) is an immunosuppressant, used mainly after allogeneic organ and bone marrow transplantation to prevent transplanted organ rejection (GVHR). This macroline was isolated from a strain of Streptomyces. Mechanism of action is similar to cyclosporine, but it is more potent and has less of some serious adverse effects\(^1\). Tacrolimus acts by the calcineurin phosphatase inhibition and so intervenes on Interleukin-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 systems\(^3\). Calcineurin inhibitors are known to their neurotoxicity, both central and peripheral\(^4\). One of the most frequent toxic effects is Posterior Reversible Encephalopathy Syndrome (PRES). Side effects related to 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 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, disorder of pupillary response to light, and later, some degree of optic nerve atrophy)\(^6\). Although they are not uncommon in ophthalmic practice, elucidating of toxic optic neuropathy demands serious and demanding approach. The diagnosis is made on the basis of exhaustive anamnesis, the disease features and course and exclusion of other possible causes. The most widely known causes of toxic optic neuropaties are antituberculotic drugs (isoniazid, etambuthol, streptomycin), some antibiotics (chloramphenicol, linezolid, sulfonamides), antimalarics (chloroquine, quinine),
antiaritmins (amiodarone, digitalis), anticancer agents (vincristine, methotrexate, cyclosporin), alcohols (methanol, ethylene glycol), heavy metals (mercury, lead, thallium) and other (carbon monoxide, tobacco) and inhibitors of phosphodiesterase 5 (sildenafil). If they are caused by drugs, majority of them recover after the therapy cessation or conversion, but in other, like optic neuropathy induced by tacrolimus, favorable outcome may be absent.

Case report
A 47 years old male patient was firstly 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 not any improvement on the subsequent checkups, he was directed to us to further examinations. This presentation was made with the patient's consent to the use of data and photographs describing his case, with his written consent.

The onset of the disease manifested with patient’s vision deterioration bilaterally, gradually, during eight to ten days before visiting an ophthalmologist. At first, he 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. He 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 wears hearing aid since twelve years ago because of bilateral sensorineural hearing loss. He had kidney transplantation in 2010, and since then he was on tacrolimus therapy (3mg 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 amloidipin. 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 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 mm Hg 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. Serum level of tacrolimus was within therapeutic doses 7.56 ng/ml (target ranges 5-20 ). Inflammatory markers (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. Biochemical analyses showed only high triglycerides (7.07mmol/L) and antibodies to viruses herpes simplex (HSV1), varicella zoster (VZV), cytomegalovirus (CMV), hepatitis B and C, human immunodeficiency virus (HIV) and Treponema pallidum (TPA) were negative. Quantiferon gold 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 homocistein (7 μmol/L) and coagulation factors levels. The laboratory results also did not point to thrombophilia. Vitamin B12 concentration was high (1131.0 pg ml\(^{-1}\)), probably as he was taking supplements for weeks, since the diseases 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 reveled maxillar sinusitis on his right side. Postcontrast magnetic resonance imaging showed infra and supratentorial cortical reductive changes and vasculopathic changes in subcortical frontoparietal regions and slightly reduced diameter of 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 not clear reasons, we performed 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 conversion from an extended-release formulation that is to be taken every 24 hours, which he had used in 3 mg dose, to the immediate-release formulation to be taken every 12 hours, 1.5mg twice daily. The rest of therapy remained the same, except the 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 dismissed hospital, we received results for Leber mitochondrial base pair mutations G11778A, T14484C and G3460A and they were negative. After a month on cyclosporine therapy his visual acuity was L+P+ on his right and fingers counting on 50 cm on his left eye. In the further course it improved a little on his right eye and now is stable on counting fingers on 50 cm on each eye, with discrete improvement of 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 amplitudes, better on the left side, where P50 was just below normal values. His optic nerves are pale. Optic coherence tomography revealed retinal nerve fiber layer (RNFL) thinning, in all sectors on 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 optic nerve after neuropathy.

He tolerates cyclosporine therapy well, without the appearance of possible side effects for a year and a half. Also, he was on latanoprost topical therapy for glaucoma, which was recently converted on dorzolamide/timolol, for better control of intraocular pressure.

Discussion

Tacrolimus is valuable immunosuppressant, but like other similar drugs, it shows numerous complications. Almost one third patients on this or similar therapy have neurological ones. Posterior reversible leukoencephalopathy syndrome (PRES), which predominantly affects the parieto-occipital 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 favourable outcome after the therapy modifications. Peripheral nerves could be affected as demyelinating or axonal form. Possible mechanisms of toxicity and risk factors are numerous.

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

It is important that all case reports find appearing of toxic optic neuropathy independently of tacrolimus blood concentration. Possible mechanisms of toxic tacrolimus influence on 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 demyelinization, vascular complications where neurotoxicity may be caused by vasoconstriction in cerebral microvasculature (like probably in PRES), or genetic variations in tacrolimus elimination mechanism from the central nervous system. The male gender and type and duration of the disease which preceded transplantation or toxic optic neuropathy may play role. 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 patient who was on this drug therapy for nephrotic syndrome, and not in GVHR disease. 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 exist an inflammatory component that provides a good response to anti-inflammatory therapy.

Our patient developed toxic neuropathy after nine years of excellent enduring of tacrolimus. The only possible side effects, until then, were high lipid level and arterial hypertension, which nephrologists expected in such patients. Both conditions were regulated by the listed therapy (amplodipin, enelapril, 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 were bilateral, now. Because of the course of his visual loss and optic atrophy, 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 toxic accumulation of 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 and especially as bilateral simultaneously occurrence\textsuperscript{17}.

According to the clinical aspect, 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 great amount of variability of clinical features, and as it appears independently of the blood drug concentration. For these reasons it is reasonable restraint of the other specialists, but from a neuroophthalmic aspect, after eliminating demyelinating and non- demyelinating inflammatory, compresive, infiltrative, traumatic, nutritive, in great extent ischemic and paraneoplastic, and even some hereditary neuropaties, our patient’s diagnosis is a toxic neuropathy. The exclusion of really all possible causes is methodologically and temporally very difficult, and is not either rational or necessary. Monitoring of a patient who has not taken good care about his eyes, until profound bilateral visual acuity loss, sets an additional aggravating circumstance in conclusion establishing.

According to the pharmacovigilance, likelihood that tacrolimus induced optic optic neuropathy, is probable (score 7), by Naranjo Adverse Drug Reaction Probability Scale (APS)\textsuperscript{18}. On the World Health Organisation-Upsala Monitoring Center (WHO UMC) scale, our case is somewhere between probable (‘‘reasonable’’) and certain.\textsuperscript{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, as well as diagnostic procedure, of course.

However, in less than two weeks, from the man who was reading, watching TV and hanging out with people, he became a person who does not recognize faces and moves precariously, while touches objects around him.

**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. Toxic optic neuropathies are under estimated in ophthalmology practice, and unfortunately, in some occasion they could be diagnosed when vision is severely damaged.

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Figures legends

Figure 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).

Figure 2. On admission, visual field deficits on the left eye is irregular and covers central and upper, more nasal region; sensitivity is low; visual field on the right eye shows perimetricaly blind field.

Figure 3. RNFL analysis shows thinning on both eyes, slightly more prominent on his right eye; poor fixation resulted in interpapillar parameters differences, which does not otherwise exist (see Fig1).
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