CASE REPORT OLGU SUNUMU

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Maculopathy After Long Term Use and Repeated Suicide Attempt with Topiramate

Topiramatın Uzun Süreli Kullanımı ve Tekrarlanan İntihar Girişimi Sonrasında Makulopati

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ABSTRACT We present the maculopathy of a 19-year-old female patient diagnosed with idiopathic generalized epilepsy after long term use and 2 suicide attempts with high-dose topiramate. The patient had used topiramate for 2 years before the presentation due to the diagnosis, and after a 2nd suicide attempt using this drug, the patient had vision loss in both eyes and severe maculopathy in the left eye. After discontinuation of topiramate, the patient's maculopathy resolved partially in both eyes. Ophthalmic examination should be kept in mind in such high doses of topiramate, which has been reported to have many ocular adverse effects even in routine clinical use.

Keywords: Topiramate; maculopathy; suicide attempt; optical coherence tomography; epilepsy

ÖZET İdiyopatik jeneralize epilepsi tanısı nedeniyle uzun süreli topiramat kullanan ve 2 kez aynı ilacın yüksek dozunu kullanarak intihar girişiminde bulunan 19 yaşında bir kadın hastanın makulopatisini sunuyoruz. Hasta başvurudan önce 2 yıl boyunca mevcut hastalığı nedeniyle topiramat kullanmıştı ve bu ilacı kullanmak yoluyla meydana gelen 2. intihar girişimi sonrasında her iki gözünde görme kaybı ve sol gözünde ciddi makulopati vardı. Hastanın topiramat ilacının kesilmesinden sonra her iki gözünde makulopatisinde kısmi düzelme izlenmiştir. Rutin klinik kullanımda bile birçok göz yan etkisi olduğu bildirilen topiramatın bu kadar yüksek dozlarında göz muayenesi akılda tutulmalıdır.

Anahtar Kelimeler: Topiramat; makulopati; intihar girişimi; optik koherens tomografi; epilepsi

Topiramate (Topamax®, mylan pharmaceuticals, US) is a carbonic anhydrase inhibitor drug that is mostly used for migraine prophylaxis and to prevent epileptic seizures. Since its launch in 1979, topiramate has been associated with the most common ocular side effects, including acute myopia and acute angle-closure glaucoma, although rare cases of maculopathy have also been reported.[1-4]

The inhibitory activity of carbonic anhydrase, inhibition of voltage-gated ion channels, inhibition of aquaporin 1 and 4, and inhibitory effect of glutamate on neurotransmitter function are thought to be responsible for the clinical efficacy of topiramate. This effect occurs after reaching a sufficient concentration at the plasma level. It has been reported that these pharmacological effects in dose increases

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may be associated with systemic and ocular side effects.[5] In our case, we report the development of bilateral maculopathy as a result of repeated suicide attempts with high-dose topiramate, who was diagnosed with idiopathic generalized epilepsy and used topiramate to prevent seizures. A case of maculopathy developing after a suicide attempt using such a high dose of topiramate has not been reported before.

CASE REPORT

A 19-year-old patient, who was followed up with the use of topiramate due to the diagnosis of idiopathic generalized epilepsy and epilepsy attacks, attempted suicide twice with Topiramate 1000 mg in April 2018 and 1250 mg in May 2019. After the 2nd attempt, the daily clinical dose of topiramate continued to be used, and she presented with the complaint of loss of vision in her both eyes. Three weeks after the suicide attempt in April 2018, the macula was misdiagnosed as a focus of retinochoroiditis in another ophthalmology clinic due to visual complaints, and the patient was started on trimethoprim 800 mg, sulfamethoxazole 160 mg, clindamycin 300 mg and prednisolone 40 mg daily for 4 months. In the follow-up, when a suicide attempt with high-dose topiramate was attempted again in May 2019, no eye examination was performed. Daily use of 100 mg topiramate was continued until November 2020, and an application was made to our clinic due to worsening vision loss.

In the examinations, the patient's best corrected visual acuity was 40/50 in the right eye and 20/200 in the left eye, and she had myopia (right eye: -2.50, left eye: -2.75). Intraocular pressures were 16 mmHg on the right and 17 mmHg on the left, there was no angle narrowing on the gonioscopy, and the anterior chamber depth was normal (anterior chamber depth right: 3.08 mm, left: 3.01 mm). Direct and indirect light reflexes were normal in both eyes and there was no relative afferent pupillary defect. Optical coherence tomography (OCT), Retina nerve fiber layer (RNFL), fundus fluorescein angiography (FFA) and visual field tests were performed on the patient who had bilateral maculopathy and pallor in the temporal quadrant of the optic disc in both eyes (Figure 1). In fundus examination, there is a slight color change in the right macula, while there is widespread macular damage and subretinal fluid image in the left eye. While the FFA image in the right eye shows no leakage in all vascular areas and the macula in the mid-late period, the FFA image in the left eye shows increased fluorescein leakage in the macular region consistent with subretinal fluid thought to be chronic in the mid-late period (Figure 2). In the OCT images, there was no finding other than a slight increase in the thickness of the outer layers of the retina in the right eye, while in the left eye, there was subretinal fluid, which was thought to have been present for a long time, with a brush border pattern appearance under the outer layers of the retina. In the visual field test, 30:2 scanning was used and there was mild peripheral visual field loss on the right, while peripheral loss was more on the left, and there was thinning of the temporal RNFL (Figure 3). We referred the pa-

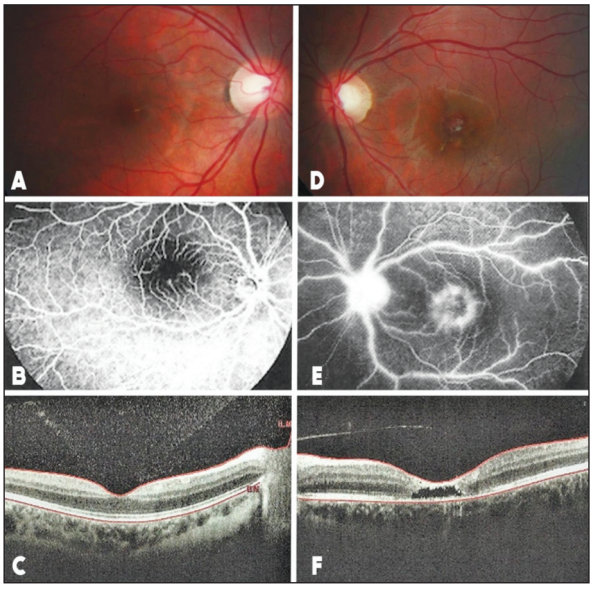

FIGURE 1: The patient's findings in November 2020; **A)** have a slight color change along with decreased pallor in her right macula. **B)** Fundus fluorescein angiography (FFA) in the right eye shows no leakage in all vascular areas and the macula in the mid-to-late period. **C)** No findings were detected in the optical coherence tomography (OCT) image of the right eye, except for a slightly increased thickness of the retinal outer layers. **D)** The fundus photograph of the left eye shows discoloration indicating extensive macular damage. **E)** In the mid-late period FFA image of the left eye, there is increased fluorescein leakage in the macular region compatible with subretinal fluid, which is thought to be chronic. **F)** In the OCT image, there is a brush border appearance under the outer layers of the retina, accompanied by long-lasting subretinal fluid.

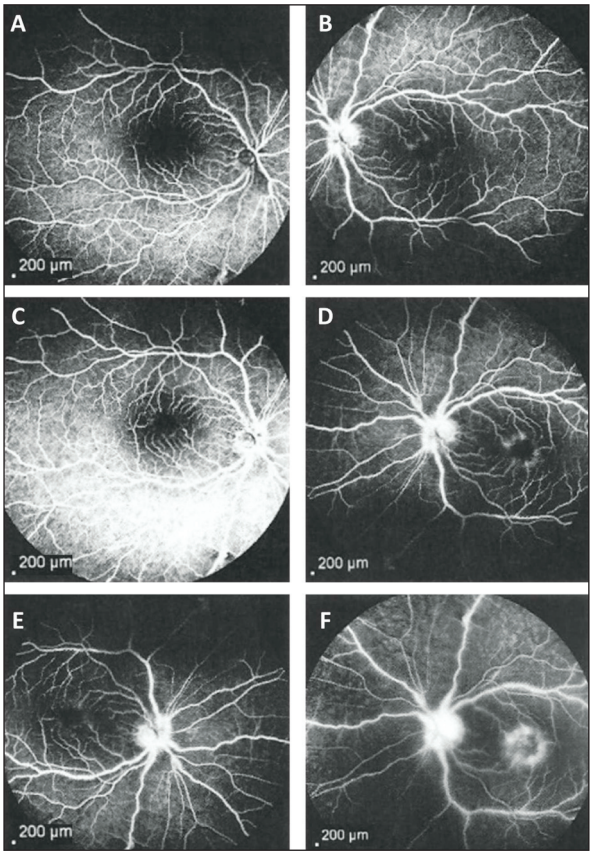

FIGURE 2: In the patient's fundus fluorescein angiography (FFA) images dated November 2020, no leakage was observed in all vascular areas and macula in the right eye in the early-mid and late periods (**A, C, and E**). In the early-mid and late period FFA image of the left eye, there is increased fluorescein leakage in the macula region, compatible with chronic macular damage and subretinal fluid (**B, D, and F**).

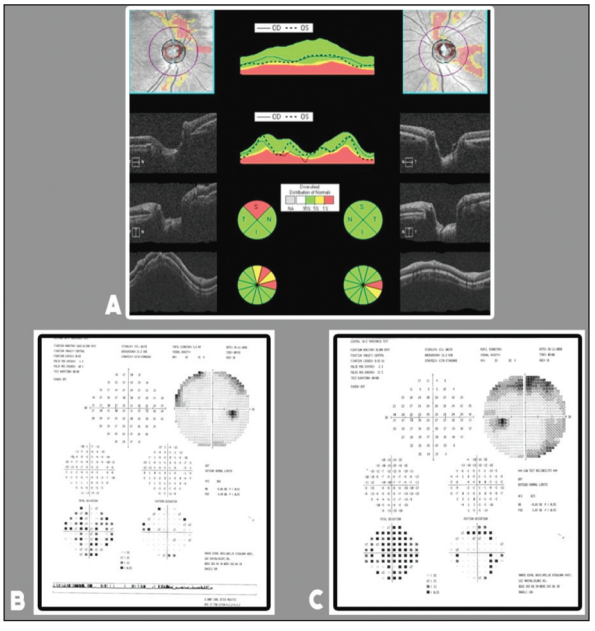

FIGURE 3: A) No pathology is detected in the retinal nerve fiber layer thickness, except for a superior thinning in the right eye and a slight temporal thinning in the left eye. In the visual field test using 30:2 scanning, **B)** there was a slight peripheral visual field loss on the right, and **C)** the peripheral loss was greater on the left.

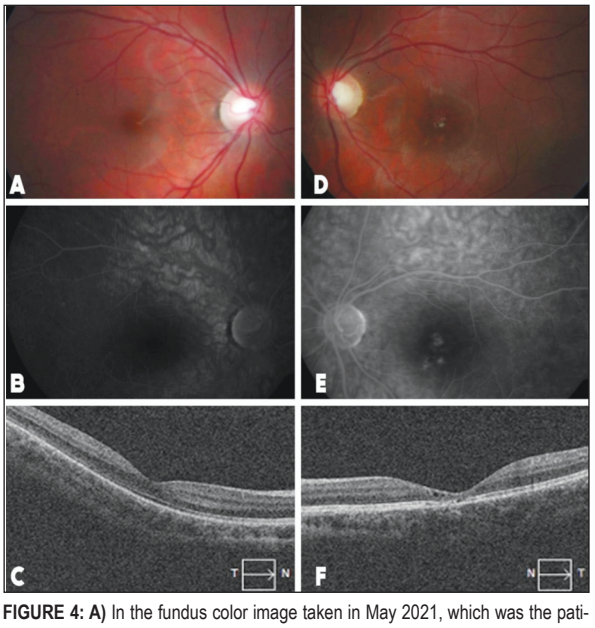

FIGURE 4: A) In the fundus color image taken in May 2021, which was the patient's last examination, a slight discoloration of the macula in the right eye is seen. **B)** Fundus fluorescein angiography (FFA) image shows no significant leakage in the late image of the right eye. **C)** Optical coherence tomography (OCT) image shows a normal macula in the right eye. **D)** In the left eye, there is a yellow-black discoloration in the macula, which was also present in the fundus color image taken 3 years ago. **E)** In the FFA image of the left eye, there is a slight leakage in the macula seen during the late filling phase. **F)** The OCT image shows that there is no more subretinal fluid in the left eye, there is deterioration in the retina pigment epitelhial line, and the macula is atrophic.

tient, whom we evaluated as having toxic maculopathy, to the neurology unit to discontinue topiramate treatment. In her examination 6 months after discontinuation of topiramate, visual acuity in the right eye remained unchanged but increased to 20/50 in the left eye. Myopia continued but reduced to -0.75 in the right eye and -0.50 in the left eye. Despite the disappearance of subretinal fluid in the left eye, maculopathy continued in the form of widespread atrophy in the inner and outer layers, foveal thinning, and retinal microcysts (Figure 4). While no leakage was seen in the right eye in the FFA images at the last follow-up, leakage secondary to macular damage was seen in the left eye in the early and late periods (Figure 5). Written informed consent was obtained from the patient for this case report.

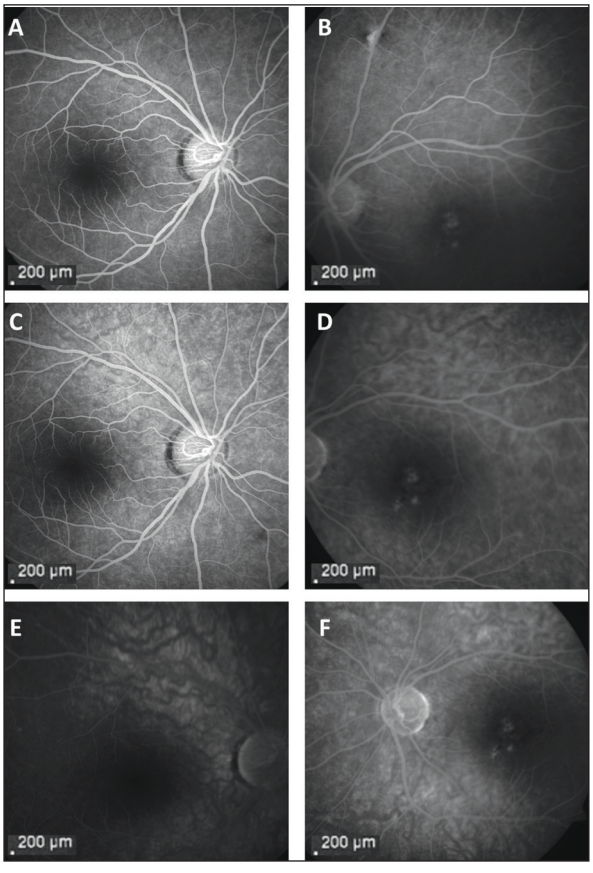

FIGURE 5: In the fundus fluorescein angiography (FFA) images of the patient's last follow-up in May 2021, no leakage was observed in all vascular areas and the macula in the early-mid and late periods in the right eye (**A, C and E**). In the early-mid and late periods in the left eye, resolution of the subretinal fluid and slight leakage around the macula were observed in the FFA image (**B, D and F**).

DISCUSSION

Topiramate is a sulfonamide derivative drug that many inhibitory mechanisms in the central nervous system and has many uses such as migraine prophylaxis, prevention of epileptic crises, bipolar disorder, obesity, and tobacco addiction. Acute myopia, secondary acute angle-closure glaucoma and maculopathy have been reported as signs of ocular syndrome caused by topiramate. Systemic side effects are somnolence, oligohydrosis, nephrolithiasis, metabolic acidosis, paresthesia and behavioral changes. Vertigo, mydriasis, confusion, and personality changes have been reported in acute overdose.[5,6]

It is claimed that the sudden increase in plasma level causes effusion by reducing the activity and function of carbonic anhydrase activity and water-selective channels, aquaporin. In the reported cases, it is thought that this effusion and the increase in fluid in the choroidal tissue, suprachoroidal region and vitreous cause acute myopia, angle-closure glaucoma and maculopathy.[5-7] In our case, subretinal fluid accumulation after the first high dose can be explained by this. While no obvious acute angle closure was observed, there was maculopathy accompanying myopic shift. It has been thought that the developing maculopathy may be the initial state of acute myopia syndrome or may develop alone with fluid passage due to effusion. Gualtieri and Janula also reported an isolated maculopathy developed with this mechanism in a case that they thought was caused by an increase in dose.[8]

Mandal et al. detected visual field defects similar to our case in two cases, which they suspected as an ocular side effect of routine daily topiramate use, and they improved after discontinuation of topiramate.[7] Asensio-Sánchez et al. showed that vision loss and maculopathy in two cases with topiramate-related maculopathy were irreversible at 1-year follow-up after discontinuation of topiramate.[9] In our case, it was observed that maculopathy continued despite an increase in visual acuity at the 6-month follow-up after the first application. In fact, in the cases published in the literature, it caused more benign retinal changes such as macular striae.[7-10] In contrast, in our case, there was severe maculopathy with subretinal fluid due to higher dose medication. While the subretinal fluid disappeared after the medication was discontinued, the retinal layer disorder in the macula remained permanent. In our case, unlike other cases, a significant difference in damage was seen between the 2 eyes. In the right eye, there was a slight color change in the fundus and a slight thickening of the outer layers of the macula, and these findings improved at the last follow-up. In the left eye, extensive chronic macular damage and subretinal fluid occurred, and continued with a macular damage that did not improve even at the last follow-up.

Although topiramate has been previously reported to be used in very high doses, these findings did not reveal ocular side effects.[11] Even slight titration increases of topiramate cause ocular side effects, but our case in which topiramate was used twice at

such a high dose and caused only ocular side effects is the first presentation. Since the increasingly widespread use of topiramate will cause more side effects, the ophthalmic examination should be done after starting the treatment, increasing the dose and of course toxications. Topiramate-related maculopathy should be kept in mind in cases of vision loss that develops under topiramate use, and drug discontinuation should be considered in suspicious cases.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ekrem Çelik, Can Demir;* ***Design:*** *Ekrem Çelik;* ***Control/Supervision:*** *Ekrem Çelik;* ***Data Collection and/or Processing:*** *Ekrem Çelik, Can Demir;* ***Analysis and/or Interpretation:*** *Ekrem Çelik, Can Demir;* ***Literature Review:*** *Ekrem Çelik, Can Demir;* ***Writing the Article:*** *Ekrem Çelik, Can Demir;* ***Critical Review:*** *Ekrem Çelik, Can Demir;* ***References and Fundings:*** *Ekrem Çelik, Can Demir;* ***Materials:*** *Ekrem Çelik, Can Demir.*

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