Case Report

Neurofibromatosis Type 1 Vasculopathy Presenting as Branch Retinal Vein Occlusion: Case Report and Review of the Literature

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Abstract

Systemic vascular occlusive disease associated with neurofibromatosis type 1 (NF1) has been reported in the aortic, cerebral, renal, celiac, and mesenteric vessels and is referred to as NF1 vasculopathy. Although retinal vascular involvement in patients with NF1 usually manifests as retinal capillary hemangiomatosis, a few cases of NF1 with retinal vascular occlusive disease have also been described. Here, we report a 2-year-old girl with NF1 who presented with branch retinal vein occlusion and peripheral retinal ischemia secondary to NF1. This case demonstrates that NF1-related retinal occlusive vasculopathy may occur in very young patients and that detailed fundus examination with fluorescein angiography is necessary in all patients with NF1.

Keywords: Neurofibromatosis type 1, NF1 vasculopathy, occlusive vascular disease, branch retinal vein occlusion

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Introduction

Neurofibromatosis type 1 (NF1) is an inherited multisystem disease that gives rise to cutaneous findings such as café au lait spots, intertriginous freckling, skin and nervous system tumors, osseous lesions, and vascular pathologies. The eye is frequently involved in patients with NF1. Iris Lisch nodules, optic pathway gliomas, neurofibromas of the orbit and eyelid, and choroidal nodules are among the most common ocular findings and serve as diagnostic criteria.[1] Recently, retinal vascular abnormalities have been shown to occur more frequently in this group of patients than previously thought.[2,3,4] Although these abnormalities mostly included structural changes and different microvascular arrangements, a limited number of reports have also documented different presentations of retinal vascular occlusion.[5,6,7,8,9]

Here, we report a unique case of branch retinal vein occlusion in a patient with NF1 and bilateral optic glioma.

Case Report

A 2-year-old girl with a known history of NF1 was referred for retinal detachment (RD) in the right eye (RE). She had a history of falling from the sofa 8 months ago, and was previously evaluated for retinoblastoma and persistent fetal vasculature as possible causes of the RD. NF1 had previously been diagnosed on the basis of multiple café au lait spots and bilateral optic nerve glioma (Figure 1A). The patient was born full term without complications. There was no history of consanguinity or ocular disease in the family.

During ocular examination, the patient showed intense objection to occlusion of the left eye (LE), indicating very poor vision in the RE. The LE could fixate on and follow small objects. Pupillary dilation was poor due to posterior synechiae in the lower quadrant of the RE (Figure 1B). The retina was behind the lens with overlying hemorrhagic fibrous membranes, no retinal break

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was detected, and ultrasonography showed a closed-funnel RD in the RE (Figure 1C). The anterior segment was normal in the LE, while fundus examination revealed subtle vascular abnormalities and mild fibrous proliferation along the distal portion of the vein in the inferotemporal arcade (Figure 2A). An examination under general anesthesia was planned. Fluorescein angiography (FA) of the LE showed delayed filling of the distal inferotemporal vein, significant surrounding capillary non-perfusion, and highly tortuous corkscrew-shaped vessels bordering the ischemic areas (SW8000 Widefield Fundus Camera, Suoer, Tianjin, China) (Figure 2C, D). The entire temporal periphery was also avascular, with vessels abruptly terminating by forming arteriovenous anastomoses and bordering the perfused and non-perfused retina (Figure 2E). FA of the RE demonstrated diffuse capillary loss in the detached retina. The inferior half was totally avascular, along with some neovascularization (Figure 1D). Tractional RD could not be ruled out in the RE because of the retinal vascular findings.

The patient underwent vitreoretinal surgery in the RE and sectoral panretinal photocoagulation of the ischemic areas and pathological vessels in the LE (Figure 2F). During surgery in the RE, following limbal lensectomy, hemorrhagic coagula and membranes were removed with forceps and scissors and the funnel could be opened from the center to reach the optic nerve head. This revealed a large macular tear within the funnel, along with avascular peripheral retina and intraretinal, subretinal, and preretinal proliferative vitreoretinopathy membranes (Figure 1E, F). After seeing the possibly traumatic macular tear-related RD, the surgery was continued mainly for anatomical preservation of the globe. Extensive membrane peeling with retinotomy and peripheral ischemic retinectomy resulted in flattening of the retina, which was tamponaded with 5000 centistoke silicone oil. The patient has been followed up without any silicone-oil related complications in the RE during 1 year of follow-up.

Discussion

Systemic vascular occlusive disease affecting the aortic, cerebral, renal, celiac, and mesenteric vessels has been previously reported in NF1.[10,11] In fact, the term "NF1 vasculopathy" has been used in the literature to describe aneurysms, stenoses, and arteriovenous malformations that occur in NF1 patients. The pathogenesis of these NF1-related vascular abnormalities is largely unknown. Previous hypotheses suggested that it may result from cellular proliferation within the vessel walls

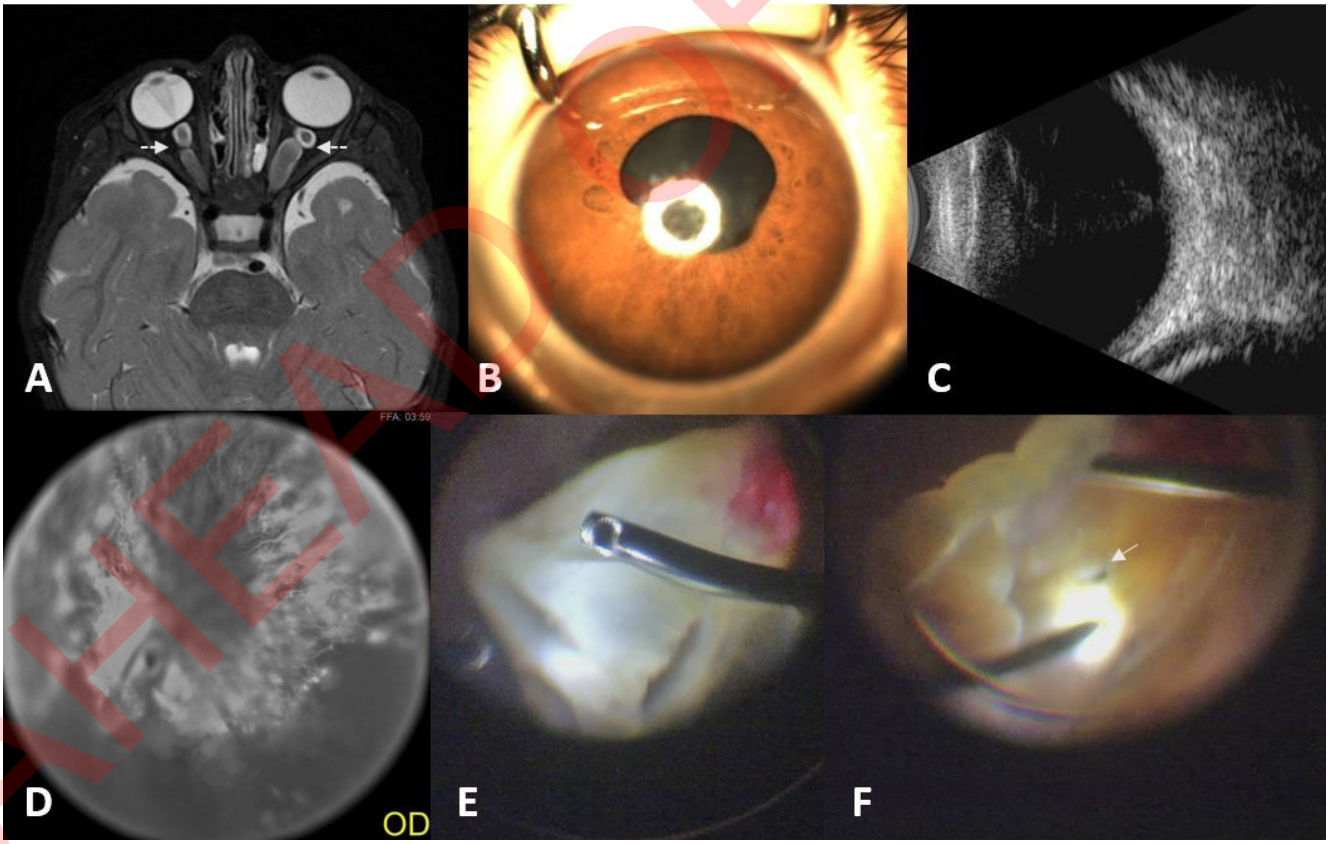

Figure 1. Cranial MRI showing bilateral optic glioma (arrows) (A). Pupillary dilation was poor due to posterior synechiae in the right eye and leukocoria was noted (B). B-scan ultrasonography demonstrated closed funnel-shaped retinal detachment (C). Fluorescein angiography showed diffuse leakage and capillary loss, which was more apparent in the inferior periphery of the right eye (D). Following lensectomy and removal of the retrolental fibrotic membranes, a macular tear was seen within the funnel (arrow) (E, F). Fundus images and fluorescein angiography images were taken with the SW8000 widefield fundus camera by Suoer (Tianjin, China)
MRI: Magnetic resonance imaging

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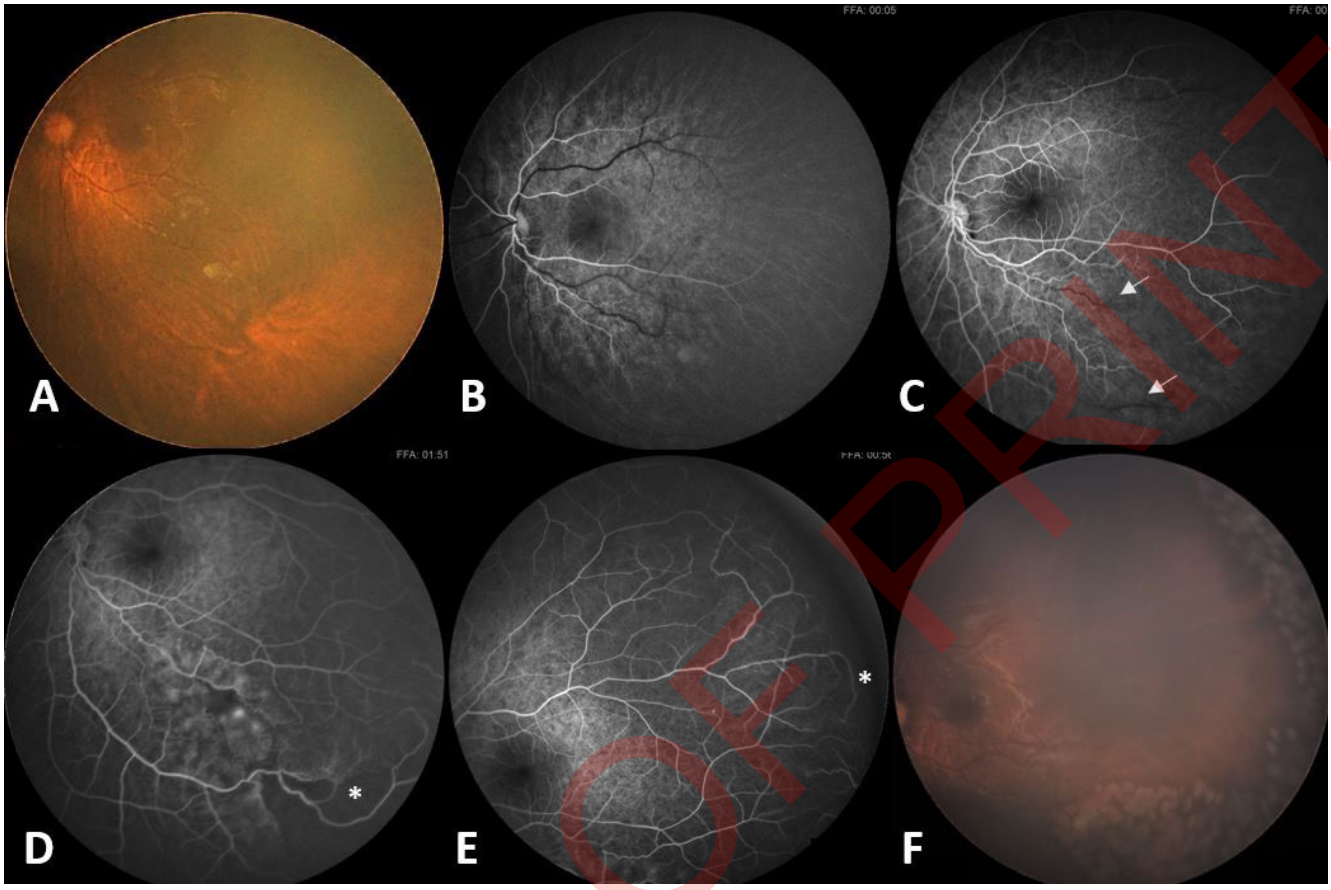

Figure 2. Fundus image of the left eye demonstrates subtle fibroglial proliferation along the distal portion of the inferotemporal vein (A). Fluorescein angiography showed normal arterial filling at 5 seconds after dye injection (B) and delayed filling of distal branches of the inferotemporal vein (arrows) at 20 seconds after dye injection (C). Areas of capillary non-perfusion and tortuous collaterals became evident in the inferotemporal quadrant in later frames (asterisk) (D). The temporal and inferior periphery were avascular, with arteriovenous communications bordering the perfused and non-perfused retina (asterisk) (E). Note that there were capillary non-perfusion areas in the tract of the inferotemporal retinal vein with a few leaking neovascular tufts at the vascular-avascular border. Fundus image of the left eye after laser photocoagulation treatment (F). Fundus images and fluorescein angiography images were taken with the SW8000 widefield fundus camera by Suoer (Tianjin, China)

or from direct compression or invasion by neural tumors.[10] However, the latter hypothesis does not seem to correlate well with clinical findings. More frequently, histologic findings indicate fibromuscular dysplasia with a predominance of intimal thickening in such cases.[11]

According to recent reports, retinal microvascular abnormalities have now been recognized in up to one-third of NF1 cases.[2,3,4] Several authors have demonstrated a spectrum of vascular abnormalities that range from simple tortuosities to the more complex corkscrew and moyamoya-like configurations.[2,3,4] While earlier studies described these lesions as congenital and stable,[2] recent ones have mentioned dynamic changes over the years.[3] Nevertheless, the clinical significance of these microvascular lesions remains unknown other than being a possible marker of NF1 disease.

On the other hand, retinal vascular occlusive diseases can also be seen in these patients, albeit rarely, and can lead to clinical consequences. The literature review yields several case reports of different types of vascular involvement in NF1 patients (Table 1). Three of these cases presented with diffuse involvement with both major and peripheral vessel occlusion and were diagnosed in the later sequelae stage.[5,6,7] They all had diffuse sheathing of retinal vessels, arteriovenous communications, avascular peripheral retina, and secondary fibroglial proliferation. One case presented with isolated macular artery involvement while the periphery was spared.[9] Two patients with peripheral retinal ischemia complicated with neovascular glaucoma have been presented as well.[12,13] Other examples included central retinal artery and ophthalmic artery occlusions during the course of NF1.[14,15]

While most of these previous reports on NF1 vasculopathy documented arterial system occlusions as the primary pathology, to our knowledge, one case of NF1 with branch retinal vein occlusion has been previously reported.[8] This was a 64-year-old woman with no systemic pathology other than NF1 who presented with superotemporal vein occlusion and areas of capillary loss at the posterior pole. Differently than this case, we observed an occlusion in a distal branch vein, and the temporal periphery was totally avascular. Moreover, previous reports emphasized the unilateral appearance of NF1 vasculopathy.[5,6,7,8,9,12,14] However, the angiographic and surgical findings in the fellow eye

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Table 1. Literature review of NF1-related retinal vascular occlusion cases

Author[ref]	Year	Age (years)	Presentation	Laterality	Vascular occlusion type
Moadel et al.[5]	1994	4	Exodeviation	Unilateral	Peripheral retinal ischemia
Thölen et al.[6]	1998	20	Routine exam	Unilateral	Peripheral retinal ischemia and BRAO
Saatci et al.[14]	1998	15	Sudden painless vision loss	Unilateral	Ophthalmic artery occlusion
Mori et al.[8]	2001	64	Gradual vision loss	Unilateral	BRVO
Kadoi et al.[7]	2003	23	Poor vision since childhood	Unilateral	Peripheral retinal ischemia
Lecleire-Collet et al.[9]	2006	26	Sudden painless vision loss	Unilateral	Macular arteriolar occlusion
Elgi et al.[12]	2010	12	Pain and poor vision	Unilateral	Peripheral retinal ischemia, NVG
Pichi et al.[13]	2013	13	Pain and poor vision	Unilateral	Peripheral retinal ischemia, NVG
Umunakwe et al.[15]	2019	36	Episodes of sudden painless vision loss	Unilateral	CRAO

BRAO: Branch retinal artery occlusion; BRVO: Branch retinal vein occlusion; NVG: Neovascular glaucoma; CRAO: Central retinal artery occlusion, NF1: Neurofibromatosis type 1

suggested possible bilateral involvement in the presented case. Vascular anomalies and ischemia observed in both eyes on FA suggested that the source of RD in the RE might not be just a standard traumatic rhegmatogenous one but might be a tractional RD. As a result, surgical intervention was considered as a potential treatment option. The presence of the avascular ischemic peripheral retina in addition to the macular tear found during the operation suggested that a rhegmatogenous RD may have developed in an already ischemic retina after trauma. Although these findings might be confusing in a patient with closed funnel RD and advanced PVR, they may indicate that unilaterality is not a rule in NF1 vasculopathy and that both eyes should be meticulously investigated. The detection of such a marked vasculopathy in a patient with a near-normal retina is also striking, emphasizing the importance of routine FA in NF1 patients.

Another issue is that our patient was much younger and had bilateral optic glioma. One might argue that direct compression of the tumor may have caused the retinal vascular disturbances if it was a central retinal vascular occlusion. However, given the occlusion of the peripheral retinal vessels, this seems unlikely. We believe the underlying pathogenesis was consistent with previous cases and likely involves vascular smooth muscle cell proliferation due to abnormal signaling between smooth muscle and endothelial cells expressing the *NF1* gene product neurofibromin, a negative regulator of mitogenic signaling.

In conclusion, NF1 may cause retinal vascular occlusions that can manifest in different ways affecting both the arterial and venous systems. Findings can be subtle, confined to small venules or located in the periphery, and can easily go unnoticed, especially in a young child, as in our case. Therefore, we recommend a detailed fundus examination and FA in all patients with NF1. Also, NF1 vasculopathy should be recognized as an etiology of retinal vascular occlusive disease in young patients.

Ethics

Informed Consent: Obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.Ö., E.Ö.Z., Concept: E.Ö.Z., Ş.Ö., Design: E.Ö.Z., Ş.Ö., Data Collection or Processing: E.Ö.Z., Analysis or Interpretation: E.Ö.Z., Ş.Ö., Literature Search: E.Ö.Z., Ş.Ö., Writing: E.Ö.Z., Ş.Ö.

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