OPEN

Retinal Cases and Brief Reports Publish Ahead of Print
DOI: 10.1097/ICB.0000000000001673

Title Retinal vascular abnormality of non-perfusion and neovascularization in a toddler with neurofibromatosis type 1

Running title Retinal vascular abnormality in NF-1

Authors and Affiliations Qiaozhu Zeng[1, 2], MD, Yusheng Hong[1, 2], MD, Tong Qian[1, 2], MD, Yong Cheng[*1,2], MD

[1] Department of Ophthalmology, Eye Diseases and Optometry Institute, Peking University People's Hospital, Beijing, China

[2] Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, College of Optometry, Peking University Health Science Center, Beijing, China

No authors have a proprietary interest.

[*]Corresponding to: Yong Cheng

Address: No.11 Xizhimennan Street, Xicheng District, Beijing

Phone number:8615120071105

E-mail: raccocheng@126.com

Funding This study was supported by Beijing Bethune Charitable Foundation (grant no. 2021-Z-07).

Declaration of competing interest The authors have no financial or proprietary

interest in the materials presented herein.

Keywords Laser photocoagulation, Neurofibromatosis type 1, Neovascularization, Retinal nonperfusion

Summary statement This case presents an unusual manifestation of neurofibromatosis type 1, characterized by peripheral neovascularization and nonperfusion. Thorough fundus examinations and systemic reviews, particularly fluorescein angiography, are essential. Additionally, we recommend conducting angiographic studies on the non-involved eye as well.

Abstract

Purpose This report describes the case of a 13-month-old boy diagnosed with neurofibromatosis type 1, who presented with retinal vascular abnormalities including extensive non-perfusion and neovascularization. We also discuss the observed

changes following photocoagulation treatment.

Methods A 13-month-old boy presented to the Department of Ophthalmology at Peking University People's Hospital with a reduction in the width of the left palpebral fissure for the past 6 months.

Results The boy exhibited more than six café-au-lait spots larger than 5 mm in diameter on his trunk and legs. Fundus examination of the left eye revealed prominent neovascularization in the temporal periphery of the retina, with late leakage and non-perfusion also noted temporally in fluorescein angiography (FA). Magnetic resonance imaging of the brain and orbits showed an enlarged left sphenoid body, a widened left cavernous sinus, and a large plexiform neurofibroma. Laser treatment was performed on the left eye. Five months later, the neovascularization was controlled.

Conclusion Careful fundus examinations and systemic reviews, especially FA, are essential. Timely laser treatment is crucial for controlling disease progression and preventing retinal detachment.

Text page 7

1. Introduction

Neurofibromatosis type 1 (NF-1) is a complex autosomal dominant disorder that affects multiple organ systems, presenting with a wide range of clinical manifestations. Common ocular manifestations of NF-1 include Lisch nodules, glaucoma, optic pathway gliomas, astrocytic hamartomas, and orbital-periorbital-plexiform neurofibromas ~~and etc~~. Herein, we report the case of a 13-month-old boy diagnosed

with NF-1, who exhibited retinal vascular abnormalities, including extensive non-perfusion and neovascularization.

2. Case report

A 13-month-old boy presented to the Department of Ophthalmology at Peking University People's Hospital with a reduction in the width of the palpebral fissure in his left eye for the past 6 months. He was born vaginally at full term, with no significant past medical history or relevant family history.

During an examination under anesthesia (EUA), intraocular pressure was measured at 12 mmHg in both eyes. The anterior segment examination of both eyes was unremarkable, with no iris Lisch nodules observed (Fig. 1). Fundus examination and fluorescein angiography (FA) of the right eye exhibited no remarkable changes (Fig. 2a). While fundus examination of the left eye revealed a large frond of neovascularization in the temporal periphery of the retina (Fig. 2b). FA of the left eye showed nonperfusion in the periphery noted temporally with late leakage.

Additionally, the boy had more than six café-au-lait spots, each larger than 5 mm in diameter on his trunk and legs (Fig. 3). Magnetic resonance imaging (MRI) of the brain and orbits revealed a spacious left sphenoid body, widened left cavernous sinus, and a large plexiform neurofibroma along the trigeminal nerve, observed in the short tau inversion recovery (STIR) sequence in the left orbit (Fig. 4). Genetic testing confirmed a pathogenic mutation, 4537C > T, in the NF-1 gene. He was the only family member with a confirmed diagnosis of NF-1.

The diagnosis of NF-1 was established based on these findings. Other pediatric retinal vascular diseases, such as retinopathy of prematurity and familial exudative vitreoretinopathy, were considered much less likely, given his full-term birth, the severe retinal vascular abnormalities ipsilateral to the large intracranial and intraorbital neurofibroma, and the genetic test results. Therefore, fundus laser treatment was performed twice on the left eye. Five and seven months later, the neovascularization showed some degree of control (Fig. 5).

3. Discussion

According to the 1987 NIH Consensus Development Conference diagnostic criteria[1], this case meets two features and qualifies as NF-1: six or more café-au-lait macules and a plexiform neurofibroma. While NF-1 commonly affects vascular structures in the kidney and brain, involvement of the retinal vasculature is relatively rare[2, 3]. Various retinal vascular abnormalities associated with NF-1 have been documented, including simple vascular tortuosity, corkscrew retinal vessels, and moyamoya-like abnormalities. In our case, we observed peripheral nonperfusion with neovascularization. The exact mechanism underlying these vascular changes remains uncertain. Rali et al.[4] suggested that besides the inherent vascular predisposition of NF-1, vascular compression by tumors could disrupt the neurovascular bundle, potentially leading to severe nonperfusion and neovascularization. Ozerdem et al. proposed that hyperproliferation of pericytes and endothelial cells may contribute to vascular occlusion and subsequent neovascularization[5].

In addition, differential diagnosis for peripheral retinal capillary non-perfusion, in different age groups should be taken into consideration when NF-1 is suspected, as shown in Table 1. In children, it is necessary to differentiate Coats, retinopathy of prematurity (ROP), and familial exudative vitreoretinopathy (FEVR) from NF-1. Rare diseases, such as Norrie disease and Incontinentia pigmenti should also be considered. While in adults, retinal vasculitis, diabetic retinopathy and retinal vein occlusion may not be neglected.

We opted to treat the severe neovascularization with photocoagulation. Similarly, documented cases of NF-1 with peripheral retinal ischemia have addressed neovascular glaucoma and neovascularization through panretinal photocoagulation (PRP) and Ahmed valve implantation[6, 7]. In cases without neovascularization but with ischemia, observation was chosen[8]. Due to the localized and severe nature of the vascular abnormalities in our patient, we initiated treatment with local photocoagulation in addition to PRP. This marks the first attempt at local photocoagulation for non-perfusion and neovascularization in NF-1 eyes. While the lesion remained stable, the neovascularization persisted. Continued close follow-up is essential to assess the long-term efficacy of photocoagulation in NF-1.

Early detection and diagnosis of NF-1 can mitigate future risks such as retinal detachment, severe pain, and vision loss. NF-1 manifestations often appear in early childhood and can even be detected in the perinatal period. Initial signs, including eye-related manifestations like neurofibromas and optic nerve gliomas, were present in 40% of perinatal cases[9]. Depending on the manifestations, interventions such as

anti–vascular endothelial growth factor injections, laser treatments, or other therapies may be considered subsequently. Given NF-1's systemic impact and varied clinical presentations, comprehensive multidisciplinary evaluation and care are essential. In a case reported by Hua et al.[8], failure to note the cystic mass during EUA would have led to further diagnostic delays in NF-1.

4. Conclusion

This case represents a rare manifestation of NF-1 involving peripheral neovascularization and nonperfusion. Careful fundus examinations and systemic reviews, particularly FA, are essential. Furthermore, we recommend angiographic studies of the unaffected eye. Timely laser treatment is crucial to manage disease progression and prevent retinal detachment.

References

1. Gutmann DH, Ferner RE, Listernick RH , et al. Neurofibromatosis type 1. Nat Rev Dis Primers 2017; 3:17004.

2. [illegible] L, Feng K, Tong A and Liang Z. Renal artery stenosis due to neurofibromatosis type 1: case report and literature review. Eur J Med Res 2014; 19:17.

3. Rosser TL, Vezina G and Packer RJ. Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. Neurology 2005; 64:553-555.

4. Rali AS, Bavinger JC, Rao P and Hubbard GB. SEVERE RETINAL ISCHEMIA

IN INFANT WITH NEUROFIBROMATOSIS TYPE 1. Retin Cases Brief Rep 2023; 17:471-473.

5. Dansingani KK, Jung JJ, Belinsky I , et al. ISCHEMIC RETINOPATHY IN NEUROFIBROMATOSIS TYPE 1. Retin Cases Brief Rep 2015; 9:290-294.

6. Pichi F, Morara M, Lembo A , et al. Neovascular glaucoma induced by peripheral retinal ischemia in neurofibromatosis type 1: management and imaging features. Case Rep Ophthalmol 2013; 4:69-73.

7. Seth A, Ghosh B, Gupta A and Goel N. Peripheral retinal ischemia in a young Indian woman with neurofibromatosis type 1. Saudi J Ophthalmol 2016; 30:60-63.

8. Hua HU, Martens R, Read SP , et al. Neurofibromatosis type 1 presenting with retinal detachment and laryngeal plexiform neurofibroma in a toddler. Am J Ophthalmol Case Rep 2021; 23:101170.

9. Isaacs H, Jr. Perinatal neurofibromatosis: two case reports and review of the literature. Am J Perinatol 2000; 17:285-292.

Table 1 Differential diagnosis for peripheral retinal capillary non-perfusion in different age groups

Figure legends

Figure 1 Anterior segment examination on the two eyes. No remarkable signs were found.

Figure 2 Fluorescein angiography of the two eyes. (a) The right eye exhibited no remarkable changes. (b) The left eye revealed a large frond of neovascularization in

the temporal periphery of the retina with late leakage.

Figure 3 Cafe-au-lait spots of the boy. Spots of larger than 5mm diameter were presented on his trunk and legs.

Figure 4 Magnetic resonance imaging of brain and orbits. Spacious left sphenoid body, widened left cavernous sinus and a large plexiform neurofibroma along the trigeminal nerve were shown in short tau inversion recovery sequence in the left orbit.

Figure 5 Follow up of the left eye after fundus laser treatment. (a) After five months. (b) After seven months.

Table 1 Differential diagnosis for peripheral retinal capillary non-perfusion in different age groups

Age groups (Mostly)	Differential diagnosis	Characteristics
Children	Coats	The first or second decades of life or adults Retinal telangiectasia with exudation Unilateral
	ROP	Preterm infants Early stage of retinal microvascular degeneration, neovascularization, and subsequent retinal detachment
	FEVR	Any age Born at full term, or preterm with a disease tempo not consistent with ROP An avascular peripheral retina which is highly variable within the same family
	Norrie disease	Born blind, often lose their vision in infancy, sensorineural hearing loss in the second decade of life Mutation in the NDP gene
	Incontinentia pigmenti	First few weeks after birth to adulthood Mainly females Skin lesions, central nervous system abnormalities, and teeth defects A mutation in the IKBKG gene, X-linked dominant disorder
Adults	Retinal vasculitis	Any age Isolated ocular condition, or associated with a systemic inflammatory disease
	Diabetic retinopathy	20-64 years old History of diabetic mellitus Diabetic macular edema and complications from abnormal retinal blood vessel growth, angiogenesis
	Retinal vein occlusion	Mostly affects individuals > 60 years old Risk factors of hypertension, hyperlipidemia, and diabetes Retinal hypoperfusion and hemorrhage result in ischemia and hypoxia

ROP, retinopathy of prematurity; FEVR, familial exudative vitreoretinopathy.