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Case Report

Pulsating Enophthalmos as an Initial Symptom of Neurofibromatosis Type 1

Aslihan Yilmaz Cebi,[1] Bilge Batu Oto,[2] Oguzhan Kilicarslan,[3] Ahmet Murat Sarici[2]

[1]Department of Ophthalmology, Cerkezkoy State Hospital, Tekirdag, Türkiye
[2]Department of Ophthalmology, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Türkiye
[3]Department of Ophthalmology, Ayancik State Hospital, Sinop, Türkiye

Abstract

We report a neurofibromatosis type 1 (NF-1) patient with pulsating enophthalmos as the first symptom. A 25-year-old female presented to us with posterior displacement of the left eye and a headache. The patient had enophthalmos with pulsations. A slit lamp examination revealed bilateral Lisch nodules and a computed tomography scan of the orbit demonstrated aplasia of the greater wing of the sphenoid bone on the left. The patient had café-au-lait macules, a history of scoliosis, and splenectomy operations. Genetic counseling confirmed the diagnosis of NF-1. NF-1 is a multisystemic, autosomal dominant genetic disease with cutaneous, neurologic, cardiovascular, and ophthalmologic manifestations. Dysfunction of tumor suppressor gene NF-1 is the main cause. Therefore, periodic screening for tumor development is required. Since NF-1 has several neuro-ophthalmological findings, ophthalmologists can play a significant role in its diagnosis and management.

Keywords: Enophthalmos, Neurofibromatosis type 1, Phakomatoses, Sphenoid bone, Tumor supressor gene

Introduction

Neurofibromatosis type 1 (NF-1) is a phacomatose with cutaneous, neuro-ophthalmological, and cardiovascular manifestations. Its prevalence is about 1 in 3000 persons. It has an autosomal dominant inheritance pattern. Dysfunction of tumor suppressor gene NF-1 is the main cause (1). Regular screening is mandatory for detecting tumor development and vascular complications. Lisch nodules, neurofibromas, optic gliomas, and the development of glaucoma are several ocular manifestations of NF-1. Management of NF-1 patients requires a multidisciplinary approach. Pulsating enophthalmos (PE) is a rare manifestation in ophthalmology practice. We report an NF-1 case with PE as the patient's first symptom. This study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient.

Case Report

A 25-year-old female patient was accepted to our clinic with complaints of headache and posterior displacement of the left eye. She had enophthalmos in the left eye and pulsations were noted [Supplementary file: Video]. The best corrected visual acuity was 20/20 bilaterally. Intraocular pressure and central corneal thickness (CCT) measurements were 12 mmHg (CCT: 552 µm) in the right eye (OD) and 13 mmHg

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Address for correspondence: Bilge Batu Oto, MD. Department of Ophthalmology, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Türkiye
Phone: +90 535 315 00 74 **E-mail:** batubilge@gmail.com

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(CCT: 555 μm) in the left eye (OS). Hertel exophthalmometer measurements were 13 and 7 mm in OD and OS, respectively. Slit-lamp examination revealed bilateral Lisch nodules (Fig. 1). Ocular motility and cover test were normal. Dilated fundus examination was normal and cup-to-disc ratio was 0.3, bilaterally. She had café-au-lait spots in the belly and back. Her medical history was positive for splenectomy and scoliosis operations, she did not have any systemic disease history. A computed tomography (CT) scan of the cranium was ordered for differential diagnosis of enophthalmos. CT scan demonstrated the aplasia of the greater wing of the sphenoid bone on the left (Fig. 2). She was referred to a genetic counselor for genetic confirmation of NF-1. A genetic test was resulted positive for NF-1 gene analysis.

Discussion

NF-1, also known as von Recklinghausen disease, is an autosomal dominant genetic syndrome with various cutaneous, neurological, cardiovascular, and ophthalmological manifestations. NF-1 is caused by a loss of function mutation in tumor suppressor gene NF-1, which codes neurofibromin. Neurofibromin works by downregulating the ras pathway and there is a lifetime risk for tumor development (1).

The diagnosis of NF-1 is based on clinical findings and requires two or more of the following criteria: At least six café-au lait macules (minimum 15 mm), axillary or inguinal freckles, optic glioma, at least two Lisch nodules, two neurofibromas or one plexiform neurofibroma, sphenoid dysplasia or tibial pseudoarthrosis, first-degree relative with NF-1. Other complications include short stature, learning disabilities, systemic hypertension, and various malignancies, such as gastrointestinal tumors (1). Regarding ocular manifestations of NF-1, the majority of nervous system gliomas are found in the optic nerves, chiasm, tracts, and radiations and known as optic pathway gliomas (2). Lisch nodules are frequent with anterior segment involvement. Conjunctival neurofibromas and corneal nerve thickening are rarely seen. Increased risk of developing glaucoma, and tumors of the posterior segment such as astrocytoma, hamartoma, and hemangioma have also been reported (3).

Our patient had café-au-lait macules, Lisch nodules, and sphenoid dysplasia; therefore, fulfilled the criteria for diagnosis. Though having café-au-lait macules, the patient had never been suspected of NF-1 in her previous medical visits. Lisch nodules were revealed during ophthalmic examination, only after she applied to our clinic with complaints of posterior

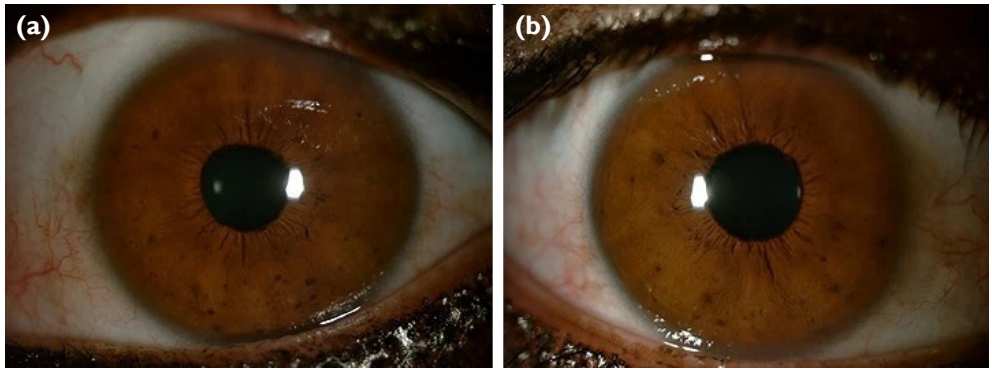

Figure 1. Lisch nodules on biomicroscopy. **(a)** Right eye. **(b)** Left eye.

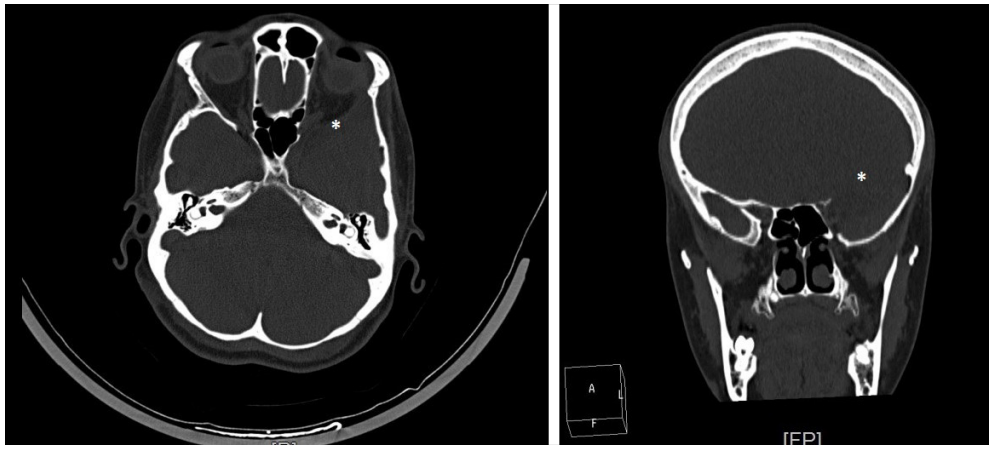

Figure 2. Computed tomography scans show the absence of the greater wing of the sphenoid bone on the left (asterisks).

displacement of the left eye. Sphenoid aplasia was discovered during the investigation for enophthalmos. Optic nerves were normal both in clinical examination and radiological imaging. Ophthalmologic findings raised the suspicion of NF-1, and only after then, the patient was referred to genetic testing. Scoliosis was evaluated as a musculoskeletal complication of NF-1. Although splenomegaly and splenic artery aneurysms have been reported in the literature (4,5), medical records of the previous splenectomy operation could not be reached.

Greater and lesser wings of sphenoid bone contribute to the formation of the lateral and the superomedial orbital walls, respectively. Impairment of this structure can lead to exopthalmos/enophthalmos, and transmission of brain pulsations. PE is a distinctive feature of NF-1. This relation was reported 3 times in the past 40 years. Only one of them, a 36-year-old woman, had PE as the only symptom like our patient (6). A 49-year-old man with known NF-1 disease was reported to have PE, visual disturbances, and neurofibromas (7), and a 64-year-old man was reported to have decreased vision and severe esotropia in addition to PE (8). PE can also be associated with orbital fractures, extensive cranio-orbital bone resections, and orbital varices (9). Comprehensive ophthalmic examination and convenient imaging techniques can reveal the etiology.

Due to neurofibromin which also modulates endothelial function; NF-1 patients may have life-threatening cardiovascular manifestations, for instance, systolic dysfunction, aneurysms, renal artery stenosis, cardiac valvular defects, and uncontrolled hypertension (10).

Conclusion

NF-1 is a systemic syndrome and its management requires a multidisciplinary approach. Regular follow-up is crucial for early diagnosis of the complications. Referral for tumor screening and systemic examination can be lifesaving. Diagnostic criteria of NF-1 include eye-related findings. As in the patient presented here, ophthalmic findings may lead to diagnosis. Ophthalmologists should keep in their mind the ocular features of systemic diseases for differential diagnosis.

Disclosures

Informed consent: Written, informed consent was obtained from the patient's family for the publication of thís case report and the accompanying images.

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