

Case Report

Optical Coherence Tomography Angiography of Retinal Microvascular Changes Overlying Choroidal Nodules in Neurofibromatosis Type 1

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Keywords

Choroidal nodules · Optical coherence tomography angiography · Neurofibromatosis type 1 · Retinal microvascular changes

Abstract

Purpose: To report 3 cases of neurofibromatosis type 1 (NF1) with choroidal nodules associated with retinal microvascular changes imaged with optical coherence tomography angiography (OCTA). **Methods:** Small case series in 3 NF1 patients. OCTA examinations were performed by a trained examiner (J.J.) after pupillary dilation. A standard scan, centered over the macula measuring 6 × 6 mm and 3 × 3 mm was obtained according to the findings on standard color photography. Additional scans were obtained in the zones with microvascular abnormalities. The segmentation provided by the machine software was used. **Results:** Cork-screw retinal vessels were observed in association with “placoid”-type choroidal nodules as shown by near-infrared reflectance imaging. In all cases, multiple lesions were found. They were second- or third-order tortuous vessels originating from the superior or inferior temporal veins. OCTA demonstrated that the tortuous venules were located in the superficial capillary plexus, and no abnormalities were found in the deep capillary plexus. **Discussion:**

Corkscrew retinal vessels are part of a spectrum of retinal microvascular alterations seen in association, sometimes overlying choroidal nodules in patients with NF1 and are visualized in the superficial capillary plexus on OCTA. We demonstrated with OCTA that they are not associated with flow loss or ischemia in the superficial and deep capillary plexus. The link between the underlying nodule remains unclear. Since neovascularization was described in choroidal ganglioneuroma, we hypothesize that corresponding secretory substances from Schwann cells, ganglion cells, or melanocytes in choroidal nodules might alter the retinal vasculature. **Conclusion:** We report on 3 cases of NF1 with choroidal nodules in association with retinal microvascular changes imaged with OCTA. OCTA demonstrated preservation of the blood flow in the deep and superficial capillary plexus of the retina. We hypothesize that angiogenic factors secreted by the underlying choroidal nodules could have an effect on the retinal vasculature. Further immunohistological studies in NF1 patients with choroidal nodules to detect angiogenic factors (such as VEGF) are necessary to confirm this hypothesis.

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Introduction

Neurofibromatosis type 1 (NF1) is a common autosomal dominant genetic disorder, with a reported prevalence of 1 in every 3,500–4,000 live births. The disease is caused by an autosomal dominant mutation in the *NF1* gene, a tumor suppressor gene, located on chromosome 17q11.2. Affected individuals are prone to develop both benign and malignant tumors in almost any organ. The best-known clinical features are café-au-lait macules and cutaneous neurofibromas [1]. Ophthalmological manifestations of NF1 are Lisch nodules, optic pathway gliomas, a distinctive osseous lesion (sphenoid dysplasia), and (orbital) plexiform neurofibromas.

The diagnosis of NF1 is made based on the clinical characteristics established by the National Institutes of Health in 1988 and/or a molecularly confirmed mutation in the *NF1* gene [2]. Choroidal nodules were recently found to be very specific for NF1, with a diagnostic accuracy of 90% if more than one nodule is present [3]. In NF1 children, choroidal nodules are seen in 71% (<12 years) to 78% (<16 years) [3, 4]. Therefore, choroidal nodules have been proposed to be added to the clinical diagnostic criteria for NF1 [3].

We report 3 cases of NF1 with choroidal nodules associated with retinal microvascular changes imaged with optical coherence tomography angiography (OCTA). OCTA is a relatively new imaging technique that generates angiographic images of the retina noninvasively.

Methods

A cohort of 34 patients with NF1 were evaluated between November 2014 and January 2016. The diagnosis of NF1 was made based on the National Institutes of Health diagnostic criteria for NF1 (34/34) and/or a confirmed molecular diagnosis (26/34). All patients received a thorough ophthalmological evaluation including multimodal imaging: standard color photography, near infrared reflectance, blue autofluorescence, near infrared autofluorescence, and enhanced depth imaging optical coherence tomography using a confocal laser ophthalmoscope type Spectralis (Heidelberg Engineering, Heidelberg, Germany). Twenty-three patients (23/34) showed choroidal nodules. In 6 patients, retinal microvascular abnormalities were observed and documented. All 6 patients had choroidal nodules. Of these, 3

patients gave their consent for an additional exam with OCTA. OCTA was obtained using AngioVue™ (Optovue, Fremont, CA, USA) or Angioplex™ (Zeiss, Oberkochen, Germany).

Results

Retinal microvascular abnormalities were identified on standard color photography in 6 patients of the study cohort (17.65%). These anomalies were located in the posterior pole and consisted of small tortuous venules. The affected small vessels were all second- or third-order venules originating from the superior or inferior temporal veins. In 3 cases, the anomalies were bilateral. The small venules presented with a tortuous corkscrew-like appearance and could be multifocal. These vessels were located overlying so-called “placoid”-type or “patchy” choroidal nodules in 50% as shown by near infrared reflectance (Fig. 1). OCTA showed the corkscrew vessels to be located in the superficial capillary plexus, and the deep capillary plexus showed a normal capillary vortex arrangement (not shown) (Fig. 2; also see online suppl. Fig. 1 and 2, www.karger.com/doi/10.1159/000469702).

Discussion

Retinal microvascular abnormalities overlying choroidal nodules in NF1 were reported previously [5, 6]. Muci-Mendoza et al. [6] reported 12 NF1 patients with corkscrew retinal vessels detected with color imaging and fluorescein angiography in 2002, but choroidal abnormalities were not studied in this cohort. Abdolrahimzadeh et al. [5] described the presence of “spiral” or “corkscrew” vascular alterations overlying placoid choroidal nodules with color photographs, near infrared images, and enhanced depth imaging optical coherence tomography. The authors reported a disturbance of choroidal vasculature overlying the nodule. The surrounding choroid but also the overlying retinal vasculature was found to be unremarkable [5].

To our knowledge, this is the first report to describe retinal microvascular alterations in NF1 patients imaged by OCTA. We observed retinal microvascular abnormalities in 26% of our cohort. This is similar to the prevalence observed in previous similar small case series (35 and 31.2%) [5, 6]. Because choroidal nodules are easily detectable with infrared fundus examination, we did not perform indocyanine green angiography. No abnormalities of retinal vascularization nor the nodules themselves are described on fluorescein angiography. Therefore we did not perform this invasive exam for comparison in our patients [7].

In our patients, and in accordance with Abdolrahimzadeh et al. [5], the abnormal retinal microvessels were observed overlying placoid-type choroidal nodules. In 50% of our patients, however, tortuous vessels were also seen without underlying nodule. OCTA allows separate visualization of the superficial and deep capillary plexus and demonstrates that the retinal microvascular alterations in NF1 patients are located in the superficial capillary plexus. The deep capillary plexus shows a normal capillary vortex arrangement without ischemic regions [8]. Retinal microvascular abnormalities are not associated with flow loss or ischemia in the superficial and deep capillary plexus.

It is difficult to determine whether there is a link between the choroidal nodules and the abnormal microvascular retinal vessels. Choroidal nodules are ovoid bodies consisting of proliferating Schwann cells arranged in concentric rings around an axon. Other histologic

studies showed hyperplastic Schwann cells, melanocytes, and ganglion cells in the ovoid bodies [9, 10].

It is speculated that disease-related disorders of vasomotor nerve cells, originating from the neural crest, such as NF1, can lead to the retinal microvascular alterations seen in NF1 patients [5].

We hypothesize that secretory substances from Schwann cells, ganglion cells, or melanocytes could have an effect on the retinal vasculature. A choroidal ganglioneuroma, a rare benign tumor in NF1 patients originating from the ganglion cells of the sympathetic and parasympathetic nervous system, can be associated with choroidal neovascularization [11]. It is suggested by Ishijima et al. [11] that angiogenic factors expressed in choroidal tumor cells may correlate with the pathogenesis of intraocular neovascularization. The retinal vessels we describe are not due to neovascularization, since no leakage is present. Another unknown mechanism must be involved. It is also unknown why it leads to tortuous venules in the superficial capillary plexus without affecting the deep capillary plexus. Possibly, secretory substances expressed in choroidal nodules such as seen in choroidal ganglioneuroma play a role in the pathogenesis of altered retinal microvasculature. Perhaps choroidal nodules are lesions that in certain circumstances evolve into a choroidal ganglioneuroma.

Conclusion

We report on 3 cases of NF1 with choroidal nodules associated with retinal microvascular changes imaged with OCTA. OCTA demonstrated preservation of the blood flow in the deep and superficial capillary plexus of the retina. We hypothesize that angiogenic factors secreted by the underlying choroidal nodules could have an effect on the retinal vasculature. Further immunohistological studies in NF1 patients with choroidal nodules to detect angiogenic factors (such as VEGF) are necessary to confirm this hypothesis.

Summary

This is the first report to describe retinal microvascular alterations in NF1 patients imaged by OCTA. We observed corkscrew retinal microvascular abnormalities in association with “placoid”-type choroidal nodules. OCTA demonstrated they were second- or third-order vessels originating from the temporal veins, located in the superficial capillary plexus. No abnormalities were found in the deep capillary plexus.

Statement of Ethics

All patients or their parents, if under 18 years, gave their written informed consent to participate in this observational clinical study. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The protocol of the study was approved by the Medical Ethics Committee of the University Hospitals of Leuven, Belgium.

Disclosure Statement

None of the authors have any potential conflict of interest or funding to declare.

References

- 1 Williams VC, Lucas J, Babcock MA, et al: Neurofibromatosis type 1 revisited. *Pediatrics* 2009;123:124–133.
- 2 National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, MD, USA, July 13–15, 1987. *Neurofibromatosis* 1988;1:172–178.
- 3 Viola F, Villani E, Natacci F, et al: Choroidal abnormalities detected by near-infrared reflectance imaging as a new diagnostic criterion for neurofibromatosis 1. *Ophthalmology* 2012;119:369–375.
- 4 Goktas S, Sakarya Y, Ozcimen M, et al: Frequency of choroidal abnormalities in pediatric patients with neurofibromatosis type 1. *J Pediatr Ophthalmol Strabismus* 2014;51:204–208.
- 5 Abdolrahimzadeh S, Felli L, Piraino DC, et al: Retinal microvascular abnormalities overlying choroidal nodules in neurofibromatosis type 1. *BMC Ophthalmol* 2014;14:146.
- 6 Muci-Mendoza R, Ramella M, Fuenmayor R: Corkscrew retinal vessels in neurofibromatosis type 1: report of 12 cases. *Br J Ophthalmol* 2002;86:282–284.
- 7 Yasunari T, Shiraki K, Hattori H, Miki T, et al: Frequency of choroidal abnormalities in neurofibromatosis type 1. *Lancet* 2000;356:988–992.
- 8 Bonnin S, Mané V, Couturier A, et al: New insight into the macular deep vascular plexus imaged by optical coherence tomography angiography. *Retina* 2015;35:2347–2352.
- 9 Kurosawa A, Kurosawa H: Ovoid bodies in choroidal neurofibromatosis. *Arch Ophthalmol* 1982;100:1939–1941.
- 10 Wolter JR: Nerve fibrils in ovoid bodies. *Arch Ophthalmol* 1965;73:696–699.
- 11 Ishijima K, Kase S, Noda M, et al: Intraocular neovascularization associated with choroidal ganglioneuroma in neurofibromatosis type 1. *Eur J Ophthalmol* 2011;21:837–840.

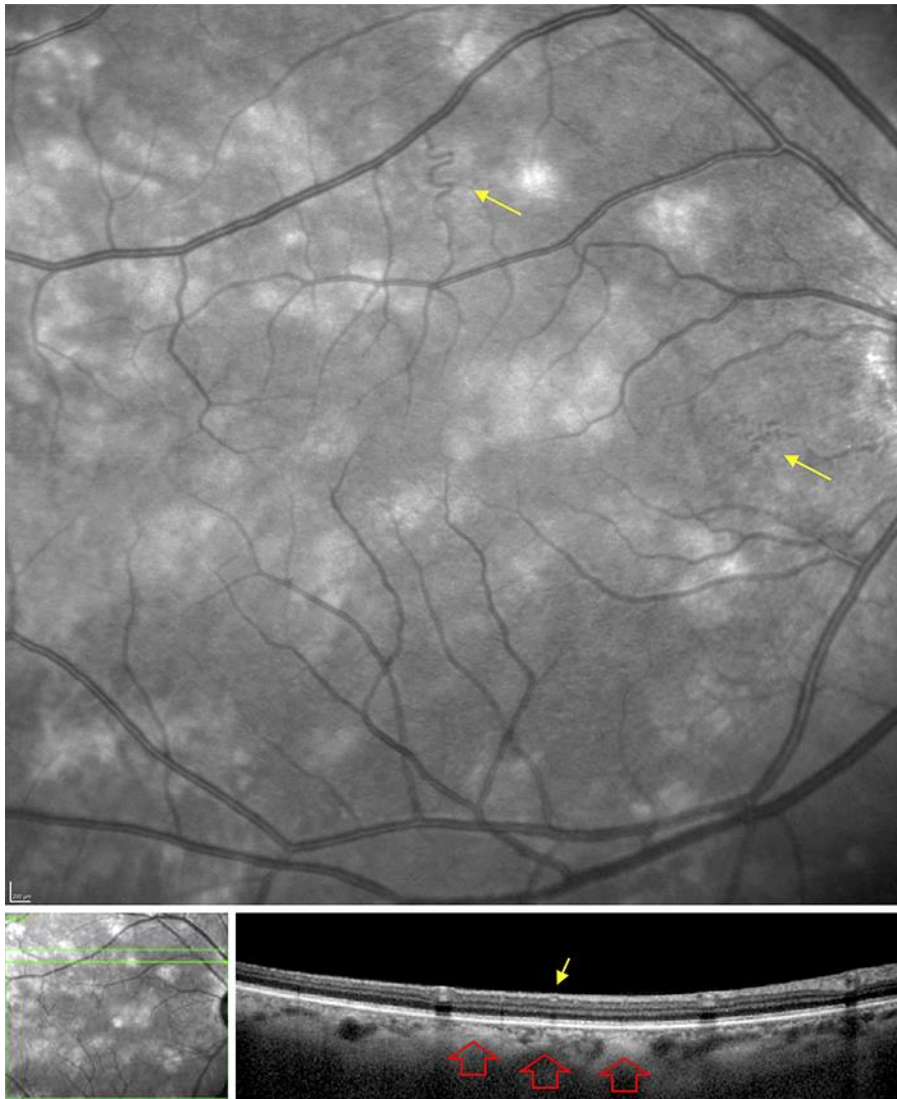


Fig. 1. Top: infrared image of the right eye of a 45-year-old female patient with neurofibromatosis type 1. Choroidal nodules are visible as patchy, irregular, ill-defined hyperreflective alterations. Multiple retinal venous microvascular abnormalities can be observed in the posterior pole (yellow arrows). The small venules have a corkscrew-like appearance and are second- or third-order venules originating from the superior or inferior temporal veins. Bottom: enhanced depth imaging optical coherence tomography at the level of the green arrow shown bottom left. The yellow arrow indicates the corkscrew venule overlying a placoid-type choroidal nodule (red arrows).



Fig. 2. Top: optical coherence tomography angiography image of the right eye (same patient as Fig. 1) showing the superficial capillary plexus. Segmentation is shown below and corkscrew retinal alterations are indicated with yellow arrows. There is no indication of flow loss or ischemia. Bottom: segmentation lines on structural optical coherence tomography.