Available online at www.sciencedirect.com
ScienceDirect
Journal of Current Ophthalmology xx (2016) 1–5
http://www.journals.elsevier.com/journal-of-current-ophthalmology

Case report

Clues from Crouzon: Insights into the potential role of growth factors in the pathogenesis of myelinated retinal nerve fibers

Giancarlo A. Garcia [a,b,*], Jack J. Tian [a,c], Supanut Apinyawasisuk [a], Sarah Kim [d], Handan Akil [a], Alfredo A. Sadun [a]

[a] *Doheny Eye Institute UCLA, Los Angeles, CA, USA*
[b] *University of California, Irvine School of Medicine, Irvine, CA, USA*
[c] *David Geffen School of Medicine, UCLA, Los Angeles, CA, USA*
[d] *Arrowhead Regional Medical Center, Colton, CA, USA*

Received 17 July 2016; revised 30 July 2016; accepted 30 July 2016
Available online ■ ■ ■

Abstract

Purpose: We present a case of bilateral extensive peripapillary myelinated retinal nerve fibers (MRNF) in an individual with Crouzon syndrome, an inherited form of craniosynostosis caused by overactivation of fibroblast growth factor receptor 2. As a secondary aim, we examine the utility of optical coherence tomography (OCT) angiography for visualization of peripapillary vasculature obscured by myelination on other imaging modalities.
Methods: A 24-year-old woman with Crouzon syndrome was evaluated for suspected optic neuritis in the right eye.
Results: Funduscopic examination and photography revealed the incidental finding of bilateral extensive peripapillary myelinated retinal nerve fibers. OCT angiography provided excellent visualization of peripapillary retinal vessels, which were partially obscured by myelination on other imaging modalities.
Conclusions: This association of Crouzon syndrome with bilateral peripapillary MRNF may lend insight into the developmental control of optic nerve myelination, the pathogenesis of MRNF, and the potential role of growth factors in these processes. Further, OCT angiography allowed for excellent blood vessel visualization in this case of MRNF.

Keywords: Myelin; Myelinated retinal nerve fibers; Crouzon syndrome; Fibroblast growth factor receptor; Optical coherence tomography angiography

Introduction

Myelinated retinal nerve fibers (MRNF) appear as grey or white striated patches with feathered borders, and are estimated to occur in 1% of the population.[1] MRNF are typically congenital, and therefore likely represent anomalies of myelination control *in utero*.[2] They are most commonly unilateral, with only 7.7% of cases estimated to occur bilaterally.[1] We present a case of bilateral extensive peripapillary MRNF surrounding the majority of the optic disc circumference in a patient with Crouzon syndrome, an autosomal dominant craniosynostosis disorder with high penetrance and variable expressivity. Crouzon syndrome is caused by mutation of the fibroblast growth factor receptor 2 (*FGFR2*) gene, leading to overactivation that promotes premature fusion of cranial sutures.[3] This can result in craniofacial and orbital structural anomalies, and has been associated with various ophthalmic manifestations including myopia, proptosis, hypertelorism,

The authors have no conflicts of interest. The authors have no disclosures. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
* *Corresponding author.* 800 Fairmount Ave., Suite 215, Pasadena, CA 91105, USA.
E-mail address: giancarg@uci.edu (G.A. Garcia).
Peer review under responsibility of the Iranian Society of Ophthalmology.

http://dx.doi.org/10.1016/j.joco.2016.07.008

Please cite this article in press as: Garcia GA, et al., Clues from Crouzon: Insights into the potential role of growth factors in the pathogenesis of myelinated retinal nerve fibers, Journal of Current Ophthalmology (2016), http://dx.doi.org/10.1016/j.joco.2016.07.008

exotropia, globe subluxation, coloboma, and optic atrophy.[4] To our knowledge, MRNF have not been previously described in association with Crouzon syndrome. We examine the potential common pathogenic mechanism for both the MRNF and craniosynostosis in Crouzon syndrome, and the role of FGFR2 in the developmental control of optic nerve myelination.

MRNF are typically asymptomatic and found incidentally on ophthalmic examination. However, because they are located superficially, MRNF can obstruct the view of underlying retinal vessels. Adequate visualization of retinal vasculature in cases of MRNF is important, as the abnormal structure and thickening of the nerve fiber layer may play a role in the development of significant retinal vascular disorders.[5–8] As a secondary aim of this report, we evaluate the use of optical coherence tomography (OCT) angiography for visualization of peripapillary vessels obscured by myelination on other imaging modalities.

Case report

A 24-year-old Caucasian woman was referred to neuro-ophthalmology clinic by her general ophthalmologist for suspicion of optic neuritis in the right eye. She had become aware of a scotoma in the superonasal visual field of her right eye over the prior six months. Additionally, she reported restricted ocular motility with binocular horizontal diplopia on left lateral gaze. She denied pain with eye movement, but described mild right-sided retrobulbar pain. The scotoma disappeared and the retrobulbar pain subsided while she was on a prior 5-day course of intravenous steroids. However, these two symptoms returned after completing the course. She denied loss of color vision and any neurologic abnormalities. She had no other past ocular history.

The patient was diagnosed with Crouzon syndrome as a child by genetic testing, which revealed mutation of the *FGFR2* gene. She previously had multiple facial and nasal corrective surgeries but no prior ocular or orbital surgeries. Past medical history also included depression and anxiety, and her only medication was escitalopram. Laboratory studies, including complete blood count, erythrocyte sedimentation rate, lupus anticoagulant panel, vitamin B12, folate, aquaporin-4 antibody, rheumatoid factor, and Lyme antibody titers performed 4 months prior were within normal limits. An outside report of a gadolinium-enhanced MRI of the brain and orbits revealed no significant abnormality of the optic nerves or other orbital structures. The patient was adopted and her family history was unknown.

On examination, the patient had craniofacial structural abnormalities consistent with Crouzon syndrome. There was no proptosis of either eye. Uncorrected distance visual acuity was 20/25 in the right eye, with pinhole improvement to 20/20, and 20/20 in the left eye. Ishihara color vision testing showed correct identification of 14 out of 14 plates in both eyes. Pupils were reactive to light, with a trace afferent pupillary defect in the right eye. Intraocular pressures were 21 mmHg in both eyes. The patient demonstrated slow adduction of the right eye. 30-2 Humphrey visual field testing (HVF, Fig. 1) revealed a superonasal visual field defect with mean deviation (MD) of −4.64 dB and foveal threshold of 35 dB in the right eye. HVF testing of the left eye was normal with MD of −1.56 dB and foveal threshold of 39 dB.

Dilated funduscopic examination revealed extensive whitish peripapillary myelinated retinal nerve fibers with irregular, feathered borders in both eyes. This finding was further visualized with color and red-free fundus photography (Figs. 2 and 3). Myelinated fibers spanned roughly three-quarters of the circumference of the optic disc (9/12 clock hours) in both eyes. The inferotemporal sector of each disc was largely unaffected, and these visible disc margins appeared crisp and with normal contour. However, most portions of the peripapillary retinal vasculature and optic disc margins underlying the myelinated fibers were not readily visible. Swept-source OCT of both optic nerve heads demonstrated a substantially thickened retinal nerve fiber layer (Fig. 3). Swept-source OCT angiography (DRI OCT Triton, Topcon Corp., Tokyo, Japan) of the optic discs revealed normal blood vessel anatomy, with no tortuosity or other structural anomalies in either eye (Fig. 3). Upon review of the previous gadolinium-enhanced MRI of the orbits, enhancement of the right posterior orbit was evident involving the medial and lateral rectus muscles and posterior intraorbital optic nerve.

A diagnosis of idiopathic orbital inflammatory syndrome (IOIS) was made, in accordance with the patient's mild limitation in ocular motility and non-specific orbital inflammation on MRI. The patient's recent-onset visual field defect, while not typical of IOIS, was nonetheless determined to have occurred as a consequence of optic nerve inflammation. The bilateral extensive myelinated retinal nerve fibers were determined to be an incidental finding associated with the patient's Crouzon syndrome, though not contributory to the patient's visual symptoms.

Discussion

This case documents a new association between bilateral extensive myelinated retinal nerve fibers (MRNF) and Crouzon syndrome. The precise etiology of MRNF is not known, however the pathogenesis is believed to involve defects of the lamina cribrosa,[9–11] or the presence of intraretinal oligodendrocytes irrespective of lamina cribrosa function.[12] Most occurrences are congenital and sporadic,[2,12] though some cases show familial inheritance.[13] Rarely, MRNF may be acquired in childhood in association with optic nerve structural abnormalities that can cause changes to the lamina cribrosa, such as optic nerve gliomas or optic nerve sheath fenestration.[14] Elbaz et al have demonstrated an association between MRNF and a history of stroke, and suggest that such cases of acquired MRNF may result from stroke-related structural changes in the lamina cribrosa, or from upregulation of growth factors and production of new myelin by oligodendrocytes after an ischemic event.[15] Of note, the patient described in the present case had no history of cerebrovascular disease.

Myelination of the central nervous system (CNS) during development is highly regulated. Proper proliferation,

Please cite this article in press as: Garcia GA, et al., Clues from Crouzon: Insights into the potential role of growth factors in the pathogenesis of myelinated retinal nerve fibers, Journal of Current Ophthalmology (2016), http://dx.doi.org/10.1016/j.joco.2016.07.008