Clinical Case Reports

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CASE REPORT

Severe open angle glaucoma in hereditary hemorrhagic telangiectasia

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Funding Information
This work was supported by the National Eye Institute Grant EY020894 (RWK), Unrestricted Grant from Research to Prevent Blindness (Vanderbilt Eye Institute) and the Vanderbilt Vision Research Center (P30EY008126).

Received: 28 April 2015; Accepted: 24 May 2015

Clinical Case Reports **2015; 3(9): 725–727**

doi: 10.1002/ccr3.324

Key clinical message

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease. Conjunctival telangiectasias and retinal vascular malformations are known ocular manifestations. We report here the first case of open angle glaucoma in a patient with HHT caused by a nonsense mutation, C471X in the ACVRL1 gene.

Keywords

glaucoma, hereditary hemorrhagic telangiectasia, transforming growth factor beta.

Introduction

Primary open angle glaucoma (POAG) is a leading cause of irreversible blindness world-wide [1]. Major risk factors for POAG include positive family history, thin central cornea, elevated intraocular pressure (IOP), and older age.

Case Report

We report here a 52-year-old white male who presented with complaint of gradual decreased vision, especially in his left eye. He was found to have elevated IOP, in the mid-30 s mmHg. His vision with moderate myopic correction was 20/40 in his right eye and 20/200 in his left eye. His central corneal thickness in each eye was normal. Slit lamp examination was unremarkable, notably with no conjunctival telangiectasia detected (Fig. 1A). Gonioscopy examination revealed normal wide open iridocorneal angles. Dilated fundus examination showed advanced cupping in both eyes, but no evidence of retinal vascular abnormality (Fig. 1B). Spectral domain optical coherence tomography (SD-OCT, Cirrus, Carl Zeiss Meditec, Dublin, CA) revealed pronounced thinning of the retinal nerve fiber layer (Fig. 1C). Humphery visual field testing (Carl Zeiss Meditec) showed advanced depression in each eye (Fig. 1D). Based on the above findings, the patient was diagnosed with severe POAG.

Due to excessive recurrent epistaxis, the patient was suspected to be affected by hereditary hemorrhagic telangiectasia (HHT), also referred as Osler-Weber-Rendu disease [2]. Multiple telangiectasias were apparent upon endoscopic examination of the nose performed by an otolaryngologist. Genetic testing revealed the patient to be heterozygous for a single-nucleotide substitution in the coding sequence of *ACVRL1*, c.1413C>A, resulting in a premature stop codon (C471X) in exon 10 (Fig. 1E). The C471X mutation in *ACVRL1* was previously identified as causative for HHT [3]. *ACVRL1* (OMIM 601284) encodes the activin-like receptor kinase-1 (also known as ALK1), which is a transmembrane receptor for transforming growth factor beta (TGFβ) superfamily ligands.

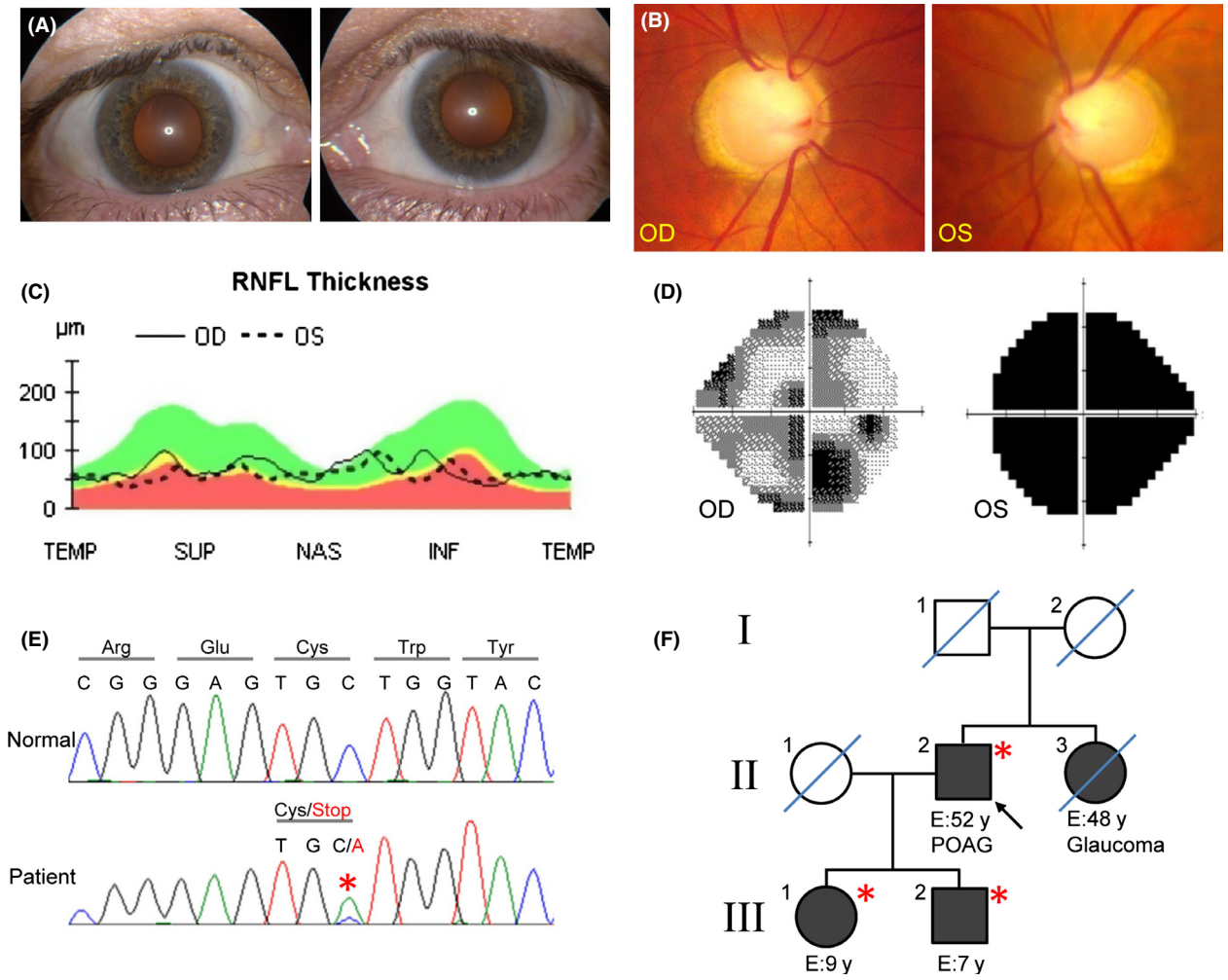

Figure 1. Severe POAG in an HHT patient carrying a mutation in *ACVRL1*, without ocular vascular malformation. Examination of the patient's eyes showed no evidence of conjunctival telangiectasia (A). Advanced cupping of the optic disk with normal retinal vasculature was apparent on dilated fundus examination (B). Severe thinning of the retinal nerve fiber layer was found by SD-OCT (C). Advanced visual field loss was apparent by Humphery visual field testing, with complete loss in the left eye (D). DNA sequencing of exon 10 of the *ACVRL1* gene revealed the patient to carry a heterozygous C to A substitution (red asterisk, E) at position 1413 of the *ACVRL1* coding sequence (c.1413C>A), which changes codon 471 from encoding cysteine (Cys) to encoding a premature stop codon (C471X). The c.1413C>A allele (red asterisks, F) found in the proband (II-2, arrow) was found in both of his children (III-1 and III-2). The proband was examined at 52 years of age and diagnosed with severe POAG (F). The sister of the proband (II-3) was affected by HHT and diagnosed with glaucoma at approximately 48 years of age (F). The children of the proband were examined at 9 and 7 years of age, respectively, and found to have no indications of glaucoma (F). OD, right eye; OS, left eye, red asterisks, confirmed c.1413C>A substitution in *ACVRL1*; filled symbols, known affected by HHT; squares, male, circles, female; E, examined; arrow, proband; blue diagonal lines, DNA samples not available.

Based on the Curacao criteria for HHT diagnosis, the patient was formally diagnosed with type II HHT (HHT2, OMIM 600376). His two children, aged 9 and 7 years, also have recurrent epistaxis. Genetic testing revealed that both children are heterozygous for the C471X mutation in *ACVRL1*. Complete eye examination of the children showed no evidence of elevated IOP or glaucomatous optic nerve damage. The patient's younger sister was also diagnosed with HHT and glaucoma at 48 years of age (Fig. 1F), although no detailed history was available.

Discussion

Two previous studies specifically investigated ocular abnormalities in HHT patients. In one report [4], 47

HHT patients aged 20–90 years were examined, with 20 cases found to have conjunctival telangiectasia and one case with retinal vascular abnormality. Another study [5] examined 20 HHT patients aged 11–68 years and found seven with conjunctival telangiectasia and two with retinal vascular malformations. Glaucoma was not reported in either study. To our knowledge, the case presented here is the first report of glaucoma in a patient with HHT.

HHT is an autosomal dominant disease caused by mutations in genes involved in TGFβ superfamily signaling [2]. Since TGFβ superfamily signaling is disrupted in HHT, it is intriguing to consider that elevated TGFβ likely plays an important role in glaucoma pathogenesis [6], suggesting a possible mechanistic linkage between HHT and glaucoma. Diagnosis of HHT and glaucoma in the patient's sister also suggests possible linkage of the conditions. As POAG is an age-related disease, the patient's young children should be monitored closely. Development of POAG in the patient's HHT-affected children would further support an association between POAG and HHT.

Based on this report, healthcare providers of HHT patients should be aware of possible development of POAG with advancing age. Surgical intervention is often needed to reduce the progression of glaucoma, especially in patients with advanced glaucoma. Caution must be taken should glaucoma surgery be required, since intraoperative choroidal hemorrhage in patients with HHT has been reported [7].

Acknowledgments

This work was supported by the National Eye Institute Grant EY020894 (RWK), Unrestricted Grant from Research to Prevent Blindness (Vanderbilt Eye Institute) and the Vanderbilt Vision Research Center (P30EY008126).

Conflict of interest

None of the authors have potential conflicts of interest related to this work.

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