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Diagnostic and Therapeutic Challenges

Edited by H. Richard McDonald

Drs. Kalpana Badami, Aliya Sultana, Babi Sinha, Raghavendra Ijeri, Chaitra Jayadev, and Stephen H. Tsang

This case is submitted by Drs. Kalpana Badami, Aliya Sultana, Babi Sinha, Raghavendra Ijeri, and Chaitra Jayadev from the Minto Ophthalmic Hospital, Bangalore, India; commented by Dr. Stephen H. Tsang, New York, New York.

Case Report

A 16-year-old female patient presented to our tertiary referral hospital with a 4-day history of sudden onset, painless decrease of vision in the right eye. She had a history of night blindness since childhood. Her family history was significant with night blindness in her maternal grandfather too. There was no antecedent history of trauma or inflammatory signs in the eye.

On presentation, her corrected distance visual acuity was perception of hand movements in the right eye and 20/120 in the left eye. She had horizontal nystagmus, and the rest of anterior segment examination was unremarkable. Posterior segment examination revealed inflammation in the vitreous with +1 cells in both eyes.

Fundus examination revealed fresh dense vitreous hemorrhage in the right eye and a hyperemic disc, normal arterioles, venous engorgement, with telangiectatic vessels in the macula, and few blot hemorrhages in the left eye (Figure 1A). The equatorial retina showed ill-defined irregular multiple confluent hypopigmented lesions interspersed with scattered pigmented scars in the periphery. There was no evidence of any bony spicules, vascular inflammation, or peripheral retinal telangiectasias.

B-scan ultrasonography of the right eye showed plenty of dot-like echoes with few clumps in the vitreous suggestive of vitreous hemorrhage with the absence of posterior vitreous detachment. The retina and choroid appeared normal. Fundus fluorescein angiogram at the time of initial presentation showed hyperfluorescence in the early phase corresponding to the telangiectatic vessels with leakage in the mid and late phases in the left eye. Minimal disc hyperfluorescence was noted in the late phase. There was no evidence of any capillary nonperfusion areas or any peripheral vascular abnormality (Figure 1B).

Optical coherence tomography of the left eye showed an altered foveal contour with intraretinal cystic spaces (Figure 2) with a normal vitreoretinal interface. An electroretinogram (ERG) showed an extinguished scotopic response and a subnormal photopic response in both eyes (Figure 3, A and B). Visual fields showed generalized depression in both eyes (Figure 4, A and B). The patient underwent all the baseline hematological and ocular investigations. Complete hemogram, coagulation profile, and peripheral smear were within normal limits. Serum homocysteine levels were normal, and sickling test was negative.

The patient was advised bed rest and was followed up at regular intervals. There was an improvement in corrected distance visual acuity with resolution of vitreous hemorrhage in the right eye (Figure 5). The left eye was stable. At the end of 4 months, vitreous hemorrhage in the right eye cleared significantly and the fundus revealed a similar picture to that of the left eye with organized vitreous hemorrhage inferiorly (Figure 6). The corrected distance visual acuity in the right eye was 20/120 and left eye was 20/60. The patient underwent a repeat fundus fluorescein angiogram, optical coherence tomography, ERG, and visual field evaluation.

A provisional diagnosis of atypical retinitis pigmentosa (RP) with macular telangiectasia was made. The patient received an intravitreal injection of bevacizumab (0.05 mL/1.25 mg) in the right eye. Partial regression of the lesion was noted within 1 week and complete regression of macular telangiectasia by 4 weeks (Figure 7, A and B). Because the results were encouraging, intravitreal injection of bevacizumab was given in the left eye, which too showed regression of the telangiectasia with a single dose. No recurrence of telangiectasia was noted in either eye at the end of a 3-month follow-up.

Dr. Stephen H. Tsang (New York, New York):

Dr. Badami presents an interesting case of a 16-year-old girl who presented with a sudden decrease of vision in the right eye. She has a history of childhood night blindness and a maternal history of night blindness as well. On initial examination, her corrected distance visual acuity was hand movements in the right eye and 20/120 in the left eye. Nystagmus was observed, but it should be clarified whether it was acquired or congenital.

Telangiectatic vessels in the macula were observed, along with vitreous inflammation and vascular abnormalities. Optical coherence tomography showed the presence of intraretinal cysts, and ERG revealed undetectable rod-specific responses and diminished photopic responses in both eyes. B-scan ultrasonography suggested the presence of vitreous hemorrhage. A diagnosis

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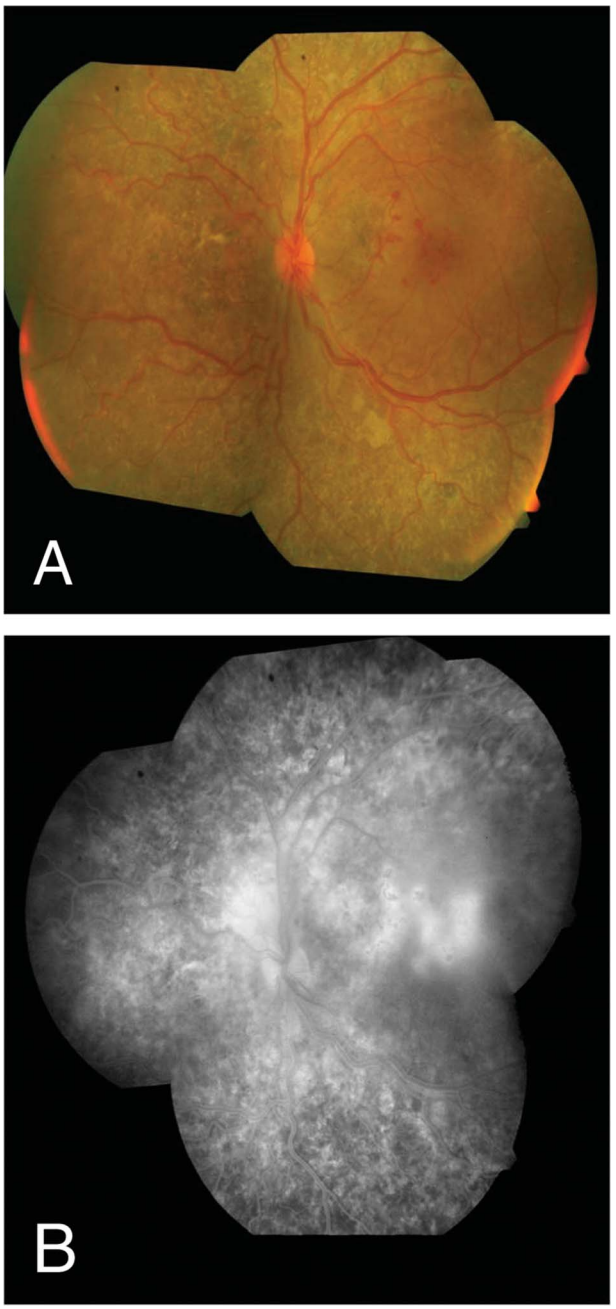

Fig. 1. A. Fundus picture of the left eye showing macular telangiectasia. **B.** Fundus fluorescence angiography showing diffuse leakage at the macula in the mid and late phases.

of atypical RP with macular telangiectasia was made, and intravitreal injections of bevacizumab resulted in complete regression of telangiectasia in both eyes after a single dose.

Although there seem to be many factors that make this case a dilemma, the ERG findings in Figure 3, A and B are pathognomonic for enhanced S-cone syndrome (ESCS), which is sometimes labeled as atypical RP. The telltale signs are: 1) the rod-specific ERG is extinguished, 2) the maximal ERG is simplified and delayed, with equally delayed photopic and scotopic waveforms, and 3) the 30-Hz flicker amplitude is lower than that of the transient photopic a-wave. Because of the characteristic ERG findings that are not found in any other disease, the differential is limited. Unusual vasculature has also been observed as a new clinical feature in some cases of ESCS.[1] The electrophysiological responses establish the diagnosis and lead to the next step of DNA testing to sequence the candidate gene *NR2E3* for disease-causing mutations.[1–3] This will be essential for the prognosis and genetic counseling of the patient.

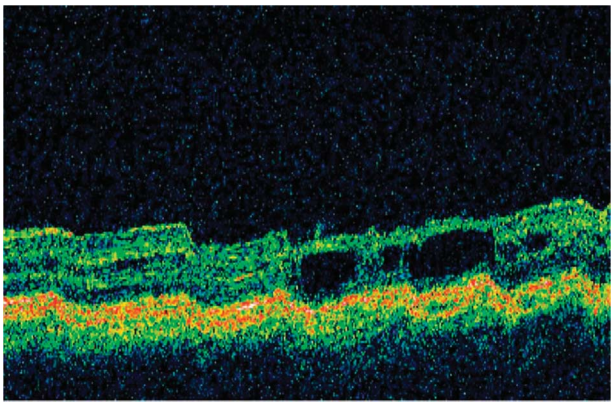

Fig. 2. Left eye optical coherence tomography showing intraretinal cystic spaces.

Although the author does not mention ESCS, the findings are potentially highly significant because of the discovery of a potential treatment, anti-vascular endothelial growth factors, for ESCS. This can be strengthened if the author can demonstrate improvements in the ERG, optical coherence tomography, and angiograms of the patient after treatment with bevacizumab. It would also be helpful if the author can provide information on whether the patient is myopic or hyperopic because patients with RP tend to be myopic and patients with ESCS hyperopic. The author's intriguing finding suggests that because the cones have a higher oxygen demand than the rods and this patient is lacking in rods, the intraretinal cysts may develop as a result of ischemic drive. Previously, carbonic anhydrase inhibitors have been used in unsuccessful attempts to treat these cysts, but because of the author's forward thinking, the standard of care for ESCS is potentially changed and randomized clinical trials are certainly merited.

The finding that anti-vascular endothelial growth factors can treat ESCS is made even more significant because of the research of Professor Joseph C. Corbo (Washington University) on reprogramming rods into cones and thereby converting RP patients into ESCS

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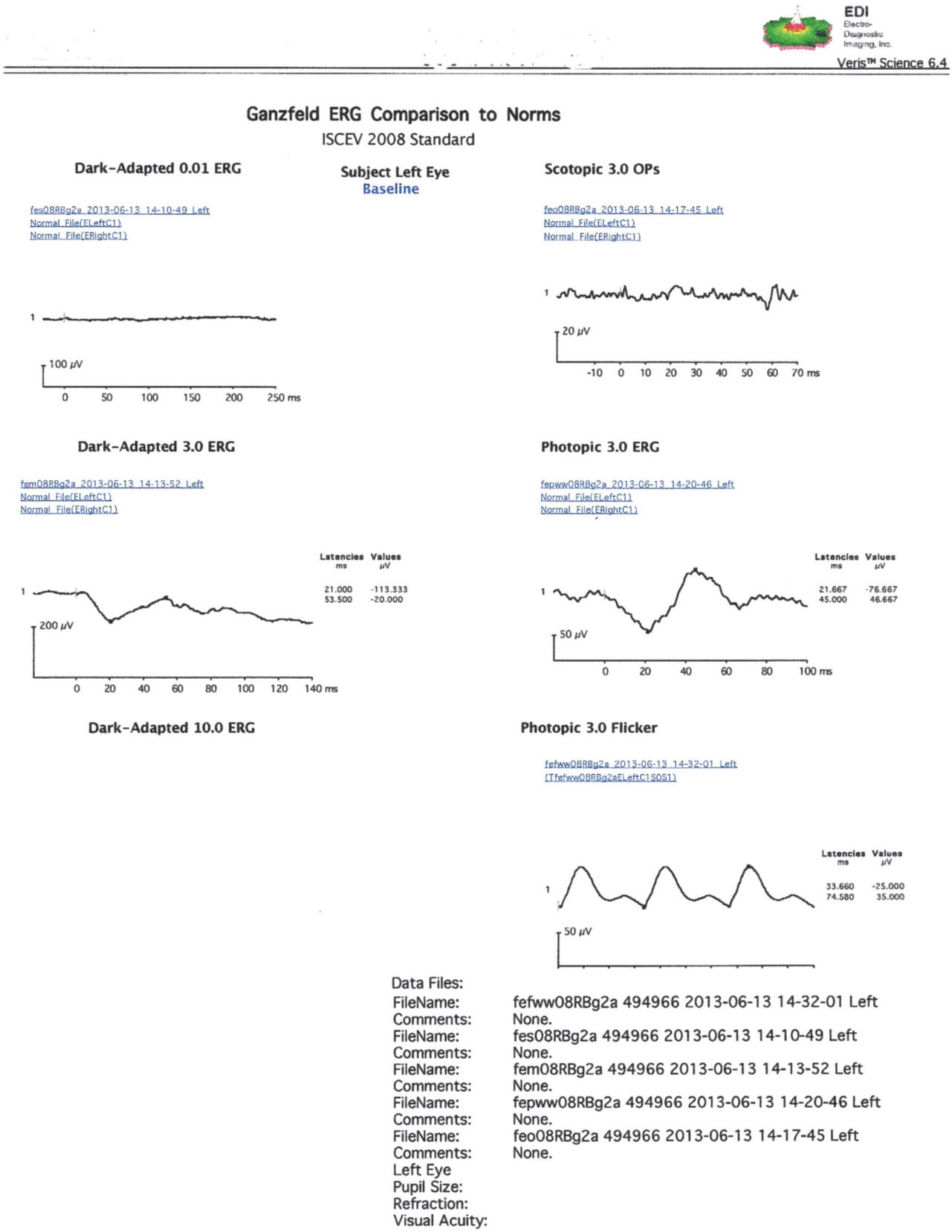

Fig. 3. Electroretinogram showing an extinguished scotopic response and a subnormal photopic response in the left eye.

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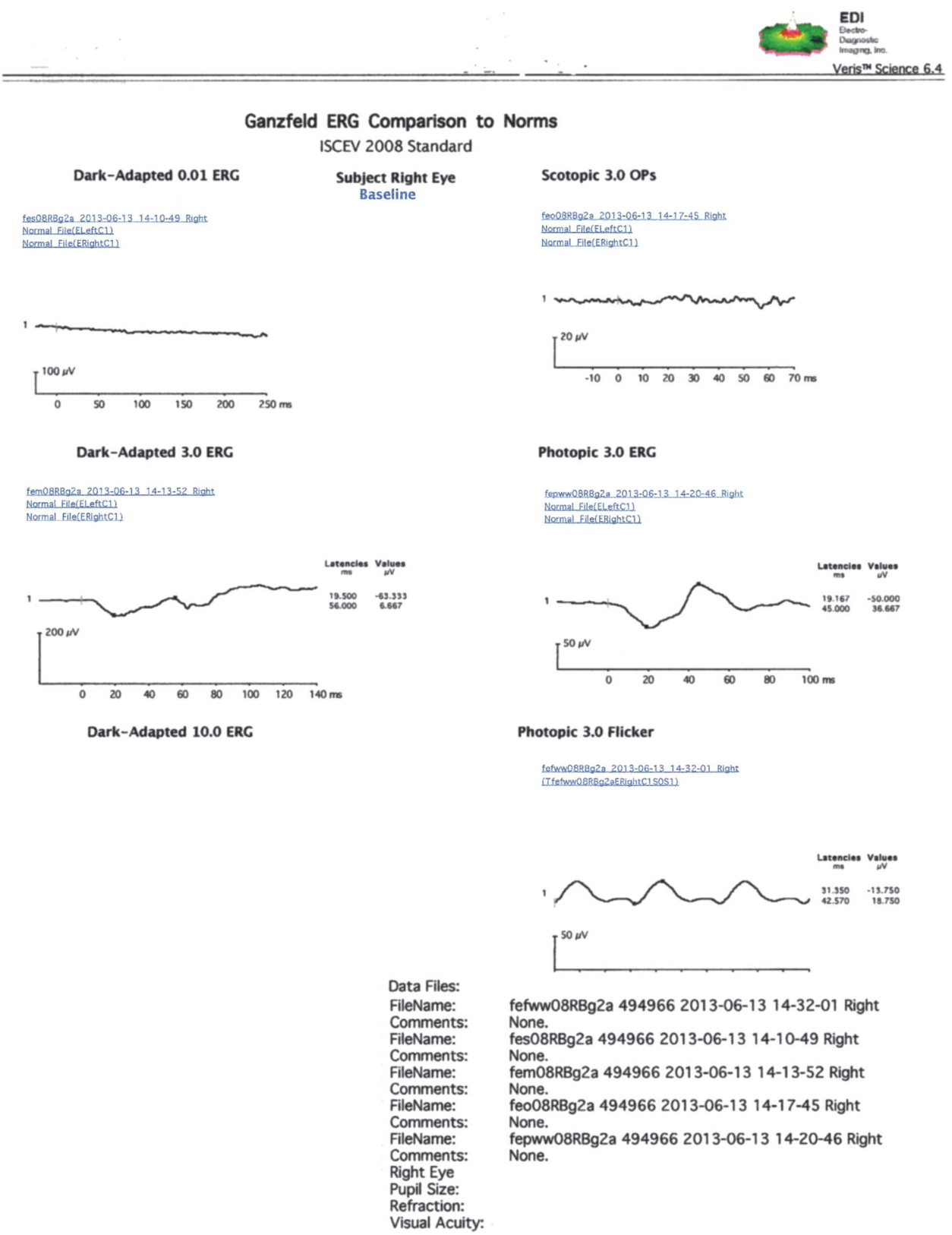

Fig. 3. Electroretinogram showing an extinguished scotopic response and a subnormal photopic response in the right eye.

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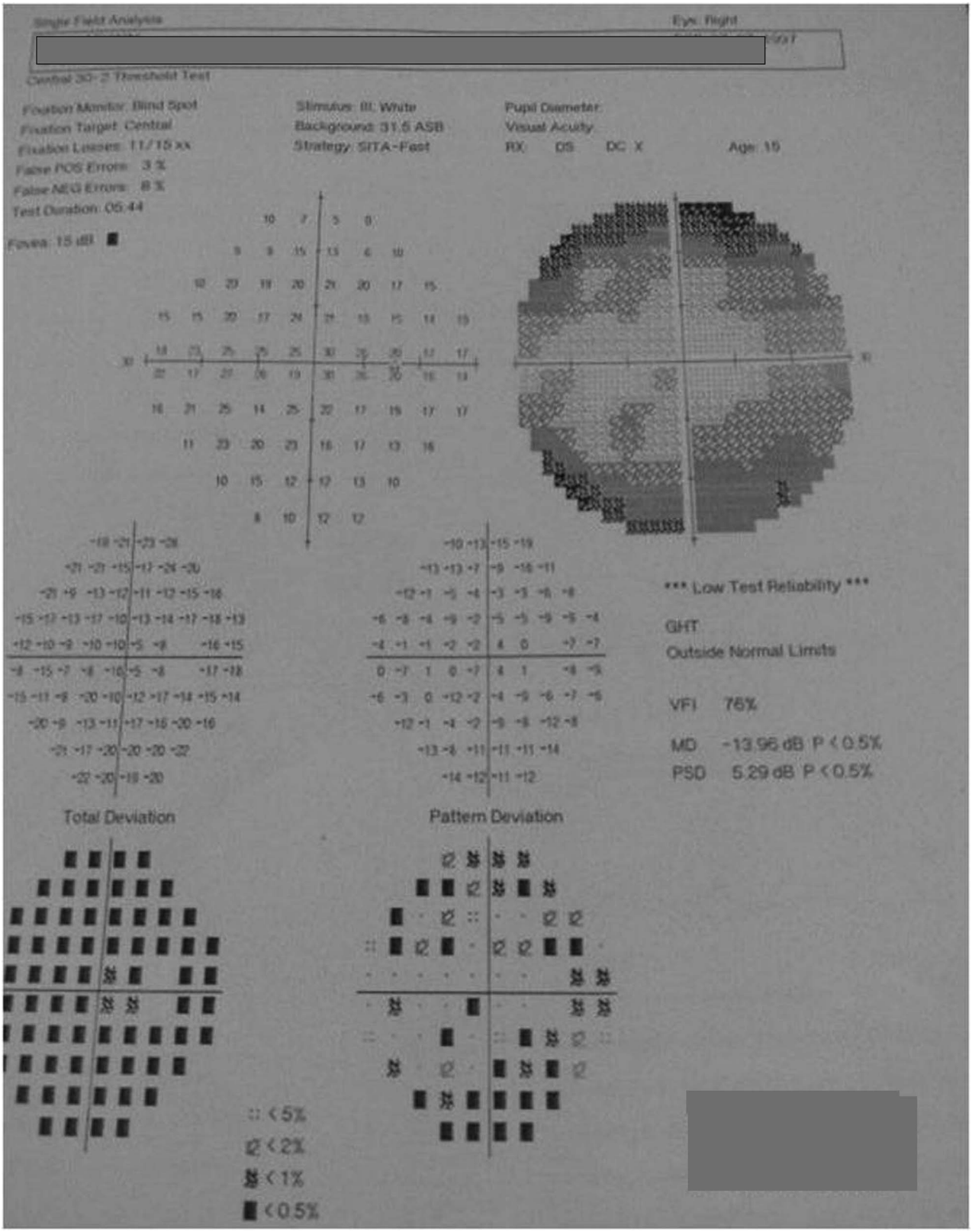

Fig. 4. Visual fields showing generalized depression in the right eye.

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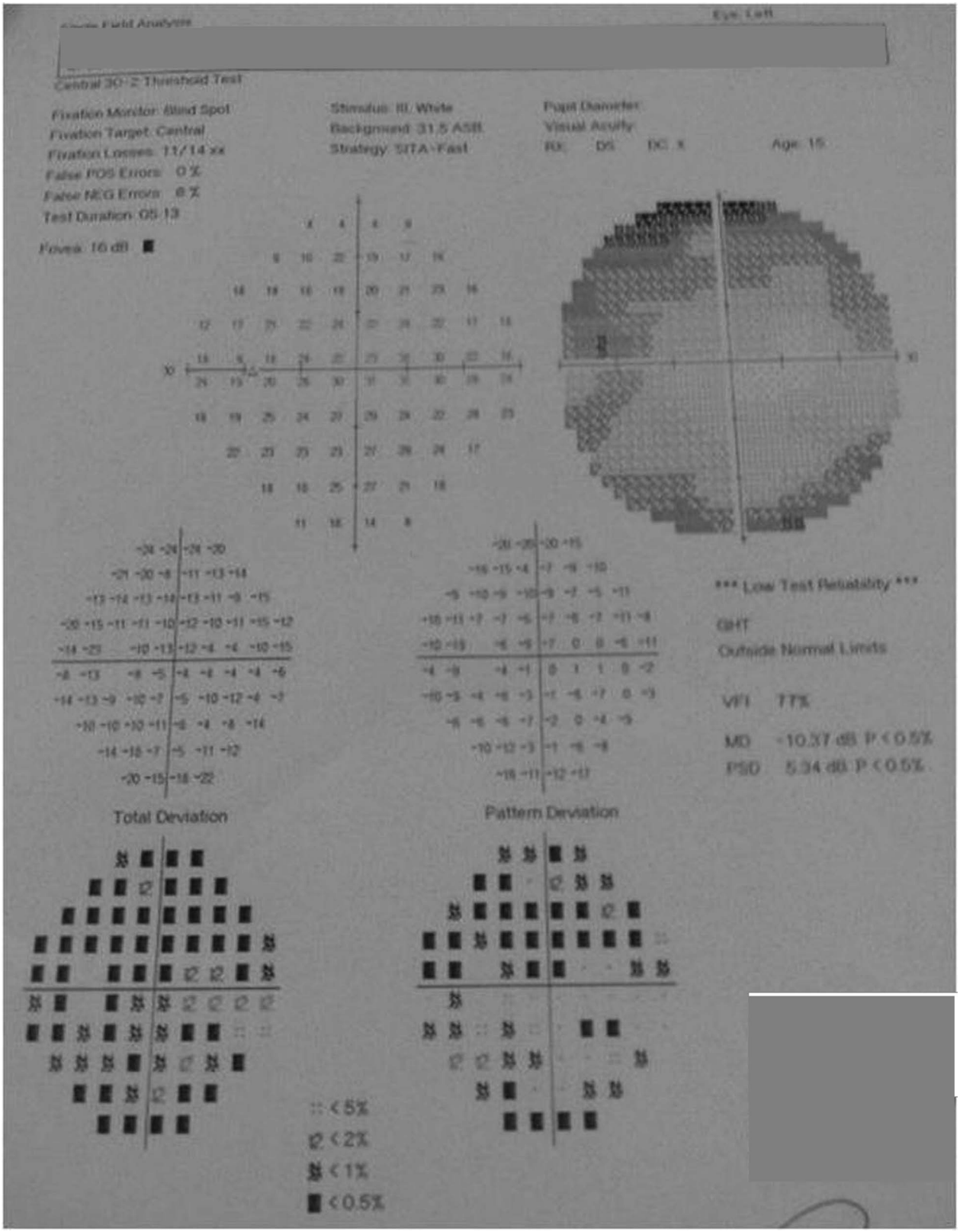

Fig. 4. Visual fields showing generalized depression in the left eye.

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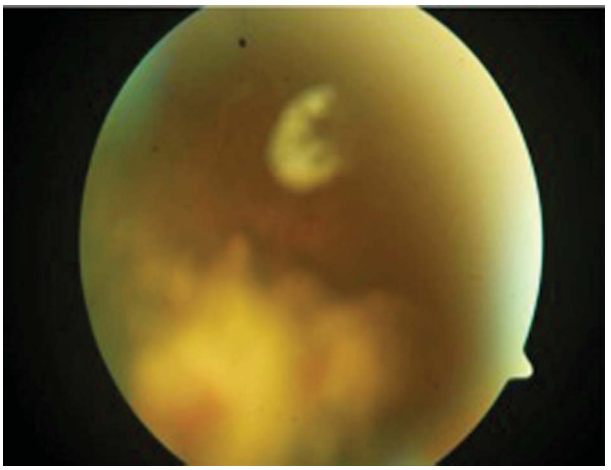

Fig. 5. Right eye fundus picture showing an organized vitreous hemorrhage.

patients as a treatment option for RP.[4] Although many ophthalmologists prefer to lump ESCS together with RP, the two diseases have different time courses, with the former progressing much slower than the latter; this is the rationale behind the Washington University team's efforts to convert RP into ESCS using gene therapy. Thus, if anti-vascular endothelial growth factors can truly be used to improve macular edema in patients with ESCS, it may have great implications for patients with RP reprogrammed to become ESCS patients as well.

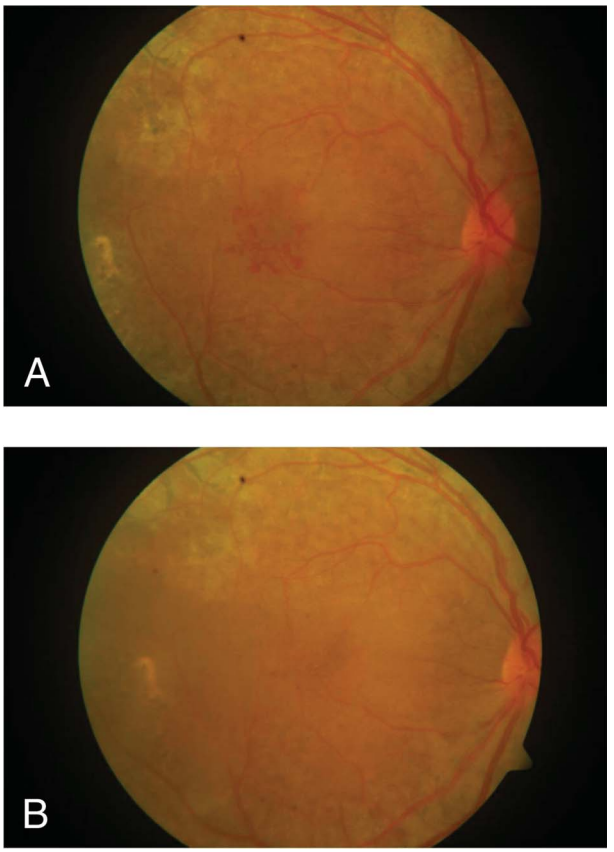

Fig. 7. Fundus picture of the right eye (**A**) showing regression of lesion, 4 weeks after intravitreal bevacizumab (**B**).

Dr. Veronika Vaclavik (Lausanne, Switzerland):

In this case, we are presented with a 16-year-old female with an acute episode of vitreous hemorrhage and painless vision loss in her right eye. She has history of night blindness, which was also mentioned in her maternal grandfather. She had horizontal nystagmus. There was no significant high error of refraction and no associated systemic abnormalities. The fundus of both eyes was remarkable with hyperpigmented dots at the level of the retinal pigment epithelium and confluent hypopigmented lesions and telangiectasia at the macula. The ERGs were in keeping with generalized photoreceptor dysfunction, predominantly rods. Optical coherence tomography revealed intraretinal cystic spaces.

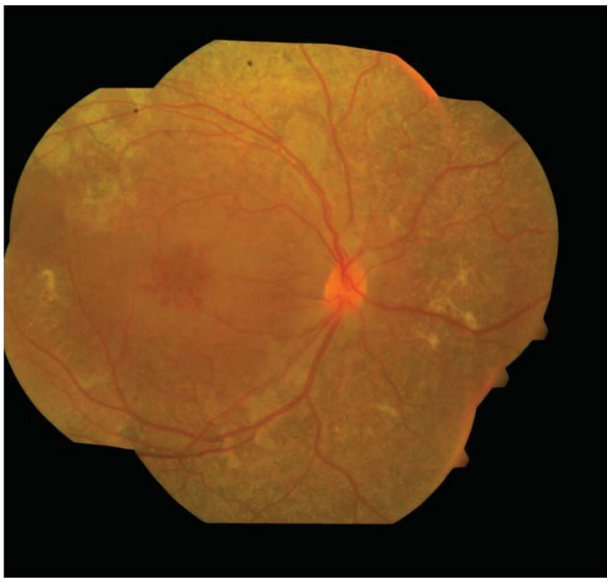

Fig. 6. Right eye fundus picture showing macular telangiectasia (similar to the left eye).

The differential diagnosis for this patient is a progressive retinal dystrophy with associated retinal telangiectasia or a chronic inflammation with vascular abnormalities. The presence of night blindness and extinguished scotopic ERGs indicate a predominantly rod photoreceptor dysfunction, which is longstanding as suggested by the nystagmus. The reduced visual acuity is explained by intraretinal cystic spaces. The absence of delay of 30-Hz flicker implicit time on ERG testing and a positive family history of nightlines indicates that a diffuse chronic inflammatory disease is unlikely. A retinal dystrophy type rod-cone

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with retinal telangiectasia is part of a spectrum of CRB1-associated phenotypes. Mutations in the *CRB1* gene have been associated with a variety of generalized retinal dystrophy ranging from RP to Leber congenital amaurosis. Retinitis pigmentosa due to CRB1 mutation presents with early onset, nystagmus, optic nerve head drusen, and nummular pigment deposits and thickened retina. Most reported cases are of autosomal recessive transmission, except one which is autosomal dominant. Vitreous hemorrhages have been reported in isolated cases of RP. In this case, we presume that the patient's grandfather has the same genetic disorder; therefore, a dominant mode of inheritance with variable expressivity of incomplete penetrance is probable, indicating a possible *PRPF8* or *PRPF31* gene involvement. My clinical diagnosis is that of an atypical retinal dystrophy with retinal telangiectasia possibly due to CRB1 mutation (alternatively a *PRP8/PRPF31* gene mutation). Mutation analysis of this gene will confirm the clinical diagnosis.

Editor's Note:

Drs. Badami, Sultana, Sinha, Ijeri, and Jayadev present a 16-year-old girl with unilateral decreased vision and a history of longstanding night blindness. A diagnosis of atypical RP with macular telangiectasis was made.

Dr. Stephen Tsang and Dr. Veronika Vaclavik have consulted on this case. Dr. Tsang notes telangiectatic vessels in the left eye, intraretinal cysts, and undetected rod-specific responses and diminished photopic responses on ERG testing. He calls our attention to the ERG findings in Figure 3, A and B. The ERG reveals classic findings for ESCS.

1. The rod-specific ERG is extinguished.
2. The maximal ERG is delayed equally in photopic and scotopic waveforms.
3. The 30-Hz flicker amplitude is lower than that of the transient photopic a-wave.

He also notes that unusual vessels are present in some eyes with ESCS and recommends DNA testing to sequence the gene *NE2E3*. Dr. Tsang credits the presenters with the observation that the telangiectatic vessels responded dramatically to anti-vascular endothelial growth factor medication. If ESCS can be tested, he states, the recent work on reprogramming rods and cones takes on even greater importance.

Dr. Vaclavik believes that the differential diagnosis includes progressive retinal dystrophy with associated retinal telangiectasis or a chronic inflammatory condition with vascular abnormalities. She focuses on the spectrum of CRB1-associated phenotypes and concludes that the patient has an atypical retinal dystrophy with retinal telangiectasias due to CRB1 mutation (alternatively a PRP8/PRPF31 gene mutation). Dr. Vaclavik believes that, in all likelihood, the patient's grandfather had the same genetic disorder, indicating a dominant mode of inheritance with variable expressivity of incomplete penetrance. She calls for mutation analysis to confirm the clinical diagnosis.

We thank Drs. Badami and co-workers for their case, and Dr. Stephen Tsang and Dr. Veronika Vaclavik for their consultation.

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