Incidence and Natural History of Retinochoroidal Neovascularization in Enhanced S-Cone Syndrome

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• OBJECTIVE: We examined the incidence and natural history of macular retinochoroidal neovascularization (RCN) in enhanced S-cone syndrome (ESCS).
• DESIGN: Retrospective case series.
• METHODS: This single-center study included 14 of 93 patients with ESCS who had signs of active or inactive RCN in ≥1 eye. We conducted multimodal retinal imaging, full-field electroretinography, and molecular genetic analysis of *NR2E3* gene. Our main outcome measures included the cumulative incidence of RCN in ESCS, type of RCN, and mode of evolution of RCN.
• RESULTS: Fourteen (15.1%) of 93 patients with ESCS had RCN in ≥1 eye at 2 to 27 years of age. All 22 RCNs (21 eyes of 14 patients) were macular. Twelve of the RCNs were active with exudates/hemorrhages. Of these, 5 appeared de novo in a subretinal location, with photographic evidence of no pre-existing lesions. The latter were compatible with type 3 neovascularization or retinal angiomatous proliferation and subsequently evolved into unifocal fibrotic nodules. The remaining active lesions all had some degree of pre-existing fibrosis and remained stable. Ten inactive fibrotic nodules, identical to end-stage de novo lesions, were found and were presumed to represent healed RCNs.
• CONCLUSIONS: RCN, a treatable condition, may occur as early as 2 years of age and may be much more common in patients with ESCS than previously estimated. It may be the primary cause of the unifocal submacular fibrosis that is commonly observed in this condition. Additional research is needed to establish the pathogenesis of RCN in patients with ESCS and its optimal management. (Am J Ophthalmol 2021;222:174–184.

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ENHANCED S-CONE SYNDROME (ESCS; OMIM# 268100) IS an autosomal recessive retinal dystrophy characterized by night blindness, hyperopia, nummular pigmented lesions around the vascular arcades, macular schisis with or without subretinal fibrosis, and a pathognomonic electroretinogram (ERG) including a supernormal photopic short wavelength (blue light) response, a nonrecordable rod response, a widened and delayed rod–cone response that is similar to the single flash cone response, and a severely reduced 30-Hz flicker amplitude that is lower than that of the single flash cone a-wave.[1–3] Histology from a single patient has shown an absence of rods and an increased number of cones, a majority of which were similar to S-cones, which are sensitive to blue light.[3] ESCS is caused by mutations in *NR2E3*, which has limited expression to the retinal outer nuclear layer. It encodes the nuclear receptor class 2, subfamily E, member 3 protein (NR2E3; OMIM# 604485) which is a transcription factor involved in photoreceptor differentiation and signaling. Mutations in *NR2E3* lead to a dedifferentiation of the photoreceptors toward S-cones rather than rods or L- or M-cones.[1–3]

ESCS is associated with various patterns of macular subretinal fibrosis.[4,5] Helicoidal fibrosis was first reported by members of our institution,[4] and other patterns were described in more detail by one of the authors (Nowilaty SR et al. Subretinal Fibrosis: A Potential Phenotypic Feature of Goldmann-Favre/Enhanced S-Cone Syndrome. PO506, 2010 Annual Meeting of the American Academy of Ophthalmology), leading us and others to suggest subretinal fibrosis as a diagnostic marker to direct *NR2E3* genetic testing.[4,5] Yet the cause of such fibrotic changes in ESCS has not been conclusively established. On the other hand, retinochoroidal neovascularization (RCN) has been described in single cases with ESCS.[6–10] However, to the best of our knowledge, the incidence and natural history of such neovascularization in ESCS have not been determined, nor have there been any attempts in the published literature to explore whether a causal relation exists between RCN and the development of subretinal fibrosis. We speculate that RCN in ESCS could either be

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TABLE 1. Baseline Characteristics of 14 Patients with Enhanced S-Cone Syndrome with Signs of Retinochoroidal Neovascularization

Baseline Characteristic	Value
Patients with ESCS, *n* (eyes)	93 (186)[a]
Patients with findings compatible with RCN, *n* (eyes)	14 (21)[b]
Median age of patients at time of diagnosis with RCN, years (IQR [range])	15 (7 [2–27])
Median follow-up time after diagnosis of RCN, years (IQR [range])	2 (4 [1–12])
Ratio of male to female patients with RCN	7:7
Patients with RCN who had pathognomonic ERG for ESCS,[c] *n/N*	11/14[d]
Patients with RCN who had homozygous mutations in *NR2E3*, *n/N*	10/14[e]
Patients with RCN in whom the ESCS diagnosis was based only on characteristic fundus features and family history of ESCS,[f] *n/N*	2/14
RCN lesions in 21 eyes with RCN, *n*	22
RCN lesions confirmed with FFA (OCT), *n* (*N*)	11 (16)
RCN lesions involving the central macula, *n*	19

ERG = electroretinography; FFA = fundus fluorescein angiography; IQR = interquartile range; OCT = optical coherence tomography; RCN = retinochoroidal neovascularization.

[a]Total of 93 patients with ESCS, who all had night blindness and characteristic fundus features, were diagnosed as follows: 1) pathognomonic ERG and biallelic mutations in *NR2E3* ($n = 45$); 2) pathognomonic ERG alone ($n = 24$); 3) biallelic *NR2E3* mutations alone ($n = 17$); 4) night blindness and typical fundus features and a known family history of ESCS ($n = 3$); and 5) night blindness and typical fundus features ($n = 4$).

[b]Twenty-two RCN lesions were diagnosed, and 1 of the patients had 2 consecutive lesions in the left eye (Figure 3).

[c]Nonrecordable rod responses with a broadened, similarly shaped dark-adapted rod-cone and light-adapted single-flash cone responses and a severely reduced 30-Hz flicker amplitude that was smaller than the light-adapted single-flash cone a-wave. These findings were present in 11 of 14 patients (patients 1–6, 8–11, and 14). In patients 12 and 13, ERG was not performed.

[d]Another patient (patient 7, Table 2) who had the homozygous c.131C>A mutation in *NR2E3* showed a nonrecordable scotopic and photopic responses in both eyes.

[e]Details presented in Table 3.

[f]Patients 12 and 13.

a precursor of fibrosis, as is well-known in other conditions featuring neovascular lesions, such as age-related macular degeneration or certain forms of uveitis, or that RCN could occur as a consequence of subretinal fibrosis, for example through a disruption of the outer blood–retinal barrier.

The purpose of this study was to examine the incidence, presentations, features, and natural history of RCN in a large cohort of patients with ESCS.

METHODS

THIS RETROSPECTIVE COHORT STUDY WAS UNDERTAKEN at the King Khaled Eye Specialist Hospital (KKESH) in Riyadh, Saudi Arabia. Ethical approval for this study was obtained from the KKESH Institutional Review Board. The study adhered to the tenets of Declaration of Helsinki.

Consecutive patients diagnosed with ESCS at KKESH between 1993 and 2019 were retrospectively evaluated for the presence of RCN. The diagnosis of ESCS was based on characteristic fundus features and was confirmed by electrophysiology or genetic analysis in most patients.[11,12] Other than serving as a background population for the purpose of estimating the incidence of RCN in ESCS, patients with no RCN were excluded from further analysis.

For patients identified with RCN, detailed information was obtained from medical records on patients' age at first presentation, gender, age at RCN diagnosis, main presenting symptoms, laterality of RCN, best-corrected visual acuity, fundus features, and multimodal retinal imaging. The latter included intravenous fundus fluorescein angiography (FFA), cross-sectional optical coherence tomography imaging (OCT; Spectralis OCT, Heidelberg Engineering, Inc, Heidelberg, Germany), and color fundus imaging (Topcon TRC-50DX, Topcon Medical Systems, Inc, Oakland, New Jersey, USA; RetCam 3, Natus Medical, Inc, Pleasanton, California, USA; or Optos PLC, Dunfermline, UK). The presence of RCN was detected by clinical fundus examination, spectral-domain OCT (for patients presenting after the year 2000), and confirmed using FFA in 11 of the lesions (Table 1). RCNs showing any one of the following were termed active: leakage on FFA, exudates or hemorrhages on fundus photography, and corresponding subretinal hyperreflective lesion on spectral-domain OCT.

Molecular genetic testing was conducted using samples of peripheral blood that were obtained for DNA extraction from leukocytes of the affected patients. Targeted next-generation sequencing was performed using retinal dystrophy panels at the molecular genetics laboratory at King Faisal Specialist Hospital (Riyadh, Saudi Arabia)[13] or at Bioscientia (Boehringer Ingelheim, Ingelheim am Rhein,

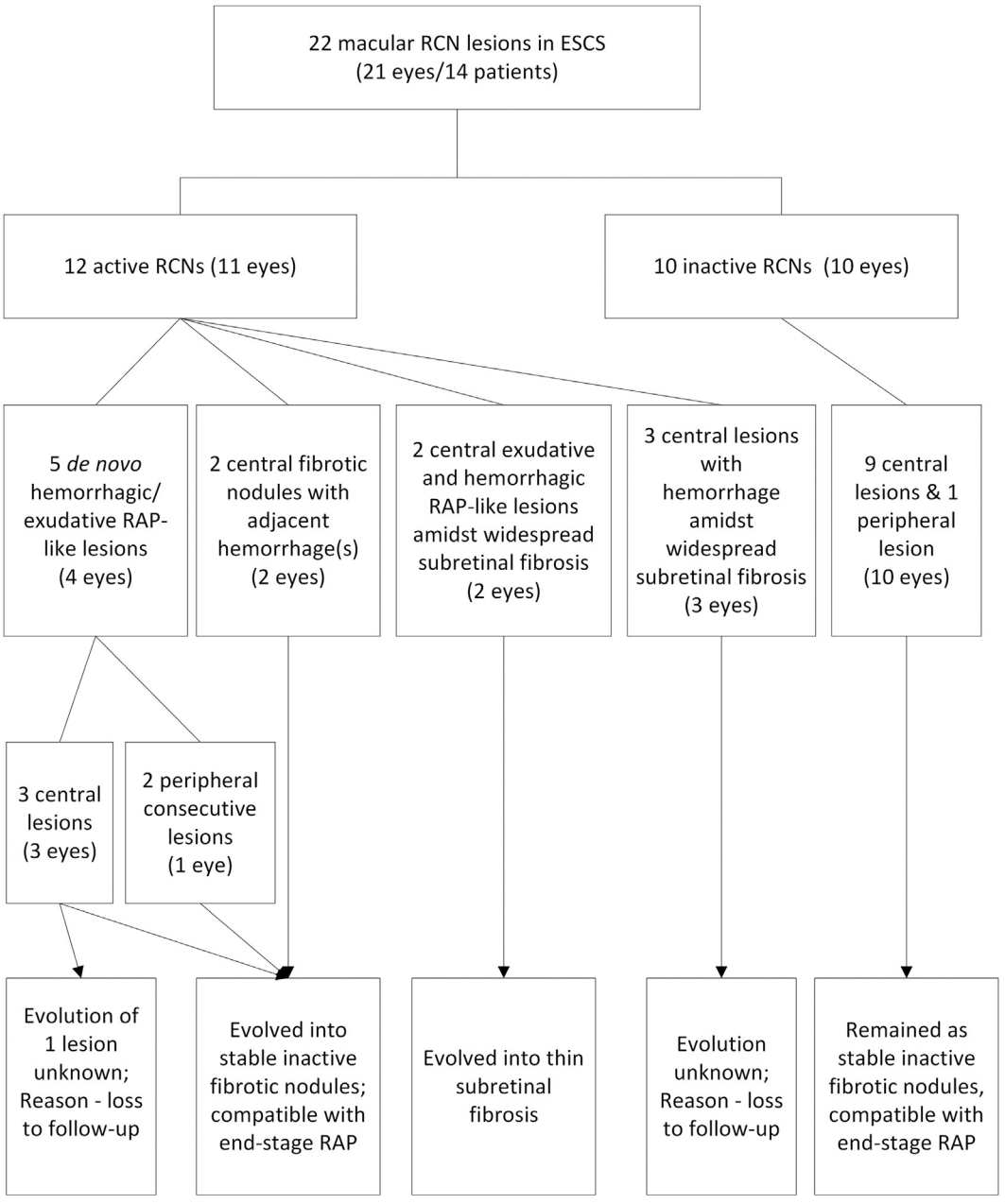

FIGURE 1. Overview of the presentation, classification, and evolution of retinochoroidal neovascularization (RCN) in 14 patients with enhanced S-cone syndrome (ESCS). RCNs showing any one of the following were termed active: leakage on fundus fluorescein angiography, exudates or hemorrhages on fundus photography, and corresponding subretinal hyperreflective lesion on spectral-domain optical coherence tomography. RAP, retinal angiomatous proliferation.

Germany; Supplemental Material Document 1). In patients with typical clinical findings, direct sequencing of *NR2E3* was performed at the molecular genetics laboratory at KKESH. Reported variants were assessed using gnomAD software (version 3; available at: https://gnomad.broadinstitute.org/).

Statistical analysis was performed using Stata software (version 16.1; Stata Corp, College Station, Texas, USA). The analysis was mainly descriptive, and no statistical testing was performed except the ϕ coefficient, which was calculated to assess the strength of association between RCN and fibrosis. Frequency and proportions were computed to describe categorical data and medians with interquartile ranges were computed to describe continuous data.

RESULTS

OF 93 PATIENTS WITH ESCS BETWEEN 1993 AND 2019, 14 (15.1%) were diagnosed with RCN in 1 or both eyes

TABLE 2. Key Findings in 14 Patients with Enhanced S-Cone Syndrome with Signs of Retinochoroidal Neovascularization[a]

Patient No.	Year at Initial Presentation, Years of Age	Age at RCN Diagnosis, Yrs (Eye), Gender	Key Findings		Length of FU from RCN Diagnosis, Yrs (Eye)	Figure
			Right Eye	Left Eye		
1	2016, 8	8 (left), 11 (right), M	Active de novo RCN compatible with RAP; lost to FU	Active de novo RCN compatible with RAP; subretinal hemorrhage was evacuated surgically[b]	3 (left) and 1 (right)	2
2	2015, 10	13 (right), M	Active de novo RCN compatible with RAP[b]	—	4	4, A–C
3	2017, 2	2 (both), F	Inactive peripheral macular fibrotic nodule compatible with end-stage RAP	Active consecutive peripheral macular de novo RCNs compatible with RAP[b]	2	3
4	1994, 24	25 (both), M	Active RCN with hemorrhage, compatible with RAP[b]	Inactive fibrotic nodule compatible with end-stage RAP	1	4, J–K
5	2019, 16	16 (both), F	Active RCN with hemorrhage and schisis[b]	Inactive fibrotic nodule compatible with end-stage RAP	1	5, A–E
6	2007, 16	16 (right), F	Inactive fibrotic nodule compatible with end-stage RAP	—	1	4, D and E
7	2009, 17	17 (left), F	—	Inactive fibrotic nodule compatible with end-stage RAP, with prominent schisis	10	5, F and G
8	2014, 14	14 (both), F	Inactive fibrotic nodule compatible with end-stage RAP	Inactive fibrotic nodule compatible with end-stage RAP	5	4, F–I
9	2014, 15	15 (left), F	—	Inactive fibrotic nodule compatible with end-stage RAP	5	—
10	2015, 23	23 (right), M	Inactive fibrotic nodule compatible with end-stage RAP	—	2	—
11	2008, 5	5 (left), M	—	Inactive fibrotic nodule compatible with end-stage RAP	5	—
12	2011, 13	13 (both), F	Active RCN with hemorrhage amidst widespread fibrosis; lost to FU after 1 year	Active RCN with hemorrhage amidst widespread fibrosis; lost to FU after 1 year	1	6, I–L
13	1995, 27	27 (right), M	Active RCN with hemorrhage amidst widespread fibrosis; lost to FU after 1 year	—	1	
14	1993, 1	15 (both), M	Active RCN with hemorrhage amidst widespread fibrosis; evolved into thin fibrosis	Active RCN with hemorrhage amidst widespread fibrosis; evolved into thin fibrosis	12	6, A–H

ESCS = enhanced S-cone syndrome; F = female; FU = follow-up; M = male; RAP = retinal angiomatous proliferation; RCN = retinochoroidal neovascularization.

[a]All RCNs were central macular except in Patient 3.

[b]Lesion evolved into unifocal fibrotic nodule compatible with end-stage RAP.

(Figure 1, Tables 1–3). The median age at diagnosis was 15 years (range 2–27 years) and the median length of follow-up after diagnosis was 2 years (range 1–12 years, Table 2). All patients were from consanguineous Saudi Arabian families. Four different homozygous mutations were identified in 10 patients (Table 3 and Supplemental Material Document 2). Two patients harbored the c.932G>A mutation, 6 had the c.119-2A>C mutation, and 1 each had the

TABLE 3. Homozygous *NR2E3* Mutations and Visual Outcome Among 14 Patients with Enhanced S-Cone Syndrome with Signs of Retinochoroidal Neovascularization

Patient No.	*NR2E3* Mutation	Eye	BCVA at Presentation	BCVA at RCN Diagnosis	BCVA at Last Follow-Up
1	c.932G>A	Right	20/20	20/300	20/300
		Left	2/200	2/200	20/80[a]
2	c.119-2A>C	Right	20/20	20/25	20/25
		Left	20/30	20/30	20/30
3	c.926G>T	Right	20/40	20/40	20/40
		Left	20/100	20/100	20/300
4	NP	Right	20/25	20/25	20/30
		Left	3/200	3/200	CF
5	c.119-2A>C	Right	20/300	20/300	20/300
		Left	20/300	20/300	20/300
6	c.119-2A>C	Right	20/300	20/300	20/300
		Left	20/50	20/50	20/50
7	c.131C>A	Right	20/300	20/300	20/300
		Left	20/300	20/300	20/300
8	c.119-2A>C	Right	20/200	20/200	20/200
		Left	20/40	20/40	20/40
9	c.119-2A>C	Right	20/30	20/30	20/40
		Left	20/30	20/30	20/80
10	NP	Right	2/200	2/200	2/200
		Left	20/100	20/100	20/100
11	c.119-2A>C	Right	20/30	20/30	20/30
		Left	20/100	20/100	20/100
12	NP	Right	20/125	20/125	20/300
		Left	20/125	20/125	20/300
13	NP	Right	20/160	20/160	20/200
		Left	20/125	20/125	20/125
14	c.932G>A	Right	F&F[b]	20/100	20/200
		Left	F&F[b]	4/200	4/200

BCVA = best-corrected visual acuity; CF = counting fingers; F&F = fixes and follows; IT = inferotemporal; NP = not performed; NR = nonrecordable.

[a]After pars plana vitrectomy for RCN and subretinal hemorrhage in the left eye. RCN developed in the right eye afterward.

[b]Patient was 1 year old at the first presentation and 15 years old at the RCN diagnosis.

c.131C>A and c.926G>T mutations. The latter (c.926G>T) was a novel missense mutation (Table 3, Supplemental Material Document 2).

All 22 RCNs (21 eyes of 14 patients) were macular (Tables 1 and 2 and Figures 1–6). All were unifocal and centrally located except in 2 eyes of the same patient (patient 3). Twelve of the RCNs were active with subretinal exudates/hemorrhages. Of these, 5 appeared de novo in a subretinal location, with photographic evidence of no pre-existing lesions (patients 1–3). Examples of such de novo lesions are shown in Figures 2–4. Each de novo lesion was compatible with type 3 neovascularization or retinal angiomatous proliferation (RAP) and was associated with ≥1 dilated retinal veins emerging from the RCN lesion and subsequently evolved into a localized unifocal fibrotic "nodule" with characteristic features, namely the presence of a pigmented spot and "dipping" retinal vessels on its surface. The remaining active lesions all had some degree of pre-existing fibrosis, and once the hemorrhages resolved the appearance of the fibrotic lesions remained stable throughout the follow-up period (Figures 4–6). Ten inactive fibrotic nodules, identical to end-stage de novo lesions, were found and were presumed to represent healed RCNs (Figures 4 and 5). There was a strong relationship between the presence of RCN and the presence or development of subretinal fibrosis ($\phi = 0.81$, $P < .001$; Supplemental Material Document 3).

In this cohort, eyes with RCN were more likely to lose vision compared with those without any known RCN. Among eyes with RCN, vision decreased in 7 eyes, improved in 1 eye, and remained the same in 13 eyes. Among eyes with no RCN, vision decreased in only 1 eye and remained the same in 6 eyes (Table 3 and Supplemental Material Document 4).

Three eyes (the right eye of patient 2 and the left eyes of patients 8 and 9) received one or more intravitreal bevacizumab injection of 1.25 mg/0.05 ml and evolved into

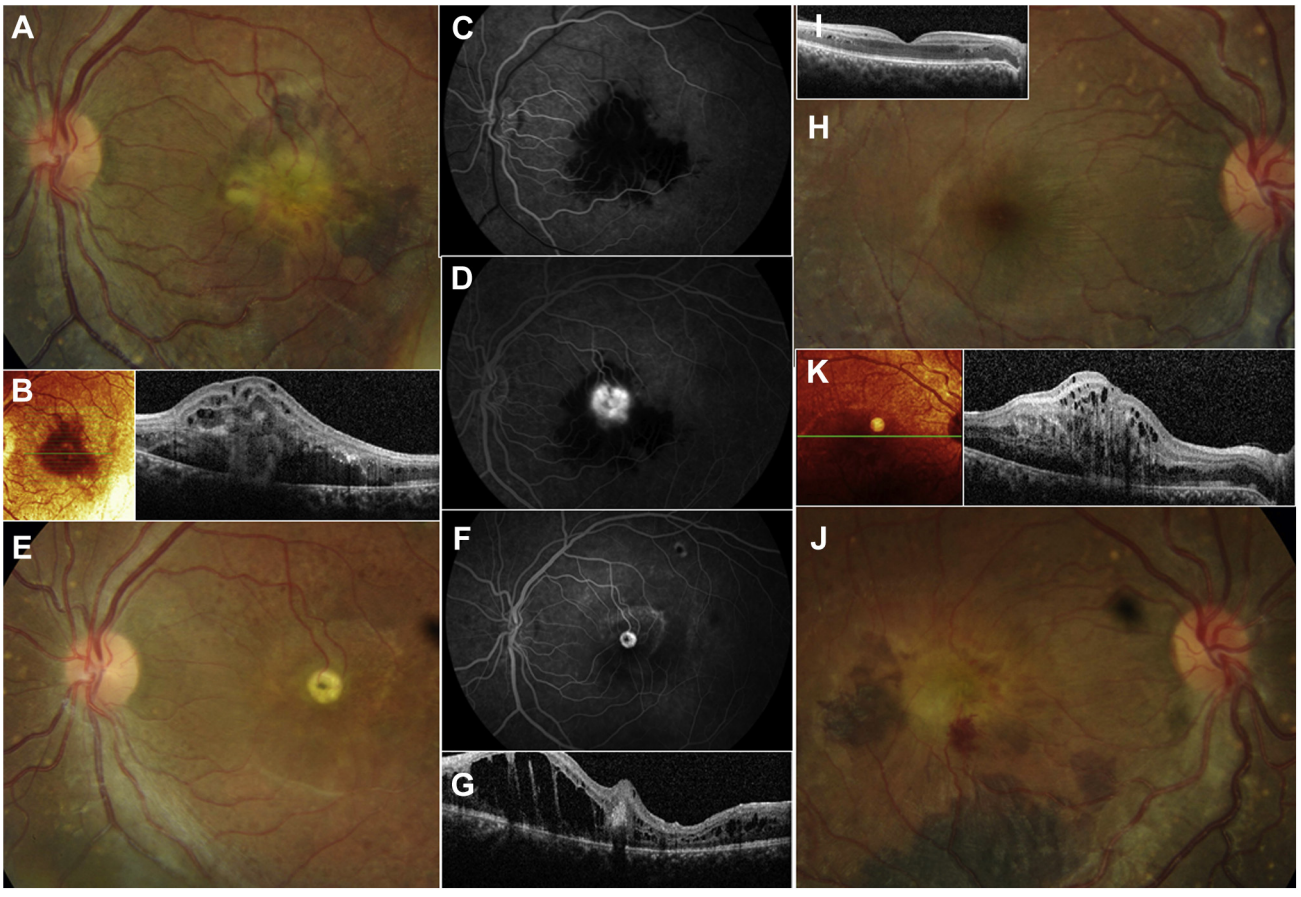

FIGURE 2. Bilateral consecutive de novo retinochoroidal neovascularization (RCN) in patient 1, an 8-year-old male with enhanced S-cone syndrome caused by a c.932G > A mutation in *NR2E3* (Table 2). A through G. Left fundus. A. Color fundus photograph shows a subfoveal RCN with subretinal hemorrhage. B. Corresponding spectral-domain optical coherence tomography (OCT) shows the RCN as a retinal angiomatous proliferation (RAP)–like lesion without retinal pigment disruption. C. The early fluorescein angiogram (FA) phase shows hypoflourescence caused by subretinal hemorrhage with, in (D) late leakage of the RCN lesion. E. One year after vitrectomy, the color photograph shows involution of the RCN into a subfoveal fibrotic nodule with tiny pigmentation and dipping retinal vessels. Note the decrease in venous congestion seen in part A. F. On FA, the fibrotic lesion exhibits staining with a hypofluorescent spot at its center corresponding to the pigment seen in part E. G. On spectral-domain OCT, the fibrotic lesion is compact and hyperreflective with adjacent macular schisis. H through K. Right fundus. H. Color photograph and (I) macular spectral-domain OCT at presentation show discrete macular schisis but no RCN. J. Color fundus photograph, 3 years later, shows a de novo RAP lesion in the central macula with subretinal hemorrhage, and (K) characteristic intraretinal disorganization and thickening on macular spectral-domain OCT.

fibrotic lesions with no improvement in vision. Of these, imaging is presented for patient 2, before and after the treatment (Figure 4). Patients 8 and 9 received their treatment in another institution and were examined by us already at a stage were the RCN had fibrosed. One 11-year-old patient (the left eye of patient 1) underwent pars plana vitrectomy with subretinal injection of 25 μg of tissue plasminogen activator for subretinal hemorrhage associated with RAP, which resulted in marked improvement in vision (Table 3). OCT angiography performed after pars plana vitrectomy confirmed the presence of a vascular lesion, but with some degree of fibrosis. The fellow eye developed a recent "de novo" RCN (Figure 2, H–K) and the patient was offered intravitreal anti–vascular endothelial growth factor injections, but the patient's father declined.

DISCUSSION

THIS IS THE LARGEST SERIES EXAMINING MACULAR RCN among individuals with ESCS. About 1 of every 7 patients with ESCS had this feature. This may be a conservative estimate considering the difficulty in assessing fundi in young children, the possibility of misinterpretation of clinical

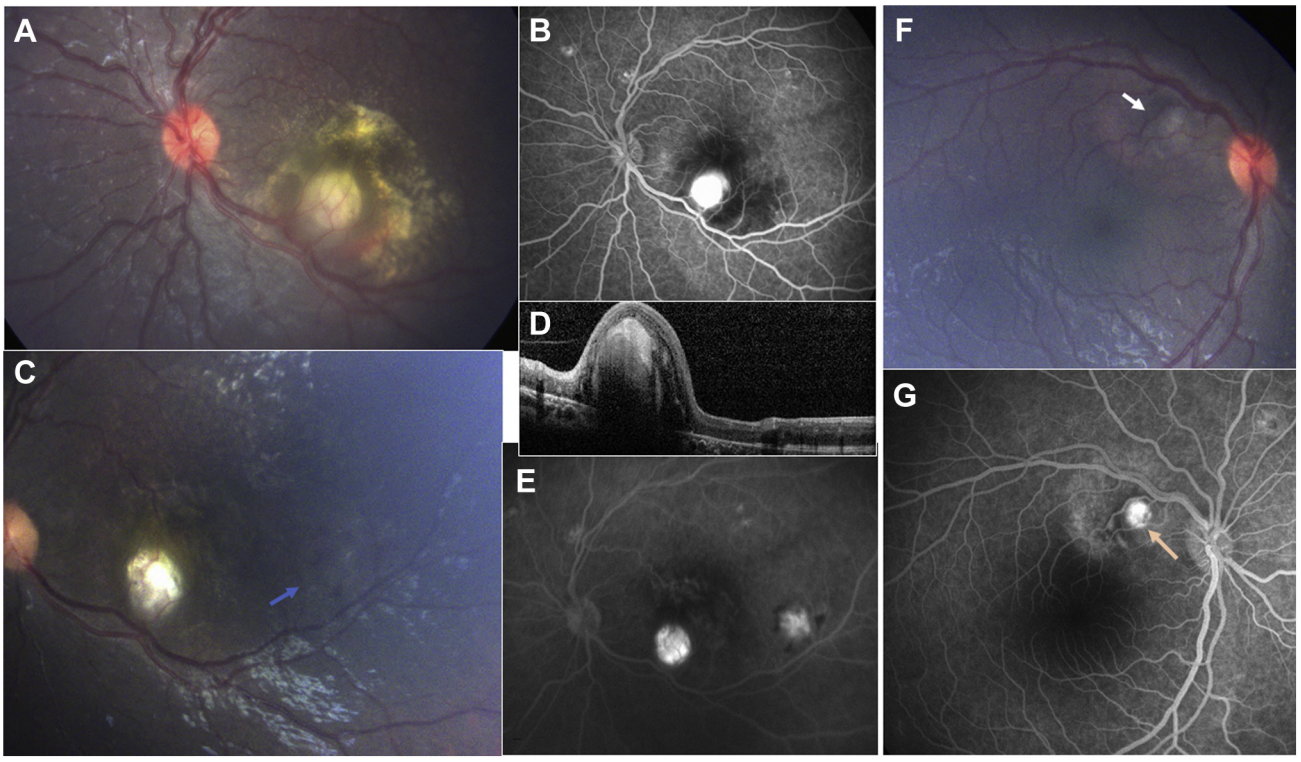

FIGURE 3. Bilateral consecutive de novo retinochoroidal neovascularization (RCN) in patient 3, a 2-year-old girl with enhanced S-cone syndrome caused by a c.926G > T mutation in *NR2E3* (Table 2). A through E. Left fundus. A. Color fundus photograph shows an exudative RCN lesion at the inferonasal macula with mild retinal venous dilation. B. The RCN lesion shows dye leakage on fluorescein angiography (FA). C. One year later, on color photography, the RCN has transformed into a subretinal fibrotic nodule. A de novo RCN with subretinal hemorrhage is seen at the inferotemporal macular border (blue arrow). D. Spectral-domain optical coherence tomography of the macula shows the fibrosis as a subretinal hyperreflective lesion. E. The FA demonstrates staining of the subretinal fibrotic lesion and dye leakage with blockage from the subretinal hemorrhage at the site of the new lesion. F through G. Right fundus. F. Color photographs show an involuted fibrosed RCN lesion at the superonasal macular border (white arrow). G. The FA shows staining of this involuted lesion and clearly depicts a hypofluorescence corresponding to pigmentation at the site of "dipping" retinal arteriole and venule (pink arrow).

findings, and the limited availability of molecular genetic testing. For example, the youngest patient in this series developed RCN at 2 years of age. It is conceivable that RCN is an inherent feature of ESCS and a potential precursor of a subsequent fibrosis. The various presentations of RCN—active, newly developing de novo lesions, evolving lesions with some fibrotic features, and inactive already fibrosed lesions—do not exclude that there is a primary RCN (which may be diagnosed or undiagnosed) that leads to a subsequent subretinal fibrosis, which in turn could trigger, or contribute to, further RCN, leading to further fibrosis.

Furthermore, this study offers insight into the presentations and natural history of macular RCN in ESCS. We showed that RCN lesions 1) are almost always located in the central macula; 2) are observed in patients as young as 2 years of age; 3) can present de novo as exudative RAP-like lesion that then evolve into the characteristic unifocal subretinal fibrotic lesions seen in ESCS (Figures 2–5); 4) can erupt among widespread subretinal fibrosis (Figure 6); and 5) can present unilaterally or bilaterally, generally in symmetrical locations, with simultaneous development in bilateral cases or delayed development in the contralateral eye, as shown in patient 1 who underwent an operation for an aggressive RCN with subretinal hemorrhage and who later developed a RCN in the other eye (Figure 2). None of our cases with unifocal fibrosis developed "new" RCN extensions adjacent to established fibrotic lesions. Furthermore, all the fibrotic lesions had a stable appearance during follow-up.

Eleven of the 22 RCN lesions we described were confirmed by angiography (Table 1). On the other hand, RCN was retrospectively diagnosed in an "inactive" stage in 10 of 21 eyes (Figure 1). These inactive lesions were diagnosed as RCN based on their identical appearance with healed, fibrosed, FFA-documented RCN (for example a healed "de novo" RCN), assuming that they had been "active" earlier. For these patients there was no strong

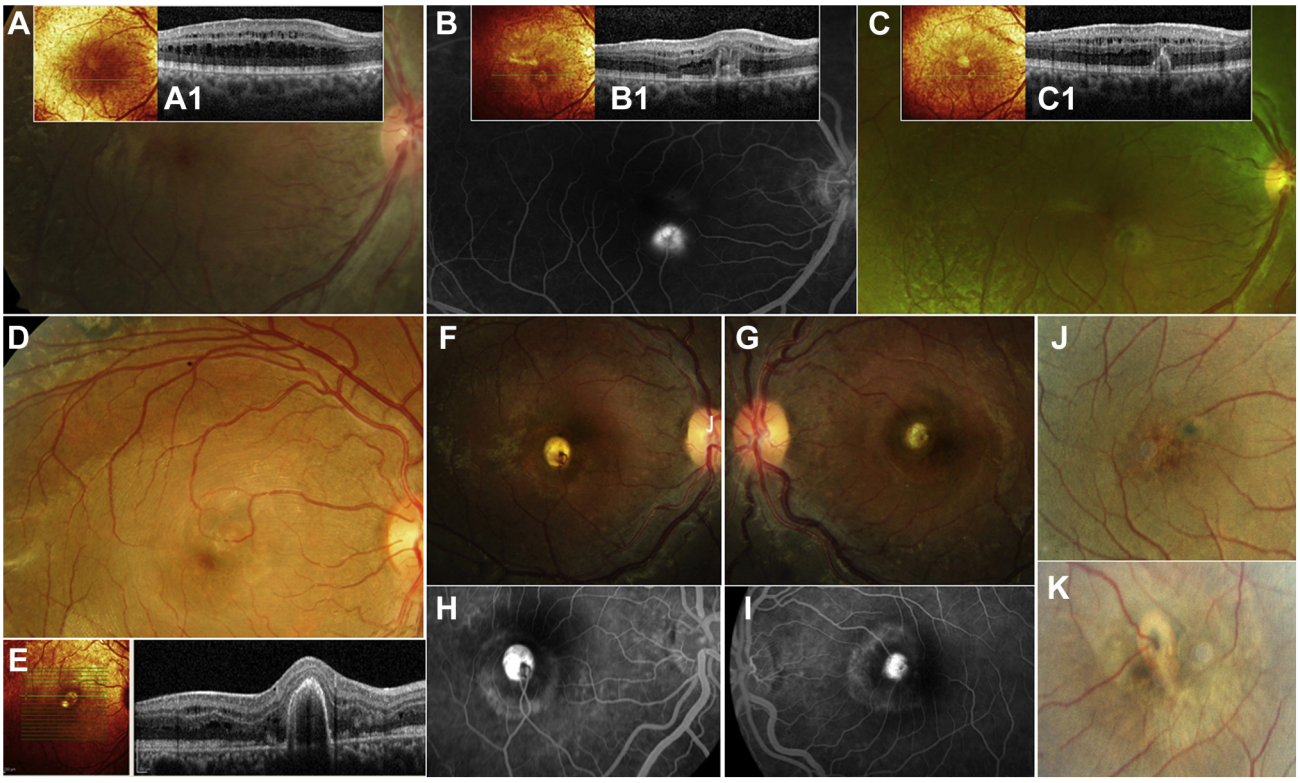

FIGURE 4. Examples of de novo and fibrosed retinochoroidal neovascularization (RCN) lesions in patients with enhanced S-cone syndrome. A. Color fundus photograph and spectral-domain optical coherence tomography (OCT; inset A1) of the right eye of patient 2, a 10-year-old male, shows macular schisis and no RCN. B. Three years later, fundus fluorescein angiography (FA) of the same eye shows a de novo RCN as a juxtafoveal leaking lesion. The corresponding spectral-domain OCT scan (inset B1) shows a hyperreflective subretinal lesion above an intact retinal pigment epithelium. C. Color fundus photography and spectral-domain OCT (inset C1) of the same eye 6 months after intravitreal bevacizumab injection showing transformation into a fibrosed RCN lesion. D. Color fundus photograph and (E) spectral-domain OCT of the right eye of patient 5, a 16-year-old female, showing an involuted fibrosed RCN lesion. F through I. Color photographs and FA of both eyes of patient 8, a 14-year-old female, showing a juxtafoveal fibrosed RCN in each eye. J through K. Color fundus photographs of patient 4, a 25-year-old man, showing a juxtafoveal evolving RCN lesion with tiny subretinal hemorrhage in the right macula (J) and a fibrosed lesion in the left macula (K). Note the consistent surface pigmentation with "dipping" retinal arteriole and venule into each lesion.

indication at presentation to perform any FFA. However, the inactive lesions were included in this study to arrive at a fair estimate of the incidence of RCNs in ESCS. Our estimate of incidence of RCN in ESCS is therefore based on the assumption that all the 22 described lesions were active RCNs at some point in time.

Although the published literature has reported few cases of choroidal neovascular membrane in ESCS, we suggest that RCN, or better yet, subretinal neovascularization, may be used as an alternative term for choroidal neovascular membrane in these cases. This is because multimodal retinal imaging uniformly showed subretinal lesions above the RPE (Figures 2–6). Furthermore, the retinal venous congestion observed in the active stage of the RCN and the frequent observation of retinal arteriole and venule dipping into the lesion with tiny pigment spot on its surface once it became fibrotic suggests that the process is akin to RAP lesions (type 3 neovascularization) in age-related macular degeneration or stage 5 macular telangiectasia type 2 lesions.

The cause of development of RCN in ESCS is not completely understood and requires further study. One may speculate whether the unique situation in the retina, with an absence of rods but an increased number of abnormal cones, could disturb the angiogenic balance in the retina.[3] On the other hand, RCN presentation at young age is not unique to ESCS but may occur also in other retinal dystrophies, such as Best disease.[14]

Our study provides further support to the idea that RCN is the cause of ≥1 pattern of subretinal fibrosis encountered in ESCS: the unifocal fibrotic "nodule." This pattern was encountered in 11 of our 14 patients (13 eyes and 22 lesions). The best support derives from the 5 "de novo" RAP-like lesions appearing in an area without previous

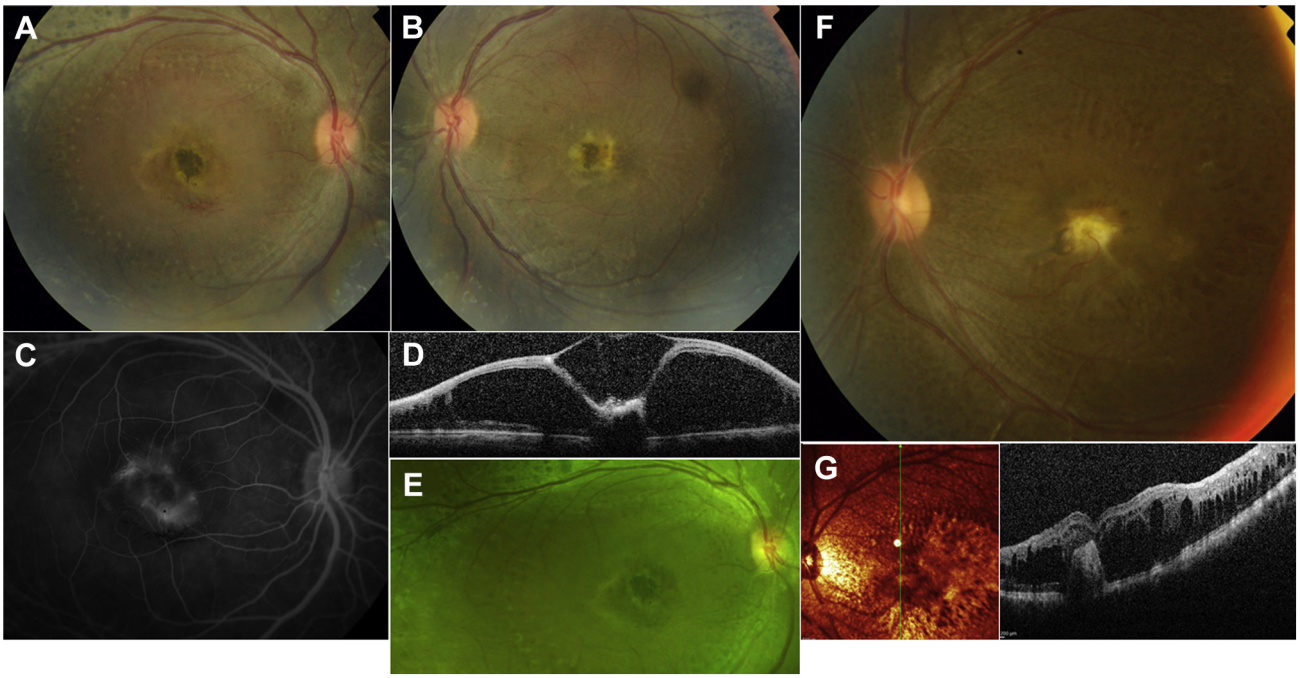

FIGURE 5. Retinochoroidal neovascularization (RCN) lesions and marked macular schisis in enhanced S-cone syndrome. A. Color fundus photographs the (A) right and (B) left eyes of patient 5, a 16-year-old female (Table 2) with a c.119-2A > C mutation in *NR2E3* showing RCN lesions with parafoveal hemorrhage in the right eye and subfoveal fibrosis in the left eye with prominent macular schisis in both eyes. C. Fluorescein angiography of the right eye reveals dye leakage of the RCN and (D) demonstrates the prominent schisis on macular spectral-domain optical coherence tomography. E. Color photograph of the RCN after resolution of the subretinal blood. F. Fundus photography and (G) corresponding spectral-domain optical coherence tomography scan of the left eye of patient 7, a 17-year-old female with a c.131C > A mutation in *NR2E3* (Table 2), depicting a subfoveal fibrosed RCN and prominent schisis.

fibrosis or distinctive features, and evolving into a characteristic unifocal fibrotic lesion with distinctive surface pigmentation and retinal arterioles and venules "dipping" into the fibrotic lesion (Tables 1–3 and Figures 2–4). Two additional cases of RCN (Figures 4 and 5) presenting with retinal hemorrhage and identical fibrotic features, as well as the 10 "fibrosed" RCN cases (Figures 3–5) featuring identical pigmentation and arteriovenous changes further support the notion that this unifocal solitary fibrotic lesion started as a RAP-like RCN. All these lesions, except in 1 patient, were located in the central macula and were fairly symmetrical when bilateral. Only one 2-year old girl (patient 3) developed RCN at the macular periphery of both eyes. Interestingly, her left eye was also the only eye in this series to develop 2 successive "de novo" RCN lesions, both situated at the inferior macular border (Figure 3 E).

A limitation of the study was the incomplete information for some patients because of the retrospective nature of the study. Moreover, all patients shared a same ethnic background, which may raise the question if the incidence of RCN or subretinal fibrosis is similar in ESCS in other populations. Several recent studies did not find RCN to be a prominent feature in ESCS.[1,5,15,16] On the other hand, similar findings with vascular anastomosis formation or type 3 neovascularization have recently been described by others.[9,17] We speculate whether some of these lesions may go unrecognized because of factors such as a very early onset in a pediatric age group, unfamiliarity with ESCS and its fibrotic features, or the unavailability or cost of genetic testing. Further limitations are that OCT angiography was unavailable when the lesions were active, and genetic analysis was not pursued further in 4 patients where the diagnosis of ESCS was based on pathognomonic ERG and a confirmed family history of ESCS. Our study shows that 8 patients had active lesions in 1 or both eyes. These are truly incident cases, whereas we cannot be sure that the remaining lesions in 6 patients ("inactive" lesions) were truly incident as opposed to prevalent. Another limitation was that the value of antiangiogenic therapy in ESCS-related RCN could not be examined in a conclusive manner.

In conclusion, ESCS was associated with RCN, which resulted in characteristic patterns of subretinal fibrosis. Considering the frequent finding of fibrosis in ESCS, and the positive association between RCN and fibrosis development, we suggest that RCN may be much more common

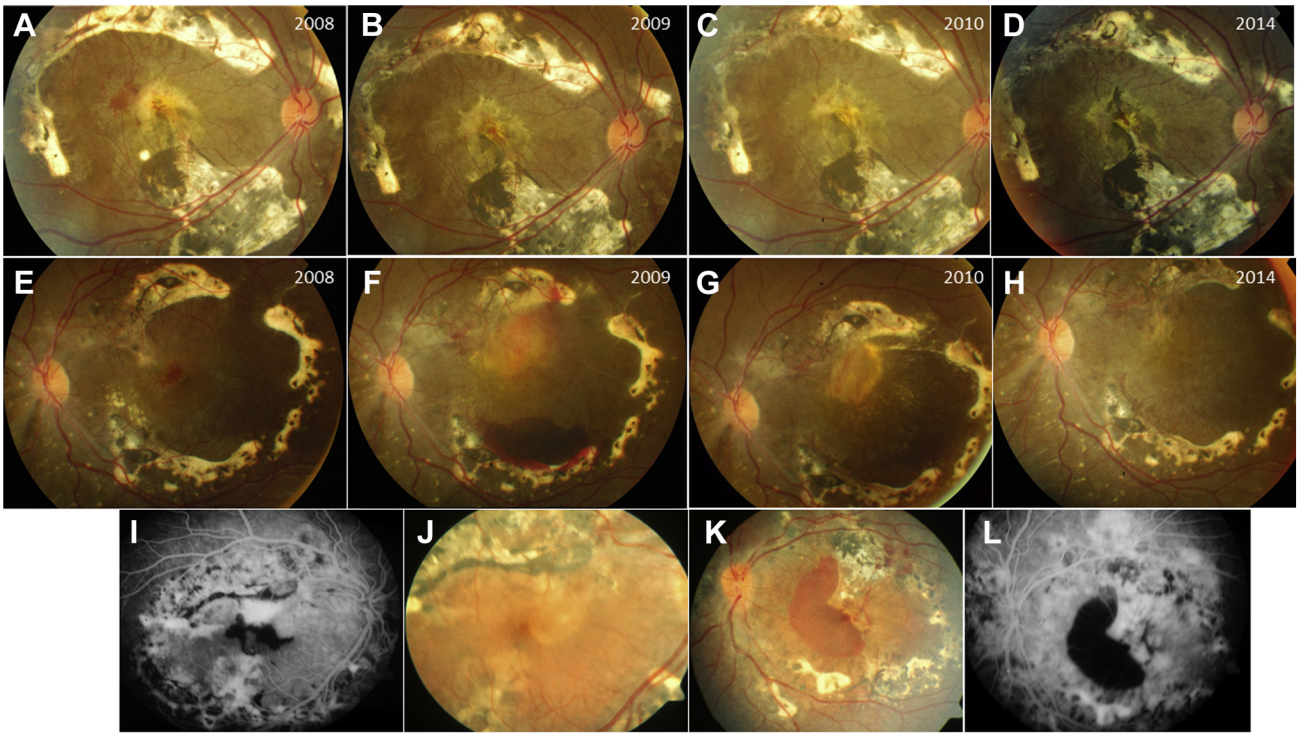

FIGURE 6. Retinochoroidal neovascularization (RCN) in eyes with widespread submacular fibrosis in enhanced S-cone syndrome. A through H. Serial color photographs of the (A through D) right and (E through H) left maculae of patient 14, a 15-year-old male with the c.932G > A mutation in *NR2E3*, depicting, at presentation, a central macular exudative RCN lesion with subretinal blood amidst widespread subretinal fibrosis (Table 2). D and H. Five years later, the exudative lesions were replaced by thin submacular fibrosis. I through L. Fluorescein angiography and color photograph of the (I and J) right and (K and L) left macula of patient 12, a 13-year-old female with enhanced S-cone syndrome (Table 2) showing central subretinal blood and widespread submacular fibrosis.

than previously estimated and may be the primary cause of the unifocal central submacular fibrotic nodule pattern that is commonly observed in this condition. Further studies are needed to understand the pathogenesis of RCN in ESCS and to establish guidelines for its optimal management. Such insight could potentially prove to be useful in other disorders with similar manifestations, such as Best disease or macular telangiectasia type 2.

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