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

Sawsan R. Nowilaty, MD, Abrar K. Alsalamah, MD, MRCSEd(Ophth), Moustafa S. Magliyah, MD, Abdulelah A. Alabdullah, MD, Khabir Ahmad, MD MSc PhD, Valmore A. Semidey, MD, Marco Mura, MD, Patrik Schatz, MD, PhD

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## Abstract

***Purpose:*** To examine the incidence and natural history of macular retinochoroidal neovascularization (RCN) in Enhanced S-Cone Syndrome (ESCS).

***Design:*** Retrospective case series.

***Methods****:*

- Setting: Institutional.
- Patient or Study Population: 14 out of 93 patients with ESCS, who had signs of active or inactive RCN in at least one eye.
- Intervention or Observation Procedure(s): Multimodal retinal imaging, full-field electroretinography, molecular genetic analysis of *NR2E3* gene.
- Main Outcome Measure(s): Cumulative incidence of RCN in ESCS, type of RCN, mode of evolution of RCN.

***Results****:* 14 (15.1%) of the 93 patients with ESCS had RCN in one or both eyes at age 2 to 27 years. All 22 RCNs (21 eyes of 14 patients) were macular. 12 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 (RAP) and subsequently evolved into unifocal fibrotic nodules. The remaining active lesions all had some degree of pre-existing fibrosis and remained stable. 10 inactive fibrotic nodules, identical to end-stage de novo lesion, 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 ESCS than previously estimated. It may be the primary cause of the unifocal submacular fibrosis which is commonly observed in this condition. Further research is needed to establish the pathogenesis of RCN in ESCS and its optimal management.

**Incidence and Natural History of Retinochoroidal Neovascularization in Enhanced S-Cone Syndrome** *Short title:* Retinochoroidal neovascularization in S cone-syndrome

Sawsan R. Nowilaty MD[1], Abrar K. Alsalamah MD, MRCSEd(Ophth)[1], Moustafa S. Magliyah MD[1,2], Abdulelah A. Alabdullah MD[1], Khabir Ahmad, MD MSc PhD[3], Valmore A. Semidey MD[1], Marco Mura MD[1,4], Patrik Schatz MD, PhD[1,5]

(Patrik Schatz ORCID 0000-0002-1747-0928)

1 Vitreoretinal Division, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia

2 Ophthalmology Department, Prince Mohammed Medical City, AlJouf, Saudi Arabia

3 Research Department, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia

4 Ophthalmology Department, University of Illinois, Chicago, USA

5 Department of Ophthalmology, Clinical Sciences, Skane County University Hospital, Lund University, Lund, Sweden.

Corresponding author: Patrik Schatz, MD PhD, Vitreoretinal Division
King Khaled Eye Specialist Hospital, Al- Oruba Road, PO Box 7191 Riyadh 11462, Kingdom of Saudi Arabia. Telephone number: Tel +966 11 482 1234 ext. 3773 | Fax +966 11 4821234 ext. 3773. Email: pschatz@kkesh.med.sa or patrik.schatz@med.lu.se
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## Introduction

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 non-recordable rod response, a widened and delayed rod-cone response which is similar to the single flash cone response, and a severely reduced 30 Hz flicker amplitude which 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 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 the *NR2E3* gene 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 de-differentiation of the photoreceptors towards 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 us (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 development of subretinal fibrosis. We speculate that RCN in ESCS could either be 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.

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

## Methods

This retrospective cohort study was undertaken at the King Khaled Eye Specialist Hospital (KKESH), Riyadh, Saudi Arabia. Ethical approval for this study was obtained from the Institutional Review Board (IRB) at KKESH. 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 and /or genetic analysis in the majority of 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 in this manuscript.

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 (BCVA), 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); color fundus imaging (Topcon TRC-50DX, Topcon Medical Systems, Inc., NJ, US, RetCam 3, Natus Medical, Inc. Pleasanton, CA), Optos PLC, Dunfermline, UK). The presence of RCN was detected by clinical fundus examination, SD-OCT (for patients presenting after 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 hyper-reflective lesion on SD-OCT.

Molecular Genetic Testing was done using samples of peripheral blood which were obtained for DNA extraction from leukocytes of the affected patients. Targeted next generation sequencing (NGS) was performed using retinal dystrophy panels at the molecular genetics lab at King Faisal Specialist Hospital (KFSH, Riyadh KSA),[13] or at Bioscientia (Bioscientia, Boehringer, Ingelheim, Germany, Supplemental document 1, available at AJO.com). In patients with typical clinical findings, direct sequencing of *NR2E3* gene was performed at the molecular genetics lab at KKESH. Reported variants were assessed using gnomAD (https://gnomad.broadinstitute.org/, v3, access date 13/12/2019).

Statistical analysis was performed using STATA 16.1 (Stata Corp., College Station, TX, USA). The analysis was mainly descriptive, and no statistical testing was performed except Phi coefficient which was calculated to assess the strength of association between RCN and fibrosis. Frequency and proportions were computed to describe categorical data and median with IQR were computed to describe continuous data.

**Results**

Of 93 patients with ESCS between 1993 and 2019, 14 (15.1%) were diagnosed with RCN in one or both eyes (Figure 1 and Tables 1-3). The median age at diagnosis was 15 years (range 2-27) and the median length of follow-up after diagnosis was 2 years (range 1-12, Table 2). All patients were from consanguineous Saudi Arabian families. Four different homozygous mutations were identified in 10 patients (Table 3 and Supplemental document 2, available at AJO.com) Two patients harbored the c.932G>A mutation, 6 had c.119-2A>C mutation, and 1 each had the c.131C>A mutation and the c.926G>T mutation. The latter [c.926G>T] was a novel missense mutation (Table 3 and Supplemental document 2, available at AJO.com)

All 22 RCNs (21 eyes of 14 patients) were macular (Table 1,2 and Figure 1-6). All were unifocal and centrally located except in 2 eyes of the same patient (Patient #3). 12 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 given in Figures 2-4. Each *de novo* lesion

was compatible with type 3 neovascularization or retinal angiomatous proliferation (RAP) and was associated with one or more dilated retinal veins emerging from the RCN lesion, and subsequently evolved into a localized unifocal fibrotic "nodule" with characteristic features, namely 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 entire follow up (Figures 4-6). 10 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 < 0.001 Supplemental document 3, available at AJO.com).

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 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 document 4, available at AJO.com).

Three eyes (patients 2-right eye, 8-left eye, 9-left eye,) received a single intravitreal bevacizumab injection of 1.25 mg/0.05 ml and evolved into fibrotic lesions with no improvement in vision. Of these, imaging is presented for patient 2, before and after the treatment, in 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 (patient 1-left eye) underwent pars plana vitrectomy with subretinal injection of 25 micrograms of tissue plasminogen activator (tPA) for subretinal hemorrhage associated with RAP, which resulted in marked improvement in vision (Table 2). OCT-angiography done after the pars plana vitrectomy confirmed the presence of a vascular lesion, however with some degree of fibrosis. The fellow eye developed a recent "*de novo*" RCN (Figure 2H-K) and was offered intravitreal anti-vascular endothelial growth factor (VEGF) injections, but the patient's father declined.

## Discussion

This is the largest series examining macular RCN among individuals with ESCS. About one out of every 7 patients with ESCS had this feature. This may be a conservative estimate considering difficulty in assessing the fundi in young children, possibility of misinterpretation of clinical findings, and limited availability of molecular genetic testing. For example, the youngest patient in this series developed RCN at the age of 2 years. It is, therefore, 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 described in this article, do not exclude that there is a primary RCN (which may be diagnosed or undiagnosed) which 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 could show that the RCN lesions 1) are almost always located in the central macula; 2) are observed in patients as young as 2 years; 3) can

present “de novo” as exudative “RAP- like” lesion which then evolve into the characteristic unifocal subretinal fibrotic lesions seen in ESCS (Figures 2-5); 4) can erupt among widespread subretinal fibrosis (Figure 6); 5) can present unilaterally or bilaterally, generally in symmetric locations, with simultaneous development in bilateral cases or delayed development in the contralateral eye as shown in our patient #1 who was operated for an aggressive RCN with subretinal hemorrhage 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 angiographically (Table 1). On the other hand, RCN was retrospectively diagnosed in an “inactive” stage in 10/21 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 indication at presentation to perform any FFA. However, the inactive lesions were included in this study in order to arrive at a fair estimate of the incidence of RCNs in ESCS. Our estimate of incidence of RCN in ESCS is thus based on the assumption that all the 22 described lesions were active RCNs at some point in time.

Although the literature reported few cases of choroidal neovascular membranes (CNVMs) in ESCS, we suggest that RCN, or better yet, subretinal neovascularization, may be used as an alternative term for CNVM 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, suggest that the process is akin to RAP lesions (type 3 neovascularization) in AMD or stage 5 macular telangiectasia type 2 (MacTel2) 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 at least one pattern of subretinal fibrosis encountered in ESCS: the unifocal fibrotic “nodule”. This pattern was encountered in 11 of our 14 patients (13 eyes/22 lesions). The best support derives from the 5 “*de novo*” RAP-like lesions appearing in an area without prior 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 (Table 1-3, Figures 2-4). 2 additional RCN cases (Figures 4-5) 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 one 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 two successive "*de novo*" RCN lesions, both situated at the inferior macular border (Figure 3E).

A limitation of the study was the incomplete information for some patients due to 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 very recently been described by others.[9,17] We speculate whether some of these lesions may go un-recognized because of factors such as a very early onset in a pediatric age group, unfamiliarity with ESCS and its fibrotic features, or 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 or ESCS was based on pathognomonic ERG and confirmed family history of ESCS. Our study shows that 8 patients had active lesions in one 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 anti-angiogenic 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 than previously estimated, and may be the primary cause of the unifocal central submacular fibrotic nodule pattern which 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 MacTel2.

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**Figure captions:**

**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 hyper-reflective lesion on spectral domain optical coherence tomography. RAP=retinal angiomatous proliferation.

**Figure 2:** Bilateral consecutive *de novo* retinochoroidal neovascularization (RCN) in an 8-year-old male with Enhanced S-Cone syndrome (ESCS) due to a c.932G>A mutation in *NR2E3* (Patient 1, Table 2).

**A-G:** left fundus. (**A)** Color fundus photo shows a subfoveal RCN with subretinal hemorrhage. **(B)** Corresponding spectral domain optical coherence tomography (SD-OCT) depicts the RCN as a retinal angiomatous proliferation (RAP)-like lesion without retinal pigment disruption. **(C)** The early fluorescein angiogram (FA) phase shows hypoflourescence due to subretinal hemorrhage with in **(D)** late leakage of the RCN lesion. **(E)** One year after vitrectomy, the color photo 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 (A). **(F)** On FA, the fibrotic lesion exhibits staining with a hypoflourescent spot at its center corresponding to the pigment seen in E. **(G)** On SD-OCT, the fibrotic lesion is compact and hyper-reflective with adjacent macular schisis. **H-K:** right fundus. **(H)** Color photo and **(I)** macular SD-OCT at presentation show discrete macular schisis but no RCN. **(J)** Color fundus photo, three years later, shows a *de novo* RAP lesion in the central macula with subretinal hemorrhage, and **(K)** characteristic intraretinal disorganization and thickening on macular SD-OCT.

**Figure 3:** Bilateral consecutive *de novo* retinochoroidal neovascularization (RCN) in a 2-year-old girl with Enhanced S-Cone Syndrome (ESCS) due to c.926G>T mutation in *NR2E3* (Patient 3, Table 2).

**A-E:** left fundus. **(A)** color fundus photo 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 photo, 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)** The macular spectral domain optical coherence tomography (SD-OCT) depicts the fibrosis as a subretinal hyper-reflective 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-G:** right fundus. **(F)** Color photos depicts 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).

**Figure 4:** Examples of *de novo* and *fibrosed* retinochoroidal neovascularization (RCN) lesions in patients with Enhanced S-Cone Syndrome (ESCS).

(A) Color fundus photo and spectral domain optical coherence tomography (SD-OCT) (in insert A1) of the right eye of a 10-year old male (Patient 2) shows macular schisis and no retinochoroidal neovascularization (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 SD-OCT (insert B1) shows a hyper-reflective subretinal lesion above an intact retinal pigment epithelium. (C) Color fundus photo and SD-OCT (insert C1) of the same eye 6 months following an intravitreal bevacizumab injection showing transformation into a fibrosed RCN lesion. (D) Color fundus photo and (E) SD-OCT of the right eye of a 16-year old female (Patient 6) showing an involuted fibrosed RCN lesion. (F-I) Color photos and FA of both eyes of a 14-year old female (Patient 8) showing a juxtafoveal fibrosed RCN in each eye. (J-K) color fundus photo of a 25-year old male (Patient 4) 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.

**Figure 5:** Retinochoroidal neovascularization (RCN) lesions and marked macular schisis in enhanced S cone syndrome (ESCS).

**A-E. (A)** Color fundus photos the right eye **(A)** and left eye **(B)** of a 16-year old female (Patient 5, Table 2) with c.119-2A>C mutation in *NR2E3* showing an 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 angiogram of the right eye shows dye leakage of the RCN and **(D)** demonstrates the prominent schisis on macular SD-OCT. **(E)** Color photo of the RCN after resolution of the subretinal blood. **(F-G)** Fundus photo **(F)** and corresponding SD-OCT scan **(G)** of the left eye of 17-year old female with c.131C>A mutation in NR2E3 (Patient 7, Table 2), depicting a subfoveal fibrosed RCN and prominent schisis.

**Figure 6:** Retinochoroidal neovascularization (RCN) in eyes with widespread submacular fibrosis in enhanced S-Cone syndrome (ESCS).

**(A-H)** Serial color photos of the right **(A-D)** and left **(E-H)** maculae of a 15-year old male at presentation and a c.932G>A mutation in *NR2E3,* depicting a central macular exudative RCN lesion with subretinal blood amidst widespread subretinal fibrosis (Patient 14, Table 2). Five years later **(D and H),** the exudative lesions were replaced by thin submacular fibrosis. **I-L** FA and color photo of the right **(I and J)** and left **(K and L)** macula of a 13-year old female with ESCS (Patient 12, Table 2) showing central subretinal blood and widespread submacular fibrosis.

Table 1 – Baseline characteristics of 14 patients with Enhanced S-Cone Syndrome (ESCS) with signs of retinochoroidal neovascularization (RCN)

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

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

[a] Total number 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), 5- Night blindness and typical fundus features (N=4).

[b] 22 RCN lesions were diagnosed, 1 of the patients had 2 consecutive lesions in the left eye (Figure 2).

[c] Non-recordable rod responses with a broadened similarly-shaped dark adapted rod-cone and light adapted single flash cone responses and a severely reduced 30Hz flicker amplitude which was smaller than the light-adapted single-flash cone a-wave. These findings were present in all 14 patients, except for patients 2, who had a non-recordable ERG, and patients 7 and 8 in whom ERG was not performed.

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

[e] Details presented in Table 3.

[f] Patients 2, 7 and 8

Table 2. Key findings in 14 patients with Enhanced S-Cone Syndrome (ESCS) with signs of retinochoroidal neovascularization (RCN).[a]

| Patient No. | Year at initial Presentation, age [years] | Age [years] at RCN diagnosis (eye), gender | Key findings | | Length of FU from RCN diagnosis, years | Figure |
|---|---|---|---|---|---|---|
| | | | Right eye | Left eye | | |
| 1. | 2016, 8 | 8 (Left), 11 (Right), M. | Active *de novo* RCN compatible with RAP. Lost to follow-up. | Active *de novo* RCN compatible with RAP. Subretinal hemorrhage was evacuated surgically.[b] | 3 (Left) 1 (Right) | 2 |
| 2. | 2015, 10 | 13 (Right), M | Active *de novo* RCN compatible with RAP.[b] | - | 4 | 4A-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 | 4J-K |
| 5. | 2019, 16 | 16 (Both), F | Active RCN with hemorrhage and schisis.[b] | Inactive fibrotic nodule compatible with end-stage RAP. | 1 | 5A-E |
| 6. | 2007, 16 | 16 (Right), F | Inactive fibrotic nodule compatible with end-stage RAP. | - | 1 | 4D-E |
| 7. | 2009, 17 | 17 (Left), F | - | Inactive fibrotic nodule compatible with end-stage RAP, with prominent schisis. | 10 | 5F-G |
| 8. | 2014, 14 | 14 (Both), F | Inactive fibrotic nodule compatible with end-stage RAP. | Inactive fibrotic nodule compatible with end-stage RAP. | 5 | 4F-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 follow-up after 1year. | Active RCN with hemorrhage amidst widespread fibrosis. Lost to follow-up after 1year. | 1 | 6I-L |
| 13. | 1995, 27 | 27 (Right), M | Active RCN with hemorrhage amidst widespread fibrosis. Lost to follow-up after 1 year. | - | 1 | |
| 14. | 1993, 1 | 15 (Both), M | Active RCN with hemorrhage amidst widespread fibrosis. Evolved into thin fibrosis. | Active RCN with haemorrhage amidst widespread fibrosis. Evolved into thin fibrosis. | 12 | 6A-H |

M=Male, F=Female; RAP = retinal angiomatous proliferation. FU = Follow up. [a] All RCNs were central macular except for Patient 3. [b] The lesion evolved into unifocal fibrotic nodule compatible with end-stage RAP.

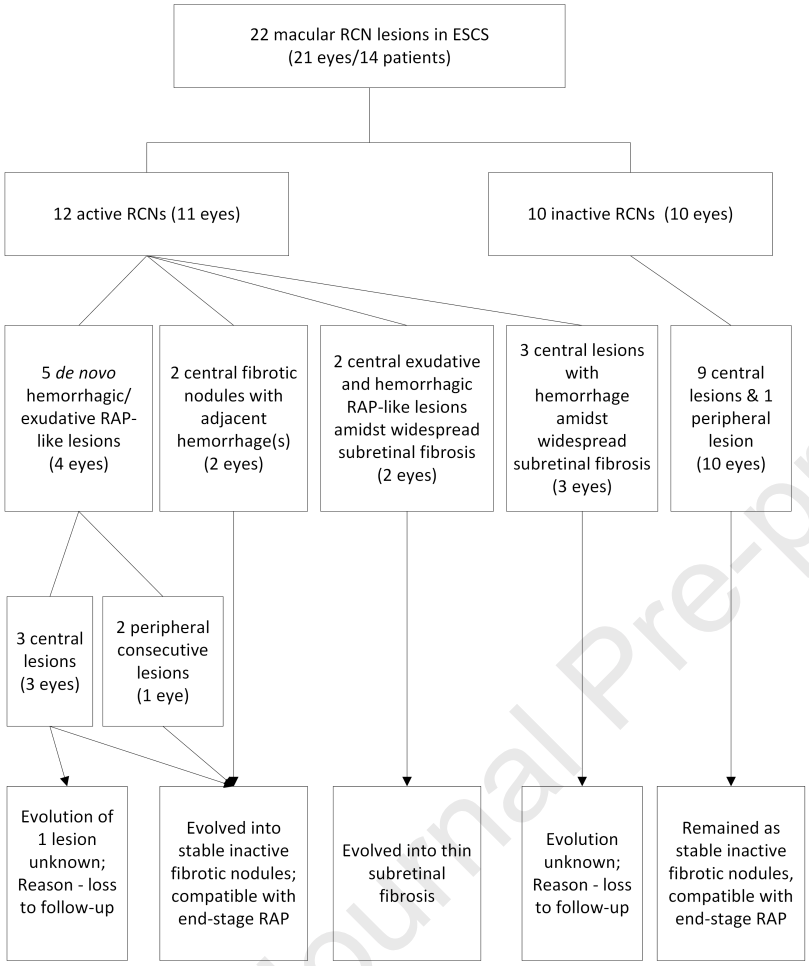
Table 3. *NR2E3* gene mutations and visual outcome among 14 patients with Enhanced S-Cone Syndrome (ESCS) with signs of retinochoroidal neovascularization (RCN). All mutations were homozygous.

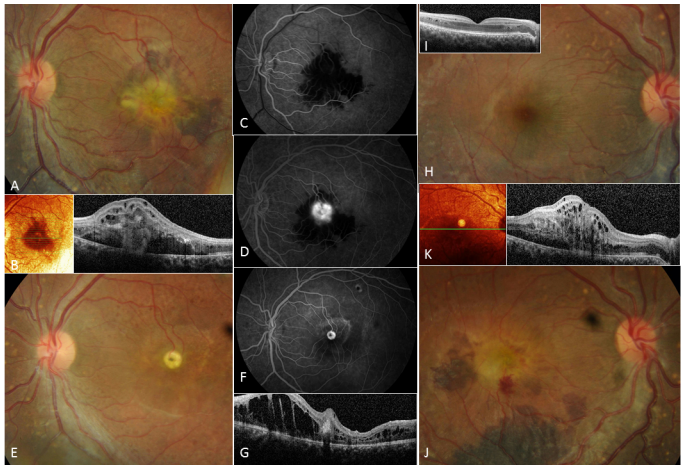
| Patient | *NR2E3* gene mutation | Eye | BCVA at presentation | BCVA at RCN diagnosis | BCVA at the last follow up |
|---|---|---|---|---|---|
| 1 | c.932G>A | Right | 20/20 | 20/300 | 20/300 |
| | | Left | 2/200 | 2/200 | 20/80[a] |
| 2 | c.119-2A>C | Right | 20/20 | 20/25 | 20/25 |
| | | Left | 20/30 | 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 |

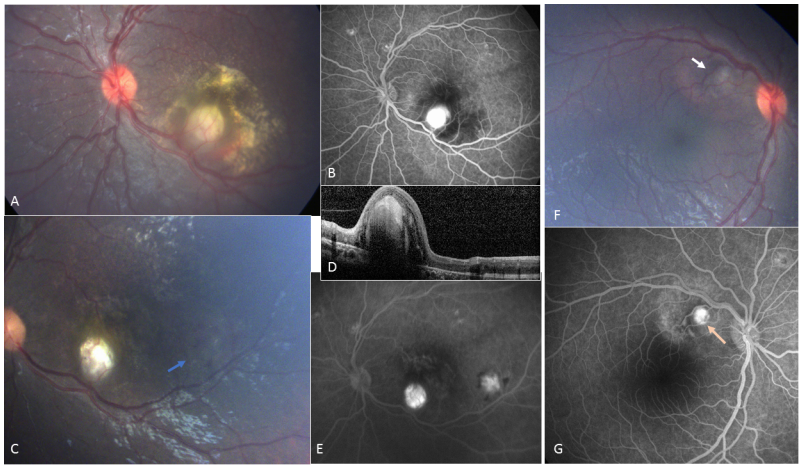
Dx= Diagnosis; BCVA= Best Corrected Visual Acuity; IT= Inferotemporal; NP= Not Performed; NR= Non-recordable; F & F: Fixes and follows

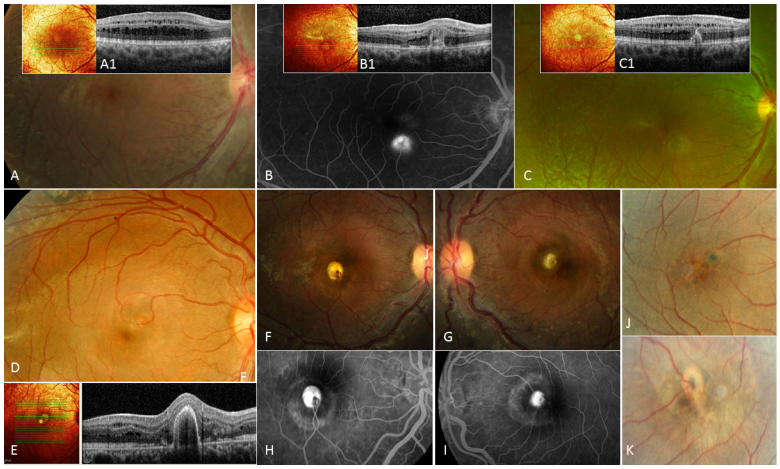
[a] After pars plana vitrectomy for RCN and subretinal hemorrhage in the left eye. Right eye developed RCN afterwards.

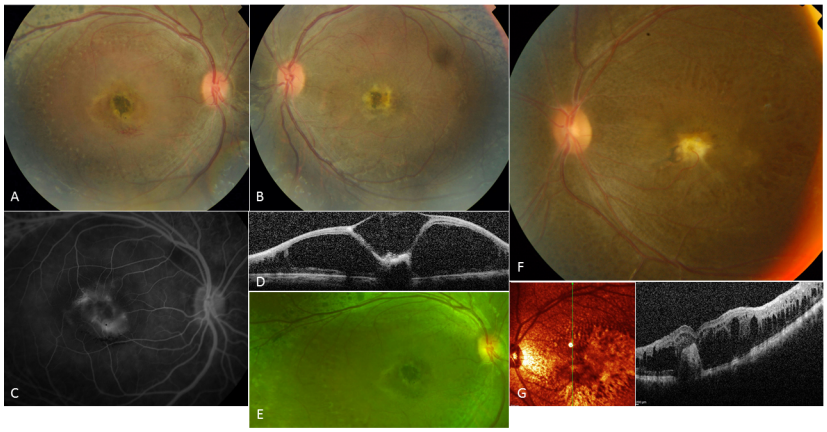
[b] Patient was 1-year old at first presentation and 15 years at RCN diagnosis.

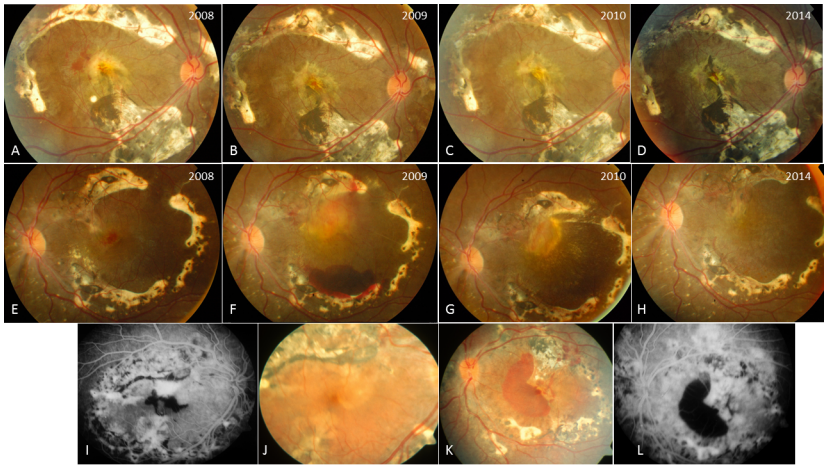












Abrar K. Alsalamah received her medical degree with First Class Honors from King Saud University and completed residency in ophthalmology at King Khaled Eye Specialist Hospital (KKESH) and King Saud University, Riyadh, Saudi Arabia. She is a Member of the Royal College of Surgeons of Edinburgh and currently pursuing her vitreoretinal and uveitis fellowship at KKESH. Her primary research interests include retinal dystrophies and degenerations, macular diseases, and uveitis.

Sawsan R. Nowilaty obtained her Doctorate Degree in Medicine from the Faculty of Medicine of Tunis. Following ophthalmology residency then vitreoretinal fellowship at King Khaled Eye Specialist Hospital (KKESH) in Riyadh, Saudi Arabia, she joined KKESH as full-time member of the Vitreoretinal Division where she is Senior Academic Consultant Ophthalmologist and the institution's past Director of Medical Education (2005-2011, 2017-2018). Her research interests include hereditary retinal degenerations, retinal vascular diseases, macular telangiectasis and posterior microphthalmos.

We found a cumulative incidence of macular retinochoroidal neovascularization in Enhanced S-cone syndrome of 15%. We describe the natural history of such lesions, which may be much more common than previously estimated.