Original Article

Enhanced S-cone syndrome: Clinical spectrum in Indian population

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Purpose: Enhanced S-cone syndrome (ESCS), a rare disorder, is often misdiagnosed as other forms of retinal degenerations, which have a poorer prognosis than ESCS. The aim of this study is to report the varied clinical features of ESCS and distinguish it from other similar disorders. **Methods:** We retrospectively scrutinized the records of patients with confirmed diagnosis of ESCS and analyzed the findings. **Results:** We included 14 patients (age range 4–39 years) who were confirmed to have ESCS according to pathognomonic electroretinography (ERG) showing reduced photopic, combined responses, and 30 Hz flicker with reduced L, M cone responses and supernormal S cone responses. The disease presented in the 1st decade with night blindness and was almost stationary or minimally progressive. Mid-peripheral fundus changes in form of nummular pigmentary alterations, yellow punctate lesions, and macular schisis were noted. The vision ranged from 6/6 to 6/36 with follow-up ranging from 1month to 22 years. **Conclusion:** ESCS shows varied clinical features ranging from unremarkable fundus to pigment clumping and atrophic lesions. It has good prognosis with patients mostly maintaining their vision. ERG is diagnostic. More awareness and knowledge about this entity can help to differentiate it from other forms of night blindness.

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First described in 1990,[1] the enhanced S-cone syndrome (ESCS) is a rare, autosomal recessive disorder demonstrating characteristic hypersensitivity of the short-wavelength-sensitive cone photoreceptors. The human retina consists of approximately 6 million cones divided into three sub-types: the long-wavelength sensitive (L) cones, the medium-wavelength sensitive (M) cones, and the short-wavelength sensitive (S) cones. In a normal individual, the S-cones constitute approximately 10% of the total cone population.[2] In ESCS, the S-cones constitute majority of the cone subtype. Patients of ESCS typically present with nyctalopia, usually in the first decade, which may or may not be associated with diminished vision.[3,4] The fundus findings are highly variable and different forms of phenotypic expression have been described. These include the typical nummular pigment deposits at the level of retinal pigment epithelium (RPE) and intraretinal cysts[1,5] to the recently described intraretinal yellow dots,[4] helicoid subretinal fibrosis,[6] and torpedo lesions.[7] Cystoid maculopathy/macular schisis is often a commonly associated feature. Because of its phenotypic similarity, ESCS is often misdiagnosed as retinitis pigmentosa (RP), juvenile X-linked retinoschisis (XLRS), and congenital stationary night blindness (CSNB).

The mutations which cause ESCS principally involve the nuclear receptor class 2, sub-family E, member 3 (NR2E3) gene, which suppresses cone differentiation during embryogenesis.[4] The diagnosis of ESCS is primarily on the basis of pathognomonic changes in the electroretinogram (ERG), i.e., similar waveform of the photopic and scotopic responses to the bright flash stimulus because of the dominance of short-wavelength sensitive mechanisms.[8] Psychophysical and genetic testing have revealed that other entities such as Goldmann-Favre syndrome (GFS) and clumped pigmentary retinal degeneration (CPRD) probably belong to the same spectrum of NR2E3 mutations demonstrating abnormal ratio of S- cone to L- and M- cone population.[9,10]

There are no significant data on the clinical profile of ESCS in the Indian population till date. The purpose of this study was to present a series of 14 patients of Indian origin diagnosed with ESCS and report their phenotypic variation along with findings of electrophysiology and ancillary imaging.

Methods

This retrospective study was conducted in the vitreoretinal department of a tertiary eye care center in South India. Institutional ethics committee approval was obtained and the study adhered to the tenets of the Declaration of Helsinki. Retrospective records were reviewed, and patients with confirmed diagnosis of ESCS according to ERG waveforms were

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selected. Patients with ambiguous diagnosis and ERG changes not conforming to the diagnostic criteria were excluded from the study. Optical coherence tomography (OCT) was performed either on the Cirrus OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) or the Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) or the swept source OCT (DRI Atlantis, Topcon Medical Systems Inc., Oakland, NJ, USA). The visual fields [30-2 Swedish interactive threshold algorithm (SITA) standard strategy] were plotted using the Humphrey Field Analyzer (Carl Zeiss Meditec Inc., Dublin, CA, USA). ERG was performed using VERIS Ganzfeld visual-evoked response imaging system, Verison 6.4.2 (Electro-Diagnostic Imaging Inc., Redwood City, CA, USA) in all the patients according to the pre-defined International Society for Clinical Electrophysiology of Vision (ISCEV) criteria.[11] A descriptive analysis was used to report the findings.

Results

The search retrieved 28 eyes of 14 patients with the diagnosis of ESCS on ERG. The cohort consisted of 7 males and 7 females. The demographic profile, presenting complaints, best corrected visual acuity (BCVA), refractive error, and fundus features at presentation have been summarized in Table 1. The age at the time of first presentation ranged from 4 to 39 years, with the mean age being 13.5 ± 11.3 years. The median age was 10 years. The disease was bilateral in all patients. The most common presenting symptom was nyctalopia (n = 10, 83.33%), with or without diminution of vision (n = 7, 50% each) and floaters (n = 1, 7.14%). The BCVA for distance ranged from 6/6 to 6/36 on the distant Snellen's chart and the near acuity from N6 to N12. Fourteen (50%) of eyes had a hyperopic spherical refractive error ranging from 1 to 7.5 dioptres with varying degrees of astigmatism.

The most common clinical finding was that of pigmentary alterations of the RPE in the mid-peripheral fundus, observed in 7 patients (50%) [Fig. 1]. Nummular patches of the RPE clumping in the mid-peripheral fundus along with varying degrees of RPE atrophy was observed in 2 patients (no. 4 and 6) [Fig. 2]. Three patients (no. 1,5, and 13) had only fine yellow punctate lesions in the mid-peripheral fundus with absence of any RPE clumping or atrophy [Fig. 3]. Two patients (no. 7, a 6-year-old female and no. 14, a 22-year-old male) had no specific changes in the fundus except for altered retinal reflex in the midperiphery. Torpedo-like lesions were observed in 1 patient (no. 4) [Fig. 4a and b]. Circumferential fibrotic scarring at the posterior pole was observed in one eye (patient no. 13) [Fig. 5]. Macular schisis documented by OCT was present in 9 of 12 patients (75%), and the macula was within normal limits in the remaining 3 patients (25%). OCT was not available in two patients. The schisis had a varied clinical picture, ranging from a few discernible schitic spaces [Fig. 2c and d] to gross thickening and separation of retinal layers [Fig. 4c and d]. Visual fields were available in 7 patients (50%). Constricted peripheral field was the consistent finding in all the patients. Among other ocular features, 1 patient (patient no. 3) had bilateral posterior subcapsular cataracts and vitreous hemorrhage in the left eye [Fig. 6]. A fluorescein angiogram (FFA) was performed to look for the cause. The view of the posterior pole was hazy because of the hemorrhage, but the peripheral fundus beyond arcades in both eyes revealed patchy hyperfluoresence corresponding to the chorioretinal atrophic patches [Fig. 6e and h] but no obvious neovascularization. The hemorrhage spontaneously resolved within 3 months. Peripheral schisis, bilateral arcus juvenilis, and intermittent divergent squint were observed in 1 patient each (7.1%).

A prototype full-field ERG in ESCS is shown in Fig. 7. The ERG consistently demonstrated non-recordable single flash rod responses in all patients. Photopic and scotopic combined responses were also delayed and had a reduced amplitude in 85.71% (n = 12) patients. The 30 Hz flicker was reduced in all patients. The dark-adapted (DA) 3.0 response had a simplified, delayed, and reduced response that was almost similar to the light-adapted (LA) 3.0 response. Cone-specific chromatic stimulation was performed in all patients. Supernormal S-cone responses were observed in all patients. L and M cone responses were delayed and had reduced amplitude in 78.5% (n = 11) patients and were nearly non-recordable in 21.4% (n = 3) patients.

Genetic testing for the causative mutation was available in 2 patients. One patient tested positive for mutation in the NR2E3 gene (patient no. 6) on chromosome 15. This patient had subtle yellow pigment deposits in the mid-periphery and macular schisis [Fig. 3]. In the other patient, mutation in the neural retina leucine zipper (NRL) gene was detected. This patient had nummular clumping of RPE in the mid-periphery with pigmentary alterations in the periphery and a few schitic spaces on OCT [Fig. 4]. The locus in both the genes was on the second exon. The details of genetic analysis of these patients are provided in Table 2.

Long follow-up was available for 10 patients (71.42%). The mean follow-up was 74.5 ± 111.1 months, and a median follow-up was of 13 months. In these 10 patients, the visual acuity remained fairly stable till the last available follow-up with no gross deterioration.

Discussion

To the best of our knowledge, this is the largest series of ESCS cohort reported from the Indian population till date. The series reports clinical features of the ESCS in 28 eyes of 14 patients, all of Indian ethnicity. Traditionally, the presentation of ESCS is usually reported to be in the first decade.[4,10] Only 5 patients in our series presented in the first decade. Most patients presented after they had already consulted elsewhere in childhood and were misdiagnosed as RP, CSNB, etc., It is possible that the onset of symptoms in these cases may have been in the first decade. The age at presentation ranged from first to fourth decades. Studies elsewhere have reported the age range from first to eighth decades.[4,7] Visual acuity at presentation ranged from normal to moderate visual impairment. Audo *et al*.[4] and Yzer *et al*.[7] have reported variable visual acuity from normal to severe visual impairment. In our cohort, the presenting visual acuity had no correlation with age, which is consistent with the findings reported by Audo *et al*.[4] Similar to other studies, nyctalopia was the most common presenting complaint and most patients had a hyperopic astigmatic refractive error.[4,7]

The classic clinical findings described in ESCS reported previously are the nummular pigment clumping with areas of atrophy in the mid-periphery and periphery,[7] but it has been reported that they are neither a consistent finding nor specific

Table 1: Demographic profile and ocular findings in enhanced S-cone syndrome

Sl. No	Age	Sex	Chief complaints	Best corrected visual acuity				Refraction		Fundus findings	OCT Macula	Visual Fields	Other ocular findings
				OD		OS		OD	OS				
				D	N	D	N						
1	7	M	Nyctalopia	6/12	N6	6/18	N6	+3.50/-2.00*10	+2.50/-2.25*150	Yellowish punctate alterations in the mid-periphery	WNL	NA	--
2	4	M	Nyctalopia	6/6	N6	6/6	N6	+0.00/-2.50*10	+0.00/-2.50*170	Mid-peripheral RPE alterations and few patches of RPE atrophy	NA	Constricted peripheral field	Atrophic retinal hole in the right eye
3	18	F	nyctalopia	6/24	N6	6/36	N6	+3.50/-4.50*10	-1.50/-2.50*170	mid-peripheral yellow and blackRPE alterations with patches of RPE atrophy	Macular schisis	NA	Bilateral cortical, posterior subcapsular cataract, vitreous hemorrhage in left eye
4	26	M	Nyctalopia and diminution of vision	6/36	N12	6/36	N12	+0.75/-0.50*40	+0.75/-0.50*10	Nummular areas of RPE clumping along the arcades and peripheral RPE alterations; torpedo lesions	Macular schisis	NA	--
5	39	M	diminution of vision	6/18	N8	6/36	N6	-0.50/-0.75*180	-0.75/-1.00*180	Yellowish punctate alterations in the mid-periphery	Macular schisis	NA	Bilateral arcus juvenalis, pseudophakia
6	12	M	Nyctalopia and diminution of vision	6/6	N6	6/9	N6	+0.75/-2.50*180	+1.00/-2.25*180	mid-peripheral RPE alterations, depigmented patches at posterior pole	Macular schisis	NA	Bilateral intermittent divergent squint
7	6	F	Nyctalopia and diminution of vision	6/12	N6	6/15	N6	+7.50	+7.25	No pigment abnormalities, altered fundal reflex in the mid-periphery	NA	NA	--
8	26	F	Floaters, nyctalopia	6/18	N6	6/24	N6	-1.00*90	+0.00/-0.50*90	Mid-peripheral RPE alterations	Macular schisis	Constricted peripheral field	--
9	7	F	Nyctalopia, diminution of vision	6/24	N10	6/9	N6	+4.00	+4.00/-0.75*180	Mid-peripheral RPE alterations	Macular schisis	constricted peripheral field	--
10	10	F	Nyctalopia, diminution of vision	6/7.5	N6	6/6	N6	+4.50/-2.50*180	+4.00/-1.50*180	Mid-peripheral RPE alterations	WNL	NA	Peripheral schisis
11	7	M	Nyctalopia	6/6	N6	6/6	N6	+0.00/-2.00*20	+0.00/-0.50*160	Mid-peripheral RPE alterations	Macular schisis	constricted peripheral field	--
12	4	F	Diminution of vision	6/24	N6	6/9	N6	-3.25/-0.75*180	-3.25	Nummular areas of RPE atrophy along the arcades, peripheral nummular RPE clumping and atrophy	Macular schisis	NA	--
13	18	F	Diminution of vision	6/9	N6	6/6	N6	+0.50/-0.75*180	+0.00/-0.50*180	Yellowish punctate alterations in the mid-periphery; circumferential fibrotic scarring at the posterior pole	WNL	constricted peripheral field	--
14	22	M	Nyctalopia	6/18	N6	6/36	N6	-1.50/-0.50*180	plano	No pigment abnormalities, altered fundal reflex in the mid-periphery	Macular schisis	Constricted peripheral field	--

OD – Right eye; OS – Left eye; D – Distance; N – Near; OCT: Optical Coherence tomography; NA: Not available; RPE: Retinal pigment epithelium; WNL: Within Normal limits

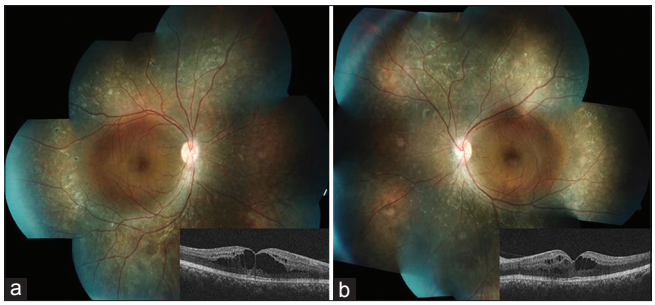

Figure 1: Fundus features of enhanced S-cone syndrome. Montage images of the right (a) and left (b) eye of patient no. 11 at the age of 19 years. Note the RPE alterations with atrophy in the mid-peripheral fundus. The optic nerve head and vessels are within normal limits. The insets show macular schisis with corresponding optical coherence tomography (OCT) images

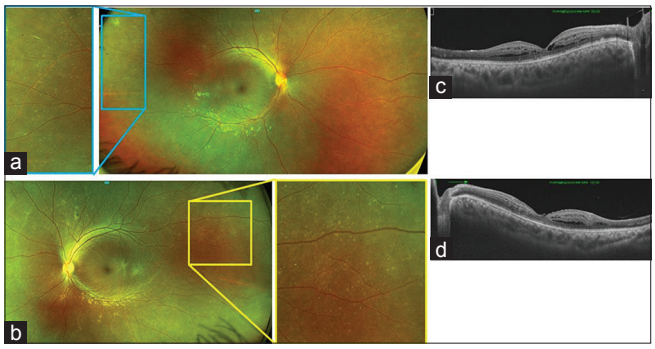

Figure 3: Intraretinal punctate yellow dots in enhanced S-cone syndrome. 7-year-old male (patient no. 1) was presented with intra-retinal yellow dots in the mid-peripheral fundus (a and b), seen more prominently in the enlarged images. Note the minimal foveal schisis on optical coherence tomography (OCT) in right eye (c) and left eye (d). Genetic testing in the patient revealed mutation in NR2E3 gene

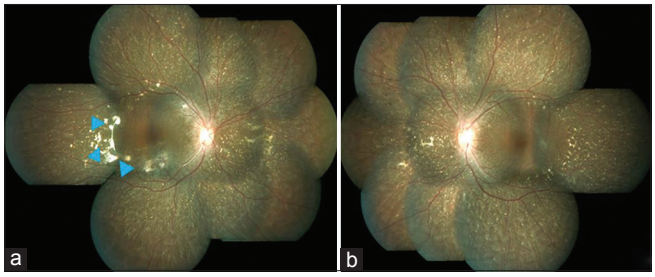

Figure 5: Circumferential subretinal fibrosis in enhanced S-cone syndrome. Intraretinal yellow dots, punctate atrophic lesions, and circumferential subretinal fibrosis (blue arrowheads) in the right eye (a) and left eye (b) of an 18-year-old female (patient no. 13). The macula was within normal limits

to ESCS.[3] In our series, nummular clumping was observed in only 2 patients, the most common finding being yellow to black irregular pigment alterations in the mid-peripheral fundus. Yzer *et al*.[7] reported novel clinical findings such as torpedo-like deep atrophic lesions, circumferential fibrotic scars at the posterior pole, around optic nerve head, and yellow dots in the normal-appearing retina. In our study, we found bilateral torpedo-like lesions in 1 patient. The torpedo-like lesions have typically been reported to consist of central depigmentation or chorioretinal atrophy with a hyperpigmented border, and

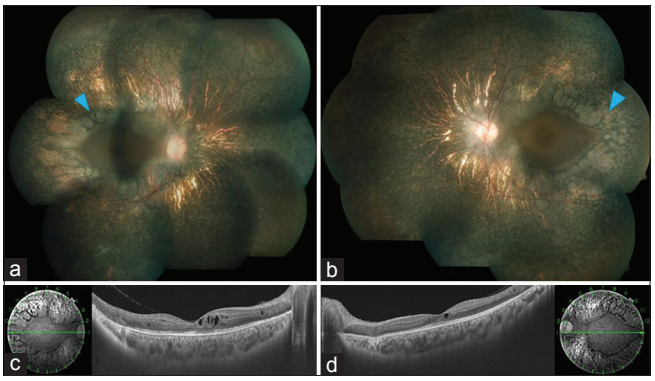

Figure 2: Nummular patches of retinal pigment epithelium (RPE) clumping in enhanced S-cone syndrome. Clinical picture in a 27-year-old girl who was presented with nyctalopia at 4 years of age (patient no. 12). (a and b) note the nummular patches of RPE atrophy (blue arrowheads) with surrounding punctate atrophic lesions in the mid-peripheral fundus. (c and d) Corresponding optical coherence tomography images showing minimal schitic spaces in the foveal region. This patient tested positive for NRL gene mutation

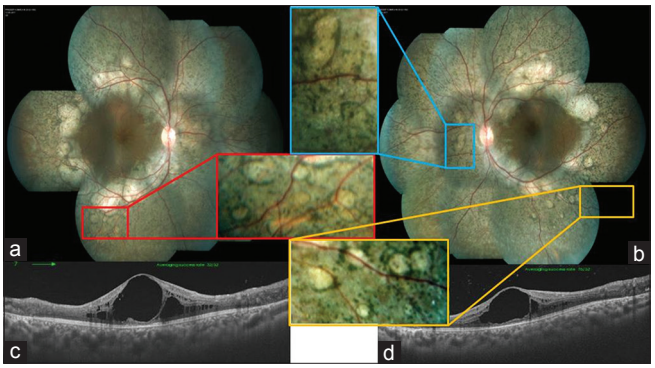

Figure 4: Torpedo-like lesions in enhanced S-cone syndrome. Torpedo-like lesions in the mid-peripheral fundus (a and b; enlarged in insets) of a 26-year-old male patient (patient no. 4). Note the large macular schisis in both eyes in the corresponding optical coherence tomography images (c and d)

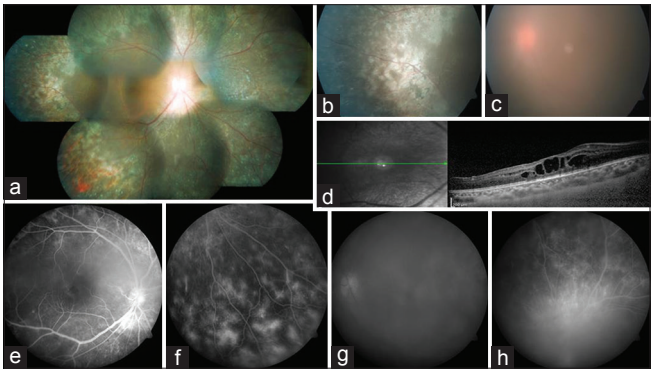

Figure 6: Vitreous hemorrhage in enhanced S-cone syndrome. 18-year-old female (patient no. 3) presenting with vitreous hemorrhage in the left eye (c).The right eye showed the typical mid-peripheral patches of RPE alterations (a), better appreciated in (b). Optical coherence tomography in the right eye revealed macular schisis (d). Fluorescein angiography corresponded to the fundus picture in both eyes (e-h), with no obvious neovascularization in the left eye (g, h)

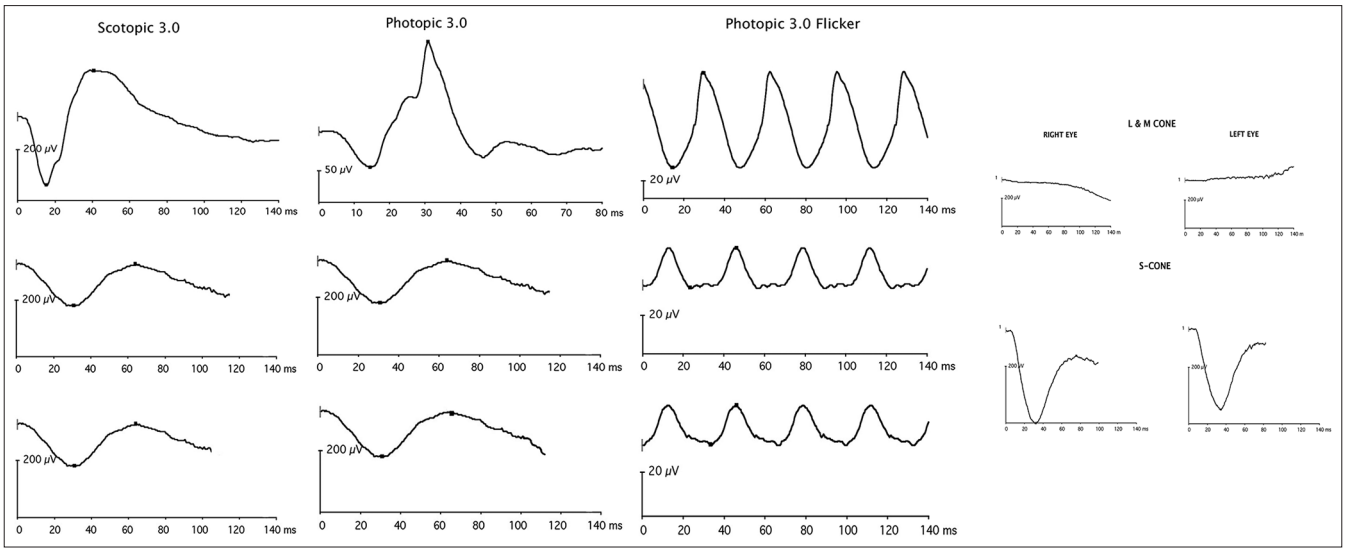

Figure 7: Typical electroretinogram in enhanced S-cone syndrome. The top row shows the ERG in a normal individual. Second and third rows show ERG of right and left eyes of a 7-year-old male (patient no. 11). The simplified scotopic 3.0 waveform [1st column] is similar to the photopic 3.0 waveform [2nd column] as both are dominated by the short-wavelength-sensitive mechanisms. Specific chromatic stimulation shows nearly non-detectable L- and M- cone responses [4th column] and supernormal S-cone responses [5th column]. Other features include delayed and reduced 30 Hz flicker[3rd column]

Table 2: Genetic mutations in patients with enhanced S-cone syndrome

Pt. No.	Gene	Identified variation	Chromosome	Protein change	Zygosity	Clinical significance
6	NR2E3/Exon 2	c.228delG	15:72103932	p.Arg77GlyfcTer29	Homozygous	Pathogenic
12	NRL/Exon 2	c.91C>T	14:24551967G>A	p.Arg31Ter	Homozygous	Pathogenic

they are observed along the arcades. Both the appearance and location of the torpedo-like lesions in this patient corroborated with the previously reported findings. The age range of patients presenting with these torpedo-like lesions was 24 to 55 years, as reported by Yzer *et al*.[7] In our cohort, the solitary patient with torpedo-like lesions was 26 years of age. Although the exact pathogenesis of the lesions is not known, abnormal choroidal or ciliary vasculature development or a fetal RPE defect has been postulated.[12,13] Intraretinal yellow dots have been reported in ESCS and other retinal dystrophies. Yzer *et al*.[7] peculiarly noted that all patients with subretinal fibrosis also had yellow dots. The location of these has been reported to be variable. In our patients, they were almost uniformly distributed in the mid-periphery of fundus. Although helicoid subretinal fibrosis was not observed, 1 patient with intraretinal yellow dots had circumferential subretinal fibrosis at the posterior pole. Although, both peripheral and macular retinoschisis have been reported in ESCS, peripheral retinoschisis is more common.[14]. In our cohort, peripheral retinoschisis was present in only 1 patient (two eyes), whereas macular retinoschisis was more commonly noted, being present in 9 patients (18 eyes). Bilateral disc edema has been reported in a recent study.[15]

Despite the variable fundus appearance, the constant finding is that of retinal degeneration in the mid-peripheral area surrounding the central field of vision. This area corresponds with the maximum S-cone dysfunction. This area also coincides with the maximum rod photoreceptor density. Hence, it is postulated that there is failure of the photoreceptors to differentiate properly and are replaced by S cones.[16] This results in visual field loss in the mid-peripheral region. The retinal degeneration is thought to be because of abnormal photoreceptor maintenance, disturbed phagocytosis, microglial proliferation, and complex gene interactions.[16]

One limitation of our study was that genotype-phenotype correlation could not be attempted in all patients as only 2 patients had undergone gene testing. NR2E3 mutations were first shown to be associated with ESCS by Haider *et al*.[17] More than 30 different variations in the NR2E3 mutations causing ESCS, GFS, CPRD, and RP have been identified.[18] Yzer *et al*.[7] attempted correlation of only those patients with common NR2E3 mutations (p, R311Q and c. 119-2A >C or IVSI-2A >C). However, they could not establish a clear genotype-phenotype relationship as the torpedo-like lesions or the subretinal fibrosis were not exclusive to any genotype. Our solitary patient with NR2E3 mutation had the pathogenic c. 228delG mutation, and the fundus had yellow dots in an otherwise normal appearing retina. The second patient had a mutation in the NRL gene. NRL mutations causing ESCS like manifestations have been reported by other authors.[19-21] Littink *et al*.[21] reported 3 patients with NRL mutation with ESCS. Phenotypically, all 3 patients had mid-peripheral pronounced RPE atrophy with nummular pigmentations and a preserved macular region. Our patient, too, showed a similar picture [Fig. 4]. The pathogenic variation of c.91C >T in the NRL gene was identified in this patient.

ESCS is one of the few disorders in which an ERG conclusively establishes the diagnosis. The ERG findings of the present cohort were in unison with the ERG described in

literature, viz., abolished or grossly reduced single flash rod responses, simplified waveform of the DA 3.0 response and its similarity to the LA 3.0 response, and a delayed 30 Hz flicker with reduced amplitude. In such scenario, specific chromatic stimulation is not necessary for the diagnosis.[4] However, all the patients in this cohort underwent specific chromatic stimulation and all of them demonstrated supernormal S-cone responses, which is in agreement with findings of Audo *et al*.[4] They observed that there was a tendency toward progressive decrease in ERG amplitudes with age, so that the older patients had lower amplitudes. However, no such trend was observed in this cohort. Pattern ERG has been reported to be delayed and reduced or even undetectable in ESCS patients.[4] Changes have also been reported in multifocal ERG, which demonstrated relative preservation of central function but reduced responses with increased eccentricity. Electrooculogram in these cases shows an undetectable light rise.[4] However, these investigations were not done in our subjects as they were not essential for diagnosis. Wherever follow-up data were available, none of the patients showed significant reduction in terms of Snellen's visual acuity. However, visual acuity cannot be the sole criterion to detect progression as longitudinal ERG data in some ESCS patients have shown slowly progressive dysfunction with gradual deterioration of visual acuity and variable visual field constriction.[4]

As mentioned earlier, ESCS is usually misdiagnosed as RP, CSNB, and XLRS. This is because most of these disorders share common features such as presentation in the early decades of life, night blindness, and mid-peripheral pigmentary changes.[8,20-27] ESCS being a rare disorder, diagnosis of this entity is a challenge because of relative lack of awareness about this condition and non-availability of electrophysiological testing at all centers. Table 3 provides a useful guide in differentiation and diagnosis of these disorders. Accurate diagnosis and differentiation are essential because the prognosis of these conditions is different. Although some disorders are rapidly progressive, ESCS is often stationary/slowly progressive.

Table 3: Differentiating features between ESCS and other common differential diagnoses

	Enhanced S-cone syndrome	Retinitis pigmentosa	Congenital stationary night blindness	Juvenile X linked retinoschisis
Age group affected/age at onset	Usually first decade	Variable		Usually 1-5 years
Prevalence	<1: 1000000	1:3000 to 1:5000	Unknown	1: 15000 to 1:30000
Mode of inheritance	AR	AD, AR, X-linked	AD, AR, X-linked	X-linked
Genes involved	Most commonly NR2E3	More than 100 gene loci identified	More than 17 genes till date	RS1
Common presenting complaints	Nyctalopia	Nyctalopia	Nyctalopia	Poor vision, strabismus, and nystagmus
Presenting visual acuity	Usually mild visual impairment	Highly variable, from near normal to profound visual impairment	Usually mild to moderate visual impairment	Highly variable, from near normal to profound visual impairment
Commonly encountered fundus features	Pigmentary alterations in the mid-peripheral and peripheral fundus, nummular pigment clumping, intra-retinal yellow dot	Bone-spicule pigment alterations in mid-peripheral fundus, attenuated retinal vessels, waxy optic disc pallor, no pigment alterations (sine pigmento)	Normal appearing fundus, golden brown fundal discoloration (Oguchi disease), white to whitish yellow deposits in mid-periphery (albipunctatus), myopic fundus (Schubert-Bornschein type)	Peripheral retinoschisis, vitreous hemorrhage, inner and outer layer retinal breaks
Macular features	Varying degrees of macular schisis	Cystoid macular edema	Macular degeneration in later life	Bicycle spoke-like schitic cavities a prominent and most consistent feature
ERG pattern	Pathognomonic. Non-detectable dim flash scotopic responses; simplified, delayed and usually reduced DA 3.0 ERG which is remarkably similar to the LA 3.0 ERG; reduced flicker ERG. Supernormal S-cone ERGs on chromatic stimulation	Not pathognomonic. Severely reduced/ abolished single rod responses, with varying degrees of reduction cone responses depending on disease severity and stage	Pathognomonic. Riggs type - non-detectable dim flash scotopic responses. Decreased a-wave and b-wave amplitude in strong flash scotopic ERG. Normal photopic ERG. Schubert-Bornstein type - similar to Riggs type except that the a-wave has normal amplitude in strong flash scotopic ERG.	Not pathognomonic. Electro-negative ERG (Reduced b-wave with a preserved a-wave)
Progression	Slow	Highly variable depending on the genotype-phenotype	Stationary/slow	Usually, schisis remains stationary

ERG – Electroretinogram; AR- Autosomal recessive; AD – Autosomal dominant; DA – dark adapted; LA – Light adapted

Conclusion

In conclusion, the ESCS is a rare disorder that can have varied phenotypic manifestations that can be confused with other conditions such as RP, CSNB, and XLRS. A pathognomonic ERG is essential to make the accurate diagnosis, which can be substantiated with documented genetic mutation. It is important to recognize this slowly-progressive condition accurately and distinguish it from other phenotypically similar disorders, as the prognosis differs significantly.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Marmor MF, Jacobson SG, Foerster MH, Kellner U, Weleber RG. Diagnostic clinical findings of a new syndrome with night blindness, maculopathy, and enhanced S cone sensitivity. Am J Ophthalmol 1990;110:124-34.
2. Curcio CA, Sloan KR, Kalina RE, Hendrickson AE. Human photoreceptor topography. J Comp Neurol 1990;292:446-53.
3. Sohn EH, Chen FK, Rubin GS, Moore AT, Webster AR, MacLaren RE. Macular function assessed by microperimetry in patients with enhanced S-cone syndrome. Ophthalmology 2010;117:1199-206.e1.
4. Audo I, Michaelides M, Robson AG, Hawlina M, Vaclavik V, Sandbach JM, *et al*. Phenotypic variation in enhanced S-cone syndrome. Invest Ophthalmol Vis Sci 2008;49:2082-93.
5. Jacobson SG, Marmor MF, Kemp CM, Knighton RW. SWS (Blue) cone hypersensitivity in newly identified retinal degeneration. Invest Ophthal Vis Sci 1990;31:827-38.
6. Khan AO, Aldahmesh MA, Al-Harthi E, Alkuraya FA. Helicoid subretinal fibrosis associated with a novel recessive NR2E3 mutation p.S44X. Arch Ophthalmol 2010;128:344-8.
7. Yzer S, Barbazetto I, Allikmets R, van Schooneveld MJ, Bergen A, Tsang SH, *et al*. Expanded clinical spectrum of enhanced S-cone syndrome. JAMA Ophthalmol 2013;131:1324-30.
8. Vincent A, Robson AG, Holder GE. Pathognomonic (diagnostic) ERGs: A review and update. Retina 2013;33:5-12.
9. Jacobson SG, Roman AJ, Roman MI, Gass JD, Parker JA. Relatively enhanced S cone function in the Goldmann-Favre syndrome. Am J Ophthalmol 1991;111:497-523.
10. Sharon D, Sandberg MA, Caruso RC, Berson EL, Dryja TP. Shared mutations in *NR2E3* in enhanced s-cone syndrome, Goldmann-Favre syndrome, and many cases of clumped pigmentary retinal degeneration. Arch Ophthalmol 2003;121:1316-23.
11. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R, *et al*. ISCEV Standard for full-field clinical electroretinography. Doc Ophthalmol 2015;130:1-12.
12. Shields CL, Guzman JM, Shapiro MJ, Fogel LE, Shields JA. Torpedo maculopathy at the site of the fetal "bulge". Arch Ophthalmol 2010;128:499-501.
13. Golchet PR, Jampol LM, Mathura JRJr, Daily MJ. Torpedo maculopathy. Br J Ophthalmol 2010;94:302-6.
14. Batioglu F. Goldmann-Favre vitreoretinal degeneration. Eur J Ophthalmol 2003;13:307-10.
15. Özateş S, Tekin K, Teke MY. Goldmann-favresyndrome: Case series. Turkish J Ophthalmol 2018;48:47-51.
16. GarafaloAV, Calzetti G, Cideciyan AV, Roman AJ, Saxena S, Sumaroka A, *et al*. Conevision changes in the enhancedS-Conesyndrome caused by NR2E3 gene mutations. Invest Ophthalmol Vis Sci 2018;59:3209-19.
17. Haider NB, Jacobson SG, Cideciyan AV, Swiderski R, Streb LM, Searby C, *et al*. Mutation of a nuclear receptor gene, NR2E3, causes enhanced S cone syndrome, a disorder of retinal cell fate. Nat Genet 2000;24:127-31.
18. Schorderet DF, Escher P. NR2E3 mutations in enhanced S-cone sensitivity syndrome (ESCS), Goldmann-Favre syndrome (GFS), clumped pigmentary retinal degeneration (CPRD), and retinitis pigmentosa (RP). Hum Mutat 2009;30:1475-85.
19. Nishiguchi KM, Friedman JS, Sandberg MA, Swaroop A, Berson EL, Dryja TP. Recessive*NRL*mutations in patients with clumped pigmentary retinal degeneration and relative preservation of blue cone function. Proc Natl Acad Sci 2004;101:17819-24.
20. NewmanH, Blumen SC, Braverman I, Hanna R, Tiosano B, Perlman I, *et al*. Homozygosity for a Recessive loss-of-function mutation of the NRL gene is associated with a variant of enhanced S-Cone syndrome. Invest Ophthalmol Vis Sci 2016;57:5361-71.
21. Littink KW, Stappers PTY, Riemslag FCC, Talsma HE, van Genderen MM, Cremers FPM, *et al*. Autosomal recessive*NRL* mutations in patients with enhanced S-Cone syndrome.Genes 2018;9:68.
22. Weleber RG, Gregory-Evans K. Retinitis pigmentosa and allied disorders. In: Ryan SJ, editor. Retina. 4th ed. Philadelphia, USA: Elsevier; 2006. p. 394-485.
23. Sikkink SK, Biswas S, Parry NRA, Stanga PE, Trump D. X-linked retinoschisis: An update. J Med Genet 2007;44:225-32.
24. Berson EL. Retinitis pigmentosa and allied diseases. In: Albert D, Miller J, Azar D, Blodi B, editors. Albert and Jakobiec, 3rd ed. Philadelphia, PA: Elsevier; 2008. Ch. 177.
25. Baldwin AN, Robson AG, Moore AT, Duncan JL. Ryan'sRetina, In: Schachat AP, editor. Edinburgh, UK: Elsevier; 2018.p. 1006-17.
26. Bijveld MM, Florijn RJ, Bergen AA, van den Born LI, Kamermans M, Prick L, *et al*. Genotype and phenotype of 101 Dutch patients with congenital stationary night blindness. Ophthalmology 2013;120:2072-81
27. Hirose T, Blodi BA. Retinoschisis. In: Albert DM, editor. Principles and Practice ofOphthalmology. 3rd ed. Philadelphia, USA: Saunders; 2008. p. 2287-304.