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Phenotypic characterisation of enhanced S Cone syndrome—a multicenter case series analysis

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PURPOSE: To characterise in detail the clinical features of enhanced S-cone syndrome (ESCS).

METHODS: A retrospective study of retinal phenotype in 34 subjects with ESCS recruited from four centres in India. All subjects had a pathognomonic electroretinogram (ERG) features diagnostic of ESCS and had colour fundus imaging. Fundus photographs, fundus autofluorescence (11 subjects) and optical coherence tomography (OCT, 22 subjects) images were graded, and correlation between their gradings were ascertained. Effect of age on visual acuity was analysed.

RESULTS: Twenty-one males (62%) and 13 females were included. The median age at presentation was 17.5 years [Interquartile range:10, 25]. Nyctalopia was the most common presenting symptom seen in 76% (26/34) of subjects. The median best corrected visual acuity at presentation was 0.35 logMAR [0.17, 0.62]. The most common retinal phenotype was a ring of non-specific pigmentary changes along the arcades with or without atrophy (41%, 28/68 eyes) followed by yellow to white dot like changes along the vascular arcades/mid-periphery (38%, 26/68). Hypo-autofluorescence with moderate diffuse or patchy changes along the major vascular arcades was seen in 37% (8/22) of eyes. OCT showed foveomacular schisis in 79% (35/44), of which 8 eyes (18%) had giant schisis(>1000 um). No correlation was observed between any of the retinal features and fundus autofluorescence subtypes, but lower visual acuity with increasing age was noted (R^2;0.122, $p < 0.05$).

CONCLUSION: This study establishes the range of retinal features associated with ESCS. Pigmentary changes with or without atrophy along the arcades was predominantly seen in our cohort unlike nummular changes described in previous studies of ESCS.

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INTRODUCTION

Enhanced S-cone syndrome (ESCS) (OMIM# 268100) is a rare autosomal recessive disorder due to biallelic pathogenic variants in the nuclear receptor subfamily 2, group E, member 3(*NR2E3*) or neural retina leucine zipper *(NRL)* genes [1–4]. *NR2E3* is more common, and the gene encodes a photoreceptor-specific transcription factor which promotes differentiation of the multipotent retinal progenitor cells to rods and all cone classes [3]. *NRL* is an upstream regulator of *NR2E3*, thus influencing the development of rod photoreceptor lineage [4]. Hence, in ESCS subjects, rods are de-differentiated to short wavelength (S) cones resulting in manifold increase in the number of S cones and the pathognomonic electrophysiologic response of the condition [1, 5–7]. Briefly, there is no rod contribution to the dark adapted (DA) electroretinograms (ERG), and the DA 3.0 ERG response is simplified, delayed and similar to the light adapted 3.0 (LA 3.0) ERG, both driven by the S-cones. Also, the LA 30 Hz flicker ERG amplitudes are usually smaller than the LA 3.0 ERG a-wave as the S-cones cannot respond well to fast flickering stimulus [7–9].

Patients present with nyctalopia and reduced vision in early childhood with or without peripheral visual field loss. These symptoms often lead to a misdiagnosis of retinitis pigmentosa [10, 11]. Common clinical findings described in ESCS include hypermetropia, foveo-macular retinoschisis and mid-peripheral retinal abnormalities that range from typical clumped nummular pigmentary abnormalities at the level of the retinal pigment epithelium (RPE) to a subtle yellow to white dots with pigmentary changes around the vascular arcades [10–17].

There are two large case series of ESCS including 56 and 31 subjects, respectively [15, 17]. Notably, most published literatures in ESCS are in Caucasian and Japanese populations [12–17] There is only one report from India describing ESCS features in 14 subjects [11]. In the current study, we extensively characterise the clinical features of 34 subjects with ESCS and further the knowledge about the natural history of the disease.

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Table 1. Grading of fundus and fundus autofluorescence appearance.

	Fundus appearance grading from Fa to Fe based on most striking feature seen.
Fa	Ring of non-specific pigmentary changes along the arcades with or without atrophy
Fb	Yellow to white dot like changes along the arcades or in mid periphery
Fc	Nummular pigmentation in mid periphery with or without atrophic patches
Fd	Altered mid peripheral reflex with no pigmentation
Fe	Normal appearance by clinical examination
	Fundus autofluorescence grading from AFa to AFe
AFa	Macular hypoautofluorescence with minimal change pattern
AFb	Hypoautofluorescence with moderate diffuse or patchy changes along the arcades
AFc	Minimal change macular autofluorescence with hyperautofluorescent flecks
AFd	Advanced peripheral hypoautofluorescence
AFe	Severe end stage macular hypoautofluorescence

Table 2. Grading of optical coherence tomography features.

	OCT Features	***N* = 44**
O1	Schisis	
	O1a: Without loss of subfoveal EZ	22 (50%)
	O1b: With loss of subfoveal EZ	4 (9%)
	O1c: Giant schisis(>1000 um) with loss of subfoveal EZ	8 (18%)
O2	Central foveal thinning(<150 um)	
	O2a: With loss of subfoveal EZ, no schisis	4 (9%)
	O2b: With loss of subfoveal EZ and presence of schisis	1 (2%)
O3	Loss of subfoveal EZ but no schisis	2 (5%)
O4	Scarred CNVM with loss of subfoveal EZ	1 (2%)
O5	Normal	2 (5%)

EZ Ellipzoid zone, *CNVM* Choroidal neovascular membrane.

METHODS AND SUBJECTS

This retrospective study was approved by the local ethics committee at each participating centre and adhered to the declaration of Helsinki. The study included 34 subjects diagnosed with ESCS based on pathognomonic ERG features on international standard testing [7, 8] and recruited from four tertiary eye institutes in South India, between 2008 and 2020. Assessments included best-corrected visual acuity (BCVA) and comprehensive ophthalmological examination including colour fundus photography (68 eyes: Optos optomap ultra-widefield (UWF^{TM}) or Zeiss clarus 500 or Zeiss FF450plus camera), fundus autofluorescence (FAF) imaging (22 eyes: Optos optomap ultra-widefield (UWF^{TM}) or Zeiss clarus 500 or Spectralis HRA + OCT), optical coherence tomography (OCT)(44 eyes : swept source Topcon or Spectralis HRA + OCT or Zeiss cirrus). ERG was performed by Metrovision monopack or LKC technologies or VERIS visual system. Limited clinical and imaging findings from the current cohort was published previously [11]. For analysis, we adapted from the findings observed by de Carvalho et al. with modifications as the fundus findings in our cohort varied (Tables 1 and 2) [15]. Foveomacular schisis with central macular thickness of >1000 µm was termed as giant schisis. Central foveal thickness of <150 µm was termed as retinal thinning. The fundus from eye each of the participant was graded based on the most striking phenotype observed.

Descriptive statistics using mean ± standard deviation (SD) and median with interquartile range (IQR) were used to elucidate the demographic data. Chi-square test and paired *t*-test (Stata software, Stata Corp. 2015. College Station, TX: Stata Corp LP) were used for the univariate analyses. Statistical difference was assessed by paired *t*-test or Wilcoxon signed rank test. Spearman correlation and linear regression were used to determine the relation between age and visual acuity, incorporating both baseline cross sectional and longitudinal data.

RESULTS

The study included 34 subjects (68 eyes) from 34 families. The median age at presentation was 17.5 years (IQR 10, 25). Majority of the subjects were males (21/34). Consanguinity was noted in 9 pedigrees (26%) and there was a family history of presumed ESCS in four of these pedigrees. The median BCVA in logMAR at baseline was 0.35(IQR 0.17–0.62). Nyctalopia was the commonest presenting symptom (26 subjects; 76%) whilst three were asymptomatic at presentation. On spherical equivalent calculation, hyperopia (>+0.5D) and myopia (>−0.5D) were noted in 57% (39/68 eyes) and 24% (16/68 eyes), respectively. Among 39 hyperopic eyes; 21, 13 and 5 eyes had mild (up to +2D), moderate (+2 to +5D) and high hyperopia (>+5D), respectively. Among 16 myopic eyes; 15 eyes had mild myopia (up to −3D) and 1 eye had moderate myopia (−3 to −6D). Asymmetric visual acuity levels (>15 ETDRS letters difference) were noted in 8/34 (23%) subjects. Linear regression analysis depicted a significant worsening of visual acuity with age ($p < 0.05$) (Fig. 1). Eleven of the subjects had follow-up visits (median follow-up duration: 4.5 years (IQR 1.3 to 9 years)). The mean age of these 11 subjects at baseline and at the last follow-up visit was 18 ± 12 years and 25 ± 11 years, respectively. Mean average BCVA of these 11 subjects at baseline and at the last follow up visit was 0.38 ± 0.29logMAR and 0.33 ± 0.28logMAR, respectively. S cone ERGs showed supernormal responses in all 18 tested subjects.

Retinal phenotype

Four patterns of fundus appearance were identified (Fig. 2 and Supplementary Fig. 1). The most common phenotype was Fa (41%,28/68) followed by Fb (38%, 26/68), Fc (15%,10/68) and Fd (6%, 4/68). Fundus appearance was symmetrical in all cases. Age did neither influence the pattern of fundus appearance ($p = 0.50$) nor the degree of pigmentary changes ($p = 0.21$). Two subjects with altered mid peripheral retinal reflex (Fd) were of 7 and 25 years of age.

Fundus autofluorescence (AF) (Figure 3)

All five patterns of AF were noted. AFb was the commoner pattern (36%,8/22 eyes) followed by equal number of AFa, AFc and AFd patterns (18%, 4/22 in each group). Two eyes (9%, 2/22) had AFe pattern. The median BCVA of subjects with the AFb pattern was 0.4 logMAR (median age—24 years). Eyes with AFb pattern had hyperautofluorescent ring within the arcades. All eyes with AFa grading had vision of 0.1 logMAR or better. There was no correlation between BCVA and other patterns of fundus autofluorescence ($p = 0.94$). No statistically significant correlation was found between any of the fundus and fundus autofluorescence sub-types.

Optical coherence tomography

Table 2 and Supplementary Fig. 2 depicts the OCT grading and features found in our cohort. Subfoveal loss of EZ (O1b, O2 and O3) was observed in subjects with a median age of 25 years (range 13–67) and their mean BCVA was 0.6 ± 0.3logMAR. The median age

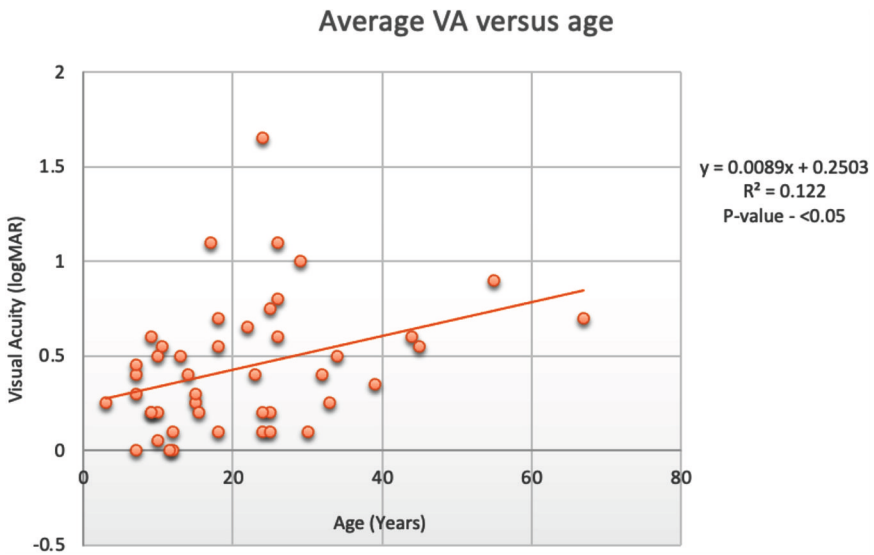

Fig. 1 Scatterplot depicting correlation between average visual acuity(VA) of both eyes (of all patients) to age.

and mean BCVA of subjects with schisis but preserved subfoveal EZ(O1a) was 15 years (range 9–25) and 0.33 ± 0.25logMAR, respectively. Giant schisis with loss of subfoveal EZ (O1c) was seen in subjects with mean age of 21 ± 5 years and mean BCVA was 1.09 ± 0.4logMAR. Chi-square analysis between OCT and fundus grading revealed significant interactions between the two categories ($p = 0.033$). However, the effect of individual grades was limited due to small sample size. One eye with choroidal neovascular membrane received monthly intravitreal bevacizumab injections (3 doses) following which the vision improved from counting fingers at 2 meters to 0.9 logMAR.

Genetic results

Genetic confirmation was available for three subjects; two had homozygous pathogenic variants in *NR2E3*(Fa category): c.143_144delinsAGTGTGCCTCCAGTGCCTCGCTCCA(p.Arg48Glnfs*66), c.228delG (p.Arg77Glyfs*29) and one had homozygous stop variant in *NRL*(Fc category): c.91 C > T(p.Arg31*).

DISCUSSION

The current study comprehensively characterises the range and relative frequencies of the various phenotypes found amongst ESCS subjects in India. Patients often presented in the second decade of life with nyctalopia and reduced vision. A ring of non-specific pigmentary changes along the arcades with or without atrophy and mid-peripheral yellow-white dots (Fa and Fb, respectively) was seen in the majority of the patients (80%). Age did not influence the fundus phenotype. Fundus autofluorescence patterns widely varied in the cohort, hypoautofluorescence with moderate diffuse or patchy changes along the arcades being commonest (AFb, 36%). Notably, eyes with macular hypoautofluorescence with minimal change pattern (AFa) had preserved vision (better than 0.1logMAR). Half of the eyes showed foveomacular retinoschisis without loss of ellipsoid zone, whilst giant schisis with EZ loss was seen in younger subjects (18%).

In a previous series by de Carvalho et al. nummular pigmentation (akin to Fc-48/56 patients,85%) was the most common finding followed by yellow white dots (similar to Fb-32/56 patients,57%). However, in our cohort Fc as striking phenotype was less frequent (15%) compared to Fa and Fb (41 and 38%, respectively). It is likely that these differences may be due to phenotypic variation in ESCS with ~130 disease causing variants in *NR2E3* gene (https://www.ncbi.nlm.nih.gov/clinvar) and additional unidentified genetic, ethnic or environmental factors [5, 6, 15–18]. In our cohort, we did not find a direct correlation of greater pigmentation (Fa and Fc grades) to older subjects. Sharon et al. hypothesised that the typical mid-peripheral pigmentary clumping at the level of the RPE appears with progressing age as the authors had observed one subject who developed these pigment clumps in later life after having noted none at the age of 5 years [6]. Other studies however refute the correlation of pigmentation to age, similar to our series [11, 15–17, 19]. Overall, pigmentary fundus changes seem to be varied and there is a subjective aspect to its ascertainment and sometimes, it is difficult to provide a quantitative consensus.

In comparison, FAF grading is objective and less varied. The patterns of autofluorescence seen in our cohort largely matched to the descriptions of de Carvalho et al. [15]. In our cohort better vision was noted in the AFa sub-type (macular hypoautofluorescence- with minimal change pattern). Further, BCVA was asymmetric in the two eyes (0.4 and 1logMAR) of the same subject with severe end stage macular hypoautofluorescence pattern (AFe). Correlation of the pattern of fundus autofluorescence to BCVA in a larger data set might be beneficial for visual prognostication.

Amongst subjects who had OCT imaging, 75% had foveomacular retinoschisis. It is noted that coalition of these schisis cavities in ESCS may progress into giant schisis with poor vision [13, 19]. Eight of our subjects had giant schisis and a BCVA of 0.79logMAR or worse. In the current cohort, BCVA did not worsen in eyes which had follow up data for a short period (4.5 years). But overall, our cross-sectional data (with patients in three decades) shows progressive loss of central vision with increasing age. Taken together, our results likely suggest slow progressive loss of BCVA in ESCS.

Retinitis pigmentosa (RP) is quite prevalent in India and across the world (1/3000–1/4000) when compared to ESCS (1 in 10^{-6}) (https://www.orpha.net/en/disease) [20–24]. Hence, general ophthalmic practitioners and retina specialists are more familiar with RP. It is striking that awareness about ESCS is lacking amongst eye specialists as none of the 34 subjects in our study were referred with the correct diagnosis. This could also be the case in other areas globally as well. Most case series have been reported only from developed countries that traditionally have less autosomal recessive disease burden (due to variation in prevalence of consanguineous marriages and smaller family sizes); hence, our results enhance the understanding about range of phenotypic manifestations that could be seen in different populations with ESCS [11–16]. The phenotypic characterisation

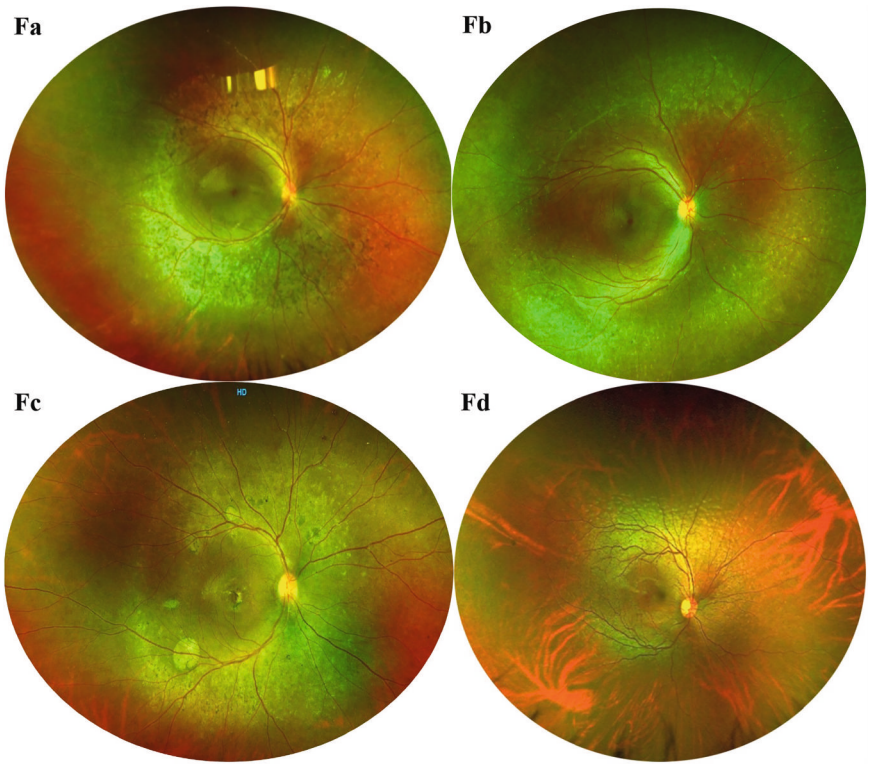

Fig. 2 Four patterns of fundus appearance (Fa-Fd; Table 1) seen in our cohort.

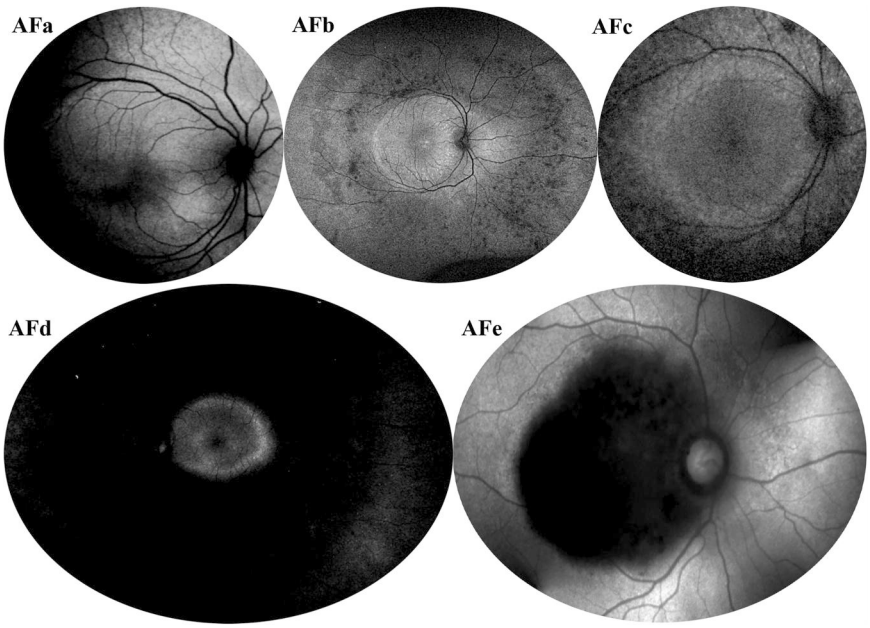

Fig. 3 Five patterns of fundus appearance (AFa-AFe; Table 1) seen in our cohort.

in the current series would help eye specialists to diagnose this slow progressive distinct condition which would help provide an accurate disease prognostication and counselling to patients even in the absence of genetic testing. The limitations of our study are its retrospective nature and paucity of genotypic validation. Due to retrospective nature of the study no standardised questions were asked about specific symptoms like nyctalopia. Further, lack of wide-field AF imaging in four subjects may have affected the relative frequencies of sub-types.

In conclusion, the current study provides the spectrum of clinical phenotype observed in ESCS in a large Indian cohort. Full field ERG is an essential tool for diagnosis of ESCS unless there is access to genetic testing as the fundus presentation is varied. In patients with nyctalopia along with fundus phenotypes described in the current study, the possible diagnosis of ESCS should be considered, along with consideration of ERG testing. This helps in ruling out other causes of nyctalopia like RP. Further studies are warranted to understand the genetic variant analysis in this

cohort and their correlation to the pattern of autofluorescence and fundus features.

SUMMARY

What was known before:

- Pathognomonic electroretinogram findings are described in Enhanced S cone syndrome (ESCS).
- ESCS studies from Caucasian and Japanese populations have reported nummular pigmentation as the predominant feature
- Fundus autofluorescence features are described in only a few reports.

What this study adds:

- A ring of non-specific pigmentary changes was predominantly observed in our ESCS cohort, in contrast to the nummular pigmentation reported in previous studies.
- Hypoautofluorescence with a minimal change pattern was associated with better vision.
- Wide phenotypic classification in the current series could aid eye specialists in diagnosing ESCS, even without genetic testing.
- Slow, progressive loss of vision can be observed in ESCS with increasing age.

DATA AVAILABILITY

Data related to the manuscript will be available from the corresponding author upon request

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AUTHOR CONTRIBUTIONS

Conceptualisation: SJ, DCP; Methodology: SJ, DCP; Data Collection: SJ, DCP, SH, SR, SD, KK, MR, DR, IA, PB, SKP, TRP. Statistical Analysis: RN, DCP, AV, SJ; Original Draft Preparation: DCP, AV, SJ; Critical Review & Editing: AV, SJ, DCP, DR

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COMPETING INTERESTS

The authors declare no competing interests.

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