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CLINICAL CASE REPORT

Novel findings in enhanced S-cone syndrome: a case with macular retinal neovascularization and severe retinal vasculitis

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Abstract
Purpose To describe a novel association of enhanced S-cone syndrome (ESCS) with macular retinal neovascularization and severe retinal vasculitis.
Methods Clinical examination, spectral domain optical coherence tomography, fluorescein angiography, fundus autofluorescence, infrared reflectance and electroretinography were used to study a 25-year-old male with a history of night blindness from early childhood and recent accelerated visual loss in right eye.
Results Pigmented lesions were observed along the arcades without peripheral retinal involvement. Intraretinal cystoid spaces, retinal neovascularization of posterior pole and severe peripheral and posterior retinal vasculitis were found on clinical examination and multimodal imaging. Based on characteristic clinical and electroretinographic findings, a diagnosis of ESCS was made.
Conclusion This case highlights novel associations of retinal neovascularization and vasculitis with ESCS.

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Keywords Enhanced S-cone syndrome · Electroretinography · Neovascularization · Retinal vasculitis

Introduction

In normal adult human retina, short-wavelength (S) cones comprise a minority of cone population. In enhanced S-cone syndrome (ESCS), a rare autosomal recessive retinal dystrophy, the rod function is absent, and majority of cones are S-cones. This syndrome has been attributed to mutations in *NR2E3* gene that encodes the nuclear receptor class 2, subfamily E, member 3 protein which suppresses cone differentiation. ESCS is characterized by a wide spectrum of clinical findings (including night blindness and variable pigmented lesions along the arcades) and characteristic electroretinography (ERG) findings [1, 2]. The perimacular elliptical ring adjacent to vascular arcades is the site of many abnormal retinal findings in ESCS. Interestingly, in normal retina, this region is predominantly occupied by rods. It has been suggested that substitution of these rods by S-cones ultimately leads to degenerative changes observed in ESCS [1]. ERG characteristically shows the absence of rod function and similar waves in both single-flash light-adapted (LA 3.0) and maximal dark-adapted (DA 10.0) responses. Photopic flicker response (LA3.0 30) is disproportionately attenuated to the single-flash

cone amplitude (LA3.0) [1]. Although retinal vascular alterations including retinal neovascularization, peripheral sea fan neovascularization and vasculitis have been reported in association with retinitis pigmentosa, there is no report of association between these findings and ESCS [3–6]. Some authors have reported subretinal neovascularization associated with ESCS [7–10].

The aim of this study is to report a novel association of ESCS with macular retinal neovascularization and severe retinal vasculitis.

Case description

A 25-year-old male presented with night blindness since early childhood and severe visual loss in his right eye for the last 4 months. His parents were consanguineous, and his father did also complain of night blindness since an early age. His best-corrected Snellen visual acuity was counting finger in OD and 20/40 in OS. Refractions were + 3.25–2.00 × 170° (OD) and + 5.50–2.50 × 175° (OS). Right exotropia was evident. Anterior segment examination was unremarkable in both eyes. Vitritis was observed bilaterally. Pigmented lesions along the arcades with cystoid macular oedema and sea fan-shaped retinal neovascularization in nasal macula and apparent optic disc swelling were observed in both eyes (Fig. 1a–d). The more peripheral retina was not affected by pigmented lesions. Multimodal imaging including fundus photograph, spectral domain optical coherence tomography (SD-OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Jena, Germany), fundus autofluorescence (FAF), infrared reflectance (IR), fluorescein angiography (FA) (Heidelberg Retinal Angiograph 2; Heidelberg, Germany) and full-field ERG (according to ISCEV standards [11]) was performed (Figs. 1, 2, and 3).

SD-OCT findings

Optical coherence tomography (Fig. 1e, f) showed evidence of vitritis (hyper-reflective particles in vitreous cavity labelled with yellow stars), cystoid spaces in inner and outer retinal layers and neovascular membranes (red arrows) on inner retinal surface in both eyes. There was a small pocket of subretinal fluid in the left eye (Fig. 1f).

FAF, IR, FA findings

FAF demonstrated (Fig. 2a, b) parafoveal mottled hyperautofluorescent lesions, more prominent in the right eye, corresponding to cystoid spaces in SD-OCT and a background hyperautofluorescence in posterior pole encircled by hypoautofluorescent lesions along the arcades. Hyperautofluorescence was also seen in

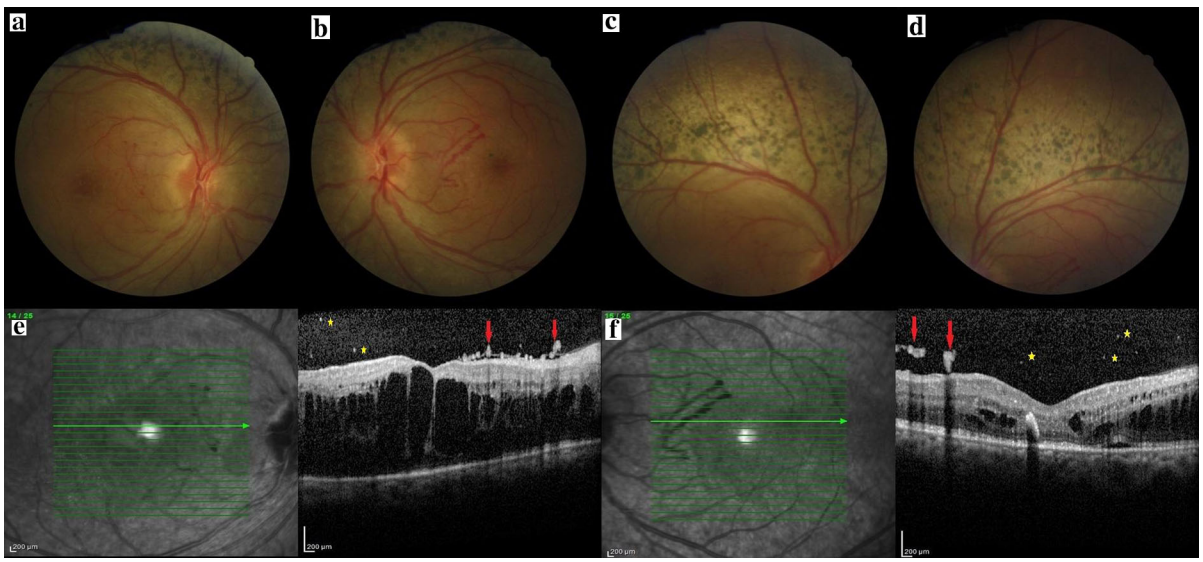

Fig. 1 Fundus photographs (**a**–**d**) and optical coherence tomography (**e**, **f**) of both eyes

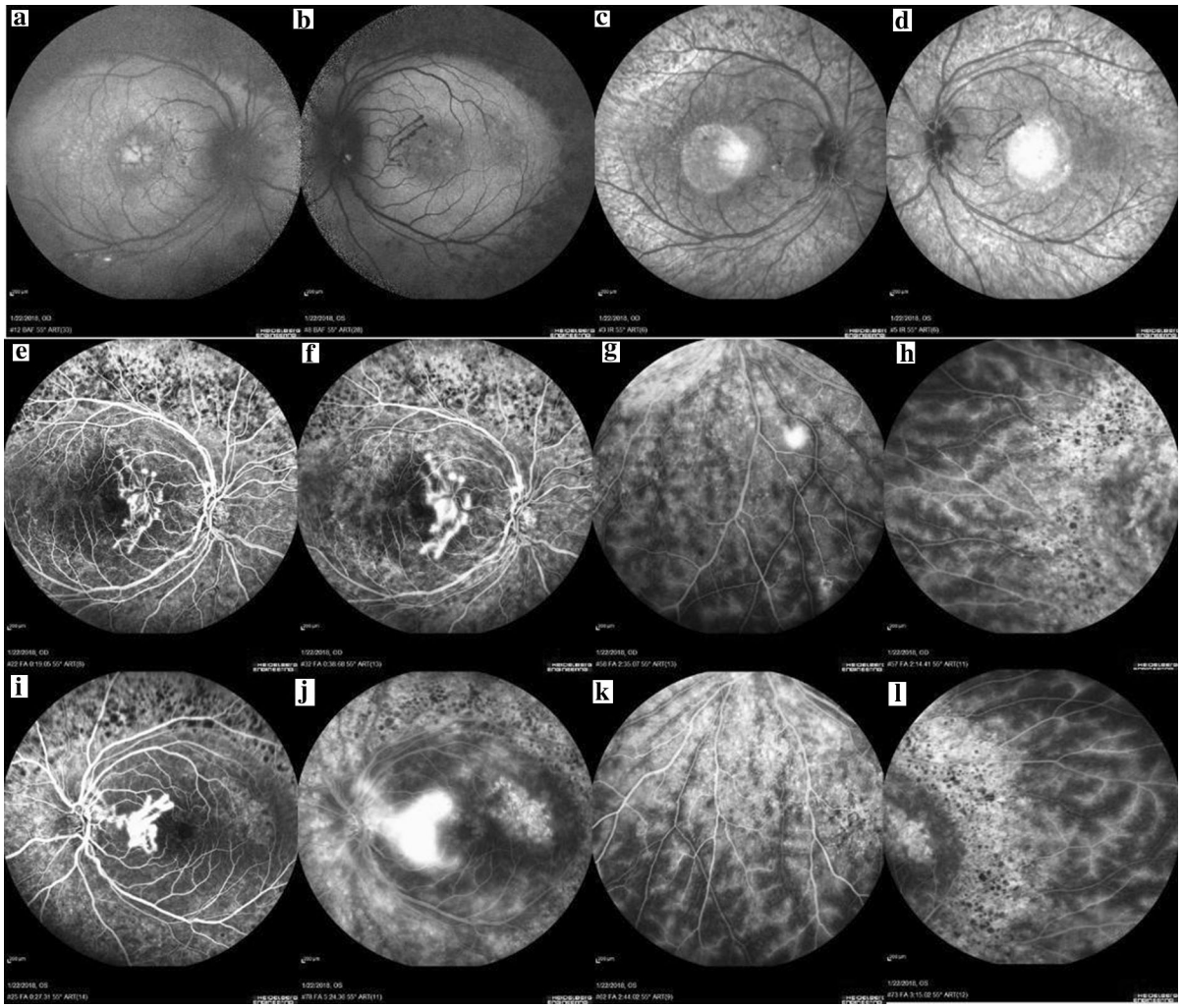

Fig. 2 Fundus autofluorescence (**a**, **b**), infrared reflectance (**c**, **d**) and fluorescein angiography (**e–l**) of both eyes. Fundus autofluorescence shows hyperfluorescent foci in optic discs suggestive of optic disc drusen

optic discs, more prominent in the left eye, possibly corresponding to optic disc drusen (ODD). Ultrasound study of optic discs revealed no evidence of calcification. IR images (Fig. 2c, d) highlighted the neovascular lesions in nasal macula. FA (Fig. 2e–l) revealed intense fluorescein leakage from macular neovascular membranes, pooling of fluorescein in macular cystoid spaces (particularly the temporal macula of the left eye) and prominent posterior and peripheral retinal vascular leakage. A focus of fluorescein leakage into the vitreous in inferonasal midperipheral retina of the right eye suggested another retinal neovascular lesion. There was no evidence of capillary dropout in FA.

Full-field ERG

Full-field ERG (Fig. 3) showed the absence of rod function, similar waves in both single-flash light-adapted (LA 3.0) and maximal dark-adapted (DA 10.0) responses, and disproportionately attenuated photopic flicker response (LA3.0 30) to the single-flash cone amplitude (LA3.0).

There were no signs or symptoms suggestive of systemic inflammatory diseases in clinical examination and review of systems. All investigations to find another infectious or noninfectious aetiology for uveitis were negative. This investigation included complete blood count and differential blood count, erythrocyte

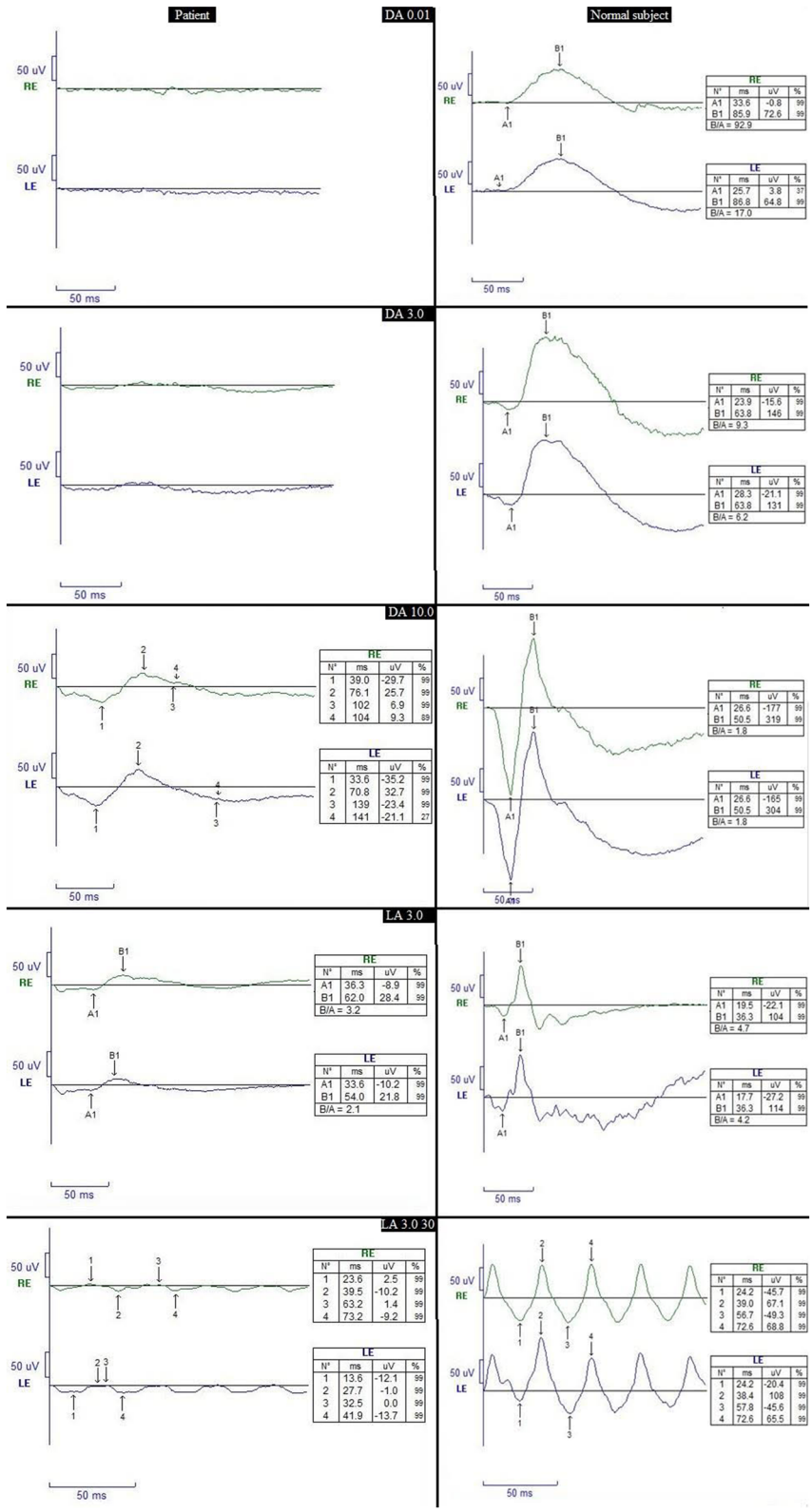

Fig. 3 Full-field electroretinogram of both eyes including DA 0.01 = rod-specific response, DA 3.0 = mixed rod-cone response, DA 10.0 = maximal dark-adapted response, LA 3.0 = single-flash light-adapted response and LA 3.0 30 = photopic flicker response

sedimentation rate, C-reactive protein, renal function tests, liver function tests, syphilis serologic tests (VDRL and FTA-ABS), tuberculin skin test, chest X-ray, antinuclear antibody, and angiotensin-converting enzyme level.

Based on characteristic clinical and ERG findings [1, 2, 12], a diagnosis of ESCS was made.

Discussion

This case presented some findings that have not previously been associated with ESCS. The patient's clinical manifestations (night blindness since early childhood and pigmented lesions with various sizes along the arcades with sparing of peripheral retina) combined with characteristic ERG findings are highly suggestive of ESCS [1, 12]. Previously reported associations of ESCS include choroidal neovascularization, subretinal fibrosis in macula or peripapillary area, subretinal haemorrhage and intraretinal yellow dots [1, 10]. Our patient showed retinal neovascularization in nasal macula of both eyes. The retinal neovascularization is reported in patients with retinitis pigmentosa (RP) [3, 5]. Kadayıfçılar et al. [3] reported a case of RP with sea fan peripheral neovascularization. In RP, retinal neovascularization has been attributed to capillary nonperfusion [3]. In our case, no evidence of capillary nonperfusion or ischaemia was seen in FA. However, considering extensive fluorescein vascular leakage that may obscure some background findings, subtle ischaemia cannot be completely ruled out. On the other hand, severe posterior and peripheral vasculitis in our patient may be attributable to the presence of neovascularization.

It is interesting that there are long-lasting speculations and evidence that presence of RP in diabetic patients may have a protective effect on development of diabetic retinopathy, especially the proliferative form [13, 14]. In contrast to such studies, a nationwide population-based cohort study from Taiwan found no statistically significant association between RP and diabetic retinopathy [15]. However, such associations have not been reported between ESCS and diabetic retinopathy, and our patient was not diabetic, after all.

Although retinoschisis cavities occur in ESCS, considering the subretinal fluid in the left eye (Fig. 1f), pooling of fluorescein in some retinal cysts and coexistence of severe extensive retinal vasculitis (Fig. 2e–l), it seems that a component of inflammatory cystoid macular oedema rather than pure retinoschisis is present in this case.

Vascular leakage and vasculitis have not previously been reported in ESCS. Kaufman et al. [5] found peripheral vascular leakage in 15 of 25 patients with retinitis pigmentosa. Interestingly, they reported that in 8 out of 13 patients with cystoid macular oedema, peripheral vasculitis was present.

One possible explanation for hyperautofluorescent foci seen in optic disc can be the presence of ODD. Although ultrasound imaging of optic discs did not show calcifications, calcification is not a constant finding in all ODDs. Unlike ESCS, association between ODD and retinitis pigmentosa has been reported previously [16]. Carlomusto et al. [16] assessed 1200 patients with retinitis pigmentosa and found that 3.6% of them had optic disc drusen.

Lack of genetic testing is a limitation of this study. However, evidence provided by clinical presentation, multimodal imaging and ERG strongly supports the diagnosis of ESCS.

To the best of authors' knowledge, this case is the first to discuss novel associations of retinal neovascularization, retinal vasculitis and presumed optic disc drusen with enhanced S-cone syndrome.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statement on the welfare of animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all participants included in the study.

Patient consent The patient has consented to the submission of the case report for submission to the journal.

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