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Goldmann-Favre/Enhanced S Cone Syndrome, 30 years mysdiagnosed as gyrate atrophy

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ABSTRACT

Purpose: Case report of a Goldmann-Favre/Enhanced S Cone syndrome (GFS/ESCS) misdiagnosed for 30 years.
Observations: Clinical case, the patient had been experiencing with poor nocturnal visual acuity since childhood. The fundus examination showed extensive areas of peripheral chorioretinal atrophy with posterior demarcation borders, and a clinical diagnosis of gyrate atrophy was established, although normal levels of ornithine should have made this diagnosis doubtful. 30 years later it was reassessed with electrophysiologic and genetic studies and diagnosed as Goldman-Favre/Enhanced S Cone Syndrome (GFS/ESCS).
Conclusions and importance: High phenotypic variability of GFS/ESCS makes it difficult to distinguish clinically from diseases such as retinitis pigmentosa, congenital retinoschisis, and gyrate atrophy. Electrophysiology and genetic studies aid in diagnosis. GFS/ESCS is a clinical diagnosis and should be suspected before molecular test. We present a novel mutation for this disease.

1. Introduction

The Goldmann-Favre/Enhanced S Cone Syndrome (GFS/ESCS) is an autosomal recessive vitreoretinal degenerative disorder described for the first time by M. Favre in two brothers.[1]

GFS/ESCS is caused by a loss-of-function mutation in the gene NR2E3 (nuclear receptor)[2] and.[3] GFS and ESCS are described as two descriptions in the spectrum of the same retinal degenerative disease.[2] We refer to this retinal degenerative disease as GFS/ESCS. ESCS has been associated with (c.508C > A; p.Arg170Ser) and (c.654del; p. Cys219Valfs*4) mutation on gene NRL (neural retina leucine zipper).[4] NRL mutations can also cause retinitis pigmentosa.[5]

GFS/ESCS show a recognizable responses in the electroretinography (ERG). There is and increased response to short wavelength (blue) when red and green cones are suppressed (orange background). Early on, the ERG shows a loss of rod function when compared to cone function. Later, the ERG response is very reduced, or almost non-detectable.

Phenotypically GFS/ESCS show peripheral pigmentary degeneration, macular cystic degeneration, peripheral retinoschisis, posterior subcapsular lens opacities, and optically empty vitreous with preretinal membranes.

2. Case report

A case report of a 59-year-old male who was recently genetically diagnosed with GFS/ESC syndrome.

He began to be monitored in our center at the age of 35. The patient is the youngest of 5 siblings, of whom he and another brother are both sufferers. There was consanguinity in his family. He reported that a paternal grandfather also had a sickness of sight. The patient has no offspring. He does not present relevant systemic diseases.

The patient described poor visual acuity at night since childhood. Initially, a visual acuity of 20/400 was recorded in right eye and 20/63 in left eye. Clinical features found were bilateral and mostly symmetrical. On slit-lamp examination cornea and anterior chamber were normal. Posterior bilateral subcapsular cataracts were found. Fundus features were described as condensed vitreous fibrillar strands, peripheral pigmentary retinopathy, with whitish foci and no vascular abnormalities. Optic disk appeared normal. Visual field testing showed a symmetrical constriction, which could be described as tunnel vision (Fig. 1).

ERG maximum response in scotopic conditions showed a decrease in the amplitude of a and b-wave, greater for b-wave. Cone response under photopic conditions presented a decrease in the amplitude of a-wave

Abbreviations: GFS/ESCS, Goldmann-Favre syndrome/ Enhanced S cone syndrome; ERG, Electroretinography.

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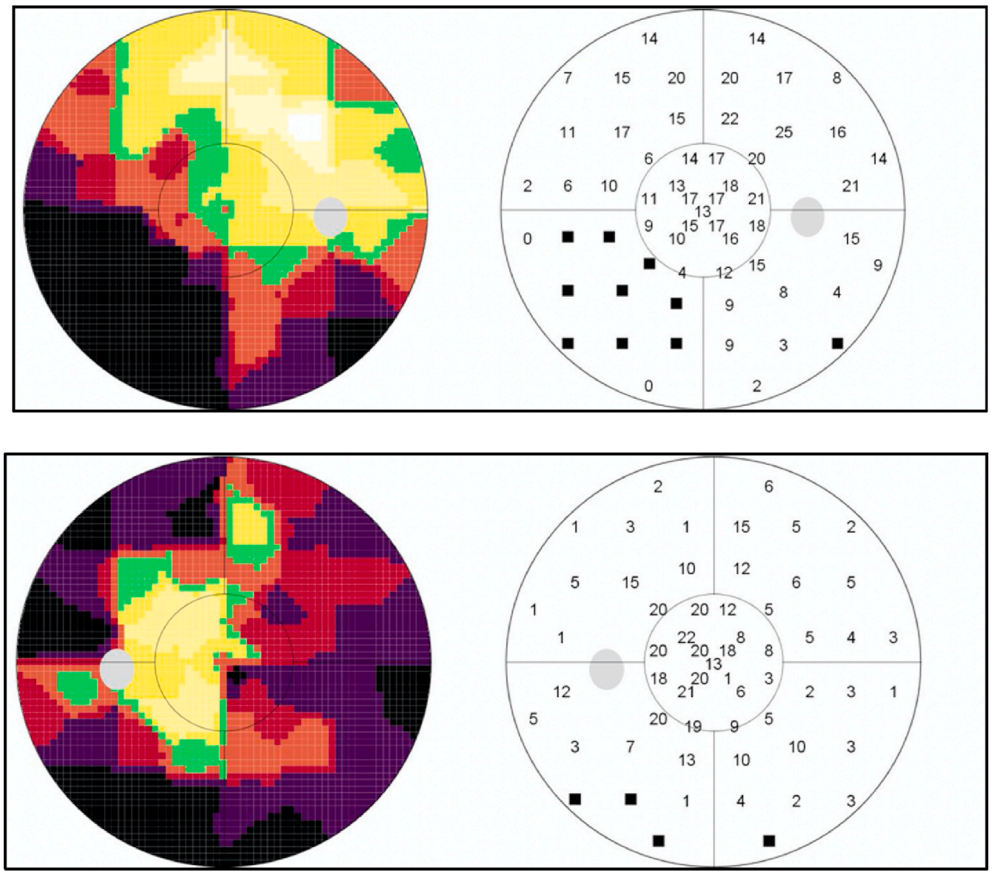

Fig. 1. Octopus perimetry central 30°, color scale of values and corrected probabilities, upper right and lower left eye, demonstrating the extensive visual field loss more in left eye. Note the concentric narrowing of visual field. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

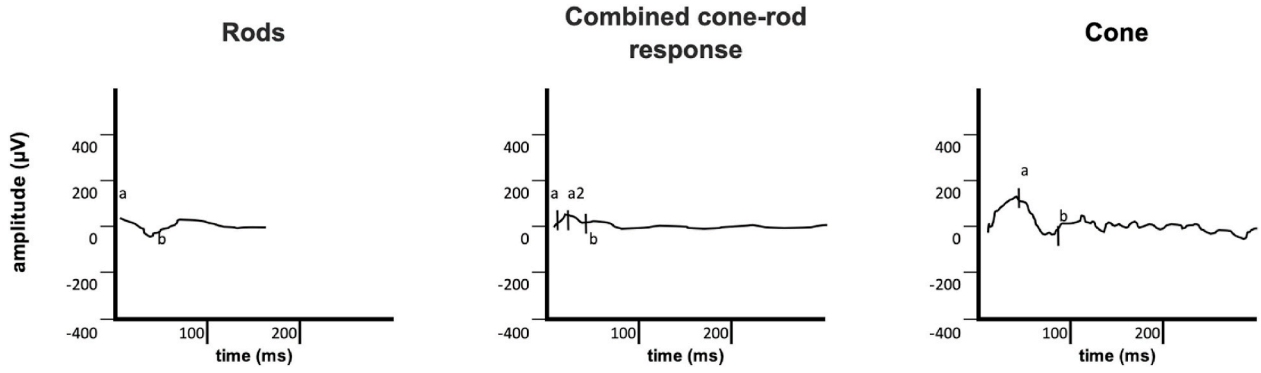

Fig. 2. Electroretinogram traces of the left eye, shows an absent rod response in scotopic conditions and little difference between the cone and máximum response waves in scotopic conditions. The response for cone, show a decrease in the amplitude of wave b (less than in the case of the response of rods).

(less than in rod response) (Fig. 2).

As initial therapeutic approach cataract surgery of both eyes was performed and medical treatment with *vaccinium myrtillus* (bilberry) was initiated. This supplement was discontinued because of lack of improvement. Bilberry has been used as a dietary supplement for its antioxidant proprieties.

Based on fundus features, gyrate atrophy was thought of as the first diagnostic possibility. Therefore, ornithine levels were requested, resulting in the high limit of normality. Therefore, treatment with vitamin B6 was not established.

Current clinical examination shows a visual acuity of 20/200 in both eyes. Comparing current retinographies with those from 1999, there is no progress in the areas of chorioretinal atrophy. The autofluorescence images show hypofluorescence at the leading edge of the peripheral area of chorioretinal atrophy, with hyperautofluorescent spots adjacent to this edge and peripapillary area (Figs. 3 and 4). Optical coherence tomography (OCT) scan shows full thickness retinal atrophy without foveal involvement (Fig. 5).

A genetic study was finally requested, which confirmed a homozygosis variant probably pathogenic c.238C > T (p.Gln 80) exon 3 in NRL gen, and thus was diagnosed as GFS/ESCS.

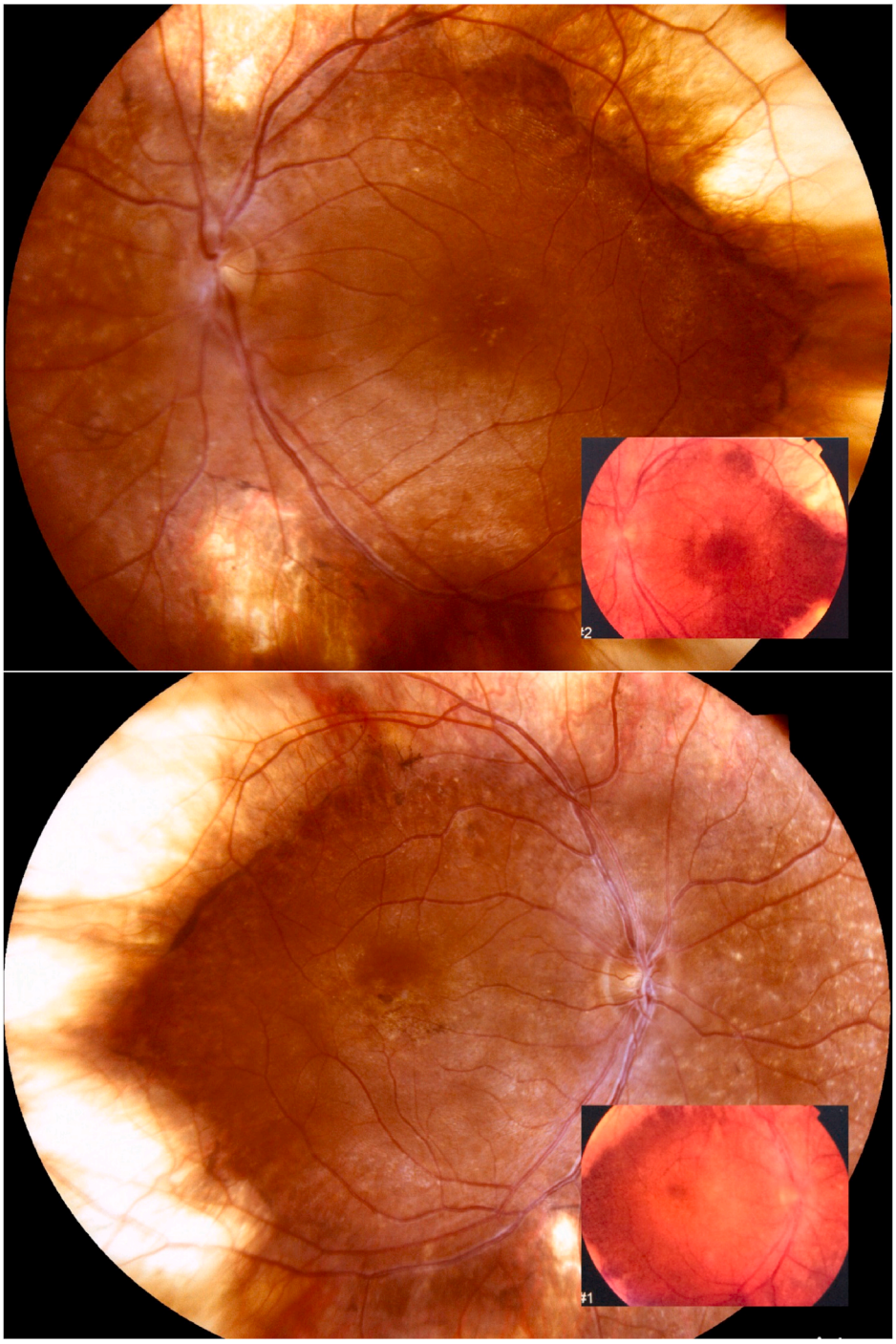

Fig. 3. Retinography images of both eyes. Recent retinography (large) and retinography dated 1999 (small). Observe the large areas of chorioretinal atrophy and nummular lesions in the peripheral retina. Highlight the stability over time.

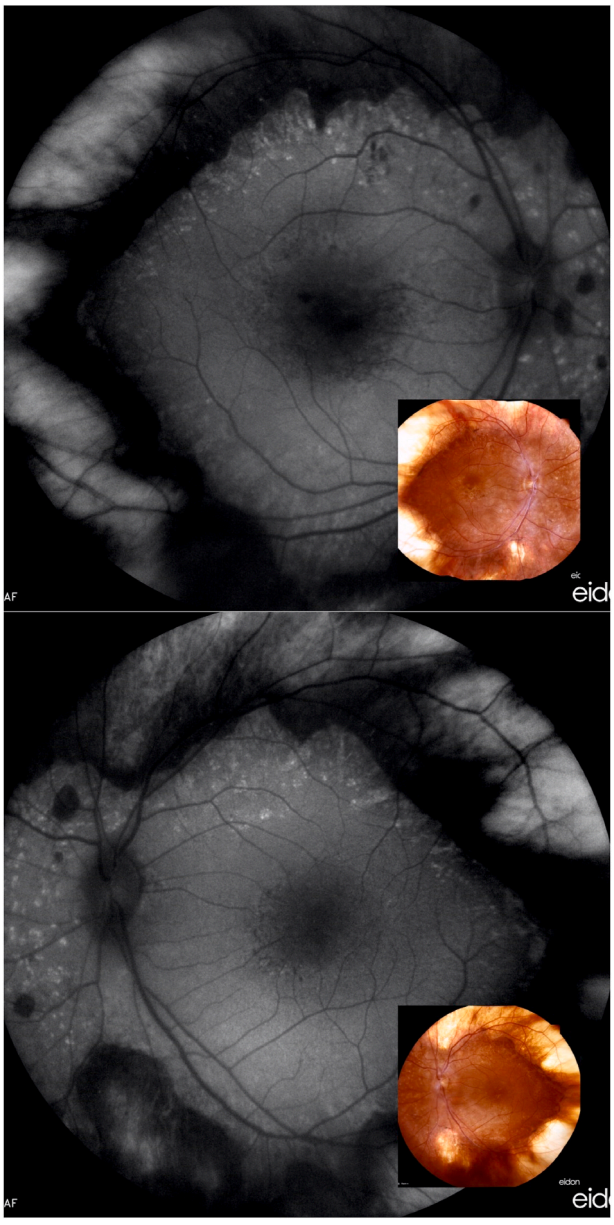

Fig. 4. Autofluorescence images of both eyes. Hypofluorescence at the areas of pigmentation, leading edge of the peripheral area of chorioretinal atrophy, with hyperautofluorescent spots adjacent to this edge and in the peripapillary area.

3. Discussion

It can be a challenge to distinguish between GFS/ESCS and other hereditary vitreoretinal disorders such as X-linked juvenile retinoschisis or chororetinal atrophies like gyrate atrophy. This situation can lead to diagnostic errors like in the case that we describe.

Reviewing the current literature there are some disagreements between Goldmann-Favre syndrome and the ESCS. Many articles identify both as the same disease. These consider that making a distinction between the two entities is redundant.[6] Others establish that Goldmann-Favre syndrome is a severe degree of the same retinal degeneration.[7]

Electroretinography findings play a major role in differential diagnosis. GFS/ESCS, shows a non-recordable ERG, with flat a and b-wave. GFS/ESCS share hypersensitivity to short wave length, presenting a similar ERG.[8] The ERG shown in Fig. 2 could correspond to the atrophic version of a specific spatial distribution in vitreoretinal degenerations.

A negative ERG, with flat b-wave and negative a-wave, is found in X-linked juvenile retinoschisis and congenital stationary night blindness (CSNB).

GFS/ESCS can be caused by NR23E gene mutation. In our case the mutation was found in c.238C > T (p.Gln 80) exon 3 in NRL gen and to the best of our knowledge this is a base-pair novel mutation for this disease.

In the case that we describe the GFS/ESCS was confused with gyrate atrophy. Although the ERG response could be similar in both diseases, normal levels of ornithine and lack of scalloped atrophy of peripheral retina should have raised the suspicion of a different diagnosis.

This case represents a diagnostic mistake. The diagnosis of GFS/ESCS is a clinical diagnosis and should be established based on clinical features and ERG, before molecular confirmation.

4. Conclusion

The low frequency of GFS/ESCS, and its high phenotypic variability, as Özateş et al.[9] shows in his article, makes its diagnosis a challenge. The GFS/ESCS also shares clinical characteristics with other retinal dystrophies. Therefore, genetic tests are an important aid that allow an accurate diagnosis and adequate genetic advice.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Patient consent

Consent to publish this case report has been obtained from the patient(s) in writing.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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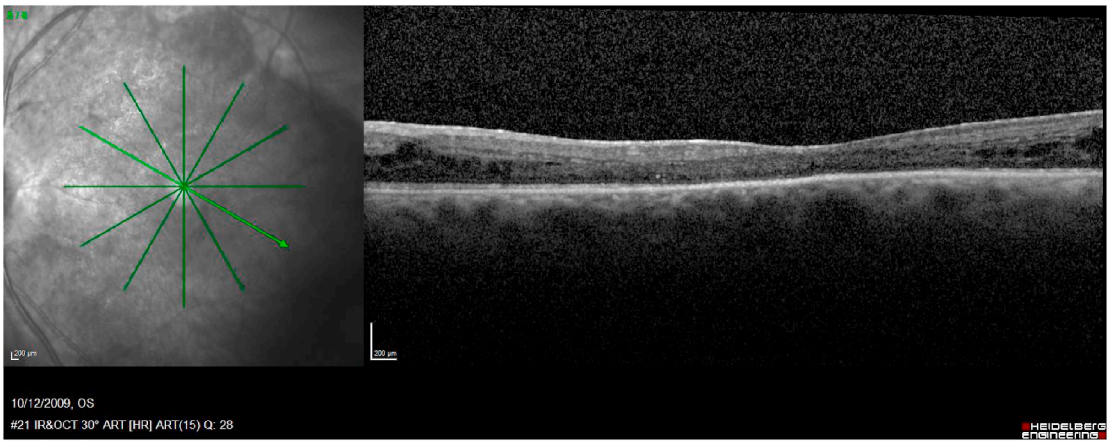

Fig. 5. Optical coherence tomography image corresponding to the right eye. Ellipsoid zone is disrupted and there is no schisis or cystoid macular edema.

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