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Case Report

Goldmann-Favre Syndrome: Case Series

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Abstract
Goldmann-Favre syndrome, which is caused by mutation of the *NR2E3* gene, is a retinal degenerative disease with a wide spectrum of phenotypic properties. Variations in clinical presentation result in difficulties in differential diagnosis. In this article, Goldmann-Favre syndrome cases with different clinical findings are presented. Clinical characteristics of our cases were reviewed and discussed in light of the literature.
Keywords: Goldmann-Favre syndrome, retina, optic coherence tomography

Introduction

Goldmann-Favre syndrome (GFS) is a progressive retinal degeneration that develops due to a mutation in the *NR2E3* gene, which has a role in the regulation of cone cell differentiation, and has an autosomal recessive inheritance pattern.[1,2] GFS and enhanced S-cone syndrome represent two distinct entities on a spectrum of retinal degenerative disease caused by mutations in the same gene.[3] The fact that these two conditions manifest with very different clinical phenotypes make it difficult to distinguish them from other diseases on the retinal degenerative disease spectrum such as retinitis pigmentosa, congenital retinoschisis, and secondary pigmentary retinopathy.[2,4,5]

In this report, the varying examination findings and clinical characteristics of patients treated in our clinic for GFS are discussed in the context of the literature.

Case Reports

Case 1

A 36-year-old woman presented to our clinic with a complaint of progressive vision loss. She reported that her low vision had been present since childhood and that her mother had completely lost her vision due to a similar history. In addition, the one male child (Case 2) and one female child (Case 3) of the patient had similar complaints. When asked about her family tree, it was learned that her parents were in a consanguineous marriage and that her spouse was also a second degree relative. Her best corrected visual acuity (BCVA) was 0.4 in the right eye and at the level of hand movements in the left eye. Anterior segment examination revealed bilateral posterior subcapsular cataract which was denser in the left eye. Fundus examination revealed widespread clumps of retinal pigment epithelium (RPE) hyperplasia surrounding the optic disc and macula of the right eye (Figure 1). There was no involvement of the macula and peripapillary area. Due to dense cataract, the posterior segment of the left eye could not be clearly evaluated. Optic coherence tomography (OCT) sections showed no pathology in the macula of the right eye. Images could not be obtained during fundus fluorescein angiography (FFA) because the patient experienced syncope.

Case 2

The 16-year-old son of the patient in Case 1 presented to our clinic with the complaint of low vision. His visual impairment

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had started at the age of 10, and his BCVA was 0.7 in both eyes with myopic correction. Anterior segment examination was normal in both eyes. Fundus examination revealed hyperplasic RPE clumps starting from the temporal retina, following the retinal vascular arcades, and extending toward the optic disc in both eyes. In addition, there were nummular lesions with atrophic centers and hyperpigmented borders in the peripheral regions of the annular lesion formed by the hyperplasic RPE clumps and the normal retina (Figures 2a, b). Fundus autofluorescence (FAF) imaging revealed punctate hyperautofluorescent lesions in the parafoveal region, nasal of the optic disc, and along the vascular arcades, and some lesions were also located in the apparently healthy retina (Figures 2c, d). OCT revealed areas of retinoschisis in the parafoveal area in both eyes despite the normal appearance of the fovea (Figures 2e, f). FFA showed hyperfluorescent window defect in areas with RPE atrophy and fluorescein blockage in hyperpigmented areas (Figures 2g, h).

Case 3

A 12-year-old female patient presented to our clinic due to low vision. Her mother (Case 1) and brother (Case 2) had similar complaints. BCVA was 0.6 in the right eye and 0.4 in the left eye with myopic correction. Eye movements, direct and indirect light reflexes, color vision, and anterior segment examination were normal on ophthalmological examination. Fundus examination revealed hyperplasic RPE clumps and areas of chorioretinal atrophy with hyperpigmented borders around the retinal vascular arcades in both eyes (Figures 3a, b). Cystoid changes and a flower-petal appearance were observed in the macula. The optic discs were raised and edematous bilaterally. No cells or haze were observed in the vitreous humor. OCT sections showed cystoid degenerative changes in the fovea and parafoveal region in both eyes (Figures 3c, d). FFA revealed extensive leakage in the optic disc and at the border between the annular area containing the lesions and the apparently healthy macular region. Widespread hyperfluorescent punctate areas of leakage were observed around the fovea and temporal of the macula in the late phase (Figures 3e, f).

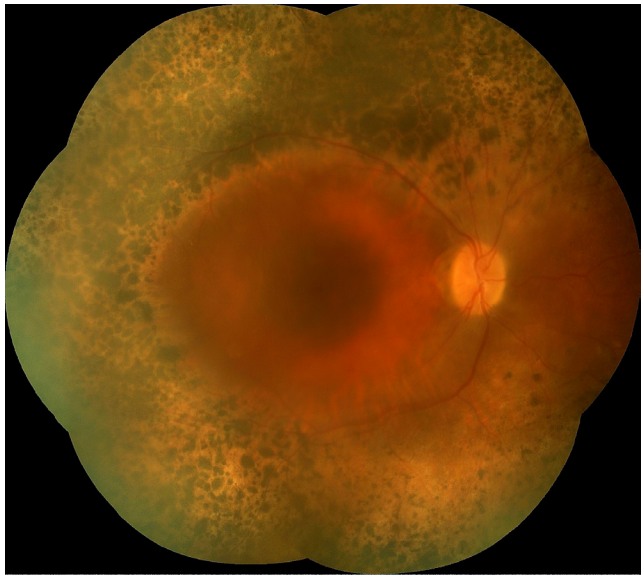

Figure 1. Case 1: Widespread retinal pigment epithelium hyperplasia around the vascular arcades

Case 4

A 31-year-old woman presented to our clinic due to poor night vision. She reported a 20-year history of low vision and restricted visual field. No one else in her family had similar complaints. She had also been followed previously for retinitis pigmentosa. On ophthalmological examination, her BCVA was 0.6 in the right eye and 0.5 in the left eye. No signs of pathology were detected in anterior segment examination. Fundus examination revealed a ring of hyperplasic RPE lesions

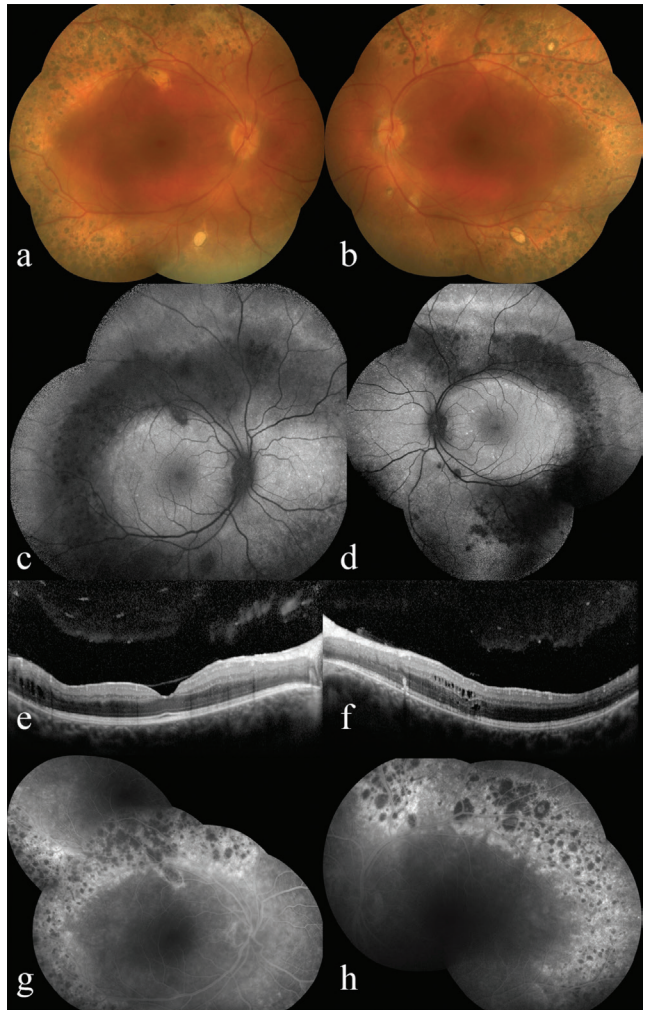

Figure 2. Case 2: Fundus photographs show nummular lesions with atrophic centers and hyperpigmented borders (a, b); fundus autofluorescence images show hyperautofluorescent spots in the apparently healthy retina (c, d); optic coherence tomography reveals areas of parafoveal retinoschisis (e, f); fundus fluorescein angiography images (g, h)

and areas of chorioretinal atrophy surrounding the optic disc and macula in both eyes (Figures 4a, b). Although there were no lesions within the retinal vascular arcades, cystoid changes were noted in the fovea. FAF revealed widespread hyperautofluorescent punctate lesions in the macula and around the arcades (Figures 4c, d). OCT showed retinoschisis at the fovea. In addition, loss of the photoreceptor layer was noted in the combined OCT sections passing through the lesion area (Figures 4e, f). FFA revealed blocked fluorescence and widespread hyperfluorescent window defect around the retinal vascular arcades, but no leakage was detected in the macula in the late phase (Figures 4g, h).

Case 5

A 12-year-old female patient with otherwise unremarkable history presented with complaints of low vision. BCVA was 0.5 in the right eye and 0.6 in the left eye. No pathology was detected in anterior segment examination. Fundus examination revealed tortuosity of the retinal vascular structures, clumped RPE hyperplasia surrounding the optic disc and macula, and widespread, yellow punctate lesions in both eyes (Figures 5a, b). Nummular lesions with atrophic centers and hyperpigmented borders were observed, particularly around the upper retinal vascular arcade. FAF imaging revealed hyperautofluorescent punctate lesions in the macula, within the annular region of affected retina, and in the periphery of the apparently healthy retina (Figures 5c, d). No pathology was observed on OCT in either eye (Figures 5e, f). The lesions could not be evaluated angiographically because the patient's parents did not consent to FFA examination.

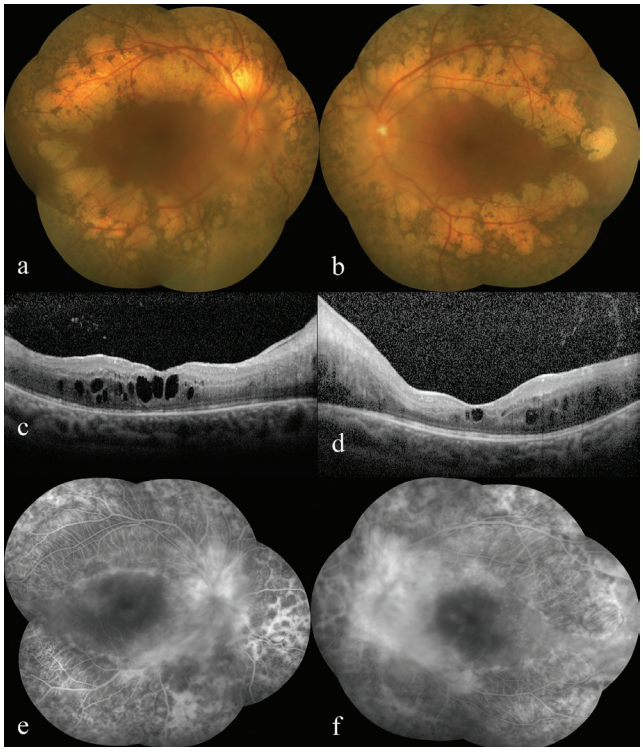

Figure 3. Case 3: Fundus photographs show widespread chorioretinal atrophy and nummular lesions with hyperpigmented borders (a, b); optic coherence tomography shows cystoid macular edema (c, d); fundus fluorescein angiography images reveal widespread leakage from the optic disc and borders of the apparently healthy retina as well as macular leakage due to cystoid macular edema (e, f)

Discussion

GFS was first described by Favre[6] in two brothers, and Ricci[7] reported that GFS follows an autosomal recessive inheritance pattern. Genetic studies have revealed that GFS occurs due to a mutation in the *NR2E3* gene, which is located on the short arm of chromosome 15.[2,5,8] The *NR2E3* gene encodes a retinal nuclear receptor involved in transcription.[9] This gene regulates the expression of cone-specific genes found in the rods and controls the differentiation of photoreceptors.[9,10]

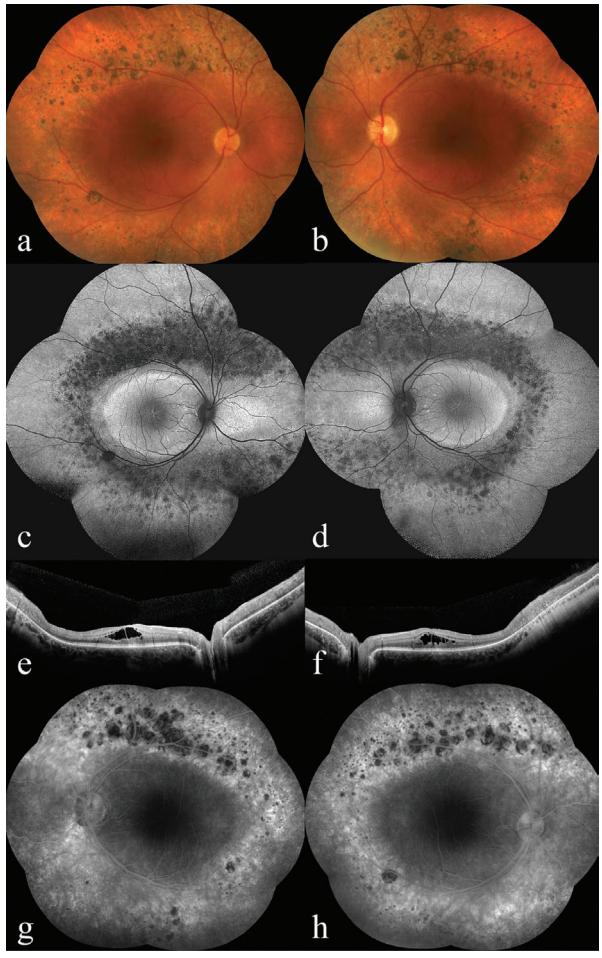

Figure 4. Case 4: Fundus photographs show nummular lesions with atrophic centers and hyperpigmented borders and RPE hyperplasia around the vascular arcades (a, b); Fundus autofluorescence images show widespread hyperautofluorescent spots (c, d); Optic coherence tomography reveals central retinoschisis and loss of the photoreceptor layer, sudden increase in retinal thickness, and loss of the retinal laminar structure in the affected peripheral retina (e, f); Fundus fluorescein angiography images (g, h)

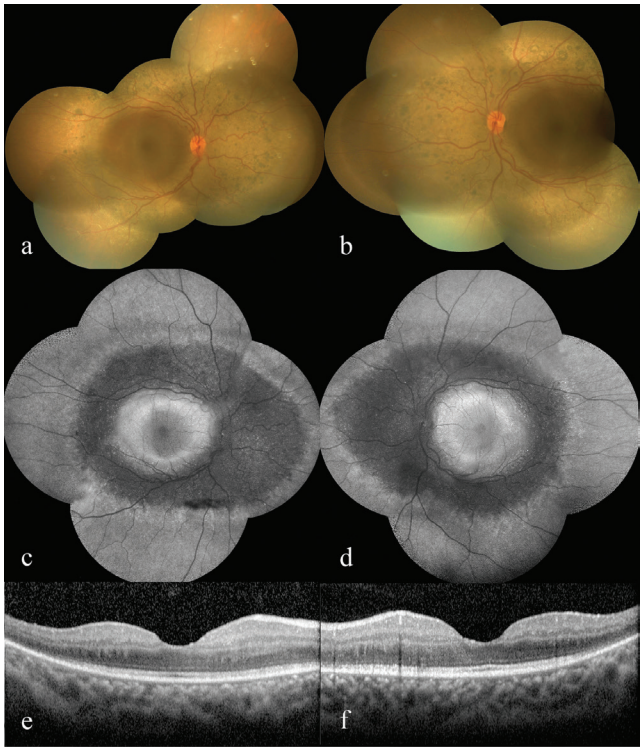

Figure 5. Case 5: Fundus photographs show yellow punctate lesions and clumps of retinal pigment epithelium hyperplasia around the vascular arcades (a, b); fundus autofluorescence images show widespread hyperautofluorescent spots (c, d); optic coherence tomography sections (e, f)

Homozygous mutations in the *NR2E3* gene result in increased and uncontrolled cone photoreceptor differentiation (especially S-cone) and a reduced number of rod photoreceptor cells during retinal development.[9,10,11]

There are case series demonstrating familial inheritance in the literature.[12,13] Familial inheritance is clearly observed in our first three cases. When taking the family history of the patient in Case 1, we learned that her mother had also had vision problems throughout her life. In addition, there was consanguinity both between the patient's parents and between the patient and her spouse. This explains how both of her children could have GFS when her spouse did not. It is reported that the phenotype of this disease may vary, despite the presence of similar mutations.[5,8,14] There was also individual variation in the nature and severity of the clinical findings and the complications experienced during follow-up in our first three cases. Studies investigating the causes of this phenotypic variability have been inconclusive.

GFS manifests as night blindness or a progressive decrease in visual acuity during the first decade of life.[4,12] It is typically characterized by hyperpigmented RPE clumps that form along the retinal vascular arcades, areas of chorioretinal atrophy, cystoid or schisis-like changes in the fovea, central or peripheral retinoschisis, vitreous degeneration, and cataract.[1,4] In addition, abnormal dark adaptation and electroretinogram results, progressive visual field loss, and color vision disorders are other accompanying symptoms.[4,12] Nummular lesions with atrophic centers and hyperpigmented borders, called "torpedo-like lesions", were first described in GFS by Yzer et al.[2] They reported that these lesions were located in the healthier areas of the retina. We also observed similar lesions in Cases 2, 3, 4, and 5 in our series. The lesions were located at the border of the apparently healthy retina in Cases 3 and 4, but were in the affected retina in Cases 2 and 5. In addition, lesions were especially prominent around the upper retinal vascular arcade in Cases 4 and 5. In GFS, rod photoreceptors are essentially replaced by S-cone photoreceptors.[12,14] There is also a reduction in the number of L- and M-cone cells due to phagocytosis of cone cells by RPE cells and as a result of the *NR2E3* gene mutation.[15] Histopathological studies have shown an increase in S-cone cells in both the perimacular area and the peripheral retina.[10] In a postmortem examination, a complete absence of rod cells and twice the normal number of cone cells was observed in the retina, with S-cone cells comprising 92% of all the cone receptors.[15] However, in experimental animal models it has been reported that the cone photoreceptors replacing the rod photoreceptors do not show a diffuse histological distribution, but are concentrated in certain regions.[16] These areas of concentration appear as pseudorosettes in histopathological examination, which may explain the round shape of these degenerative lesions.[2,16,17]

Retinoschisis is another distinctive finding of GFS.[4] Although peripheral retinoschisis is more common in GFS, central retinoschisis may also occur.[4] In our series, Case 2 had both central and peripheral retinoschisis, while Case 4 exhibited only central retinoschisis. Leakage is not seen on FFA in the area of central schisis.[4,12] However, we noted that the areas of perifoveal leakage observed on FFA in Case 3 were generally consistent with the schisis-like areas observed on OCT. Considering the widespread leakage in the optic disc and at the border of the apparently healthy retina, we believed that the lesions were caused by cystoid macular edema. Leakage is rarely observed in GFS and has been reported in a limited number of cases in the literature. Fishman et al.[12] reported three GFS cases with similar widespread leakage in the posterior pole. The leakage from both the retinal vascular arcades and the optic disc reported in those cases is consistent with the findings in our patient. GFS should be considered in the differential diagnosis of patients with a fundus appearance and leakage on FFA similar to those described.

The patients in Cases 2, 4 and 5 of our series exhibited spots that appeared yellow in color on fundus images and showed hyperautofluoresence on FAF. Similar to findings reported by Yzer et al.[2], they were located at the borderline between the affected retina and apparently healthy retina. These spots may appear as a result of phagocytosed material found in macrophages.[18]

Deterioration of the laminar organization of the retina and retinal thickening on OCT have been reported in the affected retinal area.[19] Composite OCT images from the affected retinal area in Case 4 showed loss of the photoreceptor layer at the boundary of the affected retina, followed by disruption of the laminar structure of the retina and a sudden increase in retinal

thickness. The increase in thickness and deterioration of the anatomical structure may be due to the fact that S-cone cells, which are larger than rods, are situated where the rods should be.[19] The relative decrease in choroidal thickness in the area of increased retinal thickness in the patient's left eye was an interesting finding.

The high phenotypic variability of GFS makes it difficult to distinguish from diseases such as retinitis pigmentosa, congenital retinoschisis, and secondary pigmentary retinopathy. The less common findings reported in our case series may assist in the differential diagnosis of GFS and improve our understanding the underlying pathophysiological processes.

Ethics

Informed Consent: It was taken.

Peer review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Mehmet Yasin Teke, Concept: Serdar Özateş, Design: Serdar Özateş, Data Collection or Processing: Mehmet Yasin Teke, Kemal Tekin, Analysis or Interpretation: Mehmet Yasin Teke, Literature Search: Kemal Tekin, Serdar Özateş, Writing: Serdar Özateş.

Conflict of Interest: No conflict of interest was declared by the authors.

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