

# An Interesting Case of Wrongly Diagnosed Goldmann-Favre Syndrome

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## ABSTRACT

Goldmann-Favre syndrome (GFS) is a rare vitreoretinal degeneration related to retinal nuclear receptor mutation. GFS has a wide variety of clinical features, often misdiagnosed as retinitis pigmentosa, juvenile retinoschisis, cystoid macular edema or clumped pigment retinopathy. In this study, we presented a case of Goldman-Favre vitreoretinal degeneration in 30 year-old man who was wrongly diagnosed and treated as cystoid macular edema.

**Keywords:** Goldmann-Favre syndrome, Retinoschisis, Cystoid macular edema.

## INTRODUCTION

Goldmann-Favre syndrome is an autosomal recessive disorder characterized by early-onset night blindness, increased sensitivity to blue light, pigmentary retinal degeneration, fibrillar vitreous degeneration, foveal cysts, peripheral retinoschisis and abnormal or undetectable electroretinogram.<sup>1</sup>

It is believed that Goldmann-Favre syndrome and enhanced S-cones syndrome (ESCS) share common mutations in NR2E3 gene which encodes a transcription factor, may lead to an increase S cones at the expense of M and L cones, decreased rod development, and retinal disorganization and degeneration.<sup>2</sup>

In this study, we aimed to discuss a case of misdiagnosed Goldmann-Favre syndrome.

## CASE REPORT

30-year-old-male initially presented to another ophthalmology clinic with progressive blurred vision in both eyes that started four years earlier. He had also reported history of night blindness for seven years. There was no known family history of eye diseases. In this

center between the dates of 2014-2018, he had received 2 triamcinolone injections, 18 dexamethasone implants, 12 ranibizumab injections in both eyes and one aflibercept injection in the right eye with diagnosis of cystoid macular edema. During this period, glaucoma and cataract surgery had been performed to each eye due to uncontrolled glaucoma and cataract formation.

At his first examination in our clinic in May 2018, best-corrected visual acuity was counting fingers from 5 meters in the right eye, counting fingers 3 meters in the left eye. Intraocular pressures were in the normal limits and the anterior segment examination of both eyes including lids, conjunctiva, cornea, anterior chamber and iris were unremarkable. Bilateral posterior chamber intraocular lenses were observed. Fundus examination revealed yellowish, sheen-like, round retina pigment epithelium (RPE) changes surrounding the optic disc and macula, and around the retinal vascular arcades. Cystic changes were observed in both macula but not in the peripheral retina. No cells and haze were observed in the vitreous cavity (Figure 1 a-b).

On fluorescein angiography (FFA), widespread hyperfluorescent window defect in areas with RPE atrophy and fluorescein blockage in hyperpigmented areas were

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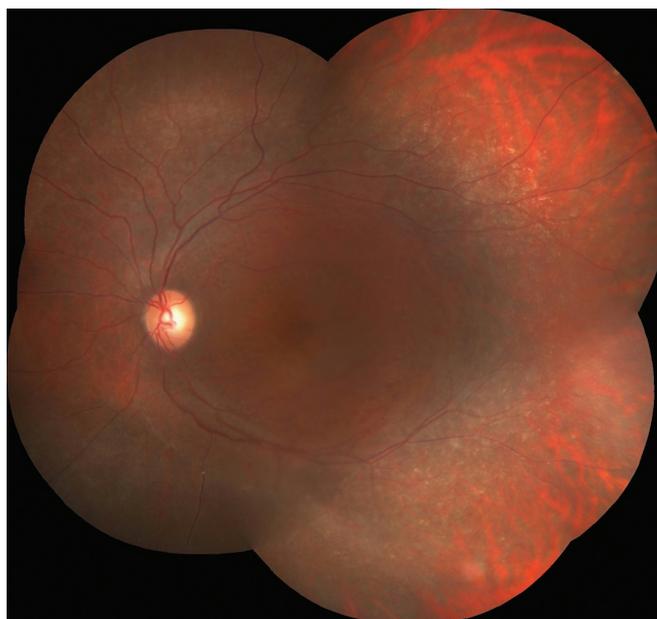
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**Figure 1 a-b:** Fundus images of the right and left eye show white-yellowish retinal pigmentary changes along the vascular arcades and cystic macular changes.

seen around the vascular arcades throughout all phases. No dye leakage was seen in the macula in the late phase (Figure 2 a-b). Fundus autofluorescence (FAF) imaging revealed punctate hyperautofluorescent lesions in the parafoveal region, nasal of the optic disc, and along the vascular arcades (Figure 3 a-b). Optical coherence tomography (OCT) evaluation demonstrated a large foveal cyst that extends from the nerve fiber layer to the outer retina in both eyes. There were cystic changes throughout all retina layers, loss of photoreceptor and retina pigment epithelium (Figure 4 a-b).

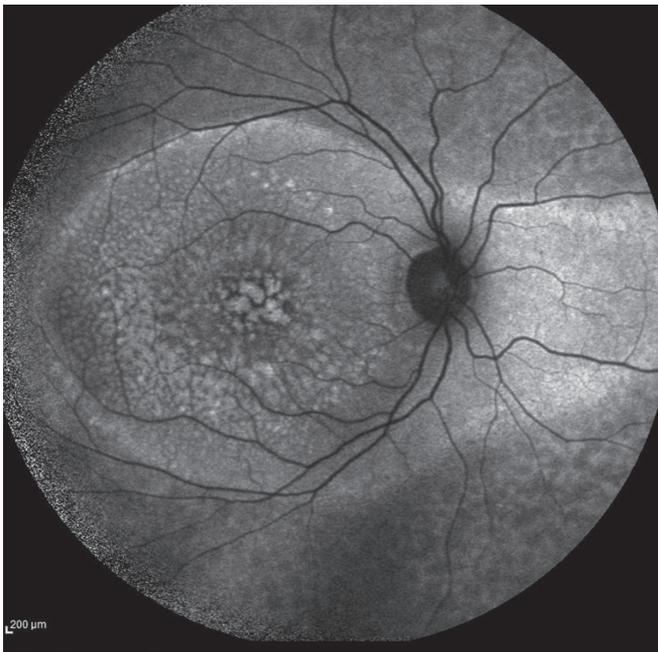
Based on the history of poor night vision, cystic macular changes that are non-leaking and unresponsive to multiple intravitreal injections, atypical RPE changes, we have considered the diagnosis of Goldmann-Favre syndrome and done genetic testing to confirm our diagnosis. The genetic testing resulted in a positive finding for a homozygous mutation in the NR2E3 gene.

## DISCUSSION

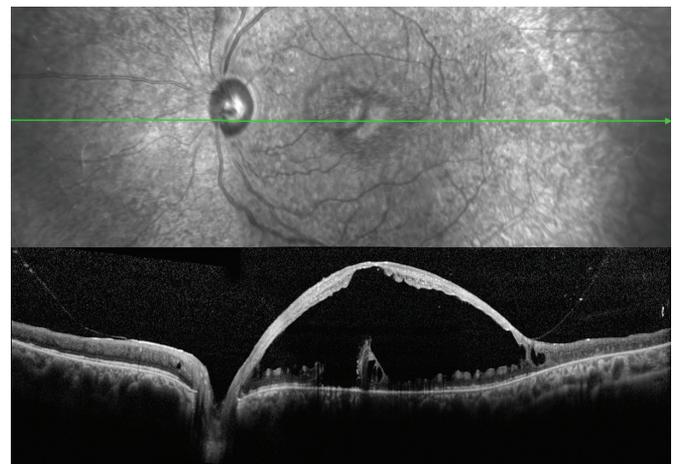
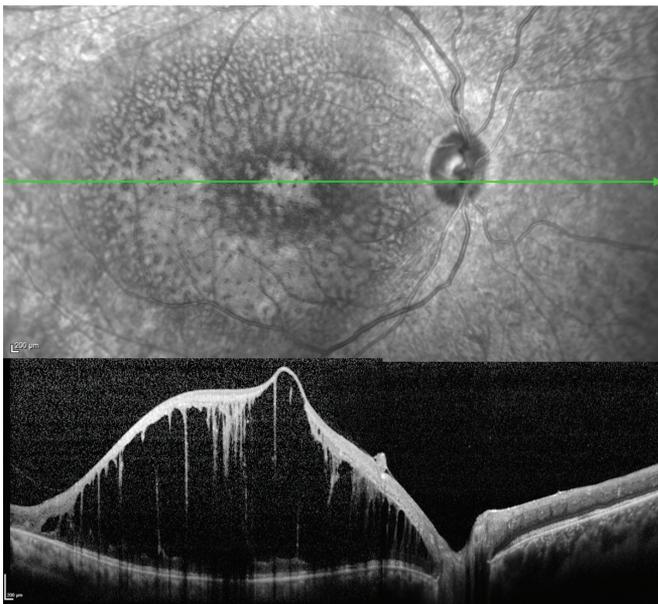
Goldmann-Favre syndrome is an autosomal recessive retinal degeneration caused by mutations in the nuclear



**Figure 2 a-b:** Fundus fluorescein angiography images reveal widespread hyperfluorescent window defect around the arcades, but no dye leakage in the fovea.



**Figure 3 a-b:** Fundus autofluorescence images show hyperautofluorescent spots around the macula and nasal of the optic disc.



**Figure 4 a-b:** Optic coherence tomography images of the right eye and left eye show foveal schisis with elevated foveal contour.

receptor gene (NR2E3) on 15q23. GFS is thought to be more severe form of ESCS. NR2E3 encodes a retinal nuclear receptor (PNR), is a transcription factor, found to the outer nuclear layer of the retina. This gene regulates proper rod and cone photoreceptor differentiation and maintenance.<sup>3,4</sup> Loss-of-function mutations in this gene result in hyperfunction and absolute increase of the S cones photoreceptor type together with decreased pathway of the rod photoreceptors.<sup>3</sup>

Characteristic features of GFS include early onset

nyctalopia, peripheral pigmentary changes, fibrillar vitreous degeneration, peripheral and less often central retinoschisis, cataract, unusual ERG and abnormal dark adaptation. Hypermetropic refraction is often noted. Presenting symptoms are usually night blindness and/or visual acuity loss in the first or second decade of life.<sup>1,5-7</sup> It is typically characterized by peripheral pigmentary changes along the vascular arcades is described spots of pigment, different from the bone spicule seen in typical retinitis pigmentosa.<sup>8</sup> Histopathologic study demonstrated

that the clumped pigment areas are due to excessive melanin accumulation in the retinal pigment epithelial cells.<sup>9</sup> Yellow-white flecks at the deep retinal layers can be an early finding of GFS. We also observed yellowish dots on the fundus images and hyperautofluorescent loci on FAF in our case. In a study of patients with NR2E3 mutation, hyperautofluorescent loci were found to be intraretinal and associated with dysmorphology of the photoreceptor layer.<sup>10</sup> White-yellow dots seen in NR2E3 mutant mice were studied and these dots were consistent with autofluorescent material within the macrophages.<sup>11</sup>

One of the characteristic features of NR2E3 mutation related retinal dystrophies is retinoschisis which could affect central or peripheral retina, resembles X-related juvenile retinoschisis. Macular cysts seen in retinal dystrophies occur as a result of disruption of retinal structure in the macula and defects in cell-to-cell adhesion. Similarly, other studies postulated that cystoid spaces in these dystrophies can be result of hybrid rod-cone cells seen in GFS that may be unable to form efficient tight junctions.<sup>12,13</sup> On the contrary, cystoid macular edema (CME) originates fluid leakage secondary to breakdown of the blood retinal barrier. While dye leakage on FFA is observed in CME, there is no dye leakage on fluorescein angiography in GFS, with some isolated exceptions. Several studies showed that carbonic anhydrase inhibitors (CAIs) are efficacious to treat non-leaking cystoid edema.<sup>13,14</sup> Nevertheless, recurrence after cessation of CAIs or no response to treatment have been reported in some studies.<sup>15</sup> The efficacy of the treatment may be dependent on the severity of schisis, duration of disorder and residual functional RPE cells.<sup>16</sup> There was non-leaking cystoid spaces on FFA in our case and he had been received a large number of intravitreal injections as diagnosis of cystoid macular edema before he came to our institute. Early onset cataract formation could be seen in patients with GFS and cataract extraction had already been performed in our case. This may be as a result of either the nature of the disorder or the side effect of multiple intravitreal steroid injections. Trabeculectomy had also been performed for glaucoma in consequence of intravitreal steroid administrations.

This case illustrates that in GFS cystic spaces may falsely be diagnosed as a cystoid macular edema. The treatment and prognosis of both conditions differ prominently and hence making a correct diagnosis is crucial.

The high variability of clinical features and various fundus appearances of this disorder may often complicate the diagnosis. Non-leaking cystoid spaces, night blindness, typical retinal pigmentary changes and pathognomonic electroretinographic features may aid in differential diagnosis of GFS.

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