Potential implications for pathophysiology in a type 1 diabetic patient affected by Stargardt disease

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Abstract. – *Purpose/Method*: To present a 35-year-old woman affected by type 1 diabetes mellitus, Stargardt maculopathy and fundus flavimaculatus. To our knowledge, this association is unusual and not yet described in the ophthalmic literature.

Results/Conclusions: Visual acuity was reduced to < 20/200 in both eyes, color vision was absent and computerized perimetry showed an absolute central scotoma. Pattern visual evoked potentials and electroretinogram (ERG) (scotopic, photopic and flicker) were considerably reduced in amplitudes. Full-field ERG was within normal limits whereas oscillatory potentials were reduced in number and amplitude. Fluorescein angiography confirmed the diagnosis of Stargardt maculopathy and fundus flavimaculatus but no diabetic retinopathy was clinically evident. Potential interactions between the diabetic microangiopathy and the retinal degenerative disorder are hypothesized and discussed.

Key Words:

Diabetic retinopathy; Fundus flavimaculatus; Maculopathy; Stargardt disease; Type 1 diabetes mellitus.

Introduction

The term Stargardt disease (STGD1 – McK 24820)[1] refers to a maculopathy with various degrees of retinal pigment epithelial changes (atrophy, dispersion, granulation) throughout the macula. Peripheral, yellowish, ill-defined pisciform (fishtail-shaped) flecks may be associated, thus representing the so called fundus flavimaculatus (FFM)[2,3].

Children between the ages of 6 and 20 years are more commonly (but not exclusively) affected, presenting a history of gradual bilateral deterioration of central vision. The probability of maintaining 20/40 or better vision in at least one eye is estimated to be 52% by age 19 and 22% by age 39. Once visual acuity drops below 20/40, it tends to decrease rapidly to 20/200, which usually occurs by the end of the third decade. No treatment is effective, although the use of antioxidants has been suggested[2,3].

In this paper, we present a 35-year-old woman affected by type 1 diabetes mellitus, STGD1 and FFM, an association that is unusual to our knowledge and not yet described in the ophthalmic literature. An updated review of this early onset macular degeneration has also been done.

Case Report

I.Z., a 35-year-old female affected by STGD1 and FFM, presented with central vision loss in both eyes (OU) lasting more than five years. The diagnosis of STGD1 and FFM had been already confirmed in the past not only clinically but also genetically by linkage to the ABCA4 gene region. Family history was negative both for diabetes and for any type of inherited degenerative retinal disorder.

The patient, also affected by type 1 insulin-dependent diabetes mellitus (IDDM), was regularly attending the Center for the Study of Diabetes (Institute of Internal Medicine II, University of Rome "La Sapienza") and classified according to the National Diabetes Data Group criteria[4]. Duration of the disease was about 25 years and glycemic control was

somewhat irregular, as demonstrated by a glycosylated hemoglobin (HbA1c) always between 9.5 and 10%. The subject was not taking other medication than subcutaneous human insulin (regular and long acting) and, despite the presence of microalbuminuria, blood pressure and serum creatinine concentrations were within normal limits. No other systemic diseases were present.

Best corrected visual acuity was < 20/200 in OU. Slit lamp examination of the anterior segment demonstrated no relevant abnormalities. The lens was transparent in OU and the intraocular pressure was normal (13 mmHg). Fundus examination and fluorescein angiography confirmed the clinical diagnosis of STGD1 and FFM, showing the typical retinal pigment epithelial atrophy in a "bull's-eye" pattern. In contrast, no clinical signs of diabetic retinopathy (DR) were present (Figure 1). Color vision was absent and computerized perimetry showed an absolute central scotoma in OU. Pattern visual evoked potentials and electroretinogram (ERG) (scotopic, photopic and flicker) were considerably reduced in amplitudes. Full-field ERG was within normal limits whereas oscillatory potentials were reduced in number and amplitude.

Discussion

The terms STGD1 and FFM are often used interchangeably to describe a degenerative retinopathy occurring within the posterior pole and in the pre-equatorial retina and both disease, which may be variations of a single disorder, are inherited in an autosomal recessive pattern[1]. Mutations in the photoreceptor ATP-binding cassette transporter (ABCR) gene (ABCA4), are responsible for this disease[5-8]. ABCR resides in the internal disc membranes of photoreceptor outer seg-
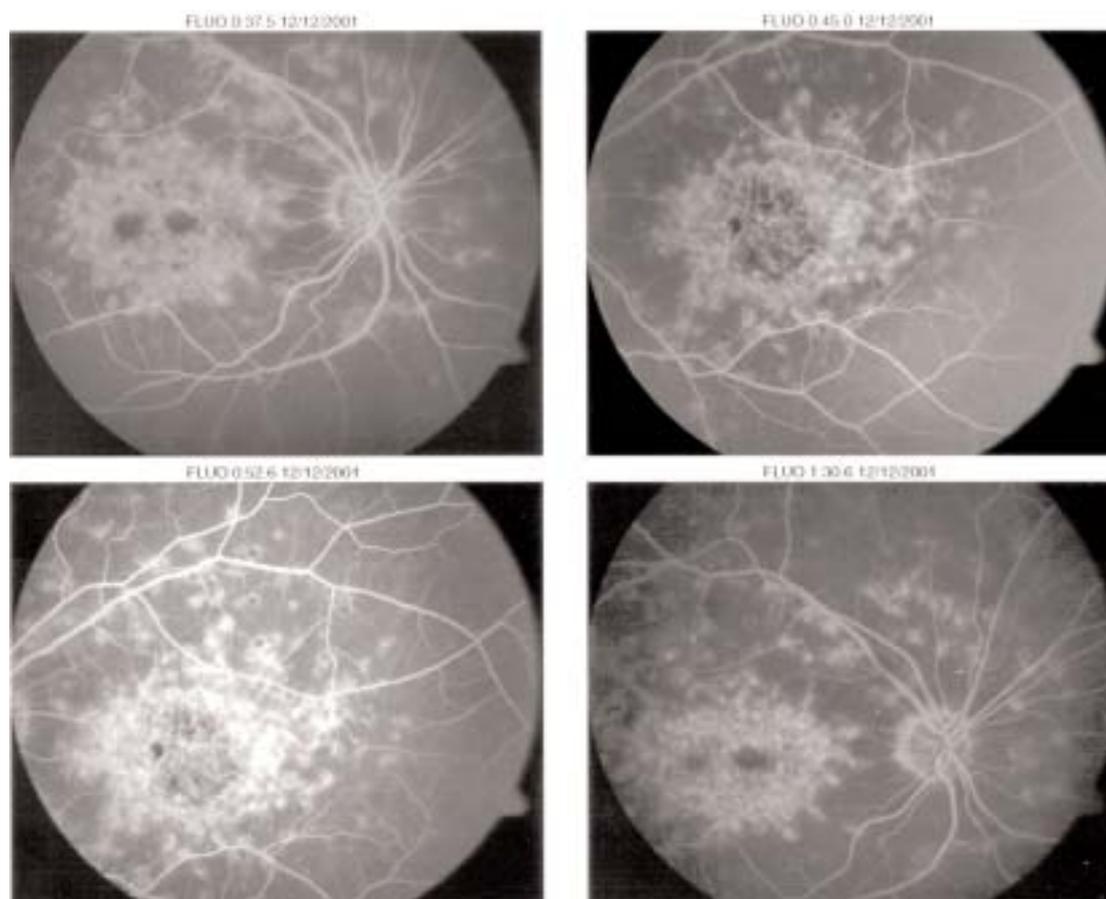

Figure 1. Stargardt disease and fundus flavimaculatus (fluorescein angiography).

ments and appears to function as a specific transporter that delivers all-trans-retinal to the enzyme retinol dehydrogenase in order to have it converted to all-trans-retinol and, thereafter, delivered to the retinal pigment epithelium (RPE) to begin the visual cycle again[9]. Approximately 250 missense, frameshift, point and nonsense mutations have been identified together with several polymorphisms and a high allelic heterogeneity[5,6]. For example, a unique sequence variation in exon 19 of the ABCA4 gene, causing an amino acid substitution T972N in the ABCR protein, has been recently found to determine a different clinical expression of the disease in two pairs of siblings with STGD1[7]. Moreover, missense mutations, mapping outside known functional regions of the ABCA4 gene, have been reported to allow a longer residual ABCR activity, thus determining a later onset of the disease[8].

A clinically similar disease, the Stargardt-like macular distrophy (STGD3 – McK 600110)[1], is genetically differentiated by the autosomal dominant inheritance and its correlated mutations (ELOVL4 gene, located on chromosome 6q16)[10-12].

Initial clinical macular changes in STGD1 include ill-defined yellowish perifoveal flecks; with progression, diffuse pigment epithelial abnormalities are recognized as a glistening area described as "beaten bronze". Foveal changes in early stages may not be clinically apparent at all and fluorescein angiography may reveal subtle central pigment epithelial defects that were not clinically obvious[2,3].

As observed in our patient (Figure 1), "choroidal silence" or dark choroid is present in some cases of STGD1-FFM and may be due to the increased filtering action of lipofuscin-laden RPE. In contrast to drusen, with which the fishtail flecks may be confused, the yellow flecks of FFM typically appear nonfluorescent; if hyperfluorescence is present, it appears in an irregular pattern that does not correspond to the flecks[2,3].

The full-field ERG is usually normal in STGD1 limited to the macula, while a delayed but otherwise normal b-wave pattern may be seen with peripheral FFM. Electrooculogram (EOG) tends to be subnormal in some patients, indicating a widespread functional disturbance of the RPE. A subgroup of patients with STGD1 develops symptoms and signs of cone-rod type retinitis pigmentosa, including nyctalopia, narrowing of retinal vessels and ERG abnormalities[2,3].

It has been recently proposed that patients with STGD1 and FFM may be classified into three different groups based on the absence or presence of generalized loss of either photopic or photopic and scotopic function[13]. In particular: group 1 – severe pattern ERG abnormalities with normal scotopic and full-field ERGs; group 2 – additional loss of photopic function; group 3 – loss of both scotopic and photopic function. It has been hypothesized that these three groups may represent distinct phenotypic subtypes of Stargardt disease[13].

Post-mortem histopathologic examination of patients with FFM demonstrated that the RPE cells are much larger and more densely packed with an intense PAS-positive substance, which is believed to be lipofuscin. The greatest concentration of lipofuscin pigment is within the posterior pole and the focal areas of cellular hypertrophy are probably responsible for the nonfluorescent yellow flecks[2,3]. One major component of human RPE lipofuscin is a diretinoid adduct, A2E, that appears to form within the photoreceptor outer segments from the spontaneous condensation of phoshatidylethanolamine and the all-trans-retinal released from the photoactivated rhodopsin. Phagocytosis of outer segments by the RPE results in accumulation of A2E within the RPE where it appears to be trapped within phagolysosomes. A2E efficiently absorbs blue light and is phototoxic to RPE cells in culture; its progressive accumulation within the RPE suggests that the RPE may become increasingly susceptible with age to the phototoxic damage. Thus, both photoreceptor and RPE photodamage may be mediated, at least in part, by retinoids or retinoid derivates and ABCR, involved in all-trans-retinal recycling, is found to be unusually sensitive to all-trans-retinal-mediated photooxidative damage in vitro[9].

Population studies have indicated that some ABCR variant alleles may enhance susceptibility to age-related macular degeneration (AMD), the most common cause of visual impairment in the elderly[14], and carrier relatives of STGD1 patients may be predisposed to develop this severe disease[15]. However, conflicting results have been found in another

study in which the ABCA4 gene did not seem to be involved in statistically significant fraction of AMD cases[16]. Finally, ABCR mutations have been suspected to predispose to retinal toxicity in patients under chloroquine or hydroxychloroquine therapy[17].

A family manifesting both STGD1 and retinitis pigmentosa (RP) has been recently observed[18] and the notion that the severity of retinal disease is inversely related to the residual ABCR activity has been confirmed in this study. On the contrary, while RP-affected diabetics have already been described in the ophthalmic literature, the association between STGD1 and type 1 diabetes mellitus, as observed in our patient, is, to our knowledge, unusual.

RP and diabetes, if associated, occur independently. However, although each condition is relatively common, the number of subjects with both conditions is quite small, usually configuring some of the classical clinical findings of Alstrom and Kearns-Sayre syndromes[3]. In these patients, DR is usually absent and the protective factor is thought to be represented by a reduction in retinal metabolism, due to photoreceptor loss, importantly rods, that require a great deal of energy and a large oxygen supply for their metabolic requirements[19]. In fact, it is certain that the diabetic retina rather than being hyperoxic, as is commonly supposed, borders on the pathological anoxia and this seems to be especially true in dark adaptation, since in such circumstances the already low retinal PO_2 markedly decreases. Moreover, there is evidence not only that a very small decrease in normal oxygen supply may affect the retinal function, but also that the diabetic retina suffers from oxygen lack before the onset of a clinically evident DR[19]. Finally, the hypoxic upregulation of vascular endothelial growth factor (VEGF), a main risk factor for DR, has been found to be largely absent in diabetics who do not develop a clinically evident retinopathy, despite the long-standing diabetes[20].

Considering all these previously published reports, the clinical case that we present should not be simply regarded as fortuitous and of limited interest, as potential interactions between the diabetic microangiopathy and the STGD1 might be hypothesized. In fact, retinal oxygen availability represents a critical point in the development both of diabetic retinopathy and of retinal degenerative disorders and this is also confirmed by the observation that hyperbaric oxygen delivery has been proposed not only for RP patients, in order to bring about the rescue of retinal photoreceptors[21], but also for high risk DR[22]. Moreover, a severe endothelial dysfunction, probably mediated by the endothelin and the immune systems, characterize the early pathophysiology of diabetic microangiopathy, even in angiographically normal retinas[23], thus representing a main cause of ischemia and hypoxia that would presumably have a greater adverse impact in patients affected by STGD1 than it would in the context of a normal ABCR function. In fact, partial loss of ABCR function produces progressive retinal disease and the hypothesis that any environmental process, leading to a decrease in ABCR function, may increase the risk or accelerate the development of retinal disease has already been postulated[9].

In conclusion, much remains to be investigated. However, we would like to emphasize the hypothesis that any factor, potentially able to reduce the retinal oxygen availability, should be seriously taken into account in the management of patients with tapetoretinal degenerations and, therefore, a systemic disease such as diabetes should be considered with caution. At the same time, our clinical case seems to confirm that degenerative retinal diseases represent a protective factor against the development of diabetic microangiopathy, even though the exact mechanism, by which a cone dystrophy such as STGD1 (unlike to a cone-rod typical RP) may act, remains to be clarified.

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