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STARGARDT'S DISEASE AND LATENT AUTOIMMUNE DIABETES IN ADULT (LADA): AN UNUSUAL ASSOCIATION AND CLINICAL IMPLICATIONS

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ABSTRACT
Stargardt's disease(STGD) is a rare condition leading to loss of visual acuity in patients in their first and second decades of life. Though multiple etiopathogenetic mechanisms have been described, its' association with autoimmune young –onset diabetes mellitus have been sparsely reported. In this article, we present a case of 35 year old male with latent autoimmune diabetes in adults(LADA) for 5 years with progressive central vision loss not corrected by glasses. His uncorrected vision was 6/12 bilaterally, and fundus examination including Optical Coherence Tomography and fluorescein angiography confirmed the clinical diagnosis of STGD, showing typical retinal pigment epithelial atrophy with "Bronze Beaten" appearance and Bull's eye pattern without clinical signs of Diabetic retinopathy were seen. Our clinical case is the first such depicting the association between LADA and Stargardt's disease, with significant clinical implications. Further our case report confirms and reiterates the finding that degenerative retinal diseases represent a protective factor against the development of diabetic microangiopathy.

INTRODUCTION
Stargardt's disease (STGD)[1] is arguably the most common hereditary recessive macular dystrophy and is characterized by juvenile to young-adult onset, evanescent to rapid central visual impairment, progressive bilateral atrophy of the foveal retinal pigment epithelium (RPE) and neuroepithelium, and the frequent appearance of yellow-orange flecks distributed around the macula and/or the midretinal periphery[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[4].

In this article, we present a 35-year-old male, affected by Latent Autoimmune Diabetes in Adults(LADA) and Stargardt's Disease, an association that is hitherto unreported in the literature[3]. Though there are case reports of associations of STGD with Type 1 Diabetes mellitus[5], but none with LADA to the best of our knowledge.

CASE DESCRIPTION
Mr SS, a 35 year old male, presented with a 5 years history of Diabetes Mellitus on oral anti-diabetic agents (Metformin, Teneligliptin and Empagliflozin) for evaluation of complications and optimization of glycemic control. There was no history of Diabetic ketoacidosis in the past, with a family history of Type 2 Diabetes Mellitus in his father and paternal uncle. His biochemical evaluation for young onset diabetes revealed an HbA1c of 7.4% with Anti GAD65 Antibody of > 2000 U/ml (reference range <5.0 U/ml) with a preserved C-peptide response (Fasting C Peptide =1.81 ng/ml, 90 minutes post meal = 7.12 ng/ml). His Ultrasound abdomen was normal and there were no pancreatic morphology abnormalities. Based on the clinical and biochemical picture, he was classified as having Latent Autoimmune Diabetes in Adults (LADA).

On further clinical examination, the patient was found to have complaints of loss of visual acuity, uncorrected by glasses in both eyes for the past 5 years, with uncorrected vision of 6/12 in both eyes. He also complained of occasional wavy vision and difficulty in adapting to dim light. Slit lamp examination of anterior segment revealed no abnormality. The lens was transparent, with normal Intraocular pressures bilaterally. Subsequently fundus

examination and fluorescein angiography showed the typical retinal pigment epithelial atrophy with "Bronze Beaten" appearance and Bulls eye pattern, suggesting the clinical diagnosis of Stargardt's Disease. He also underwent an Optical Coherence Tomography (OCT)which confirmed the initial findings . In contrast, no clinical signs of Diabetic retinopathy were seen (Figure 1a, b and c).

DISCUSSION

Stargardt's disease is also described as juvenile macular degeneration, cone-rod dystrophy and fleck retinopathy. There is still confusion about the use of the terms between Fundus Flavimaculatus(FFM) from fleck retinopathy groups and Stargardt's disease. If the disease starts later in life after the age of twenty years, flecks embracing the macula with a few macular changes and partial preservation of visual acuity exist, in which case the disorder has been described as Fundus Flavimaculatus(FFM). If the pathological visual changes starts in the first and second decades of life, the term Stargardt's dystrophy is preferable[6]. Generally, the patients are classified into different groups according to angiographic and ophthalmoscopic features[6].

Initial clinical macular changes in STGD 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[4].

As observed in our patient (Figure 1a-c), "choroidal silence" or dark choroid is present in some cases of STGD and may be due to the increased filtering action of lipofuscin-laden Retinal Pigment Epithelium(RPE). In contrast to drusen, with which the fishtail flecks may be confused, the yellow flecks of STGD typically appear nonfluorescent; if hyperfluorescence is present, it appears in an irregular pattern that does not correspond to the flecks[7].

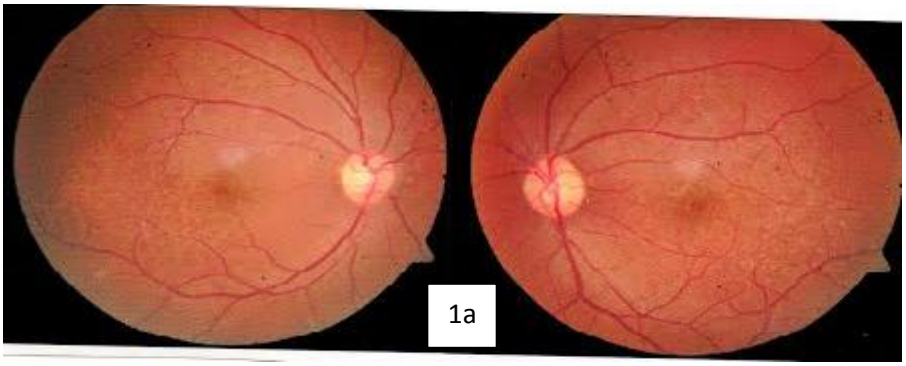
The full-field Electroretinogram (ERG) is usually normal in STGD and limited to the macula, while a delayed but otherwise normal b-wave pattern may be seen with peripheral disease.

Electrooculogram (EOG) tends to be subnormal in some patients, indicating a wide spread functional disturbance of the RPE. A subgroup of patients with STGD develop symptoms and signs of cone-rod type retinitis pigmentosa, including nyctalopia, narrowing of retinal vessels and ERG abnormalities[4,7].

Retinal degenerative disorders like Retinitis Pigmentosa (RP) and Diabetic Mellitus, 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 syndrome. In these patients, diabetic retinopathy(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[8]. In fact, it is certain that the diabetic retina rather than being hyperoxic, as is commonly supposed, borders on pathological anoxia and this seems to be especially true in dark adaptation, since in such circumstances the already low retinal PO2 markedly decreases. Moreover, there is evidence that not only 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[8]. 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[9].

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[10], but also for high risk DR[11].

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[12], thus representing a main cause of ischemia and hypoxia that would presumably have a greater adverse impact in patients affected by STGD.



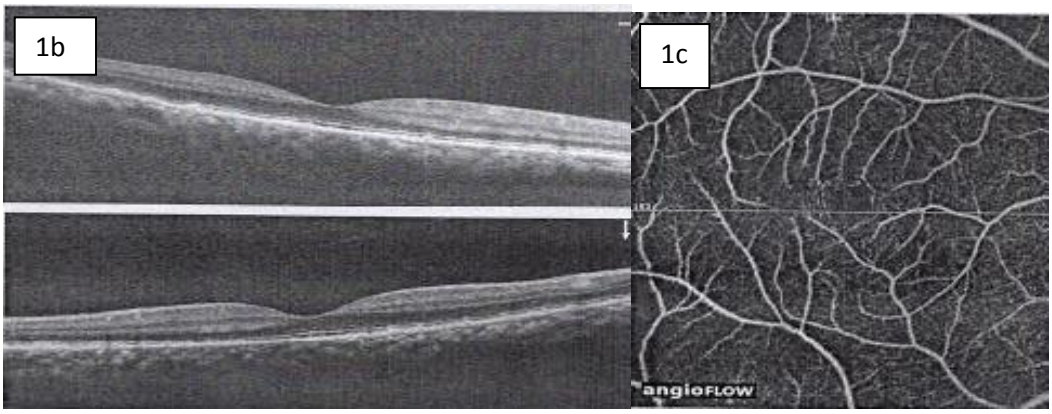


Figure 1: Detailed Ophthalmological evaluation including fundus examination(a),Optical Coherence Tomography(b) and Fluorescein Angiogram(c) reveals the presence of typical retinal pigment epithelial atrophy with "Bronze Beaten" appearance and Bull's eye pattern, suggesting the clinical diagnosis of Stargardt's Disease(STGD).

CONCLUSION

Stargardt's disease(STGD) is an uncommon yet important cause of young-onset vision loss, though much remains to be investigated regarding its' exact etiopathogenesis and treatment. Our case emphasizes 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 like STGD and therefore, a systemic disease such as diabetes should be considered with caution. At the same time, our clinical case seems to confirm and reiterate the finding(5) 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 STGD may act, remains to be clarified. Further, the association of STGD with a latent form of autoimmune diabetes in adults has not yet been reported in literature and can have important pathophysiological and therapeutic ramifications.

REFERENCES

1. Walia S, Fishman GA. Natural history of phenotypic changes in Stargardt macular dystrophy. Ophthalmic Genet. 2009 Jun; 30(2): 63-2.
2. Lewis RA, Shroyer NF, Singh N, Allikmets R, Hutchinson A, Li Y, et al. Genotype/Phenotype Analysis of a Photoreceptor-Specific ATP-Binding Cassette Transporter Gene, ABCR, in Stargardt Disease. Am J Hum Genet. 1999 Feb; 64(2): 422–34.
3. Giusti C. Potential implications for pathophysiology in a type 1 diabetic patient affected by Stargardt disease. Eur Rev Med Pharmacol Sci. 2002 Aug; 6(4): 75–9.
4. Julien S, Schraermeyer U (Oct 2012). "Lipofuscin can be removed from the retinal pigment epithelium of monkeys". Neurobiol Aging. 33(10): 2390–7.
5. Molday RS, Zhong M, Quazi F. The role of the photoreceptor ABC transporter ABCA4 in lipid transport and Stargardt macular degeneration. Biochim Biophys Acta. 2009 Jul; 1791(7): 573-83.
6. Molday RS, Zhang K. Defective lipid transport and biosynthesis in recessive and dominant Stargardt macular degeneration. Prog Lipid Res. 2010 Oct; 49(4): 476-92.7.
7. Kapadia O.D.S. Stargardt's macular dystrophy. Clin Eye Vis Care. 2000 Mar 1; 12(1–2): 71-8
8. Arden G. The absence of diabetic retinopathy in patients with retinitis pigmentosa: implications for pathophysiology and possible treatment. Br J Ophthalmol. 2001 Mar; 85(3): 366–70.
9. Marsh S, Nakhoul FM, Skorecki K, Rubin A, Miller BP, Leibu R, et al. Hypoxic induction of vascular endothelial growth factor is markedly decreased in diabetic individuals who do not develop retinopathy. Diabetes Care. 2000 Sep 1; 23(9): 1375–80.
10. Vingolo EM, Pelaia P, Forte R, Rocco M, Giusti C, Rispoli E. Does hyperbaric oxygen (HBO) delivery rescue retinal photoreceptors in retinitis pigmentosa? Doc Ophthalmol Adv Ophthalmol. 1998 1999; 97(1): 33–9.
11. Oguz H, Sobaci G. The Use of Hyperbaric Oxygen Therapy in Ophthalmology. Surv Ophthalmol. 2008 Mar; 53(2): 112–20.
12. Giusti C. Retinopathy in juvenile diabetes: a 10-year (1990–2000) review. Pediatr Diabetes. 2001 Jun 1; 2(2): 83–93.