Stargardt's vs. Inverse Retinitis Pigmentosa

Carol Ann Brunner

Associate of Science

Lincoln Land Community College, Springfield, IL 1984

Bachelor of Visual Science and Doctorate of Optometry

Ferris State University, Big Rapids, MI 1988

Abstract:

A ten year old white male was referred to the OMNI Eye Center in Lexington, Kentucky for bilateral macular changes. After our examination, he was sent to a retinal specialist for further evaluation. He believes the lesions are related to the heredomacular disorder of Stargardt's or Inverse retinitis pigmentosa. This paper compares these two entities and also identifies various other conditions which must be differentially diagnosed in patients with a bilateral macular dystrophy.

Key Words:

Stargardt's disease, Fundus Flavimaculatus, Dominant Progressive Foveal Dystrophy, Inverse Retinitis Pigmentosa

A ten year old white male presented to the clinic in January 1988 after being referred from his present optometrist for a retinal evaluation. The patient reported good vision in both eyes in the past. His mother reported he had passed several previous eye screenings; however, on a screening approximately one year ago some difficulty was noted with the left eye. The patient had recently complained of some difficulty with reading and headaches at school.

Entering unaided distance visual acuities were 20\15 in the right eye and 20\400 in the left eye. Unaided near visual acuities were J1+ in the right eye and J5 in the left eye. Refraction was +0.25 sphere in the right eye and +0.50 sphere in the left eye with no change in acuity.

Confrontation visual fields were full to finger counting. Amsler grid results were normal in the right eye and a scotomatous area was noted along the nasal border in the left eye.

Color vision testing using City University Color Plates were 10\10 in the right eye and 5\10 in the left eye. Extraocular muscles were intact. Pupils were equal, round, and responsive to light with no afferent pupillary defect.

Slit lamp examination showed normal lids, conjunctiva, cornea and anterior chamber in each eye. Applanation tonometry measured 14mm Hg in each eye.

Dilated fundus examination revealed discs, vessels, and periphery to be unremarkable. A marked disturbance of the RPE

(retinal pigmented epithelium) was noted in the macula of both eyes with some areas of RPE migration up into the retina.

This patient was then referred to a retinal specialist to further delineate the diagnosis of these bilateral macular lesions. He was seen one week later by the retinal specialist. Further discussion with the patient revealed no noticeable difference in his day or night vision. On closer questioning, his mother indicated a possibility of decreased vision in male family members on her side. Otherwise, good vision was reported in his sister, stepbrother, and stepfather.

Tests conducted revealed essentially the same results as our exam. An automated visual field (Dicon) showed normal fields in both eyes. Dilated examination showed RPE atrophy with areas of hyperpigmentation in both eyes. The left eye showed some depigmented areas nasal to the optic nerve. FIGURE 1 and 2 Due to the localization of the lesion to the macula he believed this represented "Inverse Retinitis Pigmentosa" or "Stargardt's disease" and not a viral retinitis. To differentiate these two diseases, a fluorescein angiogram and ERG were planned. With inverse RP, he expected the ERG to be extinguished. A follow-up appointment was made for these tests. However, he has not returned for the testing to date.

Since the patient did not return for the above testing no definitive diagnosis can be made at this time. Yet, a comparison can be made between Stargardt's and Inverse RP. In

such a comparison, one must have the background information of these two entities along with their differential diagnosis from other conditions. Therefore, this discussion will enable this differentiation.

Stargardt's disease was first described in 1909 as a condition in which there was a bilateral and slowly progressive lesion "confined to the macula." This lesion started in youth and led to an eventual loss of central vision which was apparently familial in nature. The age of onset is usually in the first and second decade between the ages of 8-14. 2,3

It is an autosomal recessive, progressive tapetoretinal dystrophy of the central retina. 3 There are reports of an autosomal dominant form which will be discussed later. Stargardt's is the most frequent heredomacular degeneration of the RPE and photoreceptors. It has a prevalance of 1\15,000.

Many reports and studies tend to support the notion that fundus flavimaculatus and Stargardt's are the same entity. Fundus flavimaculatus was originally defined by Franceschetti describing a bilateral disorder with yellow-white spots scattered through the posterior pole with a symmetrical appearance. They are of an irregular size and have a round, ovoid, linear, fish-like or half-moon shape and are accumulations of "PAS-positive acid mucopolysaccharide from the inner half of the pigment epithelial cells." 5 This material may go through the inner pigment epithelial cell wall to the subretinal space. 5 Further

definitions reveal fundus flavimaculatus to have extensive flecks with or without a foveal atrophic lesion. 6

Various opinions dealing with these two diseases have been made. One states that Stargardt's is marked by a macular degeneration which is progressive and begins at an early age, and fundus flavimaculatus has a "centripetal progression of a pericentral process at middle age." 7 Krill believes they are the same, but prefers fundus flavimaculatus with two different types. One with atrophic macular degeneration and one without macular degeneration. Some believe a distinction can be made on the ophthalmoscopic picture in which if the macula is involved they designate it as Stargardt's. 7 A study by Noble and Carr of 67 patients diagnosed as having Stargardt's that were in there 10-20's showed:

1. 20% had macular degeneration without flecks
2. 40% had macular degeneration with a few perifoveal flecks--Stargardt's
3. 40% had macular degeneration with diffuse posterior pole flecks--fundus flavimaculatus with macular degeneration
4. Four patients (6%) had posterior pole flecks without maculopathy--Pure fundus flavimaculatus.

Follow-up examination showed a development of flecks in some who had only a maculopathy and one patient with flecks only developed a maculopathy. Of these groups no distinction could be made between them on any other base such as "sex, race, age at onset, heredity, visual acuity, psychophysical and electrophysiologic

tests, and prognosis." 5 From this study, they concluded there was no "rational or logical distinction between Stargardt's disease and fundus flavimaculatus." 5 On the other hand, Moloney, Mooney and O'Connor showed visual loss in Stargardt's to occur within a three month period in twelve of twenty-four patients and in a one week period in three out of ten patients. The initial visual deterioration in patients with fundus flavimaculatus was never rapid and in most showed a gradual long term decrease. They also note, as did Noble and Carr, that Stargardt's and fundus flavimaculatus do not co-exist within the same family. Therefore, they suggest Stargardt's and fundus flavimaculatus are two independent diseases. 8 Thus, there is still a variety of opinions at this time concerning the differentiation of these two diseases. For this paper we will describe Stargardt's as a separate entity.

There is a variety of fundus changes involved in Stargardt's. In the very early stages, no funduscopic changes may be noted, but vision is reduced. These patients may be diagnosed as having hysteria, malingering or a brain disease. 5 The first macular sign may be a change in the foveal reflex which may disappear or become distorted with some central swelling and a possible greying or metallic appearance to the reflex. 1,9 Secondly, changes in the RPE in the form of grey, yellow, or brown spots with a granulated appearance to the fovea usually collect in masses and increase in "density" with time. 1 It may

also appear as though the fovea has a sheen or "varnish appearance."9 Occasionally, the internal limiting membrane has a very fine folded appearance radiating out. 9 A third stage or change reveals the formation of a horizontal oval of variable size, usually one-half to three disc diameters. This is sometimes called "Beaten Bronze Atrophy" and may be due to Bruch's membrane hyalinization. 1 There is an occasional peri-central involvement and rarely the whole posterior pole may be affected by the lesion. 1 The ultimate result may be an atrophic posterior pole which can resemble central choroidal atrophy. 9 Duane's reports the "process may remain central or involve the periphery as well" resembling fundus flavimaculatus.10 Late stage peripheral involvement may include round and black pigment centered within a depigmented area. As more atrophy occurs, exposure of the choroid may occur (as stated above) giving rise to a geographic atrophy within the posterior pole and a periphery resembling RP. There are many "transitional forms and a long follow-up may be needed to delineate the extent of the involvement." 10

Clinical presentation of Stargardt's patients may include a bilateral decreased visual acuity with a past history of normal vision. However, unilateral decreased vision may be present even though fundus findings are symmetric. 9 Central vision is usually less than 20/200 with no less than 20/1200. Eccentric fixation may be used successfully by patients. 1 The disease progression can be said to terminate within ten years

with a visual acuity of no less than 20\800. 4 The macular appearance does not always correlate with visual acuity and follow-up may show decreased vision with no macular changes or vice versa. 5 Other arriving complaints may include some complaint of photophobia or a form of day blindness. 1

Color vision testing will show a gradual red-green dyschromatopsia. Eventually, an achromatopsia that will become complete may be seen. 1 Yet, the most common color disturbance they will identify is a decrease in their sensitivity to the color red. 9 This can be done with a red cap comparison test between the two eyes. They will easily notice a difference in its color between the eyes when a color deficiency is present.

Visual fields reveal normal peripheral fields as long as the retinal periphery remains uninvolved. A relative central scotoma will first develop rapidly for a red target and later for green. The scotoma size depends on the size of the atrophic lesion with it rarely being greater than twenty degrees. Ultimately, an absolute central scotoma with associated eccentric fixation may occur. 9

Electrodiagnostics and fluorescein angiography are often used in differential diagnosis. Electrodiagnostic testing reveals a normal ERG and EOG which become abnormal with more extensive central and peripheral changes. The VER is subnormal even with good visual acuity and minimal fundus signs. 9,10 Therefore, an abnormal VER may be important for early diagnosis.

An ERG may be helpful when there is decreased vision with or without a foveal lesion or a lesion without flecks. In this situation, the ERG will help to rule out cone dystrophy in which cone and possibly rod ERG amplitudes would be reduced. However, ERG and EOG are not for diagnosis. A dark choroid with fluorescein angiography and the fish-tail flecks are characteristic enough to lead to the diagnosis of Stargardt's in most patients. 6

In order to diagnose Stargardt's disease various other conditions or diseases must be ruled out, one of these being Inverse RP which will be discussed later. The other conditions include Dominant Progressive Foveal Dystrophy which has been called a "Dominant Stargardt's." This is an autosomal dominant disorder having fundus findings which are the same as Stargardt's without flecks. Some believe a differentiation should be made between these two due to the different inheritance because there may be "different pathologic genes." 10 In a study of 99 family members by Cibis, Morey and Harris, it was found that there was an autosomal dominant form showing the same clinical findings as the autosomal recessive Stargardt's. This led them to conclude that there was a "variety of the genetic and allelic variations also giving the same clinical picture." 11 Other literature points out this is a much rarer form and also may be found at a later age. 10

The other conditions or diseases which must be considered include:

1. Progressive cone dystrophies which are characterized by extreme photophobia, acquired achromatopsia, subnormal photopic ERG, a macular pigment change which shows a bull's eye pattern with fluorescein angiography and contracted peripheral visual fields. 12

2. Sex-linked Juvenile Retinoschisis which has a "pathognomonic cystoid foveal alteration with radial plicae" and a subnormal ERG. 9

3. Vitelliform macular dystrophy has a characteristic cyst which breaks giving a scrambled egg appearance. The EOG is always abnormal. 12

4. Chloroquine Retinopathy can be differentiated often with a careful history. The macula will show a bull's eye appearance. Subnormal ERG and EOG, delicate foveal pigment changes in the peripheral retina, pale disc and vessel constriction are also found. 9 Blood and urine testing is also helpful.

5. Phenothiazine Retinopathy resembles chloroquine retinopathy.

6. Spielmeyer-Vogt disease may have associated cerebral manifestations distinguishing it. If not, peripheral retinal changes, vessel constriction, pale discs, ERG and EOG changes occur much earlier than in Stargardt's. Also, no perifoveal yellow-white spots are present. 9

7. Optic nerve affections which are bilateral may pose difficulty in early Stargardt's without foveal involvment. VER testing will be normal in these cases and reduced in Stargardt's. 9

8. Central areolar choroidal dystrophy may be impossible to differentiate in early and terminal stages of

Stargardt's. A dominant inheritance pattern, bilateral and symmetric lesions which show choriocapillaris atrophy on fluorescein angiography may be of some help. 9

9. Macular lipidoses can be distinguished through other associated disturbances in the patient. 9

Central dystrophies can be distinguished most often by ophthalmoscopic changes. 9 In addition, the age at which symptoms occur may be useful. Also, the patient's clinical symptoms themselves and hereditary transmission can be used in diagnosis. 7

Inverse RP must also be included in this list of differentials. Inverse RP is sometimes called Cone-Rod Dystrophy or Pericentral Rod-Cone Dystrophy. In this condition, the posterior pole develops the boney spicule pigmentation which is seen in classic RP; however, true trabeculae will not be seen in the fovea since it is avascular. It is not known whether this fundus appearance is a separate disease or if it imitates other macular dystrophies. 13 It tends to be sporadic and occasionally appears to be of an autosomal recessive origin and is usually diagnosed in the 10-20's with an ophthalmoscopic exam. 13, 10

The fundus changes with the duration of Inverse RP. Early manifestations of it involve the central retina "symptomatically, funduscopically, and functionally." 13 The earliest symptoms usually involve visual loss. The pigmentary changes occur in the posterior pole. Later manifestations will include more

involvement of the rest of the retina with frequent nyctalopia. In some cases, the peripheral involvement may be minimal with the dominant fuduscopic finding being of a macular lesion. 14, 10 Another source states it is a progressive degeneration of the neuroepithelium and the RPE in which there is a generalized atrophy of the whole retina later in the disease. 3 Also, the disc and vessels are normal until later stages of this affliction. 10 Goldberg names a condition, Central RP, which he distinguishes from Inverse RP. He believes Central RP never involves the periphery, but Inverse RP is generalized. 13 Therefore, there is another conflicting opinion of whether or not the periphery in involved.

Visual acuity and color vision will be affected eventually in Inverse RP. Visual acuity is usually normal early in this disease. Later stages will show a decrease of 20/200 or less. Color vision may also be decreased.

Electrodiagnostic testing may be used. Yet, whether these can be useful in diagnosis seems to be of a varied opinion. 13 Some say electrodiagnostic testing shows a "predominantly cone photoreceptors dysfunction" in Inverse RP. 13 On the other hand, others say ERG and EOG may be normal or only slightly decreased since the lesion is believed to be localized in the photoreceptors and RPE. 10

Visual field testing will show a constricted peripheral

field or ring scotoma if the macular lesion is a part of a more widespread retinal degeneration. 14 If not, the peripheral fields will be normal in the early stages. Later manifestations may lead to a later field constriction.

Fluorescein angiography testing will show an irregular RPE derangement and atrophy in Inverse RP. 10 In contrast, Stargardt's will show the transmission to be irregular in the RPE within the fovea. In addition, sometimes a bull's eye pattern may be seen. Yet, a choroidal nonperfusion is the most common type of transmission seen in advanced Stargardt's. 10

Stargardt's and Inverse RP can often give a similiar funduscopic picture. The age of onset is also similar. Both show decreased vision and possible decreased color vision. Their central visual fields are affected and often in later stages the peripheral fields become constricted. The ERG and EOG can be normal or only slightly decreased in both cases with the ERG and EOG being more likely decreased in Inverse RP; however, this is not always a definitive test. Fluorescein angiography appears to be the most definitive test since advanced Stargardt's has its characteristic choroidal nonperfusion. In conclusion, Stargardt's and Inverse retinitis pigmentosa may be very difficult to fully differentiate from one another, especially in the early stages, and a long follow-up may be needed to differentiate them entirely.

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Figure 1: Right eye showing macular changes in patient.

Figure 2: Left eye showing macular changes in patient.