Stargardt's hereditary progressive macular degeneration

A. RODMAN IRVINE AND FLOYD L. WERGELAND, JR

From Ophthalmology Service, Letterman General Hospital, Presidio of San Francisco, California

In a series of three papers, Stargardt (1909, 1913, 1916) described with precision and thoroughness a form of hereditary macular degeneration which has become known as Stargardt's disease. The purposes of the present paper are to review Stargardt's original observations, to argue that Stargardt's disease and fundus flavimaculatus with atrophic macular degeneration are identical, and to present a series of patients studied by fluorescein angiography consistent with the hypothesis that a late secondary or disuse atrophy of the choriocapillaris occurs in Stargardt's disease.

Stargardt described four families. The disease seemed to show recessive inheritance, being present in siblings but never in successive generations. Symptoms were usually first noted between 8 and 16 years of age, and then progressed gradually and inexorably until all macular function was destroyed some years later. The first finding was a decrease in visual acuity, often more noticeable in the bright light than in the dark, with minimal ophthalmoscopic changes. A faint irregularity in the pigment in the macular region was often all that could be seen at this stage, and the fundus might easily be passed as normal. Later, the foveal reflex was lost. Soft yellow-grey spots appeared in the macula which initially were barely distinguishable from the fundus background. As pigment epithelial atrophy and clumping progressed, these single spots became confluent and formed a rather sharply outlined lesion about 1.5×2 disc diameters in size. Yellow choroidal vessels could be seen through the base of the lesion.

In the region surrounding the macula, soft, white flecks of approximately 0.1 disc diameter in size could be seen. These are prominent in each of Stargardt's three published drawings of the posterior pole (Stargardt, 1909; Rosehr, 1954) and are described in at least one member of every family he reported. From Stargardt's descriptions and drawings, these flecks appear to be identical to what is now called *fundus flavimaculatus*. We believe the eponym "Stargardt's disease" is interchangeable with the more descriptive term "fundus flavimaculatus, type II, with atrophic macular degeneration" as used by Klien and Krill (1967). The flecks are sometimes present when visual symptoms are first noted and in other cases they appear later after macular disease has already become obvious. The similarity between Stargardt's disease and fundus flavimaculatus has been commented upon by several authors (Franceschetti, 1965; Klien and Krill, 1967). The only thorough discussion of the problem in differentiating between the two, however, is presented by Deutman (1971). Although he still prefers to separate the two entities, Deutman (1971) frankly admits there is no definite criterion for doing so. He states that perhaps the flecks appear earlier in the course of disease in fundus flavimaculatus, but he concedes that there is no documentation for this.

In Stargardt's descriptions (1909, 1913, 1916), the disc at first appeared normal but later developed mild temporal pallor. The retinal vessels remained normal throughout the

Received for publication October 29, 1971

Presented at the convention of the Association for Research in Ophthalmology, Sarasota, Florida, 26 April 1971

Address for reprints: Major A. Rodman Irvine, Box 190, Ophthalmology Service, Letterman General Hospital, Presidio of San Francisco, California 94129, U.S.A.

course of the disease. In a late follow-up of patients originally described by Stargardt, Rosehr (1954) observed loss of the choroidal vessels underlying the macula and some mild narrowing of the retinal vessels in the macular region. A striking feature of the course of this disease was the manner in which the visual acuity dropped dramatically while the macula continued to appear nearly normal. Then the visual acuity tended to remain stable at the 20/200 to 20/400 level while the observable fundus lesion progressed to "catch up" with the functional loss.

Several recent papers (François and De Rouck, 1965; Klien and Krill, 1967; François and De Laey, 1969; ffytche, Blach and Bird, 1970; Merin and Auerbach, 1970) have indicated that fluorescein angiographic or retinal function studies demonstrate that Stargardt's disease is not limited to the macula. Stargardt realized this. Besides drawing and describing the soft yellow-white spots outside the macula, he stated:

"... Earlier I believed that the process was limited to the macula and ended when this was destroyed. That may indeed be the case in some patients. Family 'S', however, shows that the disease also affects other parts of the fundus. In two members of this family, not only the region around the macula but also the periphery was affected... I would like to believe that these soft white spots are a sign that the process has already proceeded out from the macula into the surrounding region..."*

He described pigment change further in the periphery and at least one patient with abnormal dark adaptation.

We had the privilege of studying a patient who had been examined 18 years previously by the father of one of us (ARI) and 23 years previously by a prominent ophthalmologist in Philadelphia. Their records describe a progression compatible with Stargardt's disease. At the time we saw the patient, the fundus appearance bore similarities to central choroidal sclerosis. Stargardt's own patients showed such appearances in the late stages. The two diseases can be distinguished by their clinical course. In early Stargardt's disease there is marked loss of acuity with only minimal pigment granularity in the macula. In contrast, in central choroidal sclerosis, visible areas of marked atrophy precede loss of Snellen acuity (Ashton, 1953; Sorsby and Crick, 1953; Sorsby and Davey, 1955; Howard and Wolf, 1964). In addition, the typical soft white flavimaculatus flecks were present in this patient and they are seen only in Stargardt's disease and not in central choroidal sclerosis.

Fluorescein angiography documented a loss of the choriocapillaris in the macular lesion in our patient (Case 4). This finding led to a study of fluorescein angiography in the various stages of Stargardt's disease, and to an attempt to understand the relation of Stargardt's disease to the other hereditary macular degenerations which can give an identical ophthalmoscopic appearance in the end stages.

We studied four patients who represented different stages of progression of Stargardt's disease. Fluorescein angiography was performed using a Zeiss fundus camera with a Baird Atomic number 4 excitor and number 5 barrier filter. 5 ml. of 10 per cent. fluorescein were injected into the antecubital vein. Electoretinographic (ERG) testing was done under simple scotopic conditions with a pen-type tracer which was capable of measuring only the distance from the trough of the A-wave to the peak of the B-wave. B-wave dark adaptation was not measured. Dark adaptation was performed with a Goldmann Weekers adaptometer, testing a single point 15° from fixation. Results were read merely for the presence or absence of both cone and rod portions of the curve and the final level of adaptation achieved. Electro-oculography (EOG) was done according to the method of Arden and Kelsey (1962).

*Translated by ARI and FIW

Case reports

Case 1, a 10-year-old girl, was first noted to have poor vision 2 months before we saw her. She was examined because of the disease of her older brother (Case 2). Both parents have normal vision and a younger brother aged 3 years has no obvious abnormalities.

Vision was 20/40 in the right eye and 20/60 in the left, neither of which could be improved by refraction. Colour vision on the Hardy-Rand-Ritter (H-R-R) plates was normal. Dark adaptation gave a normal biphasic curve of over 4 log units. The EOG was within normal limits with light:dark ratio of 2:1. The ERG revealed a normal B-wave amplitude. Fundus examination revealed deep, soft, yellow-white flecks distributed in a circular pattern about the posterior pole. The distribution and appearance of these flecks were remarkably similar to those in Stargardt's original drawing of Paul H. (Rosehr, 1954). The macula could have been quickly passed over as normal; however, search revealed some slight granularity. Fluorescein angiography showed striking transmission of dye from the choriocapillaris in the region of the white flecks, but no transmission in the macula or loss of choriocapillaris (Fig. 1, overleaf).

Case 2, a 12-year-old boy, the brother of Case 1, first noted visual loss about 2 years ago, and his vision declined steadily to its present level of 20/200 in each eye and could not be improved with refraction. The H-R-R plates revealed only a mild red-green defect. He missed three of the screening and only one of the diagnostic red-green plates. Dark adaptation gave a normal biphasic response of over 4 log units. The EOG was judged unreliable due to poor cooperation. Fundus examination revealed a ring of white flecks around each posterior pole identical to that seen in his sister. In the macula, however, there was marked pigment atrophy and clumping. Fluorescein angiography showed patchy transmission in the macula, but no loss of choriocapillaris.

Case 3, an Army cook, was first seen by one of us (FLW) 7 years earlier (1963) when he was 23 years old. At that time his vision could be corrected to 20/40 in each eye. Fundus examination revealed "mild depigmentation of the pigment epithelium in the posterior pole in each eye with granular macular change". Vision deteriorated progressively and symmetrically so that by October, 1970, it was 20/200 in each eye. Fundus examination at this time revealed severe pigment atrophy and clumping in the macular region of both eyes. In addition multiple deep white flecks, elongated and with soft borders, were visible. In the left eye these were distributed along a line parallel to the superotemporal retinal vessels, and thus appeared strikingly similar to the first drawing in Stargardt's original article (1909). Fluorescein angiography revealed patchy transmission in the macula and also in the area around the white flecks. Most of the flecks themselves did not appear to transmit dye (Fig. 2, overleaf). No areas of loss of choriocapillaris were found. The EOG was within normal limits. The patient said he believed the vision of his parents and younger sister was good.

Case 4, a professor of mathematics, was first reported to have visual difficulty in 1947 at the age of 22 years, when he failed a vision test while in the army. He was admitted to Valley Forge Hospital and evaluated by the ophthalmology service. At that time macular changes could not have been obvious as, according to the patient, some of his doctors thought he was malingering, while others recommended pneumo-encephalography. He believes that his vision was about 20/60 at that time. He had no photophobia, but he sensed that dark glasses improved his vision. The official records have not been available to us. The next year, because his vision was deteriorating, he sought medical help from an ophthalmologist in Philadelphia whose records indicate a visual acuity of 6/40 and a 5° central scotoma in each eye. "Examination revealed an atrophic area in the macula characterized by very fine pigment disturbance." A diagnosis of heredomacular degeneration was made.

In 1953, at age 28, he was seen by an ophthalmologist in Los Angeles who found that the best visual acuity was 20/200 in both eyes. Dilated fundus examination, including the use of a Hruby lens, revealed "faint pigmented salt and pepper mottling" in the macula in each eye and some temporal disc pallor.

(a) Soft flavimaculatus flecks encircle the posterior pole of the right eye in a manner identical to that in Stargardt's original drawing of patient Paul H. (Rosehr, 1954). The macula may show slightly increased granularity but looks generally normal

(b) The left eye shows an identical appearance

FIG. 1 10-year-old girl (Case 1) whose vision is 20/40 in the right eye and 20/60 in the left

(c) Fluorescein angiography reveals patchy transmission of fluorescein in the region of the flavimaculatus flecks but not corresponding exactly with the individual flecks. No abnormalities can be detected at this stage in the macula

When we saw him in 1970 at age 45, his vision was still 20/200 in each eye. The fundus, however, now showed a much more pronounced macular degeneration. There was a large area totally devoid of pigment epithelium, presenting a fundus picture similar to central choroidal sclerosis. Around this macular lesion were several of the typical flavimaculatus deep flecks with soft borders.

(a) Right eye. A few soft flavimaculatus flecks surround a macula with obvious pigment atrophy and clumping

(b) Left eye. The flavimaculatus flecks seem to follow the course of the superotemporal vessels in a manner identical to that in Stargardt's original drawing of patient D. H. (Stargardt, 1909)

(c) Fluorescein angiography reveals marked transmission in the macular area as well as in the region of the flavimaculatus flecks. Again, the patches of transmission do not correspond exactly with the flecks. No choroidal abnormality is evident

FIG. 2 30-year-old man (Case 3) whose vision is 20/200 in each eye

Despite his large central scotomas, he was able to make out colours. On the H-R-R plates the colours all appeared faded and he tried so hard that he twice wanted to point out a figure on a part of the plate where there was none, but he only actually missed one figure on a single screening red-green plate. Dark adaptation gave a normal biphasic response of over 4 log units and the EOG

was within low normal range, having a light:dark ratio of 1.9:1.0. He stated that his parents and his only sibling, a brother 4 years younger, have had no visual difficulty.

Fluorescein angiography revealed absence of the choriocapillaris in the macular lesion. There was transmission of dye in areas adjacent to the yellow-white flecks but not through the specks themselves (Fig. 3, opposite).

Discussion

The four cases described illustrate the spectrum of the clinical course of Stargardt's disease from its earliest signs to the late stage. Although flavimaculatus flecks may not be evident in all cases of Stargardt's disease, at least not in the early stage, they were present in each of these cases. Flavimaculatus flecks are unique in appearance and can be differentiated from drusen and small chorioretinal scars by their shapes and indistinct "soft" margins. They become invisible at times if one is looking with a direct ophthalmoscope and the light does not strike them at the proper angle. With the indirect ophthalmoscope they stand out more prominently and consistently. It seems likely that Stargardt was referring to this characteristic when he stated that the flecks were only visible with his ophthalmoscope when the patient was upright and disappeared when the patient was supine (Stargardt, 1909).

Flavimaculatus flecks are also unique in their fluorescein pattern. Most of the flecks appear like deposits within the apical portion of the pigment epithelial cells which have not disturbed the deeper pigment granules and, therefore, do not transmit fluorescein. Areas adjacent to these flecks often show irregular transmission, revealing pigment epithelial damage that is not visible ophthalmoscopically. Occasional flecks, however, do seem to transmit fluorescence, as though all the underlying pigment granules had been destroyed (Klien and Krill, 1967; Gass, 1970). This was the fluorescein pattern demonstrated by each of our four patients with Stargardt's disease.

Histopathological studies of cases of Stargardt's disease are hard to find. Many reports referred to in the literature concern patients with onset of visual disturbance after the age of 50 years. On careful scrutiny these appear to be simply cases of senile macular degeneration (Behr, 1921; Klein, 1950). Only two reported cases have had early onset of visual difficulty (Paufigue and Hervouet, 1963; Vail and Shoch, 1965). One of these is suspect because of dominant inheritance (Vail and Shoch, 1965), and the other because the patient at age 35 exhibited such severe diffuse retinal degeneration that visual acuity was reduced to perception of light in both eyes. The only reference to the choriocapillaris in either of these cases is the comment that "Bruch's membrane seems to be intact, but the choriocapillaris cannot be recognized with any degree of certainty" (Vail and Shoch, 1965).

Fluorescein angiography provides a sensitive method for studying circulation in areas of pigment epithelial atrophy. Fluorescein studies in earlier stages of Stargardt's disease have been reported by several authors (Klien and Krill, 1967; François and De Laey, 1969; ffytche and others, 1970). Defects in the pigment epithelium throughout the posterior pole are made evident by fluorescein before they are visible ophthalmoscopically, *i.e.* while ophthalmoscopic findings are equivocal or limited to the macula. In Cases 2 and 3, the areas of pigment epithelial atrophy in the macula fluoresce immediately and diffusely in the early choroidal phase of angiography, demonstrating that the choriocapillaris was intact. In Case 4, however, representing the late stage of the disease, there was dramatic loss of the chorio-capillaris in the macular region. When this paper was first presented, we were unaware of the monumental work of Deutman (1970), and felt that this was the first fluorescein demonstration of loss of the choriocapillaris in Stargardt's disease. It appears, however, that our studies confirm Deutman's finding.

(a) Right eye shows atrophy of the pigment epithelium, revealing the choroidal vessels underlying the macula, and a small ring of soft flavimaculatus flecks surrounding the macula. This is similar to Stargardt's original drawing of patient H. N. (Stargardt, 1909) (b) Left eye shows a similar appearance

(c) and (d) In the early stages of fluorescein angiography the large choroidal vessels stand out prominently in the macular region, revealing a total lack of choriocapillaris except in the most temporal portion of the lesion

(e, f, g) In the later stages of fluorescein angiography, the pattern of scleral staining characteristic of central choroidal sclerosis is seen. The staining progresses centrally from the surrounding intact choriocapillaris

FIG. 3 45-year-old man (Case 4) who has had vision of 20/200 in each eye for 20 years

We question how this disappearance of the choriocapillaris in the late stage, 20 years after the loss of macular function in Case 4, is to be interpreted. If there were a loss of choriocapillaris function in the early stages of the disease, one would not expect the correlation of visual acuity and fundus appearance to show such a "lag time". One would expect a course like that seen in central choroidal sclerosis or choroideremia, where ophthalmoscopic changes and fluorescein demonstration of loss of the choriocapillaris precede or parallel visual loss (McCulloch and McCulloch, 1948; Sorsby and Crick, 1953; Sorsby and Davey, 1955; McCulloch, 1969). We believe that it is more likely that the atrophy of the choriocapillaris in the late stage of Stargardt's disease is a secondary phenomenon, a result of the long-standing loss of function and metabolic demand in the overlying retina and pigment epithelium. Precedent for such a concept of secondary atrophy of the choriocapillaris can be found in retinitis pigmentosa. This is a disease in which histological study indicates that the primary lesion is a degeneration of the photoreceptors (Cogan, 1950). In fluorescein studies of retinitis pigmentosa, however, Hyvärinen, Maumenee, Kelley, and Cantollino (1971) have demonstrated patchy areas of loss of the choriocapillaris in advanced cases. Studies of earlier cases (Berson, Gouras, and Gunkel, 1968) have failed to reveal any such choroidal abnormalities. This is identical to our findings in Stargardt's disease. A concept of secondary or "disuse" atrophy of the choriocapillaris would help explain why so many of the different hereditary macular degenerations can give an identical end-stage picture.

Blodi (1968) suggested that the best way to classify the hereditary macular degenerations was according to the histological area primarily involved. One could thus hope to separate diseases which at some time in the future may be attributed to specific enzymatic deficiencies. Starting anteriorly, we would modify Blodi's classification only slightly and propose the following categories:

- (1) The progressive cone degenerations mainly affecting the photoreceptors (Berson and others, 1968; Steinmetz, Ogle, and Rucker, 1956);
- (2) Stargardt's disease or fundus flavimaculatus Type II*;
- (3) Best's or vitelliform degeneration probably affecting primarily the basal portion of the pigment epithelial cells;
- (4) Doyme's or hereditary drusen affecting Bruch's membrane;
- (5) Central choroidal sclerosis affecting the choriocapillaris (Ashton, 1953; Howard and Wolf, 1964).

As one moves posteriorly in this progression, fundus abnormalities become apparent at an increasingly earlier stage of visual loss. Lesions in the deep pigment epithelium, Bruch's membrane, or choriocapillaris are visible, and when they are primary, fundus changes precede or parallel visual loss. Changes in the neuroepithelium are not visible ophthalmoscopically, and hence, when they are primary, there are no ophthalmoscopic lesions until secondary changes in deeper layers occur. It is the existence of these secondary changes which accounts for the fact that all the macular degenerations can look similar in their late stages. One must thus know the early course of the disease to make the correct diagnosis. Electro- and psycho-physiological evidence also supports the placing of Stargardt's disease anatomically between the cone degenerations and Best's disease. In the cone degenerations, there are early severe abnormalities in colour vision, the photopic ERG, and the cone portion of the dark-adaptation curve. In Best's disease, the EOG is

*The recent finding by Merin and Landau (1970) of fundus flavimaculatus Type I and Type II (*i.e.* fundus flavimaculatus without and with macular disease respectively) in the same family suggests that these may represent not separate diseases but different degrees of gene penetrance or perhaps a heterozygous and homozygous state.

primarily involved. Stargardt's falls between these two diseases, with more subtle and less indiscriminate involvement of all these parameters. It thus seems most suitable to consider Stargardt's a disease of the "photoreceptor-pigment epithelial complex", emphasizing the intimate anatomical and metabolic interrelations joining these two elements.

Summary

A review of Stargardt's original papers shows that the macular degeneration he described is identical to what has recently been called fundus flavimaculatus with atrophic macular degeneration. We favour retention of the eponym "Stargardt's disease" because it directs a reader back to Stargardt's original thorough and definitive work. Fluorescein angiographic studies of the various stages of the disease reveal no choriocapillary abnormality until years after the loss of macular function, at which time the choriocapillaris can disappear entirely from the macular region. We suggest that this represents a secondary, or "disuse", atrophy of the choriocapillaris. Secondary atrophy of the underlying nourishing layers may explain the similarity in the end-stage appearance of all the hereditary macular degenerations. The full course of the disease and the interval between loss of visual acuity and the appearance of such obvious macular pathology must be known if one is to classify a hereditary macular degeneration.

Dr. Eugene Hill kindly referred the patients described as Cases 1 and 2. Drs Harold Scheie and S. Rodman Irvine provided the early ophthalmological records on the patient described as Case 4. Drs Edward Tamler, Henry Metz, and Lee Stewart provided the electrophysiological studies. Mr. Ronald Eckelhoff aided greatly in the preparation of the fluorescein angiograms.

References

- ARDEN, G. B., and KELSEY, J. H. (1962) *J. Physiol. (Lond.)*, **161**, 189
- ASHTON, N. (1953) *Brit. J. Ophthalm.*, **37**, 140
- BEHR, C. (1921) *Klin. Mbl. Augenheilk.*, **67**, 551
- BERSON, E. L., GOURAS, P., and GUNKEL, R. D. (1968) *Arch. Ophthalm. (Chicago)*, **80**, 77
- BLODI, F. C. (1966) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **70**, 1047
- COGAN, D. G. (1950) *Ibid.*, **54**, 629
- DEUTMAN, A. F. (1971) "The Hereditary Dystrophies of the Posterior Pole of the Eye". Van Gorcum, Assen, The Netherlands
- FFYTCH, T. J., BLACH, R. K., and BIRD, A. C. (1970) Presented at the joint meeting of the Gonin Club and the Swiss Ophthalmological Society, Lausanne, Switzerland, 14-19 Sept., 1970 (to be published in *Ophthalmic Research*, Karger, Basel, Switzerland).
- FRANÇOIS, J., and DE LAEY, J. J. (1969) *Arch. Ophthalm. (Paris)*, **29**, 497
- and DE ROUCK, A. (1965) *Klin. Mbl. Augenheilk.*, **147**, 654
- FRANCESCHETTI, A. (1965) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **69**, 1048
- GASS, J. D. M. (1970) "Stereoscopic Atlas of Macular Diseases", p. 122. Mosby, St. Louis
- HOWARD, G. M., and WOLF, E. (1964) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **68**, 647
- HYVÄRINEN, L., MAUMENEE, A. E., KELLEY, J., and CANTOLLINO, S. (1971) *Amer. J. Ophthalm. (Chicago)*, **71**, 17
- KLIEN, B. A. (1950) *Amer. J. Ophthalm.*, **33**, 371
- and KRILL, A. E. (1967) *Ibid.*, **64**, 3
- MCCULLOCH, C. (1969) *Trans. Amer. ophthalm. Soc.*, **67**, 142
- and MCCULLOCH, R. J. P. (1948) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **52**, 160
- MERIN, S., and AUERBACH, E. (1970) *Arch. Ophthalm. (Chicago)*, **84**, 710
- and LANDAU, J. (1970) *Ophthalmologica (Basel)*, **161**, 1

- PAUFIQUE, L., and HERVOUET, F. (1963) *Bull. Soc. franç. Ophtal.*, **76**, 108
- ROSEHR, K. (1954) *Klin. Mbl. Augenheilk.*, **124**, 171
- SORSBY, A., and CRICK, R. R. (1953) *Brit. J. Ophthal.*, **37**, 129
- and DAVEY, J. B. (1955) *Ibid.*, **39**, 257
- STARGARDT, K. (1909) *v. Graefes Arch. Ophthal.*, **71**, 534
- (1913) *Z. Augenheilk.*, **30**, 95
- (1916) *Ibid.*, **35**, 249
- STEINMETZ, R. D., OGLE, K. N., and RUCKER, C. W. (1956) *Amer. J. Ophthal.*, **42**, no. 4, pt II, p. 304
- VAIL, D., and SHOCH, D. (1965) *Trans. Amer. ophthal. Soc.*, **63**, 51