Int. Ophthal. 3,2: 67-77, 1981

Chorioretinal dysplasia in young subjects with Wagner's hereditary vitreoretinal degeneration

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Keywords: Wagner's vitreoretinal degeneration, chorioretinal dysplasia, fluorescein angiography.

Abstract

Six young patients from three pedigrees with Wagner's disease were submitted to fluorescein angiography of the peripheral fundus. All eyes showed aberrant areas, characterized by: 1. localization principally in equatorial region of temporal half of the fundus. 2. whitish appearance of neuroretina with sharp demarcations. 3. absence of retinal vasculature. 4. marked atrophy of choriocapillaris and retinal pigment epithelium. 5. abnormal deflections of retinal vessels at the posterior margin of these areas. Arguments are presented in support of the hypothesis that these areas were dysplastic and not degenerative. The difference with lattice degeneration, another wellknown finding in Wagner's disease, is that retinal vasculature never developed in the dysplastic peripheral areas. It is probable that hypoplasia of the choroid has led to a too inferior structure of the overlying retina to permit development of retinal vessels. The frequent occurrence of retinal breaks in young patients with Wagner's disease, especially in the temporal periphery, seems to be a consequence of the poor condition of the retina in these dysplastic areas caused by the inferior development of both retinal and choroidal vasculature.

Introduction

The various signs of Wagner's vitreoretinal degeneration have been described by several investigators. Wagner (20) reported the following changes concerning the peripheral fundus: narrowed and ensheathed retinal vessels, retinal pigmentations, circular membranes in a liquefied vitreous attached to the equatorial retina and choroidal atrophy. Other findings such as retinoschisis (4), lattice degeneration (1, 7), retinal breaks and detachment (1, 2, 7, 9, 12, 13, 14) were added to these in later publications.

Retinal detachments caused by multiple breaks anterior to the equator are frequently found at a young age in Wagner's hereditary vitreoretinal degeneration (5, 12). In order to detect possible vascular changes associated with the poor retinal condition we examined the peripheral fundus of some young patients with Wagner's disease by means of fluorescein angiography. It is the purpose of this paper to demonstrate the deficiency of both choroidal and retinal circulation anterior to the equator present in all our patients, and to discuss its possible pathogenesis and consequences.

Subjects and methods

From three pedigrees with Wagner's vitreoretinal degeneration we selected patients not older than 30. In order to ensure a sufficient quality of equatorial fundus photography, we accepted only subjects who had no lens opacities (a rather frequent complication in even younger patients with Wagner's disease) and were capable of full mydriasis. We succeeded in making usable fluorescein angiograms of the peripheral fundus in six cases.

International Ophthalmology 3, 67-77 (1981) 0165-5701/81/0032-0067 $ 02.20

Color photographs and fluorescein angiograms of the posterior pole and peripheral fundus in different quadrants were made with a Kowa and in one case with a Cannon funduscamera. No indentation was made and no contact glass was applied for photography. In all cases the early exposures of the angiograms were made of an equatorial region selected after examination by indirect ophthalmoscopy.

Our cases I, II and III were three affected sisters from a large pedigree with Wagner's disease. Our case IV and her mother, case V, had only recently been seen for the first time and their pedigree has not yet been studied. Case VI belongs to the large family described by Jansen (13).

None of our cases had orofacial or skeletal symptoms as seen in the Stickler syndrome (3, 9, 16, 19). However only our case IV was submitted to a thorough general examination in our pediatric department, so we cannot completely rule out minimal symptoms in our other cases. Our six patients all showed an optically empty vitreous cavity pervaded by a few vitreous membranes, so typical of Wagner's vitreoretinal degeneration. Some general data on our cases are listed in Table 1.

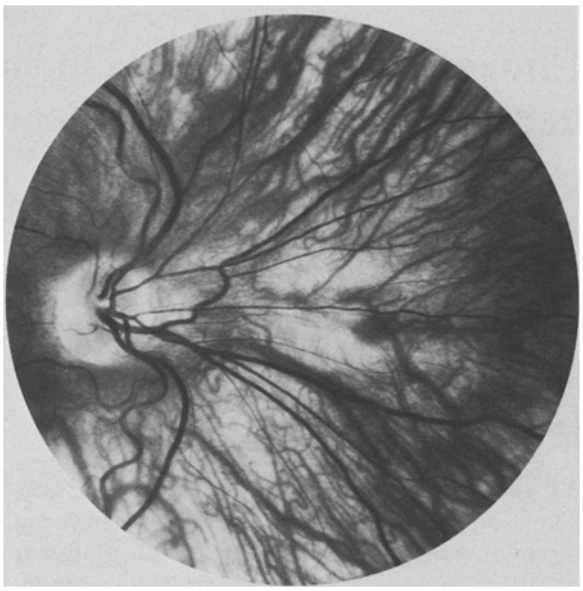

Fig. 1 (Van Nouhuys). Case I. Right eye. Inverse pattern of vessels at the disc. The choroidal vessels are clearly discernible on the nasal side of the disc.

Table 1.. Patient characteristics

	sex	age	visual acuity R.E.	visual acuity L.E.	refractive state R.E.	refractive state L.E.
Pedigree A						
Case I	f	24	6/6	6/6	-0.25sph -0.75cyl x 0°	+ 1sph - 1 cyl x 30°
Case II	f	18	6/4.5	6/4.5	+ 1 sph -1cyl x 20°	Emmetr.
Case III	f	16	6/6	6/6	Emmetr.	Emmetr.
Pedigree B						
Case IV	f	10	6/36	6/12	+ 2sph -2.5cyl x 0°	-2cyl x 0°
Case V	f	30	6/6	6/7.5	-5sph -3cyl x 15°	-6sph -0.5cyl x 170°
Pedigree C						
Case VI	m	18	6/4.5	6/4.5	-2cyl x 0°	-2.75cyl x 5°

Results

Case I

In both eyes of this 24-year old woman the larger choroidal vessels were clearly discernible in the regions adjacent to the disc at the nasal side. The vessels at the optic nervehead showed an inverse pattern (Fig. 1). A circumferential white line along which vitreous was attached to the retina was visible just posterior to the equator. Anterior to this line several large grayish-white areas of chorioretinal atrophy were situated in the temporal half of both fundi. Several clumps of pigment and small atrophic round spots, some with pigmented edges, were observed in these areas.

At early-phase fluorescein angiography of the temporal equatorial region at the 10 o'clock position of the right eye, a normal flush of the choriocapillaris was seen central to the equator, but no filling of the

choriocapillaris was observed in the atrophic area; consequently the larger choroidal vessels were clearly discernible (Fig. 2). The retinal vessels central to the

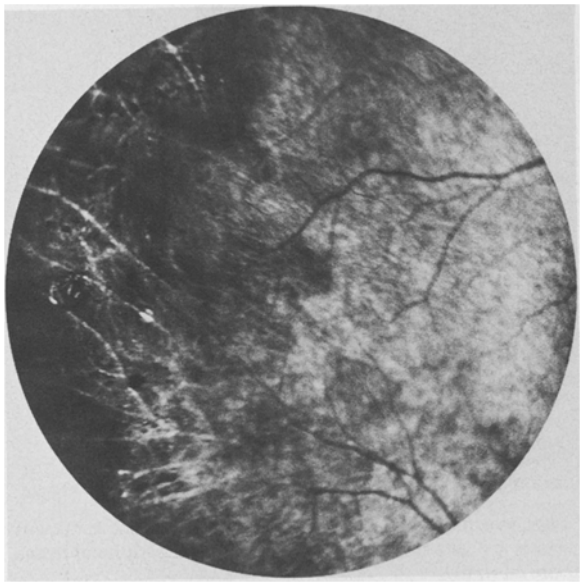

Fig. 2. (Van Nouhuys). Case I. Early-phase fluorescein angiogram of equatorial area at 10 o'clock position of right eye. Central to the equator a normal flush of the choriocapillaris is present. Anterior to the equator there is no filling of the choriocapillaris but the major choroidal vessels are perfused.

equator showed normal perfusion, but their pattern was abnormal: the superior temporal vessels curved down and the inferior temporal vessels showed an upward deviation when approaching the posterior border of the atrophic areas. The terminal branches of these vessels ended abruptly in the neighborhood of these borders, the peripheral retina being completely devoid of vasculature (Fig. 3).

Fluorescein angiography of the left eye also demonstrated extensive areas of atrophy of the choriocapillaris and pigment epithelium in the temporal half with non-perfusion of the retina (Fig. 4). On the nasal side the retina showed normal vasculature in equatorial regions and no atrophic parts of choroid and pigment epithelium were visible.

Case II

Both fundi of this 18-year-old sister of the patient described in case I showed several oblong, whitish, sharply demarcated lesions in the temporal periphery

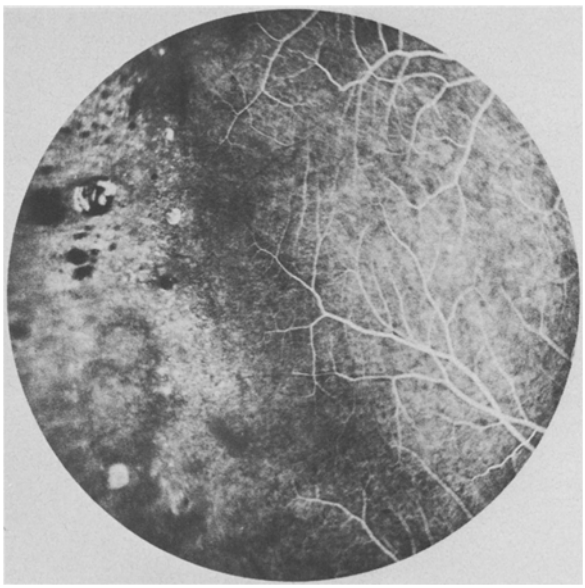

Fig. 3 (Van Nouhuys). Case I. Fluorescein angiogram of same area as Fig. 2, seven seconds later. Hyperfluorescence in the aberrant area anterior to the equator caused by atrophic pigment epithelium. Several coarse clumps of pigment are present. Note the abnormal pattern of more posterior retinal vessels and non-perfusion of the temporal periphery.

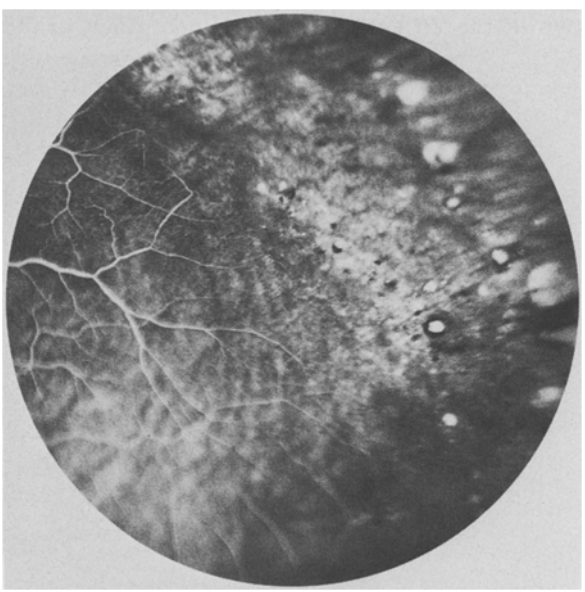

Fig. 4. (Van Nouhuys). Case I. Left eye. Late-phase fluorescein angiogram of 2 o'clock position. Absence of retinal vasculature anterior to the equator. Hyperfluorescence and mottled appearance caused by changes of peripheral pigment epithelium.

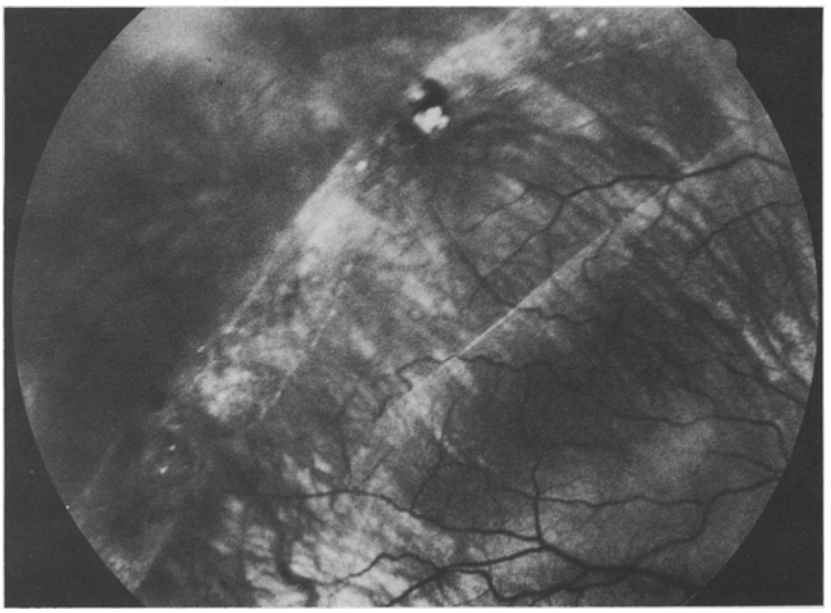

Fig. 5. (Van Nouhuys). Case II. Photograph of peripheral fundus of right eye at 10 o.clock position. Whitish atrophic areas with sharp demarcations and some accumulations of pigment. No retinal vessels are seen in these areas and the more peripheral retina. A white line along which vitreous is attached to the retina is situated more centrally.

(Fig. 5). The retina in these areas was very thin and atrophic containing a few very small holes. Early-phase fluorescein angiography at the 3 o'clock position of the left eye demonstrated poor filling of the choriocapillaris anterior to the equator. No perfusion could be observed of the retina in and anterior to the atrophic areas (Fig. 6). Late-phase fluorescein angiograms of the temporal equatorial fundus of the

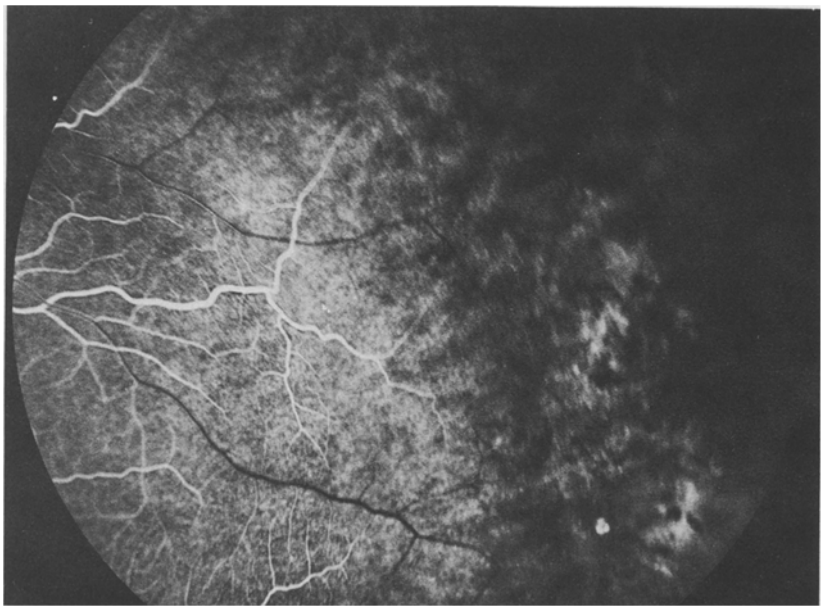

Fig. 6. (Van Nouhuys). Case II. Arteriovenous phase of fluorescein angiogram of temporal periphery of left eye, demonstrating non-perfusion of equatorial retina.

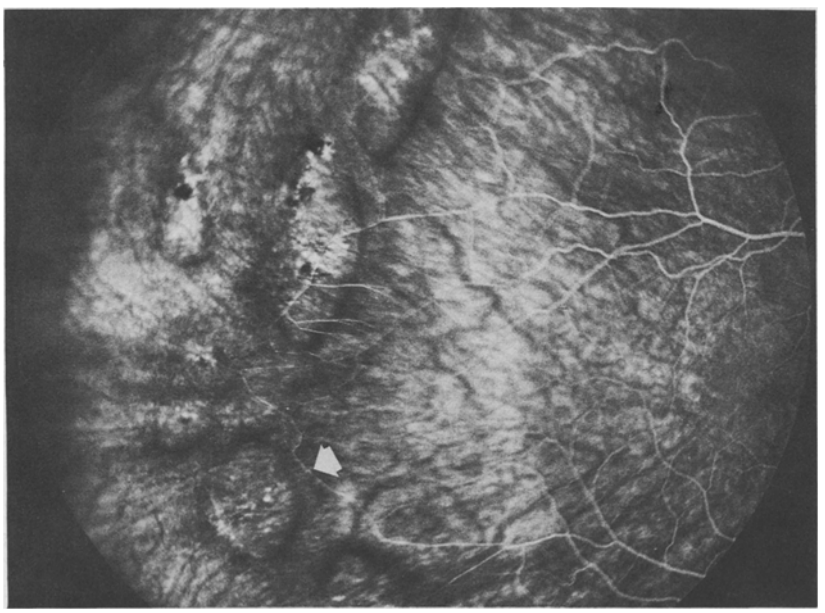

Fig. 7. (Van Nouhuys). Case II. Fluorescein angiogram of temporal equatorial region of the right eye. Note the sharply demarcated lesions with atrophic appearance. One vessel extends through part of an atrophic area. Another vessel shows deflections just posterior to the lesions (arrow).

right eye clearly showed the deviated course of the retinal vessels near the central margin of the atrophic areas. However, one vessel extended through part of an atrophic area (Fig. 7). This vessel gave off some branches in a posterior direction and showed an aberrant recurrent deviation. The retina anterior to the equator was not perfused.

Case III

This 16-year-old younger sister of the patients described in case I and II showed extensive whitish areas of chorioretinal atrophy. These were almost confined to the temporal half of both fundi anterior to the equator. Only a few delicate clumps of pigment were observed in these areas. We selected the midperiphery of the right eye at the 10 o'clock position for fluorescein angiography. Fig. 8 shows the early exposures of this area: central to the equator the greater choroidal vessels and part of the choriocapillaris were already filled with fluorescein, but no dye has entered the peripheral choroid. Three seconds later a normal choroidal flush was present centrally. Some large choroidal vessels were filled with fluorescein in the equatorial choroid as well as a few smaller ones that showed terminal branches to remnants of the almost entirely absent choriocapillaris (Fig. 9).

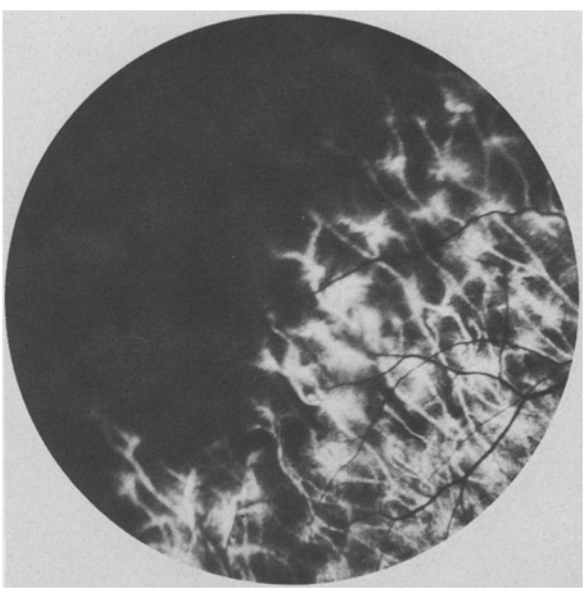

Fig. 8. (Van Nouhuys). Case III. Equatorial region of right eye at 10 o'clock position. Very early phase shows filling of choroidal vessels posterior to equator, but the more peripheral choroid is not yet perfused.

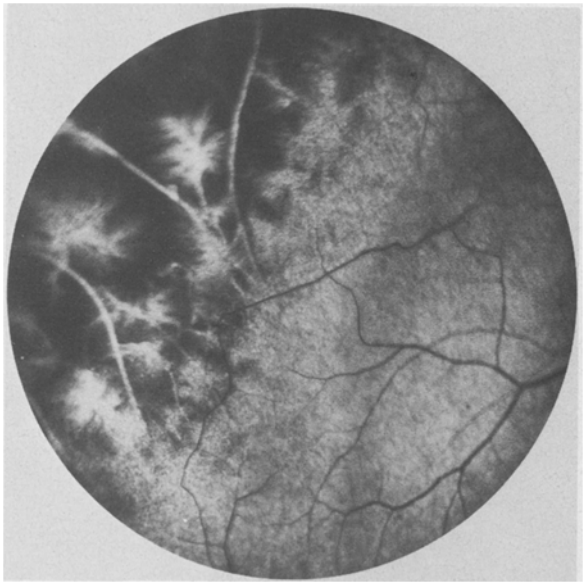

Fig. 9. (Van Nouhuys). Case III. Same area as Fig. 8, 3 seconds later. Some large choroidal vessels are filled with fluorescein in the peripheral choroid as well as a few smaller ones that show terminal branches to remnants of almost absent choriocapillaris. A normal flush of the choriocapillaris is present more centrally.

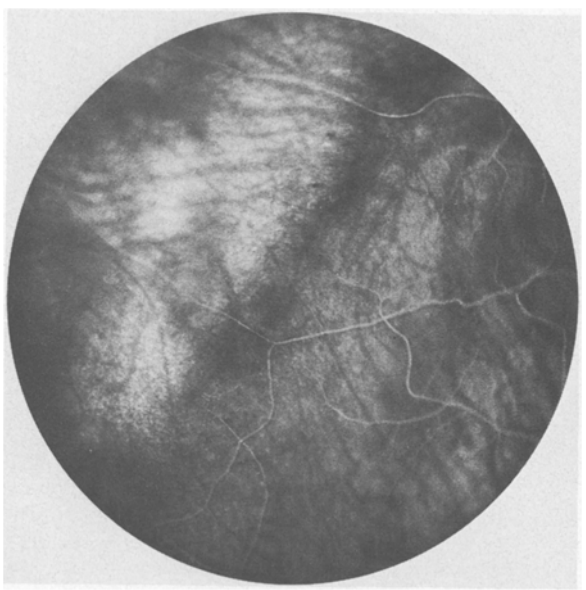

Fig. 10. (Van Nouhuys). Case III. Late-phase angiogram of temporal periphery of right eye. Hyperfluorescence caused by atrophy of retinal pigment epithelium. Two terminal branches of retinal vessels proceed to the periphery through the otherwise avascular hyperfluorescent area.

A late-phase exposure of the same region is shown in Fig. 10: anterior to the equator there was hyperfluorescence due to depigmentation of the retinal pigment epithelium. Retinal vessels showed an arrangement more or less parallel to the central margin of the atrophic periphery. Only two branches proceeded through the otherwise avascular peripheral retina. Fluorescein angiography of similar regions in the left eye was not performed because our patient became nauseated after injection of fluorescein.

Case IV

This 10-year-old girl was referred to our department with a retinal detachment in the right eye. The detachment was caused by a round hole situated in a peripheral area of chorioretinal atrophy at the nine o'clock position. A few days after a succesful encircling operation we made the fluorescein angiogram. The inverse pattern of the vessels at the discs was very pronounced. The macula was displaced to a position very close to the disc in both eyes. Marked atrophy of the choriocapillaris and pigment epithelium was present in the posterior fundus at the nasal side of the optic nervehead.

In the temporal half of both fundi peripheral areas of chorioretinal atrophy were situated equatorially (Fig. 11). Some of there areas were also found in the

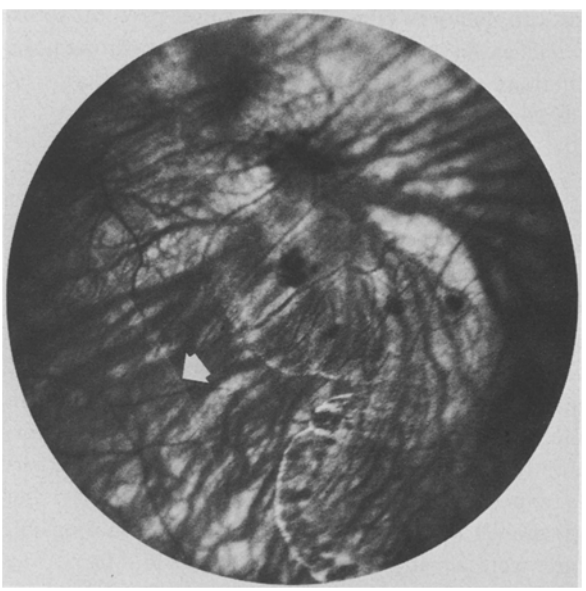

Fig. 11. (Van Nouhuys). Case IV. Left eye. Whitish sharply demarcated areas with clumps of pigment in upper temporal periphery. Attachment of vitreous membrane to the retina more centrally (arrow).

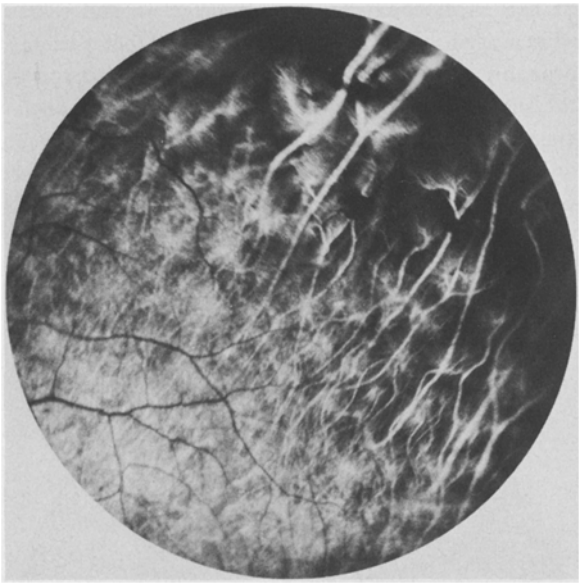

Fig. 12. (Van Nouhuys). Case IV. Same region as Fig. 11. Early-phase fluorescein angiogram demonstrates almost absent choriocapillaris anterior to the equator.

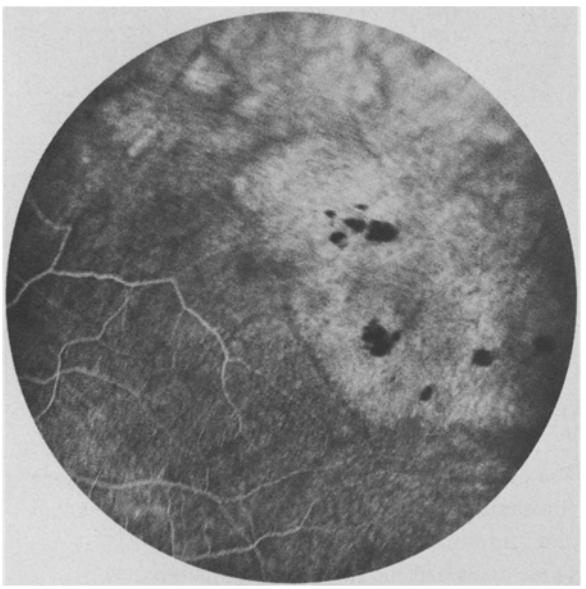

Fig. 13. (Van Nouhuys). Case IV. Late-phase fluorescein angiogram of same region as Fig. 11 and 12. The atrophic area is hyperfluorescent and is not perfused by retinal vasculature.

upper nasal quadrants. We selected the equatorial region of the left eye at the 2 o'clock position for fluorescein angiography. Early-phase exposures demonstrated a nearly absent choriocapillaris and a very atrophic pigment epithelium (Fig. 12). The late-phase showed hyperfluorescence in the atrophic area and deviant retinal vessels posterior to its central margin (Fig. 13). An interesting observation was that part of the whitish atrophic area did not show hyperfluorescence on the late angiograms (compare Fig. 11 with Fig. 13). This part with an apparently normal pigment epithelium did not display any clump of pigment.

Case V

The peripheral fundus of both eyes of the 30-year-old mother of our patient described in case IV showed even more extensive temporal areas of chorioretinal atrophy with sharply defined margins. The early-phase angiogram of the left eye at the 2 o'clock position is represented in Fig. 14: no flush of the choriocapillaris, and depigmentation of the retinal pigment epithelium anterior to the equator. The more centrally situated retinal vessels were deflected to an arrangement more or less parallel to the posterior

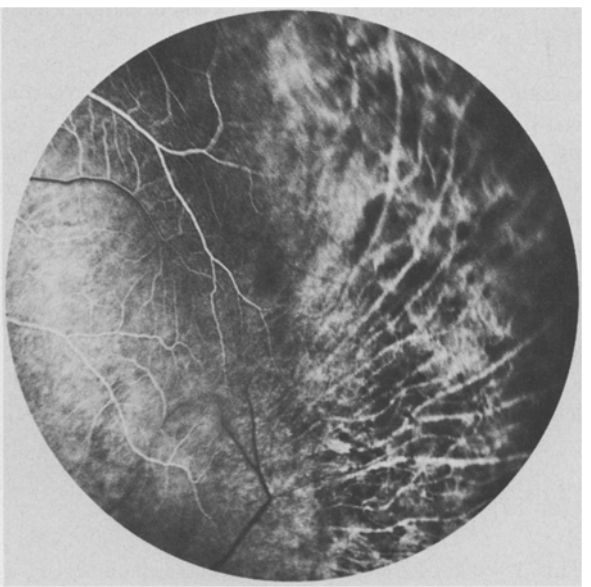

Fig. 14. (Van Nouhuys). Case V. Left eye. Arteriovenous phase of fluorescein angiogram of temporal equatorial region. Atrophy of pigment epithelium and choriocapillaris and non-perfusion of the retina anterior to the equator. Retinal vessels are deflected to an arrangement parallel to the posterior margin of the atrophic area.

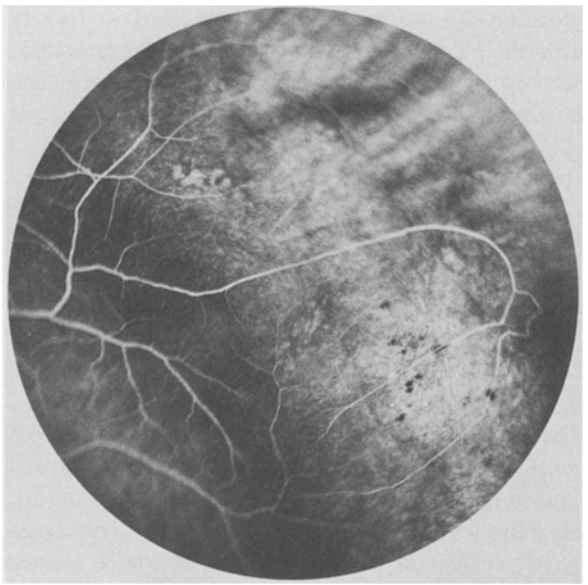

Fig. 15. (Van Nouhuys). Case V. Left eye. Fluorescein angiogram shows abnormal recurrent deflection of retinal arterial branch in atrophic peripheral area.

margin of the aberrant zone. However, a single arterial branch followed a radial course through the area of chorioretinal atrophy. Anterior to this lesion the vessel turns back, bifurcates and ends at the posterior margin after giving off a few short terminal ramifications (Fig. 15). In the upper temporal quadrant of the right eye Argon laser photocoagulation was performed in view of the degeneration of the retina, although no breaks were found. There was a similar arrangement of retinal vessels as in the left eye parallel to the posterior margins of almost avascular areas of chorioretinal atrophy.

Case VI

This 18-year-old man was an affected member of a large pedigree with Wagner's vitreoretinal degeneration. The posterior poles of both eyes showed only a slightly abnormal vascular configuration at the disc and scanty choroidal atrophy nasal to the optic nervehead. Rather large pale areas of chorioretinal atrophy were noted in the peripheral fundus in both eyes; these were virtually limited to the temporal sides. No retinal breaks were seen within these areas. Early-phase fluorescein angiograms at the 2 o'clock position of the left eye showed delayed, incomplete filling of the choriocapillaris. The larger choroidal vessels were not visible in this area as in our other patients, probably due to the less marked depigmentation of the pigment epithelium. The late-phase of the angiogram demonstrated very slight leakage from some retinal vessels, a phenomenon not observed in our other cases (Fig. 16). The configuration of the vessels with their deflections at the central border of the atrophic areas, leaving them devoid of vasculature, was similar to the pattern observed in our other patients.

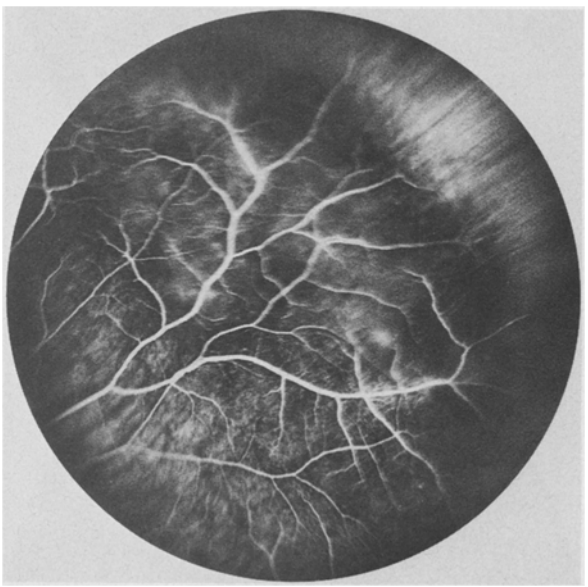

Fig. 16. (Van Nouhuys). Case VI. Left eye. Late-phase angiogram of equatorial area at 2 o'clock position. Slight leakage of dye from the most peripheral retinal vessels.

Discussion

The peripheral fundus of all our patients with Wagner's vitreoretinal degeneration showed areas with an aberrant structure of choroid and retina.

These areas had the following characteristics:

1. Situation mainly in equatorial region of temporal half of fundus. A few were found nasally, mostly in the upper quadrant. Their position was always anterior to the circumferential white line. Along this line, a well known finding in Wagner's disease, vitreous was attached to the retina.
2. Whitish appearance of neuroretina often with well-defined margins. The preretinal vitreous was

liquefied. Consequently it was not possible to distinguish vitreoretinal adhesions along these margins.
3. Coarse clumps of pigment. These were always present in at least some of the areas. No pigmentations were discovered outside these areas in the described cases. However, in other patients with Wagner's disease we have noticed clumps of pigment in more posterior parts of the fundus, often associated with degenerated retinal vessels.

The following findings were most prominent at fluorescein angiography:
1. Absence of retinal vessels and consequently non-perfusion of the retina in and anterior to the aberrant areas. In a few cases part of the areas show the presence of a single retinal vessel. The path and ramifications of such a branch generally were abnormal (Fig. 7 and 15). No signs of occluded vessels were found in the areas of non-perfusion.
2. Abnormal pattern of retinal vessels central to the posterior border of the peripheral atrophic areas. In most cases these vessels deviate from a more or less radial path to the periphery to a path parallel to the posterior border of the atrophic areas (Fig. 3 and 14). Some of the smallest branches end abruptly at the central border of the aberrant areas.
3. Absent or rudimentary choriocapillaris. This is clearly observed on the early-phase angiogram of the equatorial fundus (Fig. 9, 12 and 14). The major choroidal vessels were present in these areas.
4. Depigmentation of the retinal pigment epithelium. Late-phase angiograms showed hyperfluorescence of the atrophic areas (Fig. 13).
So far I have described the abnormal areas of the peripheral fundus as atrophic, because choroid, pigment epithelium and neuroretina show an atrophic appearance. The question arises if these changes are really caused by degeneration of a once normal choroid and retina, or if they are the result of a disorder of development. There are two important arguments in favor of the latter:
1. The aberrant areas were equally present in all our patients, even the youngest. This observation suggests a developmental disorder.
2. The completely abnormal configuration of retinal vessels at the posterior border of these areas could only be explained by a disturbed development of these vessels. The absence of occluded vessels in the not perfused temporal periphery also demonstrated that retinal vasculature never developed in this part of the fundus.

I consider these observations as evidence in support of the conclusion that the aberrant areas in the temporal equatorial part of the fundus are caused by underdevelopment. So these areas are dysplastic rather than atrophic.

The question arises as to what mechanism effectuates the blockade of developing retinal vasculature at the equator in Wagner's disease. The early-phase fluorescein angiograms of some of our patients (cases III, IV and V) showed that the smaller choroidal vessels and choriocapillaris were almost completely absent at the peripheral dysplastic areas. Before it is vascularized, the retina depends for its nutritional supply on the choriocapillaris, once regression of the hyaloid system has occurred. In my opinion one of the primary lesions in Wagner's disease must have been hypoplasia of the chorio-capillaris in equatorial areas. This hypoplasia caused damage to the pigment epithelium and neuroretina due to hypoxia before retinal vessels developed in this part of the fundus during the 8th and 9th month of gestation. When the retinal vessels reached the posterior margins of the dysplastic areas, the structure of the damaged neuroretina probably was too inferior for them to develop in it. The aspect of retinal vasculature central to the dysplastic areas suggests that there was no question of a primary disorder of these vessels themselves, as for example in dominant exudative vitreoretinopathy (6,8). The structure of the vessels generally was normal and leakage was seen in only one case. Their vitality was demonstrated by the fact that most of them proceed their path central to the blockade of the dysplastic areas or grow back in the central direction. These vessels had pushed away the more posterior vessels.
This process caused a more or less parallel arrangement with increased packing of retinal vessels at the posterior margin of the dysplastic areas (Fig. 3 and 14).

The occurrence of an inversed disc with displacement of the larger retinal arteries and veins in nasal direction is a common finding in Wagner's vitreoretinal degeneration (10, 11, 13). So far, this phenomenon has recieved little attention, and has remained unexplained. It is very unlikely that the posterior retina is really dragged to the nasal side, for in none of our cases could any cause of a tractional force in the nasal

half of the fundus be discovered. I think that there is a plausible explanation for this phenomenon: as we demonstrated retinal vasculature could not grow into the peripheral dysplastic areas, but continued its development posterior to these areas. More posterior vessels were pushed backwards in a central direction. As the dysplastic areas are mainly situated in the temporal periphery the retinal vessels in the posterior pole must have been shoved in a nasal direction. The fixation of the major vessels at the disc caused the peculiar arrangement of retinal vessels overlying the lamina cribrosa on the nasal side.

It is important to distinguish the peripheral areas of chorioretinal dysplasia from lattice degeneration. Lattice degeneration is a rather frequent finding in Wagner's disease. The equatorial position, the whitish retinal thinning with sharp demarcations and collections of pigment may lead one to mistake lattice for chorioretinal dysplasia. In lattice degeneration an arborizing network of small white blood vessels is nearly always seen. In areas of chorioretinal dysplasia no remnants of degenerated vessels are found. This is a result of the non-development of retinal vasculature in these areas as we pointed out before. Often, but not always, the areas of chorioretinal dysplasia are larger than the elongated oval lesions of lattice degeneration. A third point of discrimination is the absence of an abnormal configuration of adjacent retinal vessels in lattice degeneration. The occurrence of both chorioretinal dysplasia and lattice degeneration demonstrates the ambiguous character of Wagner's disease: it is a developmental as well as a degenerative disorder.

Another common finding in Wagner's disease is the presence of pale-yellow areas of atrophy of choriocapillaris and pigment epithelium in the posterior pole. These are mostly situated adjacent to the disc on the nasal side (Fig. 1). These central atrophic areas are different from the peripheral areas of chorioretinal dysplasia in the following repects:

1. No sharp demarcations.
2. No whitish appearance of the neuroretina.
3. Normal retinal vasculature.
4. No coarse pigmentations.

The most conspicuous finding in Wagner's disease is extensive liquefaction of the vitreous. Wagner (20) already regarded this abnormality as a disorder of development, because it was present in the youngest patients. Although there is still some speculation about the origin of the secondary vitreous, most investigators hold that it is produced by the Müller cells of the retina. The dysplastic peripheral areas of the retina may have contributed to the production of aberrant vitreous. In normal eyes the most peripheral vessels of the retina differ from the more posterior capillaries in that they have a perivascular coat. Spitznas (18) demonstrated the occurrence of collagen fibrils and the formation of a limiting membrane with the morphologic characteristics of the inner limiting membrane of the retina in this perivascular coat, suggesting that Müller cells contribute to the formation of both the cortical vitreous and the perivascular coat. From this point of view it is attractive to speculate about deficient Müller cells in the peripheral retina giving rise to the disturbed development of both secondary vitreous and retinal vasculature in Wagner's disease.

Histopathologic studies of Wagner's vitreoretinal degeneration have been described in a few cases (1, 3, 4, 15). Reports mention cystoid degeneration in the peripheral retina, accumulations of pigment, especially around retinal vessels, increased thickness of the walls of vessels, atrophy and even absence of the choriocapillaris. As most of the preparations were from eyes removed after late complications such as glaucoma, retinal detachment or general atrophy, these studies have contributed little to our knowledge about the histology of choroid and retina during early life and the pathogenesis of the disease.

The frequent occurrence of retinal breaks in Wagner's disease is well known. Of 79 eyes examined by Hirose (12) and co-workers, 59 showed a retinal break with or without retinal detachment (75%) and surprisingly many cases were found in young patients. Retinal breaks were much more common in the temporal half of the fundus (67%) than in the nasal part (33%). Many patients had multiple breaks at different distances from the ora serrata. It is likely that this predilection of breaks for the temporal periphery is the consequence of the temporal localization of the peripheral areas of chorioretinal dysplasia. In these areas the retina is very thin due to the combination of poor choroidal and absent retinal blood supply. This atrophy of all layers of the retina may easily give rise to a break. In our patients described in case II and IV we observed small round retinal holes in the

peripheral dysplastic areas. The retinal detachment of our case IV was caused by such a break. The frequent occurrence of retinal breaks in young patients supports my theory that these breaks are caused by a congenital failure of circulation in the peripheral choroid and retina. However, it is probable that in older patients equatorial degeneration and lattice contribute to the formation of retinal breaks.

Non-perfusion of the peripheral retina, especially in the temporal half of the fundus is a charactaristic feature of dominant exudative vitreoretinopathy (6, 8, 17). We studied 5 pedigrees with this desease. Retinal breaks in the avascular retina do occur in this condition, but seem to be less frequent than in Wagner's disease. This difference may be the consequence of the fact that in dominant exudative vitreoretionopathy only the retinal circulation is affected, whereas in Wagner's disease a disorder exists of both retinal and choroidal vasculature in the dysplastic areas.

More studies of the peripheral fundus are necessary to prove a causal relation between the dysplastic areas and retinal breaks. Examination of members of other pedigrees with Wagner-like syndromes will answer the question of whether the aberrant circulation of choroid and retina is a general feature in these related syndromes.

Acknowledgement

I am indebted to Mr. Albert aan de Kerk for his photographs of the peripheral fundus.

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