Autosomal dominant vitreoretinochoroidopathy (ADVIRC)

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SUMMARY We report the second family recognised to have autosomal dominant vitreoretinochoroidopathy. The clinical features were (1) autosomal dominant inheritance; (2) peripheral, coarse pigmentary degeneration of the fundus for 360°, with a relatively discrete posterior border in the equatorial region (this finding may be pathognomonic); (3) superficial punctate yellowish-white opacities in the retina; (4) various vascular abnormalities; (5) breakdown of the blood-retinal barrier; (6) retinal neovascularisation; (7) vitreous abnormalities; and (8) choroidal atrophy. Visual reduction was mainly due to macular oedema or vitreous haemorrhage.

In 1982 Kaufman and associates reported for the first time a condition we termed autosomal dominant vitreoretinochoroidopathy. Its main features were: (1) an autosomal dominant hereditary pattern; (2) peripheral pigmentary retinopathy for 360°, with a discrete posterior boundary near the equator; (3) punctate whitish opacities in the retina; (4) vitreous cells and fibrillar condensation; (5) blood-retinal barrier breakdown; (6) retinal arteriolar narrowing and occlusion; (7) retinal neovascularisation; (8) choroidal atrophy; and (9) presenile cataracts. This unique combination of features indicated that this disorder was a distinct nosological entity. Although it is apparently rare, we have detected a second family with this disease in our clinic. This family is unrelated to the first and is reported here.

Materials and methods

Each available blood relative of the proband was examined with the following methods: (1) ocular and systemic history; (2) refraction; (3) external eye examination; (4) slit-lamp examination; (5) applanation tonometry; (6) dilated fundus examination with direct and indirect ophthalmoscopy; (7) screening for skeletal defects, including inspection and palpation of the palate, inspection of the spine, and examination for joint hyperextensibility and joint enlargement. In addition the following examinations were performed on the proband, his parents, his siblings, and some of his other blood relatives: (1) Goldmann field examination; (2) fundus photography and fluorescein angiography; (3) vitreous fluorophotometry; (4) electroretinography; (5) Goldmann contact lens biomicroscopy and gonioscopy; (6) blood and urine testing for amino acids. Vitreous fluorophotometry was performed after an injection of 14 mg/kg of fluorescein sodium using a modified Haag-Streit 360° slit-lamp or the Fluorotron Master (Coherent Radiation, Palo Alto) as previously described. The values 3 mm anterior to the chorioretinal peak were normalised to a blood fluorescein level of 10 μg/ml.

Fig. 1 Pedigree.

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Electroretinography was performed as previously described. Both white and chromatic stimuli were used to differentiate between rod and cone function. Both single and flicker stimuli were used.

Family study
See Fig. 1. No consanguinity was known. The paternal side of the family was of Italian origin, the maternal side of Polish. All family members had normal pregnancies and deliveries with the exception of the proband, who is described below. No systemic abnormalities were noted, including the results of careful clinical screening for skeletal abnormalities. The electroretinogram was normal in all family members. Urine and blood amino acid levels were normal, including those of ornithine.

Case reports

Patient III-3
The proband was first seen in 1976 as a 13-year-old white male because of recurrent vitreous haemorrhage in the right eye. Four months earlier he had received focal laser therapy for new vessels above the right optic nervehead by another ophthalmologist. He denied nyctalopia but did admit that his day vision was better than his night vision. He denied photophobia and colour vision problems. He had weighed 2100 g at birth and required supplemental oxygen for 3 days. The vision was 20/30 in each eye without correction. The external examination and slit-lamp examination of the anterior segment were normal; both lenses were clear. The vitreous contained 3+ cells in each eye, but no optically empty space was observed. There appeared to be a posterior vitreous detachment in the left eye. The applanation pressures were 18 and 19 mmHg in the right and left eyes respectively. Gonioscopy was unremarkable.

On funduscopic examination several abnormalities were seen bilaterally. There was marked, peripheral, coarse pigmentary mottling that extended for 360° around the retinal periphery (Fig. 2). It had an abrupt border approximately at the equator, posterior to which the fundus looked relatively normal. Occasionally, the pigment was arranged in bone spicule configurations. Numerous yellowish-white dots were visible, which appeared to be in the region of the internal limiting membrane. These were most frequent in the area of the pigmentary changes. There were also many nodules on the internal limiting membrane in the area of the pigmentary disturbance. Occasional beading, sheathing, whitening, and occlusion of veins was seen, especially peripherally, where there was a generalised paucity of vessels. The retinal arteries appeared to be somewhat attenuated (Fig. 3A). There was greyish discoloration of the inner retina along the inferior temporal vascular arcades which was due to retinal oedema as determined by angiography. In the right eye there

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Fig. 3 Right optic disc region of proband, patient III-3. A. Prepapillary fibrous tissue and a scar from previous photocoagulation are seen. Mild arterial narrowing is present. Note the greyish discoloration of the retina along the inferotemporal arcade. B. The angiogram shows fine microvascular anomalies (arrowheads), particularly near the photocoagulation scar, and the disc shows late hyperfluorescence. Note staining of vein walls (double arrows).
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Fig. 2 Peripheral fundus of the proband, patient III-3. There is coarsely mottled retinal pigmentation that occasionally assumes a bone spicule pattern. The posterior boundary is relatively discrete. Multiple yellow dots (black arrowheads) and nodules (black and white arrowheads) are seen. Note the white vein (open arrow) which is occluded on the angiogram (see Fig. 5).

Fig. 4 Colour photograph of right macular area of proband, patient III-3. A focus of preretinal new vessels is present superotemporal to the macula near the arcade (arrow).

Fig. 7 Left macula of proband, patient III-3 in 1982. There is considerable pigmentary mottling in the foveal region. Note also the yellowish-white dots (arrowheads).

Fig. 11 Peripheral retina of patient III-5. Coarse pigmentary retinopathy with a relatively discrete posterior boundary (arrowheads) is seen. Some bone spicule pigmentary configurations are present.

Fig. 12 Peripheral retina of patient III-1. Coarse pigmentary retinopathy with a discrete posterior boundary. Yellow dots are present (arrowheads).
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was prepapillary fibrotic tissue, a scar superior to the disc due to previous photocoagulation, and fine microvascular abnormalities near the scar. Irregular staining of the vein walls was also seen (Fig. 3B). An area of retinal neovascularisation was seen superotemporal to the macula near the arcade (Fig. 4). Extensive vitreous haemorrhage was seen from the inferior arcade to the ora serrata extending from 5.00 to 8.00 o'clock.

Fluorescein angiography showed marked window defects peripherally with multiple foci of blocked fluorescence (Fig. 5). Posterior to the boundary of the marked pigmentary change there was fine pigmentary mottling. Subtle abnormalities of the calibre of the retinal capillaries were seen, including some at the perifoveal capillary net. There was late staining at the optic disc and in the region of the new vessels (Fig. 6). Mild depression of the visual fields was determined by Goldmann perimetry, and in addition there was a superior field defect in the right eye corresponding to the area of vitreous haemorrhage. The electroretinogram's photopic and scotopic responses were normal in amplitude and implicit times. It was initially thought that the patient might have some form of arrested retrolental fibroplasia, until examination of other family members revealed the hereditary nature of the disease.

The patient was next seen in June 1979. The vision at that time was 20/50 OU with a correction of -2·25 OD and -2·50 OS. The macula appeared to be displaced somewhat inferiorly and temporally in each eye. The vitreous haemorrhage in the right eye had mostly resorbed, leaving a white intravitreal clot inferiorly. The focus of retinal neovascularisation along the superior temporal arcade was slightly enlarged as compared with the previous examination. A fluorescein angiogram showed that macular pigmentary changes had developed in the interim. There was moderate leakage along the arcades near the disc and some late disc staining.

In January 1982 the patient developed a black central spot in the central field of the left eye. The best corrected vision was 20/60 (−4·25+0·50×130) in the right eye and 20/300 (−5·00+0·75×75) in the left eye. There was a defect on Amsler grid testing OS. The anterior segment examination was changed only in that slight band keratopathy was noted at 3.00 o'clock near the limbus OS. On funduscopy examination there was increased pigmentary mottling at the maculas of both eyes (Fig. 7). Yellowish-white dots could be seen in the maculas, and considerable macular thickening, especially in the left eye, was noted. Fluorescein angiography showed marked leakage from the radial peripapillary capillaries and at the foveas (Fig. 8). On this examination some intravitreal bands were noted as well as vitreous condensation over the peripheral pigmented zone. A focus consistent with hypertrophy of the retinal pigment epithelium was observed at 4.00 o'clock in the left eye posterior to the boundary of the peripheral pigmented zone. As expected in a patient with marked leakage of fluorescein into the macula,
The external examination both in eyes showed a product of differences in tensions of the vitreous. Yellowish-white dots were seen in the region of the internal limiting membrane and were similar to those in his brother's eyes. The retinal arterioles were somewhat attenuated, and in some areas there were mild-calibre irregularities of the veins. There was preapillary fibrous tissue without visible vessels in both eyes. Mild pigmentary changes at the macula were questionably present in each eye. The fluorescein angiogram showed a broad band of window defect with a fairly discrete posterior boundary near the equator. Coarse foci of blocked fluorescence were seen in this region and corresponded to the pigmented areas in the retina. Posteriorly there was fine mottling to the background choroidal fluorescence. The visual fields showed mild generalised depression. The electroretinogram was normal.

The patient was again examined in May 1982. At this time his vision was 20/40 OD (-7.00+1.50×110) and 20/30 OS (-6.50+0.25×120). Milder posterior embryotoxon was seen OU. The fundus examination was similar to that at the previous examination except that occasional whitish nodules were seen on the internal limiting membrane, the large choroidal vessels could be seen even at the centre of the macula, and the retinal vessels over the peripheral pigmented zone were either not visible or white lines. Fluorescein angiography showed fine microaneurysmal changes at the perifoveal capillary ring, late leakage at the macula and optic nervehead, and the pigmentary changes seen previously. The vitreous fluorophotometry result was markedly elevated. The electroretinogram remained normal.

**Patient III-1**
The 22-year-old brother of the proband was first seen in 1982. He had no symptoms, no nyctalopia, no colour vision problems, and no history of prematurity. The vision was 20/30 OD (-9.00+1.00×70) and 20/25 OS (-9.75+0.75×120). The external examination, applanation tonometry, and slit-lamp examinations were normal except for slight peripheral posterior cortical opacities in each lens. With slit-lamp biomicroscopy 1+ vitreous dots, translucent lines, and posterior vitreous detachments were seen. On indirect ophthalmoscopy the posterior segment examination showed a band of pigmentary degeneration extending for 360° in each eye, as in his brothers (Fig. 12). Yellow-white dots near the internal limiting membrane were observed, but no nodules were seen. There was increased visibility of the choroidal vasculature even at the macula of each eye. A fluorescein angiogram revealed late leakage from the discs,
Fig. 9A

Fig. 9B

Peripheral window defects, and areas of blocked fluorescence. The retinal arterioles appeared to be slightly attenuated. There was slight depression on visual field testing in both eyes. The vitreous fluorophotometry results were markedly elevated in both eyes. The electroretinogram was normal.

Patient II-2
The 45-year-old father of the proband denied any ocular symptoms. His vision was 20/20 OU (−3·50 OU). The external examination, applanation tonometry, and slit-lamp examination were unremarkable except for mild punctate cortical flecks in the lenses. The gonioscopic examination was normal. Biomicroscopy of the vitreous using a Goldmann lens showed slight vitreous degeneration and syneresis, no vitreous cells, and posterior vitreous detachment OU. Peripherally, fine yellow dots were seen in the region of the internal limiting membrane in some areas. The fundus examination revealed several peripheral foci of pigmented blotches OU. The fluorescein angiogram, visual fields, vitreous fluorophotometry, and electroretinogram were normal.

Patient I-2
The 76-year-old paternal grandmother of the proband was asymptomatic. She refused to come to the hospital, so she was examined at home. An external examination by flashlight was unremarkable except for a few cortical spokes and mild nuclear sclerosis of both lenses. The dilated fundus examination with direct and indirect ophthalmoscopy showed several
pigmentary disturbance. and a excludes differentiating familial appears it cystoid hemorrhage breakdown to be prominent feature of this may be seen. We have original a seeing nivation of which seemed peripheral pigmented blotches 3600 macular drusen. The recording 1982. Fig. 10 Electroretinogram of proband, patient III-3 in 1982. The recording was taken under scotopic conditions with a white light. It is normal in amplitude and timing.

peripheral pigmented blotches and a few yellow dots which seemed more discrete, more yellow, smaller, and rounder than drusen. There was mild choroidal atrophy as evidenced by increased visibility of the large choroidal vessels even in the macula. No macular drusen were seen. There was a prominent 360° peripapillary conus in each eye with a tilted disc in the left eye.

Discussion

We have described the second family with autosomal dominant vitreoretinocchoroidopathy. Our recognition of a second affected family so shortly after seeing the original family suggests that the condition may be more common than we had assumed. Although peripheral pigmented retinopathy was a prominent feature of this disease, visual loss appears to be related mainly to macular oedema due to breakdown of the blood-retinal barrier or vitreous haemorrhage due to retinal neovascularisation. Cystoid macular oedema has been severe and recurrent in the probands of both this pedigree and of the one we initially reported.1

When all of the features of this ocular disease are present, diagnosis should be straightforward because it appears that this combination of findings is unique. The major characteristics which are useful in differentiating this condition from others are as follows: (1) Familial pattern. This feature, for the most part, excludes a wide variety of retinal vascular diseases that could produce breakdown of the blood-retinal barrier and retinal neovascularisation. (2) Peripheral pigmentary disturbance. We know of no other con-

dition where there is a broad band of marked pigmentary degeneration, which extends from a discrete posterior border in the equatorial region to the ora serrata for 360°. It may be a pathognomonic sign of this disease. (3) Yellow-white dots. These dots appeared to be in the retina or on the internal limiting membrane and not at the level of the pigment epithelium. They sometimes appeared to glisten, and diameter was approximately 30 μm. They were usually seen peripherally in the region of the coarse pigmentary disturbance, but also could be seen in the posterior pole. Similar foci are known to occur in a variety of retinal degenerative conditions.5 (4) Prominent vascular abnormalities. These included vascular leakage, arteriolar attenuation, venous beading, venous sheathing, venous occlusion, focal venous staining, microaneurysm formation, and retinal neovascularisation. (5) Absence of significant nystagmus. This effectively rules out various forms of congenital stationary night blindness, such as fundus albipunctatus, and progressive rod-cone dystrophies, such as choroideremia and retinitis pigmentosa. (6) Normal electroretinogram. This eliminates most forms of retinitis pigmentosa, Goldmann-Favre disease, and congenital retinoschisis. (7) Absence of prominent systemic features. This excludes a variety of syndromes which potentially could be confused with this one, such as Stickler syndrome⁶ and the metabolic tapetoretinal degenerations.⁷

The conditions which we considered most seriously in the differential diagnosis were autosomal dominant cystoid macular oedema and snowflake deposition in hereditary vitreoretinal degeneration. Autosomal dominant cystoid macular oedema is a recently described condition characterised, as its name suggests, by autosomal dominant inheritance and cystoid macular oedema.⁸ Additional abnormalities include leakage from the optic disc capillaries, mild peripheral pigmentary retinopathy,⁹ vitreous opacities, subnormal electrocoelulography values, and normal electroretinograms at least during the initial stages. In our family the peripheral pigmentary abnormalities were severe and were more frequent than was frank macular oedema. In autosomal dominant cystoid macular oedema the peripheral pigmentary changes are not very prominent, and are much less frequent than are the macular changes. Furthermore the reported pigmentary changes did not have the characteristics seen in our cases, where there was extensive peripheral pigmentary mottling for 360° with a relatively discrete posterior boundary.

Hereditary vitreoretinal degeneration with snowflake degeneration was described by Hirose et al.⁵ It is characterised by autosomal dominant inheritance and a sequential evolution of changes consisting of (1) extensive white-with-pressure, (2) snowflake
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degeneration, (3) sheathing of retinal vessels and pigmentation, (4) increased pigmentation and disappearance of vessels. Fibrillar vitreous degeneration progressed along with the fundus changes. Five of their 15 cases developed rhegmatogenous retinal detachment. The peripheral pigmentation, yellow-white dots (snowflakes), and vascular changes are reminiscent of the condition we have seen. However, snowflake degeneration is not characterised by intense pigmentation having a discrete posterior boundary. Hirose et al. also did not describe significant macular oedema, microvascular changes, or retinal neovascularisation. Prominent white-with-pressure, the evolution of changes that they described, and rhegmatogenous retinal detachment were not seen in our patients. We also excluded Bietti's tapetoretinal degeneration with marginal corneal dystrophy,11 the disease described by Wagner,12 and familial exudative vitreoretinopathy13 because of the marked vascular decompensation and characteristic pigment distribution seen in our patients. However, marked vascular leakage occasionally occurs in the latter condition.14

We have included the father and paternal grandmother of the proband as being affected by the condition, even though they did not have the extensive changes seen in the proband and his 2 brothers. We consider these 2 to have minimally expressed disease. However, their mild changes possibly could be nonspecific. If so, it would be impossible to determine conclusively the hereditary pattern of the disease in this family.

It is difficult to determine the primary site of the underlying disease process in this condition. The vitreous is involved with mild degenerative changes, vitreous cells, vitreous strands, and early posterior vitreous detachment. The retina is involved with vascular changes and pigmentary abnormalities. The choroid is abnormal because some choriocapillaris atrophy must be present for the large choroidal vasculature to be visible in the foveal region. It may be that the primary sites of involvement are the retinal pigment epithelium and the retinal vessels, and that the other changes are secondary, including presenile cataract.1 This would explain the abnormal vitreous fluorophotometry and normal electronegogram results in our patients.

In summary, we present the second family with autosomal dominant vitreoretinochoroidopathy, a disease with protein manifestations in the ocular posterior segment. So far this disease has been recognised only in Chicago, Illinois, although the 2 kindreds were not related. Visual loss appears to be related to vitreous haemorrhage or macular oedema and may be severe. Variable expressivity may be present, as in most dominant traits, and suggests that examination of family members may aid in establishing the diagnosis in questionable or minimally affected cases. Because the term autosomal dominant vitreoretinochoroidopathy is cumbersome, we suggest the acronym ADVIRC as a convenient name until the precise pathogenesis and primary anatomical locus of involvement are established.

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