Atypical vitelliform macular dystrophy in a 5-generation family

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SUMMARY Five generations of a family with autosomal dominant atypical vitelliform macular dystrophy (A-VMD) were studied. This dystrophy is similar to autosomal dominant Best's vitelliform dystrophy (B-VMD) but clinically more closely resembles sporadic pseudovittelliform macular degeneration (P-VMD). Of the family members who were 14 years or older 43 (24 females and 19 males) of the 101 at risk (43%) were affected. Vision varied from 20/20 to 20/200. Field defects and tritan colour defects were invariably present only when vision was $\leq 20/200$, but these defects were sometimes present when vision was good. The electrooculographic studies (LP/DT ratios) in this family were found to be normal or reduced and did not correlate with visual acuity. Minimal retinal findings consisted of macular or extramacular punctate yellow lesions or both in the retinal pigment epithelium, which were hypofluorescent by angiography, and retinal pigment epithelial defects in the temporal nerve fibre bundle, which were hyperfluorescent by angiography. Fluorescein angiographic changes were invariably present when retinal lesions were noted, and this was the most reliable test in identifying genotypically affected family members with minimal phenotypic expression.

Autosomal dominant retinal pigment epithelial (RPE) dystrophies include Best's vitelliform macular dystrophy (B-VMD),¹ butterfly-shaped epithelial dystrophy (BED),² foveomacular dystrophy (FMD),^{3,4} and drusen.⁵ Establishing a correct diagnosis in RPE dystrophies may be difficult in that B-VMD and BED may be a continuum.⁶ Further, the diagnosis may be confused because of sporadic conditions. Pseudovittelliform macular degeneration (P-VMD) is similar morphologically to B-VMD, but is sporadic, shows a normal or slightly abnormal electro-oculogram, has a later age of onset, shorter period of evolution of the lesion, and a discrete atrophic lesion as the end stage.⁷

This paper presents a large family with an autosomal dominant RPE dystrophy which is an atypical vitelliform macular dystrophy (A-VMD). There is complete penetrance but extreme variability of phenotypic expression, with different appearances to the primary lesions, multifocal lesions, and

variable age of onset and rate of progression. The electro-oculogram is not always diminished in affected family members and cannot be used for genetic counselling. Fluorescein angiographic changes are invariably present when ophthalmoscopic lesions are identified, and are thus more valuable than electro-oculography in detecting *genotypically* affected family members with minimal *phenotypic* expression.

Patients and methods

Thirty-eight individuals in 4 generations of a single family were shown by examination (1981) to have A-VMD, and 6 more were ascertained by review of ophthalmological records. In addition 71 unaffected relatives were examined. Both affected and unaffected family members had the following examinations (1981): visual acuity best corrected, external examination, motility examination, examination by a hand-held slit-lamp, examination by direct and indirect ophthalmoscopy, and fundus photography.

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Fig. 1 Pedigree of family with atypical vitelliform macular dystrophy. Squares, males; circles, females; open symbols, unaffected; solid symbols, affected; vertical lines in symbols, unexamined; slash through symbols, deceased.

Table 1 Clinical data for 44 affected family members

Patient	DOB	Sex	Visual acuity (OD-OS)	Colour	EOG (OD-OS)	Fundus photographs	Fluorescein angiograms
I*	14 Jul 1870	F	[[poor vision]]				
II ₁	05 Feb 1893	F	[20/80 20/200]			3A 3B 3C	†
II ₂	30 Nov 1895	F	[[poor vision]]				
II ₄	23 Mar 1902	M	[20/40 20/60]		2-2/2-2	1A 2B 0C	†
II ₅	09 Aug 1909	F	20/200 20/200	‡	1-6//1-7	3A 3B 1C	†
II ₆	14 Nov 1913	F	[20/25 20/30]		2-2/2-0	2A 3B 2C	†
II ₇	22 Jun 1915	M	20/30 20/30			1A 2B 3C	†
III ₅	14 Sept 1917	F	20/100 20/200			2A 3B 3C	§
III ₆	08 Apr 1920	F	20/20 20/20			1A 2B 0C	§
III ₇	14 Dec 1926	M	20/30 20/30		2-4/2-8	2A 2B 3C	†
III ₈	15 Mar 1929	F	20/20 20/20			1A 3B 0C	§
III ₉ *	07 Mar 1930	F	20/30 20/20	‡		1A 2B 0C	†
III ₁₂	18 Nov 1916	F	20/30 20/200		3-2//2-6	3A 2B 0C	†
III ₁₃	18 Apr 1918	M	20/20 20/100			2A 2B 2C	§
III ₁₄ *	15 Jan 1920	M	20/40 20/30	‡		1A 1B 0C	†
III ₁₅ *	08 Aug 1922	F	20/30 20/40			1A 2B 1C	†
III ₁₆	12 Dec 1924	F	20/30 20/30	‡		1A 1B 1C	†
III ₁₇ *	29 Jun 1926	M	20/200 20/200	‡	2-4//2-3	3A 1B 1C	†
III ₁₈ *	31 Jul 1928	M	20/20 20/30	‡		1A 1B 0C	†
III ₂₃	06 Jun 1927	M	20/200 20/200		1-6/1-5	3A 2B 1C	†
III ₂₅	07 Sept 1932	F	20/20 20/60			1A 2B 0C	†
III ₂₆ **	30 Sept 1949	F	20/20 20/20	†		1A 1B 2C	†
IV ₁₆	06 Jan 1948	F	20/20 20/20			1A 2B 0C	§
IV ₂₂ **	14 Dec 1952	M	20/20 20/20	†		1A 1B 1C	†
IV ₂₄ **	28 Jun 1962	M	20/20 20/20	†		1A 1B 0C	†
IV ₂₈	28 Dec 1943	F	20/30 20/70			1A 2B 0C	§
IV ₂₉	18 Jan 1946	M	20/200 20/100		2-2/2-2	2A 2B 0C	†
IV ₃₄ *	01 Jun 1952	F	20/20 20/20			0A 1B 1C	†
IV ₃₆ **	16 Jan 1957	F	20/20 20/20			0A 1B 1C	†
IV ₄₀ **	14 Sept 1945	M	20/20 20/20			1A 1B 0C	†
IV ₄₂	08 Jan 1953	F	20/20 20/20			1A 2B 0C	†
IV ₄₅ **	08 Nov 1957	F	20/20 20/20			0A 1B 2C	†
IV ₄₆	13 Nov 1958	M	20/20 20/20			1A 1B 0C	†
IV ₄₈	24 Jul 1961	M	20/20 20/20			0A 2B 1C	†
IV ₅₁	08 Aug 1951	F	20/30 20/25			1A 1B 0C	†
IV ₅₇ **	26 Aug 1962	F	20/20 20/20	†	2-7/2-5	1A 2B 0C	†
IV ₅₈ **	03 Jun 1965	M	20/20 20/20			1A 2B 0C	†
IV ₅₉ *	13 Dec 1951	M	20/20 20/20			1A 2B 1C	†
IV ₆₀ **	05 Jul 1953	F	20/20 20/20			0A 1B 1C	†
IV ₆₂ *	26 Feb 1958	F	20/20 20/20			1A 1B 0C	†
IV ₈₃	24 May 1953	M	20/20 20/20			1A 1B 1C	†
IV ₈₉	14 Dec 1953	F	20/20 20/20			1A 2B 0C	§
IV ₉₂	22 Nov 1956	M	20/25 20/25		1-6//2-1	2A 2B 1C	†
V ₁₉ **	26 May 1967	M	20/20 20/20			0A 2B 1C	§

DOB=Date of birth. EOG=Electrooculogram (light peak to dark trough ratio). OD=Right eye. OS=Left eye. *=GPT1 Type 2-1, i.e. doubly heterozygous, with children. **=GPT1 Type 2-1, i.e. doubly heterozygous, without children. M=Male. F=Female. [[]]=Died prior to 1974 studies. []=Died prior to 1981 studies. †=Normal. ‡=Abnormal. §=Not performed. 0=Normal. 1=Minimal. 2=Moderate. 3=Severe. A=Macular. B=Peripapillary. C=Peripheral. Fig. 1 shows the position of each patient in the pedigree. || Marks information given in Figs. 2-7.

Twelve affected patients had central visual field testing, 10 affected patients had 100-hue colour testing, 10 affected patients had electro-oculograms (1974),⁸ and 34 affected and 16 unaffected patients had fundus fluorescein angiography (1974 and/or 1981).

Results

The family pedigree (Fig. 1) showed the segregation of A-VMD to be consistent with an autosomal

dominant inheritance pattern with complete penetrance and 7 instances of male to male transmission. Of the 44 affected members 25 were females and 19 were males. Slightly fewer than 50% of the family members at risk who were older than 14 years were known to be affected (43%; 43 of 101). Family members were designated as affected on the basis of moderate or severe retinal lesions seen ophthalmoscopically with or without fluorescein angiography, or on the basis of minimal retinal lesions

Fig. 2 Colour abnormalities in 2 affected family members. Left, patient III₁₆ (age 61 years; visual acuity OU: 20/30). Right, patient III₁₇ (age 54 years; visual acuity OU: 20/200).

seen or suspected ophthalmoscopically and substantiated by fluorescein angiography (See Table 1). All family members except 3 in generation IV (IV₉₄₋₉₆) were older than 14 years, while only 3 family members in generation V (V₁₉₋₂₁) were at least 14 years of age. Visual acuities in the affected family members ranged from 20/20 to 20/200, with only 6 family members having a visual acuity of 20/200 or less in one or both eyes (II₅, III₅, III₁₂, III₁₇, III₂₃, and IV₂₉).

Amsler grid visual fields were performed on 12 affected family members. A central visual field defect was noted only in those family members whose visual acuity was markedly reduced.

A complete or partial tritan colour defect was found in 6 of 10 of the affected family members

tested. There was no correlation between visual acuity and the colour defect (Fig. 2); however, in 2 family members whose visual acuity was 20/200 or less the tritan colour defect was present.

Electro-oculograms were performed in 1974 on 10 affected family members. The electro-oculogram was abnormal (Fig. 3, top) in only 3 affected family members (ages 16 to 65 years at the time of examination). Visual acuities in these 3 family members ranged from 20/25 to 20/200. In the 7 affected family members (ages 12–72 years at the time of examination) with normal electro-oculograms (Fig. 3, bottom), visual acuities ranged from 20/20 to 20/200. Thus decreased visual acuity did not correlate with an abnormal electro-oculogram.

Fig. 3 Electro-oculograms of 4 affected family members. Top left, patient IV₆₂ (age 16 years; visual acuity OD: 20/25). LP/DT ratio 1.6. Top right, patient II₅ (age 65 years; visual acuity OD: 20/200). LP/DT ratio 1.6. Bottom left, patient III₁₂ (age 58 years; visual acuity OD: 20/30). LP/DT ratio 3.2. Bottom right, patient III₁₇ (age 47 years; visual acuity OD: 20/200). LP/DT ratio 2.4. Normal LP/DT ratio 1.7–4.0. Each dot represents the average of 7 to 10 ocular rotations at a rate of one rotation per second. Shaded area = dark adapted testing. Unshaded area = light adapted testing.

Fig. 4 Mild central retinal abnormalities in 2 affected family members demonstrated by fundus photography and fluorescein angiography. Left, patient III₁₈ (age 53 years; visual acuity 20/20). The macular region of the left eye appears normal ophthalmoscopically and there is only a slight defect in the nerve fibre bundle temporally (top). However, there are foveal fluorescence and peripapillary retinal pigment epithelial defects angiographically (middle and bottom). Right, patient III₁₄ (age 61 years; visual acuity 20/30). The macular region of the left eye has a slight yellow appearance ophthalmoscopically and there is a defect in the nerve fibre bundle temporally (top), and there are foveal fluorescence and peripapillary retinal pigment epithelial defects angiographically (middle and bottom). (Asterisks mark camera artefact.)

Fundus photographs and fluorescein angiograms were used to document the variable phenotypic expression of the dystrophy of the retinal pigment epithelium. The multifocal nature of this dystrophy with both central and peripheral lesions is shown in minimal (Figs. 4 and 5), moderate (Fig. 6), and severe (Fig. 7) forms.

Minimal changes consisted of small yellow lesions in the macular and/or peripheral retina and small defects in the temporal peripapillary region. Moderate changes included elevated ('fried egg') yellow lesions in the macula or peripheral retina, and defects (usually 90°–180°) in the temporal peripapillary region. In minimal and moderate cases the yellow lesions were hypofluorescent in early but hyperfluorescent in late fluorescein angiograms,

while the peripapillary lesions were uniformly hyperfluorescent. Severe changes included advanced vitelliform macular or peripheral lesions which had depigmented centres and pigment clumping around the edges without hypertrophic scarring, and large (usually 360°) retinal pigment epithelial defects in the peripapillary region. In these cases the fluorescein angiograms showed the defects as hyperfluorescent areas from early to late. Some patients had minimal central lesions and severe peripheral lesions simultaneously (and vice versa). In some cases retinal lesions advanced from minimal to moderate or from moderate to severe from 1974 to 1981, and in 2 cases visual acuity decreased from normal to legal blindness in one eye during this period (III₁₂ and IV₂₉).

Fig. 5 Mild peripheral retinal abnormalities in 2 affected family members demonstrated by fundus photography and fluorescein angiography. Left, patient IV₄₃ (age 28 years; visual acuity 20/20). A small yellow dot (arrow) is apparent in the right eye ophthalmoscopically (top), less apparent (arrow) by early angiography (middle), but well demonstrated (arrow) by late angiography (bottom). Right, patient III₁₆ (age 57 years; visual acuity 20/30). A few small yellow lesions (arrow) are apparent in the right eye ophthalmoscopically (top), hypofluorescent (arrow) by early angiography (middle), but hyperfluorescent (arrow) by late angiography (bottom). (Asterisks mark camera artefact.)

Discussion

The ophthalmoscopic appearance of B-VMD may be polymorphous,^{9,10} multifocal lesions may occur,¹¹ and the age of onset and rate of progression of the dystrophy may vary considerably even within single families. In B-VMD fundus lesions have been reported at birth, but they are more typically discovered between ages 3 and 15 years. There have been good reports that the lesions can develop late in life, and that the age of clinical onset may vary considerably within a single family. Electro-oculography,¹²⁻¹⁴ fluorescein angiography,¹⁵⁻¹⁷ and pathological studies have all localised the pathology in B-VMD to the retinal pigment epithelium.¹⁸ Recent reviews¹⁹⁻²¹ have emphasised that the main

criteria for the diagnosis of B-VMD are family history (autosomal dominant pedigree), visual loss in advanced cases (with high variability in appearance of the lesions), and a diminished electro-oculogram.

In contrast P-VMD is generally sporadic, except in 2 instances of apparent autosomal dominance in two generations.^{3,4} The lesions are usually smaller than those of B-VMD, the electro-oculogram is normal or slightly decreased, the onset is later in life, with a slower progression, and an end stage which is atrophic (not hypertrophic).^{7,22-27}

This family with A-VMD demonstrates extreme variability of expression, including differences in appearance and location of the lesions, and in their variable age of clinical onset and progression. Inconsistent abnormalities were found with field and

Fig. 6 Moderate central and peripheral retinal abnormalities in 2 affected family members demonstrated by fundus photography and fluorescein angiography. Left, patient IV₂₉ (age 28 years; visual acuity 20/30). The macular region of the right eye has a vitelliform lesion ophthalmoscopically (arrow) and a defect in the temporal nerve fibre bundle. The (arrow) early (middle) and (arrow) late (bottom) fluorescein angiography confirm these abnormalities. Right, patient IV₄₅ (age 24 years; visual acuity 20/20). The periphery of the right eye has a depigmented area ophthalmoscopically (arrow). This area demonstrates hypofluorescence (arrow) early (middle) and hyperfluorescence (arrow) late (bottom). (Asterisk marks camera artefact.)

colour tests, and these tests were invariably positive only when visual loss was advanced. The electro-oculogram was also inconsistent in this family, since even severe visual loss was not necessarily associated with an abnormal electro-oculogram. Thus this family, which meets all the criteria for autosomal dominance, represents the first instance of normal electro-oculograms in patients with a dystrophy similar to B-VMD.

It is estimated that in B-VMD only two-thirds of the genetically affected individuals have phenotypic expression consisting of visible macular changes and that in those with macular changes only 10% have vision $\leq 20/200$.⁹ This family with A-VMD is similar to that estimate, since in the 38 living affected persons in this pedigree only 9 eyes of 6 patients above the age of

14 years have vision of $\leq 20/200$ (12%). The other third of the genetically affected individuals with B-VMD with no visible macular changes have been called 'carriers' and have been identified by their position in a family pedigree and/or by abnormally low electro-oculograms. These individuals are not really carriers, since they have the same genetic composition as the affected patients.

Accurate genetic counselling can be given only if individuals with the affected genotype can be recognised phenotypically. Further, linkage analysis can only be performed if disease status is correctly designated for all family members considered. In order to analyse the linkage data without prejudice it was felt necessary to have a consistent point to cease study of the patients both ophthalmologically and

Fig. 7 Advanced central and peripheral retinal abnormalities in 2 affected family members demonstrated by fundus photography and fluorescein angiography. Top left, patient III₁₂ (age 58 years; visual acuity 20/30). The macular area of the left eye has an advanced vitelliform lesion ophthalmoscopically and defects in the peripapillary region are extensive. Bottom left, the fluorescein angiograph demonstrates these lesions. Top right, patient III₁ (age 48 years; visual acuity 20/20). The peripheral retina of the right eye has a large peripheral depigmented scar as well as several small yellow lesions similar to those seen in less advanced cases. Bottom right, the fluorescein angiograph demonstrates these lesions.

genetically. Fourteen years was selected because at the time of the initial study of 70 individuals in 1974 the youngest ophthalmologically affected patient was found to be 16 years old.

In 1981 an examination of 105 individuals identified the youngest ophthalmologically affected patient to be 14 years old, and a preliminary linkage study of blood samples obtained from these family members suggested linkage to the soluble glutamate pyruvate transaminase (GPT1) locus. It was felt desirable to confirm the linkage. Therefore, it was decided to study as many offspring of the doubly heterozygous family members (affected members with GPT1 type 2-1) as possible, since these individuals yield most of the information in a linkage analysis.²⁰ For this reason, more examinations were performed in 1981 with special attention given to the offspring of the doubly heterozygous family members, including fluorescein angiography to confirm their disease status. During this study 23 additional examinations were performed, and their blood samples were also collected. This included all such potentially informative individuals except IV₂₃ and IV₄₃. Selecting the age of 14 years as a consistent point to cease studying patients also virtually eliminated generation V without prejudice.

Variable expressivity has been well recognised as an obstacle to the establishment of linkage, and all methods available must be employed to demonstrate mild phenotypes who are nonetheless genotypically affected.²⁸⁻³² In this family, linkage between A-VMD and GPT1, thought to be on the short arm of chromosome 16, was established by means of maximum likelihood analysis ($Z=4.33$, that is, odds favouring linkage 22 000 to 1).³³

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