Hereditary macular degeneration in three generations

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Hereditary macular degeneration has a multifarious ophthalmoscopic appearance but is usually characterized by a sharply-defined, dense, homogenous, avascular disc resembling the intact yolk of a fried egg (Sorsby, 1940; François, 1961; Braley, 1966). The appearance of the macula, however, may range from mild pigmentary degeneration to dense scarring with pigmentary hyperplasia. The clinical course of the macular lesion, the degree of visual impairment, and the age at onset of ocular symptoms also vary within and between families (Sorsby, 1940; Grimm and Tedford, 1963; Braley and Spivey, 1964).

In spite of the polymorphism of the macular lesion, probably all forms of macular degeneration represent the same fundamental degenerative process (Berkley and Bussey, 1949; François, 1961; McKusick, 1971).

This paper describes a family in which eight members in three generations have macular degeneration; two affected brothers also have alopecia congenita, one in addition has coarctation of the aorta, and their mother, who has macular degeneration, also has congenital aortic stenosis.

FIG. 1 Pedigree
Case report
The pedigree of the family is shown in Fig. 1.
Eight relatives (III,6 to III,13) were not available for examination, but eighteen relatives have been investigated, eight of whom have macular degeneration. Clinical details of these eight affected individuals are given below and in the Table.

Table Clinical features in the eight relatives with macular degeneration

<table>
<thead>
<tr>
<th>Pedigree reference</th>
<th>Relationship to propositus</th>
<th>Date of birth (yrs)</th>
<th>Onset of visual symptoms (yrs)</th>
<th>Visual acuity</th>
<th>Appearance of macula</th>
<th>Colour vision</th>
<th>Other abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV, 6</td>
<td>Propositus</td>
<td>1.2.64</td>
<td>5</td>
<td>6/36 6/9</td>
<td>Sharply-defined yellowish avascular oval lesion Pigment stippling</td>
<td>ABN</td>
<td>Alopecia congenita Coarctation aorta</td>
</tr>
<tr>
<td>IV, 7</td>
<td>Brother</td>
<td>4.5.68</td>
<td>2-3</td>
<td>—</td>
<td>Bilateral pigment stippling</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>IV, 8</td>
<td>Brother</td>
<td>4.5.68</td>
<td>2-3</td>
<td>—</td>
<td>Bilateral loss of foveal reflex Pigment stippling</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>III, 3</td>
<td>Mother</td>
<td>16.4.37</td>
<td>30</td>
<td>6/12 6/24</td>
<td>Bilateral sharply-defined oval lesion with central pigmented area</td>
<td>ABN</td>
<td>ABN</td>
</tr>
<tr>
<td>II, 1</td>
<td>Maternal grandfather</td>
<td>20.11.09</td>
<td>41</td>
<td>6/80 6/80</td>
<td>Central areolar choroidal atrophy</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>II, 4</td>
<td>Maternal great-aunt</td>
<td>20.11.05</td>
<td>38</td>
<td>6/9 6/6</td>
<td>&quot;Moth-eaten&quot; appearance with small clumps of pigment</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>III, 2</td>
<td>Maternal uncle</td>
<td>16.12.34</td>
<td>—</td>
<td>6/9 6/9</td>
<td>Clumps of pigment around the fovea</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>IV, 5</td>
<td>Maternal first-cousin</td>
<td>16.7.62</td>
<td>4-5</td>
<td>6/24 6/18</td>
<td>Fine pigment stippling</td>
<td>ABN</td>
<td>ABN</td>
</tr>
</tbody>
</table>

L = left  R = right  N = normal  ABN = abnormal  NE = not examined

IV, 6. Propositus (date of birth: February 1, 1964), the eldest of a sibship of three (Fig. 2), first seen when aged 5 years with defective vision ascertained at a routine school medical examination.

FIG. 2 Sibship (IV,6—IV,8). Propositus (IV,6) and his younger brother (IV,8)—left and right respectively showing alopecia congenita.

Ophthalmoscopic examination of the right macular region shows a sharply-defined oval lesion, yellowish and avascular, with little surrounding pigment and approximately half-a-disc in diameter (Fig. 3, overleaf)—an appearance similar to that of a ruptured vitelliform cyst. The left macula shows only pigment stippling. There are no refractive errors: visual acuity 6/36 (right) and 6/9 (left). Accurate assessment of the visual fields was not possible because of poor fixation. Colour vision is normal in the left eye but probably defective in the right. Over 3 years of periodical outpatient observation, the visual acuity has not deteriorated.
This patient also has alopecia congenita (Fig. 2); the scalp hair was absent at birth and for the past 4 years he has worn a wig. There are no clinical features of ectodermal dysplasia. Teeth, nails, and sweating are normal. Coarctation of the aorta, diagnosed at birth, was confirmed at the age of 4 years by cardiac catheterization.

IV, 7 and 8. The younger sibs are twins (date of birth: May 4, 1968). They have identical blood groups (A2, CDe/CDe; MS; Pi; Lu^a--; Le^a--; K--; k+; Kpa^+; Kpb--; Fya+; Fyb++; Jka++; Jkb++; Cw--; Wra--). Each twin has a normal male chromosomal constitution (46, XY). The parental blood groups are available, and from the blood groups and the dermatoglyphs, the probability of this pair of twins being monozygotic or dizygotic was calculated, as suggested by Smith and Penrose (1955), as 0.9683 and 0.0317 respectively.

IV, 7. This 4-year-old boy has macular degeneration; both fundi at the macular region show pigment stippling. He also has a left concomitant convergent strabismus, first noted at the age of 2 years. Clinical examination revealed no other abnormality; in particular, the nails, teeth, hair distribution, and cardiovascular system are normal.

IV, 8. The co-twin of IV, 7 also has macular degeneration, characterized by a bilateral loss of the foveal reflex and pigment stippling of both maculae—an appearance similar to that observed in Stargardt's disease (Fig. 4).
Like his eldest brother (IV,6), he has alopecia congenita (Fig. 2). There are no other abnormalities; in particular, the cardiovascular system is normal.

III,3: The mother (date of birth: April 16, 1937) of IV,6–8, has defective vision first noted when she was 30 years old. Fundus examination showed identical lesions in each eye; in the macular area, there is a sharply-defined oval lesion of approximately one disc diameter, with a central pigmented area surrounded by a lighter halo (Fig. 5). Visual acuity is 6/24 (right) and 6/12 (left). Visual field examination shows a right central scotoma and on the left a smaller U-shaped scotoma. She also has a severe red-green colour vision defect. During 18 months of continual surveillance, visual acuity has deteriorated; it is now (January, 1972) 6/60 (right) and 6/24 (left). She can read N5 with a high reading addition. A congenital aortic stenosis was successfully treated (May, 1970) by aortic valve replacement. The distribution of hair, and the teeth and nails are normal.

Fluorescein studies in the mother (III,3) and her three sons (IV,6; IV,7; IV,8) showed fluorescence of the areas of the macular degeneration, probably auto-fluorescence. No evidence of vascular abnormality or leakage could be demonstrated.

**FIG. 5** Mother (III,3). Left fundus with a sharply-defined pigmented oval lesion surrounded by a lighter halo at the macular region.

**FIG. 6** Maternal grandfather (II,1). Left macular area with an appearance similar to areolar choroidal atrophy.

II,1. The maternal grandfather (date of birth: November 20, 1909) has defective vision, first noted when he was aged 41 years. The visual acuity in each eye is 6/60. Fundus examination shows typical central areolar choroidal atrophy (Fig. 6). No other ocular or physical anomaly is present.

II,4. A maternal great-aunt (date of birth: November 20, 1903) has noticed deterioration of vision for the past 30 years. The visual acuity is 6/9 (right) and 6/6 (left), with correction +6 D sph. right and +5 D sph. left. Both maculae have a "moth-eaten" appearance with small clumps of pigment. The colour vision is normal. There are no other physical or ocular abnormalities.

III,2. The maternal uncle (date of birth: December 16, 1934) has no ocular symptoms. The corrected visual acuity for each eye is 6/9. Fundus examination showed a bilateral loss of the foveal reflex and small clumps of pigment around the fovea—an appearance similar to early senile macular degeneration. The colour vision is normal. No other physical abnormalities are present.

IV,5. The daughter of III,2 (date of birth: July 16, 1962), like the propositus, has been referred because of defective vision detected during a routine school medical examination. The visual acuity is 6/24 (right) and 6/18 (left); there are no refractive errors. Both macular lesions are characterized by fine pigment stippling. She has a red-green colour vision anomaly and a pendular nystagmus.
Of the remaining relatives investigated, only two males (III,5; IV,4) show ocular abnormalities; each has a severe red-green colour vision defect.

**Discussion**

Hereditary macular degeneration has considerable polymorphism in the ophthalmoscopic appearance, the clinical course of the degeneration, the degree of visual impairment, and the age at onset of ocular symptoms (Sorsby, 1940; François, 1961; Grimm and Tedford, 1963; Braley, 1966; Braley and Spivey, 1964). We consider that the family presented in this paper has many of the characteristic features of hereditary macular degeneration. The appearance of the macular lesions in the eight affected individuals show marked polymorphism. The propositus, aged 5 years, has typical vitelliform degeneration of the right macula but only pigment stippling of the left macula. Other affected relatives have varied macular lesions, from mild pigment stippling to an appearance similar to early senile macular degeneration (Table I). The maternal grandfather, aged 61 years, has typical central areolar choroidal atrophy. Although this lesion is usually considered distinct from heredo-macular degeneration, in view of the family history, it is consistent with hereditary macular degeneration (François, 1972). Although there may be more than one variety of macular degeneration, evidence is not adequate for delineating more than one entity. Several authors (Sorsby, 1940; François, 1961; McKusick, 1972) have suggested the existence of a single hereditary form, since transitional forms and apparently different types of macular degeneration may be observed in the same family. The multifarious macular lesions in eight affected relatives in the family presented in this paper are consistent with the concept of a single hereditary entity.

The age at onset of visual disability also shows considerable variation (Davis and Hollenhorst, 1955; Braley, 1966). The family presented in this paper also illustrates this feature; visual disability was manifest in the four affected members of the fourth generation (IV,5 to IV,8) during the first 5 years of life, whereas other affected relatives did not develop visual symptoms until the third and fourth decades. On the other hand, the maternal uncle (III,2), with an ophthalmoscopic appearance similar to early senile macular degeneration, admits to no visual disability.

Since Best (1905) described the first pedigree of congenital macular degeneration, many families have been reported (Best, 1905; Vossius, 1921; Weisel, 1922; Jung, 1936; Sorsby, 1940; Falls, 1949; Davis and Hollenhorst, 1955; François, 1961; Grimm and Tedford, 1963; Braley and Spivey, 1964; François, 1971), the majority having autosomal dominant inheritance (McKusick, 1971). In the family described by Best (1905), eight of 300 members examined had macular degeneration. This family was re-investigated by Vossius (1921), Weisel (1922), and Jung (1936), who observed macular degeneration in 22 out of 300 members. Autosomal dominant inheritance has been confirmed by others (Davis and Hollenhorst, 1955; Grimm and Tedford, 1963; Braley and Spivey, 1964; François, 1971) observed macular degeneration in a father and son, in a mother and two sons, and in a mother, daughter, and son. Macular degeneration in our family shows autosomal dominant inheritance; eight (5 males; 3 females) of eighteen relatives investigated in three generations are affected. There is male-to-male transmission (Fig 1; II,1 and III,2).

Few twins concordant for macular degeneration have been reported; Neame (1944) described heredo-macular degeneration in female twins whose father was affected, and Falls (1949) also reported twins concordant for macular degeneration. In our family the
twins who are concordant for macular degeneration are likely to be dizygotic in spite of being concordant for blood groups; the maximum likelihood that they are dizygotic is 0.0317. Several members, however, have a number of features additional to macular degeneration. Two sibs (IV,6 and IV,8) have alopecia congenita and one of these (IV,6) and his mother (III,3) have congenital heart abnormalities. These may be chance findings or, alternatively, stigmata comprising a distinct entity which must be distinguished from others with similar aggregation of findings. These are: ectodermal dysplasia—but neither individual shows any abnormality of teeth, nails, or sweat glands; incontinetia pigimenti—but this can easily be distinguished on clinical grounds; and the cases described by Albrectsen and Svendsen (1956)—but here, additional to the alopecia and retinal lesions, there are hand abnormalities. We consider that the alopecia in this family is a coincidental, as six other relatives with macular degeneration have normal hair distribution. Isolated alopecia congenita is rare. Sly and Treister (1967) reviewed thirteen families from the literature and added one of their own in which six of thirteen sibs were affected. They concluded that isolated alopecia congenita is inherited as an autosomal recessive trait. In our family, inheritance of alopecia congenita is probably autosomal recessive. Congenital aortic stenosis in the mother (III,3) and coarctation of the aorta in her son (IV,6) are also probably chance findings and unrelated to the macular degeneration.

Summary
A family is described in which eight of eighteen relatives in three generations have macular degeneration with marked variation in ophthalmoscopic appearance and in the age at onset of visual disability. Inheritance is autosomal dominant. Two affected sibs also have alopecia congenita, which is probably unrelated to the macular degeneration, inheritance being autosomal recessive. Besides the macular degeneration, a mother and her son have congenital heart abnormalities, also considered to be chance findings.

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