GENEALOGICAL AND GENETICAL STUDIES OF HEREDITARY MACULAR DEGENERATION IN THE COUNTY OF VÄSTERBOTTEN, SWEDEN

by

Stefan Nordström
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This dissertation is based on the following separate papers, which will be referred to in the text by their Roman numerals:


INTRODUCTION

Hereditary macular degeneration is a defect of the retina of the eye, more precisely of the macula lutea, and it seems appropriate to include here a short anatomical description of this organ.

The multi-layered human retina is separated from the underlying choriocapillaris by Bruch’s membrane. Nearest to this membrane is a pigment epithelium (tapetum nigrum). Then follows the neuro-epithelial layer of rods and cones, and after that nuclear, reticular, and ganglion layers. (Waardenburg et al., 1963, p. 1719)

The retina has a very high rate of metabolism. Its nutritional needs are served by retinal as well as choroidal vessels. (Henkind, 1971)

The organization of the central part of the retina - the fovea - differs from that of other parts. It lacks a ganglion layer and a nuclear layer and it is much thinner in the most central part - the foveola. It also lacks rods in the neuro-epithelial layer. There are no retinal vessels in the central fovea and the major share of foveal nutrition comes from the underlying choriocapillaris. (Henkind, 1971, and others).

The terminology is somewhat obscure; according to Waardenburg, the macula lutea (the yellow spot) occupies a small part of the central fovea (Waardenburg et al., 1963, p. 1723). According to other authorities, the fovea lies in the centre of the macula lutea (Henkind, 1971). Merin and Auerbach (1970) state that the macula lutea, strictly speaking, "... is not part of the retinal neural network. It represents only that area which contains
a pigment accumulation in front of the retinal receptors in whose approximative center the fovea is located". "The clinician uses the term 'macula' but means the fovea". According to Blach (1973) "The macula is that part of the retina in which the ganglion cell layer is more than one cell thick and therefore represents an area some 5.5 mm in diameter. The fovea is a depression at the centre of the macula ...". Potts (1966, b) suggests that "Perhaps the most meaningful compromise is to equate the macula with the cone-rich area centralis ... extending with a 3 mm radius around the fovea".

Only man, monkeys, and birds have a true fovea (Maumenee, 1971). In man the specialized foveal structures begin to develop from the end of the 6th fetal month. (Waardenburg et al., 1963, p. 1720).

**Macular degeneration**

The macula lutea is responsible for the sharpest vision. It is, however, also more vulnerable than the remaining part of the retina to processes of aging (Dobbie, 1972) and to lesions caused by sun-gazing (Ewald & Ritchy, 1970), drugs (Potts, 1966a), inflammation etc. There are also many other diseases and syndromes which affect the macular region (Maumenee & Emery, 1972).

Senile macular degeneration occurs frequently in old people. According to Heinrich (1973), Kornzweig in America found macular degeneration in 24 % of 65-year-old subjects and in 36 % of 80-year-old subjects. In the Västerbottian population as well, senile macular degeneration occurs frequently (II, Tables 1 and 3).
Histological examination of eyes with senile macular degeneration reveals changes in Bruch’s membrane (Heinrich, 1973). According to Cogan (1965) the primary abnormality in most degenerations of the macula appears to be in the pigment epithelium or Bruch’s membrane. Krill et al. (1966) postulate that hereditary macular degeneration is initially a disease of the region of the innermost portion of Bruch’s membrane and the pigment epithelium.

Blach (1973) states that "Atrophy of the various retinal elements is seen especially in the hereditary and degenerative conditions .... It is often unknown whether the choriocapillaris, Bruch’s membrane, the pigment epithelium or the receptors are primarily involved as these structures are metabolically interdependent. In degenerative myopia there is some evidence that the pigment epithelium is primarily involved. In the hereditary juvenile macular degenerations electrical studies often suggest that there is widespread involvement of the retina and indeed fluorescein angiography in Stargardt’s disease does show that the pigment epithelium is widely affected".

Krill and Deutman (1972) report two families with a dominant macular degeneration in which pronounced acquired diffuse cone disease was the common abnormality among all affected members.

Potts (1966, b) discusses the involvement of the circulatory system of the eye in macular diseases.

A comprehensive anatomic classification of diseases of the macula is presented by Maumence and Emery (1972)
Hereditary macular degeneration

Cases of hereditary macular degeneration have appeared in the literature under a variety of designations such as: congenital macular degeneration, central exudative detachment of the retina, macular cysts or pseudocysts, congenital vitelliform cyst of the macula, exudative central detachment, central cystoid dystrophy, and hereditary vitelliform macular degeneration (Krill et al., 1966). The macula in early stages of degeneration has been described as looking like "an egg with sunny side up" and at a somewhat later stage like a "scrambled egg". Therefore Krill et al. (1966) suggest the term "vitelliruptive macular degeneration" (vitellus = egg yolk, ruptus = broken into fragments).

According to Waardenburg the term degeneration of the macula should be abandoned as a description of hereditary macular dystrophies. It is erroneous, firstly because macular degenerations usually extend over the entire fovea and adjoining parts and are not limited to the macula, secondly because "... the term degeneration is used by pathologists for deteriorating cell processes, which have nothing to do with heredity". Waardenburg suggests the term "central tapetoretinal dystrophy" for "a mostly bilateral, symmetrical, slowly developing process at the centre of the retinae, affecting one or several members of a sibship or a family stock". (Waardenburg et al., 1963, p. 1723).

Cogan (1965) suggests that it is the choroid which is primarily involved in some cases of hereditary macular degeneration and the pigment epithelium in others. He claims that it would not be difficult to suggest a more correct nomenclature "... but until a better correlation of the ophthalmoscopic and pathologic findings is possible, it is probably
wise to adhere to the catchall designation macular degeneration". The term "hereditary macular degeneration" is also frequently used by clinical ophthalmologists and is used in most of the references studied. This term is therefore also employed in this dissertation.

As early as 1875 Hutchinson and Tay observed similar presenile macular degeneration in three sisters (Remky et al., 1965). Some other cases of familial macular degeneration were also reported toward the end of the 19th century. They were all, however, considered to be inflammations and were consequently diagnosed "central chorioditis" or "central retino-chorioditis" (Waardenburg et al., 1963, p. 1724 f.)

Such diagnoses have also been frequent in subjects with hereditary macular degeneration in pedigrees from the county of Västerbotten (See Appendix).

When Best in 1905 reported congenital macular degeneration in 8 members of one family, inheritance of the disease was manifested. Follow-up studies in the 1920's and 1930's (Vossius, Wiesel and Jung) increased the number of recognized affected members in this family to 22 out of 300 individuals (Krill et al. 1966). Since then a number of disorders of the macula have been stated to be hereditary. Many attempts have been made to classify the hereditary macular degenerations, but these have met with great difficulties. A classification based on the age of onset is suggested by Behr (1920) and later by Falls (1966). Such a classification, however, is not reliable. Age of onset can be very variable within the same family (c.f. Barkman, 1961). Classification on the basis of the ophthalmoscopic appearance of the lesions is also impossible (II, p.8 and Table 8).
Blodi (1966) states that age of onset and the ophthalmoscopic appearance of the lesions, as well as resulting defects in colour vision, alterations of the electroretinogram and the mode of inheritance have proved unsuitable and unreliable as bases for classification. "It would, therefore, be most desirable if a clear order could be brought into this protean group of diseases by finding characteristic morphologic changes on pathologic examination. At present we can make such a classification only with regard to the tissue mainly involved: the choroid, Bruch's membrane, the pigment epithelium or the retina".

Braley (1966) and Maumenee and Emery (1972) also suggest a classification of macular degenerations based on the tissues involved. A comprehensive discussion of attempts to classify hereditary macular degenerations is published by Remky et al. (1965).

In Finland Forsius and Eriksson (1970) have successfully used parish records in genealogical studies of families with tapetoretinal degenerations. They discuss the possibility that very variable clinical manifestations of tapeto-retinal degeneration among Åland islanders are caused by the same mutation.

In Sweden Larsson (1932) reported three families with Stargardt's progressive familial macular degeneration. The inheritance was recessive. A Swedish pedigree of hereditary macular degeneration inherited as an autosomal dominant trait, presented by Barkman (1961), is of great interest inter alia from the aspect of population genetics. Barkman traced a total of 69 cases (39 men and 30 women) with "central tapetoretinal degeneration" in the province of Dalecarlia (County of Kopparberg). 63 of the cases (36 men and 27 women) belong to the same pedigree. In the Dalecarlian population as a whole the trait is rare. The province has 284 000 inhabitants.
HEREDITARY MACULAR DEGENERATION IN THE COUNTY OF VÄSTERBOTTEN.

MATERIAL AND METHODS

The first of the three papers in this dissertation (I) is a methodological study, in which the method of using parish catechetical meeting examination records (PCMER) to trace persons in earlier generations suspected of having impaired visual acuity is presented. This study was followed by a more detailed population survey in the county of Västerbotten (II). As many probands as possible were traced in the population. 8 probands came to my attention through continuous personal contact with ophthalmologists and other clinicians. Another 13 probands were found by:

1. Study of case records of patients born 1st - 8th of each month, examined 1966-1970 (and partly 1971) at the Department of Ophthalmology, the University Hospital, Umeå (7982 patient-records) - 6 new probands.

2. Study of records from the Adviser for the Weak-sighted in the county of Västerbotten; Membership-record (300 members) - 3 new probands.
   Social record (612 recorded patients) - 1 new proband.

3. Study of case records of patients born 1900 or later with a disease of the retina and/or the optic nerve examined in 1971 at the Department of Ophthalmology, the University Hospital, Umeå. The records were sorted out by means of a computer (693 patients) - 3 new probands.

From the 21 probands a total of 124 patients with hereditary macular degeneration, 95 of them residing in the county of Västerbotten, were traced. This search included a total of 241 ophthalmologically examined individuals. PCMER made it possible to establish a connection between 102 of the 124
subjects traced, 75 of them residing in the county of Västerbotten.

A urinary metabolic study of 40 affected and 40 non-affected subjects in the same family was done in an attempt to confirm results presented by Lefler et al. (1971) concerning an association between hereditary macular degeneration and aminoaciduria (III).

**PCMER as a means of tracing sight defects**

PCMER are unique for Sweden, Finland and to some extent the Baltic countries, that is for countries belonging to Sweden during the so-called "stormaktstiden" (great power period) (1611-1718). In Sweden PCMER and other parish records are collected in provincial archives. Microfilmed copies are available at county libraries. PCMER from a given parish contain a great deal of information about the parishioners, such as removal into and departure from the parish, occupation, character, intellectual capacity, and ability to read (Johansson, 1973; Widén, 1973). Sometimes there are marginal notes, for instance 'weaksighted' as an explanation of why a parishioner could not learn to read. In Sweden information from parish records is now being collected in a "demo- graphic data-base" to be used for various research purposes (Johansson & Åkerman, 1973). The information in the parish records on the woman who brought the disease into the pedigree1-family according to I, Fig. 1 (III:5) is obscure. Her birth-year varies in different records, and it was difficult to find information about her birth-place. Data on her and four of her seven children in PCMER, however, indicate that they probably had impaired visual acuity. It was therefore of great interest to establish who this woman really was and where she came from. Although she had been married twice before, she had only one
child from the earlier marriages. When consulting the parish records regarding her first marriage, it was finally found that she was a daughter of a settler in the village of Hacksjö in the parish of Vilhelmina. By tracing the descendants of other children of this settler, it was possible to connect most families with an autosomal dominant hereditary macular degeneration in the population into one family.

RESULTS AND CONCLUSIONS

The two pedigrees in the first paper (I) are incomplete. Many new cases were found by continued investigations (II). One of the original cases in the first survey (I, Fig. 2, V:6) was not accepted as a case of hereditary macular degeneration in a renewed examination. The theory about illegitimacy in family 2 (I) was proved to be erroneous. The chief result of the first study was the demonstration that it is possible to use PCMER as sources of information useful for tracing persons in earlier generations suspected of having impaired visual acuity.

A short summary of the results of the population survey (II) will be presented here:

1. The Vilhelmina-family Pedigrees 1-3

   **Diagnosis:** Hereditary macular degeneration
   **Inheritance:** Autosomal dominant
   **Expressivity:** Very variable
   **Penetrance:** High but not complete
   **Age of onset** (deterioration of sight): Any age from early childhood to after the age of 50. A bimodal distribution with one maximum before and one after puberty.
Number of cases: 125, 65 men and 60 women. 23 are dead, 27 do not reside in the county of Västerbotten. An under-representation of trait-carriers in later generations indicates that there may be about 30 more subjects who will be affected later (when they reach their age of onset).

Genealogy: The disease has been traced back to a settler in the parish of Vilhelmina in the 18th century, descendant from the province of Dalecarlia (county of Kopparberg), and probably related to a Dalecarlian family with hereditary macular degeneration (Barkman, 1961).

Convergent strabismus with irregular dominant inheritance, weak penetrance, and variable expressivity occurs in the family.

2. Pedigree 4

Diagnosis: Hereditary macular degeneration  
Inheritance: Autosomal dominant?  
Number of cases: 3 - son, mother and grandfather. The grandfather does not reside in the county of Västerbotten. The degeneration is unilateral in the son.

Genealogy: The family is descendant from the county of Jämtland. It has been traced to the beginning of the 19th century. No connection with the Vilhelmina-family has been found. However, this family may also be related to the Dalecarlian family (Barkman, 1961).

3. Pedigree 5

Diagnosis: Hereditary senile (?) macular degeneration  
Inheritance: Autosomal dominant?  
Number of cases: 3 - son, father and grandmother. The degeneration in the son is regarded as incipient.

Genealogy: The family has been traced back to the beginning of the 19th century. Västerbotttnian ancestry. No connection with the Vilhelmina-family has been found.
4. **Pedigree 6**

   **Diagnosis:** Hereditary macular degeneration.
   Stargardt's disease (flavimaculatus with atrophic macular degeneration)?
   **Inheritance:** Autosomal recessive? (autosomal dominant?)
   **Number of cases:** 3 - two brothers and a son of one of them. The son may have macular degeneration caused by a cerebral atrophy.
   **Genealogy:** The family is traced to the beginning of the 19th century. Västerbottian and Finnish ancestry.

5. **Pedigree 7**

   **Diagnosis:** Hereditary macular degeneration
   **Inheritance:** Autosomal recessive?
   **Number of cases:** 3 - brother and sister and a daughter of a first cousin. The brother and the sister both have diabetes mellitus. There are no signs, however, of retinopathia diabetica. Their parents are first cousins

6. **Pedigree 8**

   **Diagnosis:** Hereditary macular degeneration
   **Inheritance:** Autosomal recessive?
   **Number of cases:** 2 - male first cousins

7. **Pedigree 9**

   **Diagnosis:** Hereditary macular degeneration (tapetoretinal degeneration?)
   **Inheritance:** Autosomal recessive?
   **Number of cases:** 2 - male and female cousins - the female does not reside in the county of Västerbotten.
   **Genealogy:** This family is fairly inbred. It has been traced to the 18th century. The two affected subjects are first cousins, as their fathers are brothers. Nothing, however, suggests inheritance of the macular degeneration from their fathers. Through their mothers the two subjects are both second and fourth cousins.
8. Pedigree 10
**Diagnosis:** Hereditary macular degeneration
**Inheritance:** Autosomal recessive?
**Number of cases:** 2 - brother and sister

9. Pedigree 11
**Diagnosis:** Hereditary macular degeneration
**Inheritance:** Autosomal recessive?
**Number of cases:** 2 - brother and sister

10. Pedigree 12
**Diagnosis:** Hereditary macular degeneration - central choroidal sclerosis?
**Inheritance:** Autosomal dominant?
**Number of cases:** 2 - father and son

In 7 cases, 2 men and 5 women, with the diagnosis "hereditary macular degeneration" or "macular degeneration of a hereditary type", no inheritance was found.

The occurrence of hereditary macular degeneration in the county of Västerbotten is estimated to about 0.4 per thousand. The "Vilhelmina-degeneration" occurs in more than 0.3 per thousand in the population. The frequency of the gene inducing macular degeneration in the Vilhelmina-family is estimated to 0.2 per thousand.

**Urinary metabolic studies (III)**

A prominent association between aminoaciduria and an autosomal dominant type of hereditary macular degeneration was observed by Lefler et al. (1971). An attempt to confirm their results was made at the Department of Paediatrics, University Hospital, Umeå. Urinary metabolic studies by means of high-voltage paper electrophoresis (HVPE) and some qualitative chemical
tests were performed in 40 affected and 40 non-affected members of pedigree 1 (II). A normal pattern on HVPE and negative reactions in all qualitative chemical tests were found in all urine samples. Consequently, the results published by Lefler et al. were not confirmed.

Migration

Macular degeneration in the Vilhelmina-family has been traced to a settler, descendant from the province of Dalecarlia, and probably related to a Dalecarlian family with hereditary macular degeneration (II). The disease has been found in 125 of the descendants of this settler, who moved to the parish of Vilhelmina in the 18th century. Seven of the affected members of the family still reside in the Vilhelmina-region, one of them (6th generation) in the same village as the original settler. 24 subjects, all of them descendants of a son of the settler, reside in the Storuman-region. 13 subjects, all of them descendants of a daughter of the settler, reside in the Åsele-region. 20 subjects are residents of the Umeå-region, 11 subjects live in other parts of the county of Västerbotten and 27 subjects in other parts of Sweden. 23 subjects were dead when the survey was finished (II, Fig. 6, Table 7). Still more patients with hereditary macular degeneration, related to the Vilhelmina-family, may be discovered in other counties in Sweden. For example, many members of the 4th generation (II, pedigree 3) departed to the county of Jämtland in the 19th century.

In the last half of the 19th century and the beginning of the 20th century, many Swedes emigrated to America. Among the emigrants from Västerbotten were members of the Vilhelmina-family. American
reports on hereditary macular degeneration are mostly concerned with the northern states in which there are many inhabitants of Swedish stock. An Iowan family reported by Braley and Spivey (1964) has a Dutch ancestry. A Swedish ancestry cannot be excluded in some of the other families reported (Fall, 1949, Michigan, Davis & Hollenhorst, 1955, Minnesota, Krill et al., 1966, Illinois, Vail & Shoch, 1965, Illinois).

Genetic counseling

Persons affected with unfavorable traits and their close relatives naturally wish to know whether their future children are likely to have the same traits. Unfortunately, and quite unnecessarily they sometimes experience a sense of shame at having such traits in their family. They feel uncertain and their lack of knowledge about inheritance worries them. Such persons ought to have the opportunity of discussing the problem with competent medical geneticists, who often can give them reassuring information.

The results in this dissertation should be of some value as a basis for genetic counseling, especially in the Vihelminna-family. The macular degeneration in this family may lead to many problems due to loss of central vision. The disease is, however, never so grave that it is genetically inadvisable to have children, even if there are risks of transmitting the unfavorable gene.

When the inheritance of a genetic trait is dominant, affected persons will transmit the allele to one-half of their children. Irregularity of phenotypic expression, however, implies that macular degeneration may appear among the offspring even if the parents are non-affected.
Final comments

The Vilhelmina-family represents a unique material for further investigations of hereditary macular degeneration. In 102 affected members the same gene has very variable phenotypic expression. Further, about 30 members of the family probably have the gene, but have not yet developed the disease.

Classification of hereditary macular degenerations as well as other forms of macular degeneration according to the anatomic structures involved, has been suggested by many authorities (Blodi, 1966; Braley, 1966; Maumenee & Emery, 1972). Eyes with macular degeneration obtained for histologic study, however, mostly come from patients of advanced age. Consequently, pathologic studies are mainly concerned with senile macular degenerations (Vail & Schoch, 1965; Heinrich, 1973). There is a scarcity of early histopathologic material (Maumenee, 1971; Blach, 1973).

In the Vilhelmina-family, many eyes could be obtainable for histological studies. The ophthalmologist should arouse the patient's "... interest in donating his eyes for research. He should stimulate the relatives and family of the patient to do the same" (Braley, 1966).

Fluorescence angiographic, electroretinographic, and electrooculographic studies are also recommended in the literature. (Krill, 1966; Francois, 1971; Merin & Auerbach, 1970; Hammerstein, 1971; Schwartz et al., 1971; Hilsdorf, 1972; Schmidt, 1973; Eriksson & Forsius, 1973).

Investigation of the possibilities of medical treatment of the disease should be furthered. Barkman (1961) observed improvement of vision after steroid treatment. Braley and Spivey (1964) agree that "... the administration of systemic steroid
may have certain beneficial effects. If the end result is not good central vision, it may delay the severe visual loss until a later date". It has, however, been suggested that the improvement reported by Barkman may be due to spontaneous alterations (Remky et al., 1965).

Visual aids can greatly assist patients with macular degeneration. There is, however, need for much more training of the patients in order to get successful results with such appliances. A recent study with close circuit television indicates that this may be an extremely effective aid in the future (Silver, 1973).
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REFERENCES


APPENDIX

SOME EARLIER DIAGNOSES IN PATIENTS WITH HEREDITARY MACULAR DEGENERATION IN PEDIGREES FROM THE COUNTY OF VÄSTERBOTTEN

<table>
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