Choroideremia in a Female

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[WITH COLOUR PLATE ON FACING PAGE]

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It is generally accepted that the choroidoretinal degeneration known as choroideremia is under the control of a gene transmitted on the X chromosome. The fully developed condition is confined to males who present with progressive visual loss. The age of onset, speed of progression, and degree of this visual loss are all variable, but it is to be expected that an affected male will have serious visual disability at least in adult life. Characteristic minor abnormalities of the fundus have been described in heterozygous females and they may progress to cause a mild degree of visual loss in adult life (Kurstjens, 1965; Krill, 1967); the disability in such carrier females is, however, never severe, nor do the fundus appearances develop to the stage seen in affected males. In this communication a case of advanced choroideremia causing serious visual loss from early childhood is described occurring in a female. The family history (see family tree) is consistent with the hypothesis that she is a heterozygote for the gene causing choroideremia who manifests the condition in very severe form.

Clinical Findings

The *proposita* (IV 2) was ascertained during a survey of the causes of visual handicap among 776 children in special schools in England and Wales. An extensive report of this study has appeared (Fraser and Friedmann, 1967), and the *proposita* is Case A 107 of that report. At the time of ascertainment she was 20 years old and was completing her education at a technical college for children with severe visual handicaps. Her poor vision had been noted at the age of 3 years after a bout of pneumonia; the disability had always been aggravated at night and was accompanied by photophobia. With some difficulty she had followed a normal course of education to the age of 14, at which time she had moved to a school for partially sighted children, whence she had been transferred to the school where she was first seen by us.

She had been noted to be myopic and had worn glasses from the age of 9, when her visual acuity was 6/36 in each eye, which could be corrected with glasses to 6/18 (right) and 6/12 (left). At the age of 14 her corrected visual acuity was only 6/60 in the right eye and remained 6/12 in the left. At that time an extensive choroidoretinal degeneration was seen, and it was noted that her fields of vision were very restricted. At the time of our examination at the age of 20 the findings were typical of advanced choroideremia (Colour Plate, Fig. 1).

In view of this exceptional occurrence of choroideremia in a female an extensive family study was undertaken. The similarly affected male relative (III 14) was visited; he too had appearances typical of advanced choroideremia (Colour Plate, Fig. 2). He dated the onset of his visual trouble at the

age of 20 years. Initially his disability was greater at night. When seen at the age of 54 he still managed to remain in employment, though with some difficulty. His corrected visual acuity was 6/36 in the right eye and 6/60 in the left and his fields of vision were extremely restricted. Two other male relatives of the *proposita* (I 1; III 10) had had visual symptoms consistent with choroideremia but were not alive at the time of the family study.

A total of 18 female relatives of the *proposita* were seen, and of these six showed fundus appearances characteristic of the carrier state for choroideremia (see Colour Plate). Only one of these (II 6) had had objective visual difficulties, apparently since early adult life. At the time of examination, however, she was 85 years old and still had excellent vision in the right eye. Her left eye had always been amblyopic and she had been inconvenienced for many years by photophobia, on account of which she wore tinted glasses. It should be noted that all four females in this pedigree who are obligate heterozygotes, in that they are mothers or daughters of affected persons (II 2, II 6, III 7, IV 9), showed fundus changes characteristic of the carrier state.

Karyotype Studies

The occurrence of a sex-linked condition, usually found only in males, in the daughter of a heterozygous female and of a normal male may most readily be explained on the basis of an abnormality of the X chromosomes of the type of Turner's syndrome. Such an explanation was, *a priori*, all the more appealing in this case, since IV 2 had had only two periods at the age of 16 years. There were several points, however, militating against a diagnosis of Turner's syndrome. Though short, she was not excessively so (5 ft.; 152 cm.), and in fact apart from her menstrual irregularity she showed no signs or symptoms usually associated with this condition.

LEGENDS TO PLATE

Fundus photographs of the girl (IV 2) and her affected male cousin (III 14) contrasting the findings in fully developed choroideremia with the minor changes characteristic of heterozygotes—in this case the mothers of the two affected individuals III 7 and II 6.

FIG. 1; IV 2. The mid-periphery of the fundus, showing the typical pale background with some isolated pigment.

FIG. 2; III 14. The disc is crowded and surrounded by a pale fundus with the typical red macular area.

FIG. 3; III 7. The right superior quadrant with white dots and a fine pigment dispersion, more marked near the vessels.

FIG. 4; II 6. Fine pigmentary changes around the disc, at the macula, and near the retinal vessels.

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FIG. 1

FIG. 2

FIG. 3

FIG. 4

Furthermore, the results of a diagnostic uterine curettage at the age of 20 showed "endometrial hyperplasia with a typical swiss-cheese pattern," which is not the appearance usually associated with Turner's syndrome. Nevertheless, extensive studies were made of her chromosomal status. They all afforded normal results. In particular, she had normal amounts of sex chromatin bodies in buccal smears and skin fibroblast cultures, and repeated examination of chromosome preparations derived from both blood and skin did not show any deviation from a normal female karyotype.

Discussion

The finding of manifesting heterozygotes in a wide variety of X-linked conditions normally occurring only in males has been interpreted as providing support for the Lyon (1961) hypothesis of the random inactivation of one X chromosome of females of some mammalian species, including mouse and man. However, clinical involvement of heterozygous females has on the whole been moderate, and cases in which the severity of these conditions in such females has been comparable to that seen in affected males are rare. Examples have been reported of severely affected and presumably heterozygous females in the case of haemophilia A and B (Kerr, 1965; Whissell, Hoag, Aggeler, Kropatkin, and Garner, 1965; Rozman, Castillo, Ribas-Mundo, and Surós, 1967), protan and deutan types of colour blindness (Franceschetti *et al.*, 1963), and glucose-6-phosphate dehydrogenase deficiency (Beutler, Yeh, and Fairbanks, 1962). Another possible condition in which fully affected female heterozygotes may occur is Pelizaeus-Merzbacher disease (Merzbacher, 1910; Spielmeyer, 1923; Zeman, Demyer, and Falls, 1964), but sex-linked inheritance is not unequivocally demonstrated in this disease.

It is noteworthy that the fully mutant phenotype has not been previously described in heterozygous females in the case of various sex-linked conditions affecting primarily the retina—ocular albinism, choroideremia, and a group of choroidoretinal dystrophies allied to retinitis pigmentosa—though patchy and partial involvement of the ocular fundus is common. In the case of choroidoretinal dystrophies allied to retinitis pigmentosa, families have been described in which clinical manifestations of some severity occurred in female heterozygotes (Merritt, Myers, and Wilbrandt, 1963; Hoare, 1965), but in no case were these females affected as seriously

as males. Similar partial involvement of adult females has been reported in the case of choroideremia (Kurstjens, 1965; Krill, 1967); the two alleged examples of fully affected females (Grimsdale, 1917; Shapira and Sitney, 1943) cannot be evaluated, since neither clinical nor family information is adequate.

It has been suggested that the expression of the mutant phenotype in heterozygous females is due to the fact that by chance all the X chromosomes bearing the normal allele are inactivated. This suggestion implies the subsidiary hypothesis that the number of precursor cells present at the time of random inactivation must be small; thus, if these are as many as 20, the chance of all the normal alleles being inactivated is only $1/2^{20}$, or approximately one in a million. This explanation is not entirely satisfactory and other suggestions have been made. Some of these are quite independent of the Lyon hypothesis, such as absence of one X chromosome (XO karyotype), illegitimacy (probably in the case of a rare condition accompanied by incest), and mutation of the paternally derived normal allele so that the affected female is a homozygote rather than a heterozygote. The last two explanations must be regarded as, *a priori*, highly unlikely and the first has been excluded in the present case.

It is not, however, possible to exclude the possibility of a subtler abnormality of the X chromosomes in Case IV 2. Thus, for example, she may be a XX/XO mosaic, with loss of the paternally derived X chromosome in the eye tissues but without detectable mosaicism in circulating leucocytes and skin fibroblasts. Then, again, it may be that she is the product of the fertilization of an XX ovum in which homozygosity has occurred at the choroideremia locus by a process of non-disjunction during the first or second meiotic divisions (Stern, 1959). Such fertilization might have been by a X-chromosome-carrying sperm or by a sperm which had lost its sex chromosome.

In the first case the paternally derived X chromosome may have been lost at an early mitotic division, and the XX cells subsequently may have outgrown the XXX cells; the possibility cannot be excluded, however, of undetected XX/XXX mosaicism. This mechanism is formally equivalent to that proposed by de la Chapelle, Hortling, Wennström, Niemi, and Johansson (1965) as an explanation for their finding of two males with XX sex-chromosomal constitution by the loss of a Y chromosome from a hypothetical XXY zygote. It is of some interest to note that in both these cases studies using the Xg blood group showed that both X chromosomes

Pedigree of family in which a female heterozygote (IV 2) manifests choroideremia. This girl is Case A107 of the report of Fraser and Friedmann (1967) and we are much indebted to the Johns Hopkins Press for permission to reproduce this pedigree from that publication.

were maternally derived. This blood group was determined also in the present family, but the findings were non-contributory, since the proposita and her parents were all of the phenotype Xg(a+).

The second case implies the fertilization of an abnormal ovum by an abnormal sperm. This coincidence may not be as unlikely as it seems, since there may be some means whereby the fertilization of XX ova by sperm lacking a sex chromosome is favoured, so that the occurrence of zygotes with an unbalanced sex-chromosome complement is minimized.

Yet another possible explanation of the loss of the paternally derived normal allele at the choroideremia locus which does not necessarily invoke the Lyon hypothesis is that suggested by Ferguson-Smith (1966). This is based on the hypothesis that parts of the X and Y chromosomes are homologous and that interchanges may take place between them during meiosis, giving rise to a sperm carrying an X chromosome of which part, including the choroideremia locus, has been replaced by a piece of Y chromosome not carrying the normal allele in question.

The hypotheses of an undetected cytological abnormality of the X chromosomes and of inactivation may also be combined. Thus in man it is probable that abnormally constituted X chromosomes—for example, isochromosomes—are uniformly rather than randomly inactivated, while in the mouse the converse situation has been described (Lyon, Searle, Ford, and Ohno, 1964) in that in the presence of a certain X-autosomal translocation the normal X chromosome is uniformly inactivated. While the X chromosomes of IV 2 seemed to be normally constituted, a minor abnormality of one of them leading to uniform inactivation of the paternally derived X chromosome cannot be excluded.

Lastly, it remains to consider the possibility that the clinical history in the case of IV 2 could be a result of the aggravation of the usual minor manifestations of choroideremia in heterozygotes by other factors, whether genetical or environmental. For example, modifying genes could exist whose effect interacts with that of the abnormal allele for choroideremia. Again, IV 2 was premature—her birth weight was 3 lb. 4 oz. (1,475 g.)—but, in fact, no untoward events in the perinatal period such as might affect the development of the retina were reported; unfortunately the hospital notes concerning this birth are not available.

Whatever the mechanism of the production of choroideremia of this girl, it is clear that this entity must be added to the growing list of conditions in the human species in which the mutant phenotype occurs in the probably heterozygous female. Grüneberg (1967a), in his critique of the Lyon hypothesis as applied to man, has suggested that there is no evidence that heterozygotes for X-linked genes as a whole show any greater variability than heterozygotes for autosomal recessive conditions, and indeed it is undoubtedly true that normal overlaps are common in both cases. In the case of autosomal recessive conditions in man, however, there is no authenticated example of a heterozygote manifesting the fully mutant phenotype, and the occurrence of such a phenomenon in the case of choroideremia and other sex-linked conditions demands an explanation whether in terms of the Lyon hypothesis, in terms of the hypothesis of

partial inactivation of both X chromosomes advanced by Grüneberg (1967b), or in yet other terms.

Summary

A family affected by an intermediate recessive sex-linked disease, choroideremia, is described in which a female carrier is as severely affected as the male, whereas usually such females show minimal visual and retinal changes. Though the genetic mechanism of the production of this condition in a female carrier cannot be exactly defined, some possible explanations are discussed, especially with reference to the Lyon hypothesis of the inactivation of one X chromosome.

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