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Von Hippel–Lindau Syndrome: A Report on Three Kindreds

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Von Hippel–Lindau syndrome is characterized by angiomatous cysts of the retina, cerebellum, abdominal organs (principally the kidneys and pancreas), and epididymis. Von Hippel (1904) first described angiomatous formation in the retina. Lindau (1926) was the first to recognize the related occurrence of haemangioblastomata of the cerebellum and abdominal organs. Phaeochromocytoma with hypertension has been reported in some patients (Chapman and Diaz-Perez, 1962).

The angiomatous cysts in both retina and cerebellum have been attributed to proliferation of mesodermal remnants with intimately related ectodermal changes (Michaelson and Hill, 1949). Cerebellar tumours engender a rise in intracranial pressure with the usual sequelae as well as specific neurological loss with localizing signs (Cushing and Bailey, 1928), while retinal cysts ultimately result in blindness (Rados, 1950). The combination of hypertension with angioma may lead to subarachnoid haemorrhage. The response to therapeutic irradiation is variable (Isaac, Schoen, and Walker, 1956), and the prognosis is usually poor. The clinical aspects of the syndrome were comprehensively reviewed by Melmon and Rosen (1964).

The familial nature of the syndrome has been noted and autosomal dominant inheritance suggested as the likely mode of transmission (Pratt, 1953). In this communication three independent cases are reported, one from an extensive kindred with seven affected individuals. The modes of inheritance seem to include simple autosomal dominance, autosomal dominance with incomplete penetrance, and autosomal recessive transmission.

Present Investigation

Our patients who came for genetic counselling included the following cases.

Case 1. A 26-year-old man displayed the salient features of the syndrome. By the age of 25, he had undergone 14 ocular operations for retinal cysts and was completely blind in both eyes. He had had six craniotomies performed between the ages of 18 and 24 for excision of cerebellar tumours. Pathological examination revealed, as expected, benign haemangioblastoma. For the past two years he has been under radiotherapy with no evidence of recurrence. The father of the propositus had recurrent haemangiomata of the cerebellum which required repeated operations. Before his recent death, at age 48, he had been incapacitated for some 12 years. The pedigree is shown in Fig. 1.

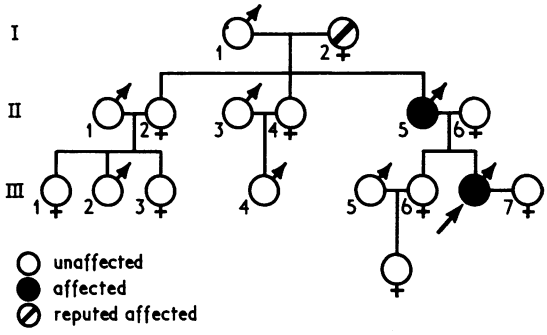

FIG. 1. Pedigree of Case 1 showing autosomal dominant inheritance.

Case 2. A 40-year-old man in whom the most prominent manifestation of the syndrome has been cerebellar cysts which first presented as severe headaches and spells of drowsiness 12 years ago. Three intracranial operations were required for the relief of the symptoms of these space-occupying lesions. Retinal involvement was limited to transient papilloedema associated with raised intracranial tension. This was promptly relieved after excision of the cerebellar cysts. Examination of the parents of our patient (II.6 and II.7, Fig. 2) revealed no detectable clinical or radiological sign of the disease.

Case 3. A woman of 22 years: the most salient feature of the disease in this case has been retinal involvement. Her visual problems date as far back as the age of 12 years. She is already completely blind. Only

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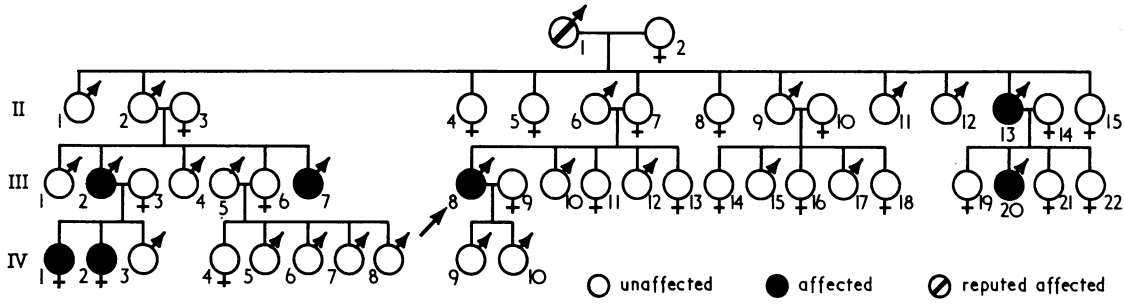

FIG. 2. Pedigree of Case 2 showing autosomal dominant inheritance with incomplete penetrance.

lately has she begun to complain of vague headaches; neurological examination has disclosed no evidence of intracranial lesions.

The above three families were investigated and the clinical and radiological findings verified on all the affected and other relevant individuals by the author.

Discussion

The above cases are presented for two reasons. First, the mode of inheritance of Von Hippel–Lindau syndrome has been considered to be autosomal dominance as indeed is the situation in the family of Case 1 (Fig. 1). As shown in Fig. 2, autosomal dominance with incomplete penetrance also seems to be the mode of transmission in the family of Case 2. However, in the family of Case 3, in Fig. 3, autosomal recessive inheritance appears to be the most feasible form of transmission to account for the observed findings.

No consanguinity could be ascertained but there was a complete absence of the manifestations of the disease in the parents, grandparents, or more distant ancestors of our proposita (index case). It is extremely unlikely that the appearance of the trait in Case 3 represents the advent of a new mutation, since the same disorder manifests elsewhere in the family. Two sibs (V.2 and V.7, Fig. 3) who are second cousins of our patient, suffer from the affliction, and both developed retinal and cerebellar angioblastomas in their late teens. In this regard, it is noteworthy that, (a) they are the offspring of a consanguineous mating (parents are second cousins); (b) neither their parents nor any of their ancestors seem to be affected; (c) 2 out of 6 members in this sibship are affected, a frequency that does not deviate significantly from the predicted ratio of 1 in 4 based upon autosomal recessive inheritance.

This pedigree shows convincingly that autosomal recessive inheritance can operate as an alternative mode of transmission of Von Hippel–Lindau syndrome. It further illustrates that even if hitherto a condition has always been known to follow a certain type of inheritance, the risks of recurrence quoted to the patient or relatives as well as the genetic counselling rendered should be based upon a thorough analysis of the particular pedigree in question.

Secondly, the cases are of further interest because

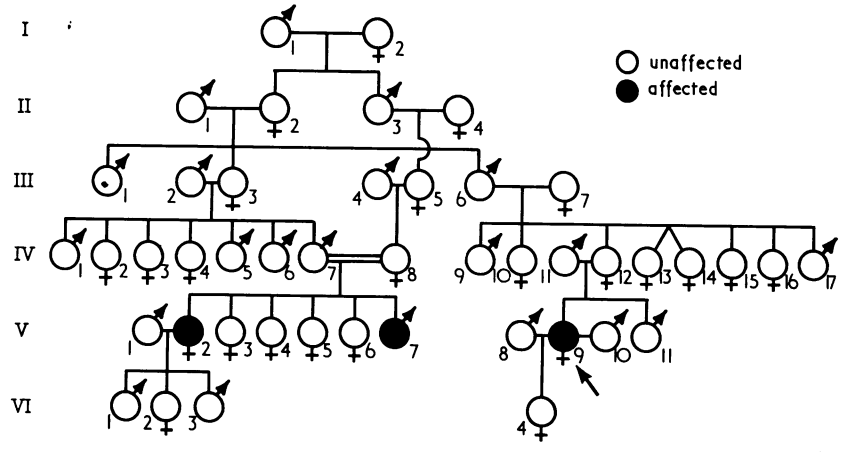

FIG. 3. Pedigree of Case 3 showing autosomal recessive inheritance.

the variable expressivity, for which the syndrome has been noted, is clearly shown by comparing its manifestations in the three index cases. Whereas blindness and cerebellar tumours appear to be the prominent features of the syndrome in Cases 3 and 2, respectively, Case 1 combined both manifestations. Further, in the family of Case 2, IV.1 and IV.2 (Fig. 2) suffered blindness as a result of recurrent angiomatous cysts of the retina at the ages of 26 and 24 years, respectively, without any evidence of cerebellar implication.

Summary

Three independent pedigrees showing transmission of Von Hippel–Lindau syndrome are reported. Autosomal recessive inheritance seems operative in one case. This is in contrast to the mode of inheritance hitherto reported, namely, autosomal dominant transmission. Variable expressivity of the syndrome is also noted.

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