Genetics and Neurology

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Foreword

'Reading maketh a full man, conference a ready man, and writing an exact man.'

Francis Bacon

Because of its extreme complexity it is not surprising that so many of the disorders which affect the nervous system should have a genetic basis. The establishment of a precise diagnosis is all important and often calls for considerable skill and experience both in neurology and genetics. Though developments in biochemistry, and more recently in recombinant DNA technology, are beginning to provide precise and objective diagnostic tools for some of these disorders, clinical acumen still remains of paramount importance. Few are better qualified than Dr Sarah Bundey to review this complicated field for she is not only a practising medical geneticist but has also researched widely in neurology over many years. The result is a scholarly yet compact work which should be especially useful to medical geneticists and neurologists in training as well as to others who, from time to time, may be required to give genetic counselling in one of these disorders.

1985 A.E.H.E.

Preface

I have directed this book to clinical geneticists and to registrars in paediatrics, neurology and genetics, and have assumed that they have a basic knowledge of genetics. The book is meant to provide practical information regarding clinical delineation of different entities, their genetic mechanisms, and the recurrence risks useful for genetic counselling. I have aimed to interest neurologists in some of the intricacies and fascination of genetics and I have tried to simplify for clinical geneticists and paediatricians the clinical distinctions between different neurological diseases. In some instances the genetics of a particular disorder are unclear, and where this is so I have given my own assessment and interpretation of existing data rather than present every controversial aspect. Although the book is largely intended for doctors in training I hope that consultant neurologists, to whom the clinical descriptions of diseases will appear superficial, will find the risks of recurrence useful.

I have not attempted to enumerate the many neurological genetic disorders that have been described in single families, unless there is a particular interest in their biochemistry or natural history, or to the differential diagnosis from another somewhat similar disorder. The exception is that I have attempted to list all X-linked disorders in Appendix 3. This is because in advising female relatives of an isolated male patient it is important to consider whether or not his condition could be X-linked.

Neurological genetics is a diffuse subject and not all aspects can be covered in a book of this size. I have chosen to omit the amino-acid disorders; the organic acid disorders; multiple malformation syndromes; psychiatry (apart from dementia) and mental deficiency since these are well covered in other books. Most of the methodology relating to practical clinical genetics is to be found in Emery's *Methodology in Medical Genetics*, an earlier book in this series, published in 1976. However I have discussed two further aspects of genetic methodology in Appendices 1 and 2.

I am very pleased that Dr E. M. Brett was able to contribute: his wide experience of degenerative disorders in children will make his chapter very valuable.

Finally, I must record my gratitude to the late Professor C. O. Carter, who taught me the importance of precision in genetics, how to carry out genetic studies and how to assess critically the studies of others.

1985 S. B.

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Contents

1

Malformations of the central nervous system

Introduction

Malformations of the central nervous system are relatively common, occurring in 3 to 4 % of early spontaneous abortuses (Creasy & Alberman 1976) and in about 0.6% of births in the U.K. (Leck 1974). Congenital malformations of the brain are found at autopsy in between 20 and 30% of mentally retarded patients (Freytag & Lindenberg 1967).

The gross malformations have started to appear by the end of the third month of gestation and must therefore be caused by factors acting early in pregnancy. The first embryological landmark is the development and then the closure of the neural tube which occurs between 18 and 28 days after ovulation. Posterior defects in the neural tube give rise to anencephaly, spina bifida and related malformations; while anterior defects produce the holotelencephaly group of malformations. The cerebral and optic vesicles and the choroid plexus start to form at four to five weeks' gestation and soon afterwards the primordia of the cerebellum appear. The ventricles are well formed by about eight weeks and the corpus callosum develops at about 10 weeks. From about five to 25 weeks' gestation there is cellular migration and proliferation; abnormalities in these processes lead to the formation of abnormal gyri, to ectopic positioning of nervous tissue (cortical and cerebellar heterotopias) and to the development of phakomas and other cerebral tumours. From 25 weeks of gestation until one to two years of postnatal life, there is cellular maturation, the formation of synapses, the development of specific cellular patterns in different parts of the brain, and myelination. Noxious influences at this time produce defects in cellular architecture and in myelination, and from about seven to nine months of gestation will cause destructive or degenerative changes rather than developmental abnormalities. For reviews of the embryology of the nervous system see Hamilton et al (1972) and Gabriel (1974).

Many malformations of the nervous system carry no recurrence risks. Attention will primarily be given in this chapter to those conditions where there is a risk of the same malformation occurring again in relatives. For more comprehensive reviews on congenital malformations see Warkany et

al (1981) and Bergsma (1973). Multiple malformation syndromes will not be covered in this section, for they also have been adequately reviewed elsewhere (Holmes et al 1972; Smith 1982).

ABNORMALITIES OF CLOSURE OF NEURAL TUBE

These malformations include anencephaly, iniencephaly, encephalocoele, myelomeningocoele and meningocoele but not isolated hydrocephalus. They arise as a result of failure of the neural groove to form a tube and close at each end, a procedure which normally occurs between 18 and 26 days after ovulation (Hamilton et al 1972). Thus, any teratogens which may cause neural tube malformations must act during this short period. Epidemiological and genetic studies have shown that the malformations are aetiologically related, in that an increased incidence of one is accompanied by a similar increase in the others, and that the increased risk that occurs for relatives of patients with one of these malformations is for any of the other malformations as well as for the same one. Therefore they are usually grouped together as neural tube defects, or NTD.

It has been shown that spinal dysraphism (Carter et al 1976) and multiple congenital vertebral anomalies (Wynne-Davies 1975) should also be included as neural tube defects, since the incidence of anencephaly and spina bifida in first degree relatives is as high in these conditions as if the index patient had anencephaly or spina bifida. However, they have not been included in earlier epidemiological studies.

The incidence of neural tube defects varies from one area to another and also from one race to another (Table 1.1). It is interesting that on migration, races tend to keep the incidence of their country of origin.

Genetics

The pattern of recurrence of neural tube defects in the families of index patients demonstrates that this group of malformations is polygenically

Table 1.1 Some incidences of neural tube malformations per 1000 Births (data from Carter et al 1968; Leck 1972; Carter & Evans 1973)

South-East England (London)	2.9
Wales	7.6
Northern Ireland	8.9
Northern India	6.0
Egypt (Alexandria)	5.4
Africa	<1.0
Japan	<1.0
English in Birmingham	3.7
Irish in Birmingham	5.6
Indians in Birmingham	4.3
Negroes in Birmingham	1.0
Whites in U.S.A cities	2.4
Blacks in U.S.A. cities	0.9

Table 1.2 Incidences of neural tube malformations in relatives (data from studies in South-East England: Carter & Evans 1973; Carter 1976)

Full sibs	1 in 22
Half sibs	1 in 50
Children	1 in 22
Aunts, uncles, nephews, nieces	1 in 70
Cousins*	1 in 148
Incidence in population from which index patients came	1 in 340

* in fact, mothers' sisters' children

inherited (Carter et al 1968; Carter & Evans 1973). For example, in South-East England (Table 1.2) the incidence in first-degree relatives is about 1 in 22, that is, about 15 times the population incidence; the incidence in second-degree relatives is about five times the population incidence and the incidence in third-degree relatives is about twice that of the population.

The family studies show that, on average, 60 to 70% of the causation of neural tube defects is genetic, leaving about 20 to 30%, which on average is due to environmental factors. It is now clear that one of the environmental factors that can cause the development of a neural tube defect in a fetus which is genetically predisposed is poor nutrition. Periconceptional dietary supplementation by vitamins has been shown to prevent the recurrence of neural tube defects in the offspring of women at high risk, that is, those women who have previously had an affected child (Smithells et al 1980, 1983). However, different environmental factors may be important for different individuals and different races.

Prenatal detection of babies with neural tube defects is now largely possible through the measurement of amniotic fluid alpha-fetoprotein in women at increased risk, through measurement of serum alpha-fetoprotein in all pregnant women, and through ultrasound examination of the fetal head and spine.

Meckel syndrome

This is a condition, fatal at or soon after birth, in which polycystic kidneys are present, together with microcephaly or anencephaly, usually an occipital encephalocoele, and sometimes premature fusion of some cranial sutures. Other variable features include eye anomalies (microphthalmia, colobomata), cleft palate, post axial polydactyly, congenital heart disease and abnormalities of genitalia. Necropsy also reveals hypoplasia or dysgenesis of the cerebral cortex and cerebellum and sometimes absence of olfactory bulbs or optic nerves or absence of the corpus collosum (Fried et al 1971; Hsia et al 1971; Meckel & Passarge 1971).

The condition is inherited as an autosomal recessive with a 1 in 4 recurrence risk for sibs. Parental consanguinity has been reported in some families and the condition is perhaps commoner in Jews. Observations from Seller

(1979) suggest that Meckel syndrome may be commoner than previously thought, accounting for 5 to 10% of abnormal fetuses who are aborted because of raised levels of alpha-fetoprotein. She emphasized the need for autopsy of a fetus or infant with a neural tube defect, in order to determine whether other stigmata of Meckel syndrome are present, as the occurrence risk of Meckel syndrome is appreciably higher than the 1 in 20 risk given for uncomplicated neural tube defects. Prenatal diagnosis of the Meckel syndrome is possible, through ultrasonic detection of polycystic kidneys and/or raised levels of alpha-fetoprotein in the amniotic fluid.

ABNORMALITIES OF CLEAVAGE

Holotelencephaly and related malformations

These form a heterogenous group of malformations where the common factor is failure of cleavage of the forebrain. The cerebral anomalies, of which at least one must be present, include: one cerebral hemisphere and ventricle; poorly developed or absent frontal lobes; defective formation of olfactory and optic nerves; and abnormalities of the corpus callosum, hippocampus, basal ganglia, pituitary and hypophysis. Manifestations of these cerebral malformations in the few patients who survive are mental and physical retardation, epilepsy and spasticity. Most patients usually die from complications of associated facial malformations. The most severe of these is the cyclops deformity where there is a single midline eye, and a blindly ending proboscis above this, instead of a nose. The next severe facial abnormality is ethmocephaly where there are two separate orbits, close together, and above them a blindly ending proboscis. Cebocephaly is the condition where there is orbital hypotelorism, a nose in its normal position, but with a single nostril which does not communicate with the nasopharynx. In some patients orbital hypotelorism and trigonocephaly, with or without a cleft lip, may be the only facial malformation; and in the family reported by Khan et al (1970), there were no facial abnormalities, fusion of the cerebral hemispheres and associated malformations being discovered at post mortem.

Genetics

These brain malformations, together with facial and other malformations, have been described in association with trisomy of chromosome 13 or of 18, and the 18p- syndrome. Chromosome studies should be performed in all patients.

Familial occurrence in sibs with normal parents has been occasionally observed when the malformation has been associated with a normal karyotype; for example, holotelencephaly with the cyclops malformation (Cohen & Gorlin 1969); with cebocephaly (James & Van Leeuwen 1970; Holmes

et al 1974); with orbital hypotelorism and a blind ending nose (DeMyer et al 1963; Hintz et al 1968); or without any facial abnormalities (Khan et al 1970). In these familial cases there were no structural abnormalities outside the face and brain. In the absence however of a large series, it is difficult to know what recurrence risk to give for an isolated case with normal chromosomes; probably the recurrence risk is low. In lambs this group of malformations may be environmentally caused (Babbott et al 1962) and teratogenic agents might be responsible for some human cases (Mollica et al 1979).

Septo-optic dysplasia

A related malformation is that of septo-optic dysplasia, in which are present hypoplastic optic nerves, agenesis of the septum lucidum, and secondary hypopituitarism. Reported cases have been isolated but Smith (1982) advises examining close relatives for hypoplastic optic discs.

MALFORMATIONS OF THE CORPUS CALLOSUM AND NEIGHBOURING STRUCTURES

The commissures bearing fibres connecting the two halves of the brain arise from the lamina terminalis, which is the thickened plate at the site of the closed anterior neuropore. The first commissure to be formed (the anterior commissure) connects the two olfactory bulbs. Caudal to this develops a separate hippocampal commissure, which connects the hippocampal areas. This becomes the primordium of the corpus callosum at about the ninth week after fertilization, when fibres connecting the early cortex develop behind it (Hamilton et al 1972; Fig. 1.1). As the cerebral hemispheres

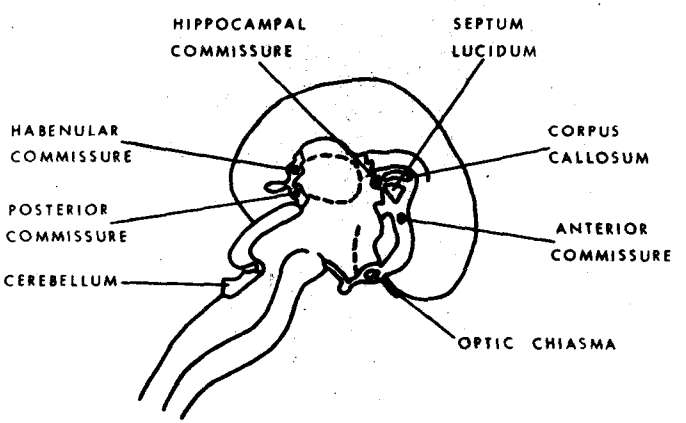

Fig. 1.1 Sagittal section through the brain of a 9-week human embryo (redrawn after Hamilton et al 1972; Fig. 464d, with permission from the publishers MacMillan Ltd)

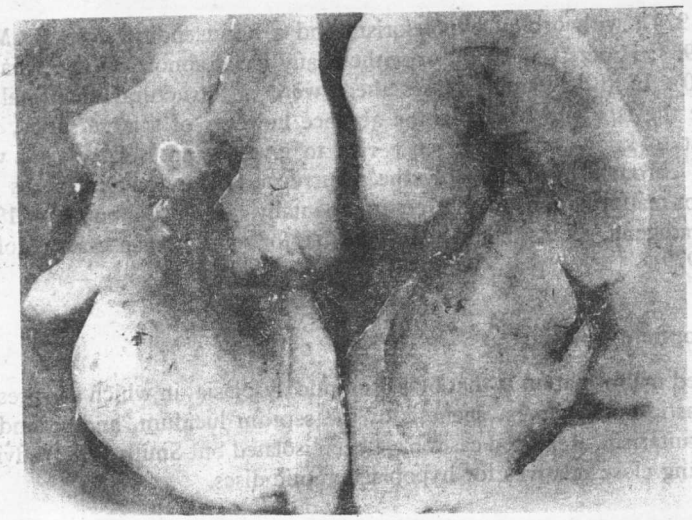

Fig. 1.2 Coronal section through the brain of a 4-day-old male infant who had been born after 28 weeks of a pregnancy complicated by hydramnios. The section shows the absence of any tissue (i.e. corpus callosum) joining the medial surfaces of the cerebral hemispheres in the mid-line

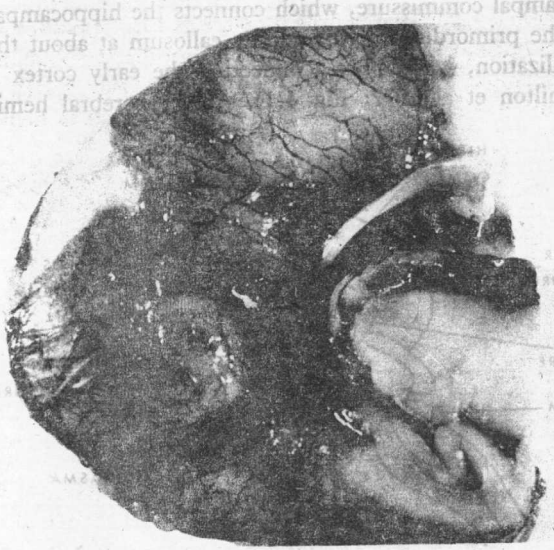

Fig. 1.3 Sagittal section of the occipital pole of the same premature infant as in Figure 1.2 showing absence of the corpus callosum