Genetic diseases in general practice

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SUMMARY. Genetic diseases are important to family doctors. I have analysed my role as a Dutch general practitioner in caring for patients with such disorders and describe this with some examples.

Introduction

THE Expert Committee of the World Health Organization on Human Genetics (1969) in its third report states: "In the present state of medical knowledge the proportion of people in the population who might benefit from genetic advice is not large, but by no means negligible. It is probable that, in all countries, no less than four per cent of all live-born individuals suffer from genetic or partly genetic conditions and might benefit from genetic counselling."

Thus any general practitioner will meet genetic diseases, by which I mean disorders or abnormalities which are wholly or partly due to the patient's genetic disposition.

Types of genetic disease

There are several types of genetic diseases:

1. *Chromosome abnormalities*

An abnormal number of chromosomes or a displacement, inversion, or loss of parts of chromosomes can lead to serious congenital abnormalities, such as Down's syndrome, or spontaneous abortion.

2. *Monogene abnormalities*

These are due to transmission of a mutated single gene or gene pair, and according to Mendel's classical laws they can be transmitted to another generation by a dominant, recessive, or X-chromosomal mechanism. All these monogene abnormalities are rare in general practice, but owing to their genetic pattern they may be seen as a cluster in several members of one family. Many of these diseases involve inborn errors of metabolism, such as cystic fibrosis, phenylketonuria, glucose-6-phosphate dehydrogenase deficiency, and many other rare diseases. McKusick (1975) lists 583 dominant, 466 recessive, and 93 X-chromosomal diseases with a proven heredity factor.

3. *Multifactorial disorders*

These include: malformations at birth, due to several genetic factors and external causes such as spina bifida, anencephaly, club foot, hare lip, and cleft palate; and disorders mainly due to external causes, but where genetic factors also have unmistakable influences. This group includes a large number of more common diseases, such as essential hypertension, ischaemic heart disease, diabetes mellitus, peptic ulcers, atopy and asthma, and rheumatoid arthritis. Usually, these diseases are not present at birth, but appear later in life. Carter (1969) defines a common disease as one which occurs in a population with a frequency of one per cent or more.

4. *Mother-child incompatibility*

Differences in blood group between mother and child give rise to the production of antibodies in the mother which can harm the child in utero or immediately after birth, as in Rhesus antagonism.

Since the publication of the WHO report in 1969, more recent figures on the prevalence of genetic diseases have become available. Trimble and Doughty (1974) have listed rates per 100 live-born children in British Columbia, Canada (Table 1).

Identifying genetic diseases

Genetic diseases are quite rare. They are like poisoning: we know they exist, we hope they will not occur, and yet we always have to be prepared to consider their possibility.

Are there indications which suggest the genetic character of the disease to the general practitioner (or specialist)? In my opinion there are six circumstances

Table 1. Prevalence of genetic diseases per 100 live-born children (WHO, 1969).

	Minimum	Adjusted*
Dominant	0.06	0.08
Single gene recessive	0.09	0.11
X-linked	0.03	0.04
Chromosomal	0.16	0.20
Malformations at birth	3.58	4.28
Other multifactorial causes	1.58	4.73**
Unknown	0.60	2.70
Total	6.10	12.14

*These figures have been corrected to allow for bias due to delay in disease onset, migration, and incompleteness of ascertainment.
**The most common traits in this category are diabetes mellitus, epilepsy, strabismus, and asthma (Trimble and Doughty, 1974).

which can lead us to consider the possibility of gene influence:

1. The presence of serious abnormalities at birth.
2. Serious mental deficiency, especially when combined with other abnormalities; this condition is mainly due to a chromosomal aberration.
3. Repeated abortion or stillbirth without evidence of obstetrical or internal causes may be caused by a chromosomal aberration.
4. When several members of the same family have rare abnormalities without clear evidence of external causes, this gives rise to suspicion of transmission by monofactorial or multifactorial heredity.
5. Frequent occurrence of certain important diseases or syndromes in the same family.
6. Severe icterus or anaemia at birth or soon after often points to a mother-child incompatibility.

Many genetic diseases are not present at birth but develop later in life.

Referral and support

If a genetic disease is suspected, the general practitioner's main task will often be to refer the patient to a clinical specialist. Further referral to a (university) genetics centre, in consultation with the specialist—who often knows as much or as little about modern genetics as the general practitioner himself—will often be necessary.

An absolute precondition for genetic counselling is that the diagnosis should be established. Before starting genetic counselling the general practitioner should determine whether the patient or the family is well motivated and the time chosen is apt for counselling. According to Carter and his colleagues (1971), genetic counselling will be useless without these conditions.

Before, during, and after the genetic investigations the general practitioner should continue his personal and continuing care for the patient and his family, for he has more knowledge of their specific circumstances than any specialist or counsellor.

After the genetic advice has been given the main task of the general practitioner should be to fit it into the particular circumstances of the family concerned. Spence's dictum (1970) that there should be three kinds of diagnosis—the nature of the disease, what the patient (or his family) thinks about it, and whether the patient (or his family) understands what the doctor tells him about it—is particularly true of genetic diseases.

Such diseases are almost certain to raise questions which members of the family will put to their trusted family doctor. These questions not only refer to their need for information but also to their fears and feelings of guilt. "The more the physician understands the background of his patients the more he will be able to help them with difficult problems" (Emery, 1975).

Examples from general practice

Nancy A., born in 1971, is the second child of healthy parents. No diseases are known in the family. The parents are not related to one another. The elder sister is quite normal. The early stages of Nancy's development were also normal, but several attacks of convulsions at the age of eight months called for further investigation in a neurological clinic. The condition was diagnosed as metachromatic leukodystrophy, an autosomal-recessive genetic error of metabolism. It was explained to the parents that each subsequent child they had would have a 25 per cent chance of having the same disease as Nancy: a high risk for a severe disease.

It now fell to me to answer the many questions of Nancy's parents: What would the future bring for her? How old might she become? What should be done in cases of severe fits or repeated infections of the respiratory tract? Would it be wiser to refrain from making use of all the therapeutic means offered by modern science, or should everything be done to keep Nancy alive? What form of contraception would the parents use? What aid could the family receive from the social services? In the meantime the mother, supported by a district nurse, has taken upon herself the task of caring for her severely handicapped child with admirable courage and devotion. Oral contraception is used and the regular 'Pill' checks by the family doctor provide the mother with an opportunity to discuss outstanding problems. The parents do not want any more children, even after I suggested the possibility of prenatal diagnosis for this disease and selective abortion of an affected fetus.

Prevention

There has recently been a marked trend in medical thinking towards the idea of preventing diseases before they manifest themselves. Such prevention may be undertaken not only in an attempt to reduce incidence of children with severe inherited handicaps (primary prevention), but also attempts to reduce the complaints

associated with genetic diseases (secondary prevention). The preventive work carried out by the general practitioner will be differently orientated for each disorder.

I had known Mrs B. for eight years when she came to my consulting room one day in 1970, when she was 32, and told me that her sister had died rather suddenly of "an acute attack of a family disease". Further information revealed that the sister had died of an attack of porphyria. Other members of the family, including my patient, appear to have a latent form of porphyria variegata. This disease is inherited in an irregular dominant pattern, but in general it does not give clinical symptoms apart from a rise in the coproporphyrin and protoporphyrin levels in faeces and urine. The dangerous aspect of the disease is the risk of an acute attack of porphyria, especially when certain medicaments are given, such as barbiturates, sulphonamides, oestrogenic steroids, and methyldopa. In order to ensure that Mrs B. did not get medicine on her 'forbidden list' from other sources, I furnished her with a medical information card specifying the medicaments she should not receive. When contraception was discussed, the couple decided on sterilization, as oestrogenic steroids were contraindicated.

The task of the family doctor here mainly consisted of collecting information about diseases in close relatives and informing the patient and her family about the consequences of such diseases. For this purpose he must gain more insight into the diseases in order to give as good advice as possible.

A problem of secondary prevention occurred as follows: Mr C. had a myocardial infarction at the age of 36; before this he had appeared to be quite healthy. Further investigations of himself and his family revealed that he had familial hypercholesterolaemia type 2. According to experts this must be regarded as a dominant autosomal disease, which may lead to early death as a result of repeated coronary accidents. Mr C. was not spared this fate: he died at the age of 45 from severe decompensation of the heart in spite of treatment by a cardiologist.

Preventive care is offered to his two children, now 19 and 17, who both have high cholesterol levels in their blood. They follow a low cholesterol diet, take medicine to keep their cholesterol low, and undergo regular blood tests. Further preventive measures are not possible at present.

Prevention also includes the possibility of prenatal diagnosis by means of amniocentesis. By investigation of the amniotic fluid it is possible to diagnose a chromosomal aberration or a number of inborn errors of metabolism at an early stage of fetal life. In the Netherlands prenatal diagnosis is performed at the Erasmus University, Rotterdam, and also at the Universities of Amsterdam and Groningen.

The general practitioner must know the indications for prenatal diagnosis. Emery (1973) considers that amniocentesis and the possibility of selective abortion might be offered to parents only when the risks of an abnormal child exceed five per cent, or in exceptional circumstances where parental anxiety is an overriding consideration. Emery (1973) and Niermeyer (1975) give the following indications:

1. Advanced maternal age (38 or over); because of a higher risk of trisomy-21 (Down's syndrome) and other chromosomal aberrations.
2. Mothers who have previously given birth to a child with a chromosomal aberration.
3. Pregnancies where one of the parents is a balanced carrier of a chromosomal rearrangement (translocation, inversion).
4. Pregnancies at risk for one of those inborn errors of metabolism (about 50) where the affected fetus can be diagnosed in utero.
5. Sex prediction in X-linked recessive disorders, where it is not yet possible to detect the homozygous affected male in utero.
6. Pregnancies at risk for an open neural tube defect (anencephaly, spina bifida).

Detection and surveillance of high risk groups

The examples illustrate detection and surveillance of high risk groups in general practice. "By identifying vulnerable groups, early diagnosis is carried out when it is most needed and most likely to lead to effective action". This is how the family doctor's task is described in *The Future General Practitioner* (RCGP, 1972).

The general practitioner often detects a disease at an early stage by knowing the pattern of diseases in a particular family, such as essential hypertension, ischaemic heart disease, diabetes mellitus, peptic ulcers, cholelithiasis, atopy and asthma, and rheumatoid arthritis, to mention just a few. The pathogenesis of these diseases is to be sought in a combination of external influences and polygenic hereditary factors.

When these diseases occur several times in one family, the family as a whole can be considered as a high risk group for the disease in question. For example, Carter (1969) estimates that the risk of ischaemic heart disease is six times as high in first-degree blood relatives of patients as in the population as a whole.

Every observant general practitioner will sometimes have found strikingly high frequencies of some diseases in some families. In Britain, Kuenssberg (1964) has investigated the occurrence of 'clusters' of certain diseases in his practice by keeping a register of familial diseases, his 'F-book'. I have also published a report on some striking examples (Aulbers, 1963). Taking a good family history can be a great help in detecting some syndromes or diseases.

Ethical problems

Genetic counselling can involve the general practitioner in ethical problems. The most important is the requesting and supplying of information about patients. In the Netherlands it is usual for doctors to apply to the general practitioner or specialist when they want any

medical information about a patient, having first asked the patient's permission.

Another ethical problem may arise in prenatal diagnosis; for example, when the parents decline therapeutic abortion on religious or ethical grounds, even in a case of marked abnormalities in the fetus. In these cases the parents must have the final decision.

Other problems concern sterilization, contraception, artificial insemination, euthanasia, and 'genetic engineering'. The Dutch Secretary of State for Public Health has quite rightly asked for advice on these matters from a committee of the Dutch Health Council. Such a report will, of course, not give binding decisions, but only guidelines. In the meanwhile, family doctors must wrestle with decisions about a particular patient with a particular problem now.

The role of the family doctor in genetic diseases

In genetic and congenital disorders, the role of the family doctor may be summarized:

1. To consider constantly the possibility of a genetic disorder.

2. To examine a newborn child for possible congenital defects.

3. To refer the child to a specialist, if congenital or genetic defects are found or suspected.

4. To consult with a clinical specialist about whether further genetic investigation is desirable.

5. To help the family before, during, and after specialist and genetic investigation by showing concern and giving information and practical advice (to provide personal care).

6. To relate the genetic advice to the particular circumstances of the patient and his family.

7. To advise about contraception.

8. To know the indications and possibilities of prenatal diagnosis.

9. To take a good family history when a gene-involved disease is suspected.

10. To perform blood tests in cases of Rhesus-negative gravidae between the 32nd and 36th week, and after the delivery in cases of serious neonatal icterus or anaemia.

11. To carry out appropriate medical examinations before marriage (if genetic disease in the family is suspected, the advice of a geneticist should be sought).

12. To recognize his continuing educational needs in human genetics.

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Medical certificates

The Minister for Police, Mr T. Newberry, has advised the College that under Rule 33(4) of the Police Rules, the Commissioner for Police has issued an instruction requiring members of the police force, when obtaining medical certificates, to ensure that the nature of the illness is shown on such certificates.

The Australian Medical Association, Queensland Branch, has repeated, for the information of its members, advice given to members in 1971 on medical certificates. We strongly recommend these guidelines to College members:

1. It is a breach of professional confidence to supply to any third party, without the consent of the patient, information concerning that patient's medical condition, unless there is an overriding statutory obligation to do so, e.g. in the case of notifiable infectious diseases.
2. It is not a breach of professional confidence to hand a certificate containing a statement of the nature of his disability to the patient himself.
3. If the patient does not wish the nature of his illness to be stated on the certificate, this is his right, and words such as 'on medical grounds' are perfectly in order.
4. In the absence of any such request it is equally his right to be assisted in his claim by the provision of a certificate which will not be rejected by his employer.
5. Any member who feels reluctant as a matter of principle to include a diagnosis in medical certificates is quite entitled to ask every patient for whom he writes a certificate whether that patient does or does not wish the nature of his illness to be stated.
6. He does not discharge his obligation to his patients if he refuses on all occasions to state the nature of the illness in the certificate.

Reference

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