Pediatrics Seminar

Down's Syndrome

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Down's syndrome, formerly called mongolism, is one of the most important causes of mental retardation. It accounts for 5-15% of institutionalized mental defectives in the U.S.A., and is encountered once in every 600-700 births.

The earliest known description of mongoloid patients goes back to 1866, though it is quite likely that this specific condition was noticed by other physicians before that time. Dr. Langdon Down, an English physician, coined the term «mongolism» while he was attempting to classify mental defectives on an ethnic basis. This term is unsatisfactory for both medical and social reasons, especially since the condition apparently occurs with the same frequency in all ethnic groups. The name has recently been changed to Down's syndrome in honor of the physician who first described the condition as an entity.

Incidence

Down's syndrome, a relatively common condition, occurs with a frequency of one in 600-700 births. One of the striking features is the relation between the incidence of the condition to the mother's age when the child is born. For mothers under 20 years of age, it occurs once in approximately 2,300 births. The risk increases slightly for mothers in the 20-30 year age bracket, and then rises sharply thereafter to one in 46 births for women over 45 years of age.[1] (Table 1).

The Cause of Down's Syndrome

As early as 1932, it was suggested that mongolism may be due either to an excess or to a deficiency of chromosomes. This, however, was only one of the many different hypotheses advanced, and the chromosomal

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TABLE I

RISK OF GIVING BIRTH TO A MONGOLOID CHILD FOR DIFFERENT MATERNAL AGE GROUPS. INCIDENCE PER 1,000 BIRTHS. (COLLMAN AND STOLLER)

AGE GROUP	INCIDENCE	O %
15-19	1/2,3co	0.43
20-24	1/2,6oo	0.61
25-20	1/1,2co	0.82
30-34	1/880	1.13
35-39	1/290	3.45
40-44	1/1oo	10.co
45-49	1/46	21.76
All Ages	1/696	1.44

basis of the condition was not obtained until recently. In 1959, it was convincingly demonstrated that mongoloid patients have 47 chromosomes instead of 46 (or 23 pairs), which is the normal number for man. This extra chromosome is one of the smallest and has been designated as No. 21 (chromosome pairs are numbered in decreasing order of size, No. 1 being the largest). Since there are three size No. 21 chromosomes in Down's syndrome instead of the normal two, the term trisomy 21 has also been applied to this condition. (Trisomy literally means «three bodies».)

Although the great majority of Down's syndrome patients are trisomic for chromosome 21, exceptions are known to exist. These have the equivalent of an extra No. 21 chromosome, but the extra chromosomal material is fused to yet another chromosome (a process known as translocation). The net result is that the number of separable, countable chromosomes may not be increased, but, nonetheless, there is an increase in the overall genetic material within the individual cells. Since the actual amount of extra, genetic material is believed to be the factor which determines the appearance of Down's syndrome, individuals with the translocation type chromosome do not differ in appearance and prognosis from the more common trisomic Down's syndrome type.

Characteristic Features of Patients with Down's Syndrome

Besides the appearance of the eyes, which was responsible for the designation «mongolism», there are many other symptoms commonly seen in patients with Down's syndrome. For instance, they are somewhat shorter in stature than normal people, and have small, round heads, short noses

small, round, low-set ears and narrow eye openings. The upper eyelids look somewhat puffy, with a fold of skin at the inner corners, called an epicanthic fold, and wrinkles (fissures). Yellow or yellow-gray speckling of the iris may also be seen. They have stumpy limbs, with broad hands and feet. Often a single horizontal crease may be seen in the palms of the hands, as well as a single crease, rather than the usual two, on the little finger. They may have umbilical hernias, congenital heart disease and decreased muscle strength. While all these features may not be present in one child, the general appearance of all children with the syndrome is strikingly similar.

Various Types of Down's Syndrome in Regard to Their Chromosomal Makeup

1. Trisomy 21 (47 chromosomes in each cell):

The great majority of mongoloid children fall into this category. Approximately 91 per cent of patients born to mothers under 30 years of age, and 98 per cent of those born to mothers over 30, were found to have an extra chromosome (47 chromosomes).[2]

A discussion of the possible ways in which this extra chromosome finds its way into the mature egg is beyond the scope of this paper.

2. Translocation Mongolism:

This appears to be relatively more frequent in children born to young mothers. For instance, in the same study as mentioned above, 9 per cent of affected infants born to mothers of less than 30 years of age had a translocation, as compared to approximately 2 per cent in the older group, which indicates that the advancing age of the mother as a cause of mongolism is not very significant in these patients.[2] An interesting finding in this type of mongolism is that the condition may be familial in a certain number of cases, e.g. about 25 per cent when the maternal age is under 30, and 15 % when it is over 30.[2] This means that one of the parents may be carrying the fused or translocation chromosome. In these cases chromosome studies of the carrier parent usually reveal only 45 chromosomes instead of 46. Since the large chromosome is actually made up of 2 chromosomes, as explained above, this accounts for the carrier's being completely normal.

3. Mosaicism

This term indicates that the patient carries more than one cell line. For instance, he may have cells with 47 chromosomes as well as cells with 46. The ratio between the normal and abnormal cells varies from case to case. Patients with this type of Down's syndrome may have almost normal intelligence if a significant majority of the cells of his tissues carry chromosomes normal in number and structure.

The Risk of Having a Second Child with Down's Syndrome

The risk can vary from slightly higher than that for the general population, to a highly unlikely, but hypothetically possible, situation in which all offspring will be affected. For this reason, the question of the risk of a recurrence of the syndrome must be considered on the basis of the available laboratory information on any given patient. The various possibilities are as follows:

1) If no information is available on the chromosome makeup of the patients.

Here only a general estimate can be given, but the risk in such a case will be increased approximately two and a half times compared with the risk for that particular maternal age group as shown in Table 1. However, it should be emphasized that in general the risk of a second affected child is still not very high, with the exception of mothers in the last age group.

2) If the affected child has trisomy 21 (the standard, common type of mongolism). This group is divided into two sub-groups for discussion:

a) Both parents have normal chromosomes.

Here the risk of future siblings being affected is theoretically the same as for parents in the general population, increasing with the mother's age.

However, most experts in this field seem to believe that there is, in fact, a slight additional risk for these mothers, though not high enough to be considered significant.

b) One parent is mosaic for trisomy 21.

The exact risk figure cannot be given for the families in this particular sub-group. However, if the mother is known to be mosaic trisomic there is a significantly increased risk of another child being similarly affected.

3. Translocation mongolism of 13-15/21 type.

a) Both parents have normal chromosomes.
The risks are similar to 2a.

b) One parent is the carrier of the translocation.
This group must be sub-divided for discussion.

1) If the mother is the carrier, the risks are serious:

1/3 of the children will be mongoloid.
1/3 of the children will be normal but carriers.
1/3 of them will be entirely normal.

TABLE 2

THE RISK OF HAVING A SECOND CHILD WITH DOWN'S SYNDROME

Chromosomal Makeup : First Child with Down's Syndrome	Mother	Father	The Risk for the Second Child
Unknown	Unknown	Unknown	Approx. 2.5 x risk for the mother's age group
Trisomy G	Normal	Normal	Slight additional risk, though not significant
Trisomy G	Mosaic	Normal	Fairly high risk
Trisomy G	Normal	Mosaic	Not established as yet
Translocation D/G 13-15/21	Normal	Normal	Slight additional risk, though not significant
Translocation D/G	Carrier	Normal	One-third
Translocation D/G	Normal	Carrier	One-twentieth
Translocation G/G	Normal	Normal	Slight additional risk, though not significant
Translocation G/G - 21/22	Carrier	Normal	One third
Translocation G/G - 21/22	Normal	Carrier	One twentieth (risk increasing with paternal age)
Translocation G/G - 21/21	Carrier	Normal	All children will be affected
Translocation G/G - 21/21	Normal	Carrier	All children will be affected

2) If the father is the carrier:

1/20 will be monogoloid.
1/20 will be normal, but carriers.
18/20 (or almost all) the children will be normal.

If the parent carries the translocation in mosaic form, the risk of having another mongoloid child would be even less than the figures given above.

4. The affected child has a translocation of the 21/22 type.

a) Both parents have normal chromosomes.

The risks are similar to 2a; that is, the same as for the general population. However, there is a suggestion that advancing paternal age may increase the risk slightly.

b) One parent carries the translocation.

If the translocation is of the 21:22 type, the risks are as described in 5b. If the father carries the translocation, however, the risks seem to increase with advancing paternal age.

If the translocation is of the 21/21 type, all children will be affected.

5. Other special situations.

These are extremely rare, and therefore will not be mentioned in this paper.

Ackowledgement

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