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Chromosomal Aneuploidy, Mosaicism and Eugenics

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Introduction

Aberrations from the normal (euploid) number of chromosomes are very frequent, one in about 200 live births having a chromosomal number other than 46 in all or some cells. Chromosomal aneuploidies such as monosomy X, trisomies, and polysomies represent one category of gametopathy. They are caused by nondisjunction or chromosomal loss during meiosis, presumably meiosis I, although French authors (Grémy et al, 1967) have recently proposed that errors of meiosis II are a more likely cause. The various chromosomal mosaicisms are due to postzygotic mitotic errors, and may be classified under the blastematoses. Gametopathies and blastematoses are generally sporadic events, as are most aneuploidies and mosaicisms. It is therefore unusual, even exceptional, to find more than one case of aneuploidy in a family. Nevertheless, this does occur.

Because of the high overall incidence of chromosomal aberrations, every physician dealing with this type of disease will at some time encounter familial agglomerations of cytogenetic disorders. Experience has shown that most familial chromosomal aberrations are not transmitted according to the mendelian rules of single gene inheritance. Two questions thus arise: How are they transmitted? How great is the risk of their recurrence within a given family? In this presentation, we shall study the transmission patterns of cytogenetic diseases and discuss the possibilities of their recurrence within a family.

Familial chromosomal aberrations can be divided into four categories: (1) aneuploidy due to a similar aberration (other than interchange) in a parent; (2) aneuploidy due to parental interchange; (3) agglomerations of aneuploidies which occur although the parents are euploid; and (4) familial mosaicism.

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1. Cases with Parental Aneuploidy or Mosaicism

The reproduction rate of individuals affected with Turner's syndrome, Klinefelter's syndrome, trisomy D_1, trisomy E, and of mongoloid males is, for all practical purposes, nil. Mongoloid females can reproduce. It can be assumed that 50% of the ova of 21-trisomic females are disomic, and, therefore, that the zygotes resulting from fertilization of such ova are trisomic. Since only one in three 21-trisomic zygotes reaches the end of gestation, we can calculate that a mongoloid woman has a risk of about 25% of having a mongoloid child. Indeed, 5 of 16 children born to mongoloid mothers have been mongoloid, the 11 others being of normal physical appearance and intelligence (Zellweger, 1964). Since mongoloid females run a fairly high risk of producing mongoloid children, sterilization of mongoloid girls who lack appropriate protection is warranted.

Both men and women with chromosomal mosaicism containing a 21-trisomic clone may have mongoloid offspring. We cannot predict how many they may have since we do not know the ratio of trisomic to euploid gametic stem cells (ovogonia or spermatogonia) in a gonad and thus cannot determine the number of disomic gametes. Nevertheless, mosaic parents with a 21-trisomic clone have an increased risk of having one or several mongoloid children, and they should be counseled accordingly.

Although infertility among XYY men and X-polysomic women is probably more frequent than among men and women with normal sex chromosomal complements (Kohn et al, 1968) the majority of them can reproduce. Theoretically, we would expect that half of their offspring would have an aneuploid karyotype. Experience has shown, however, that offspring of XYY men and XXX women are more often euploid than aneuploid, suggesting a selective advantage of the euploid gametes. Among the aneuploid children of women with trisomy X or an X-trisomic clone are an XYY male (Rosenkranz, 1965) 2 XXY Klinefelters (Rosenkranz, 1965; Fujita et al, 1967) an XXYY Klinefelter (Rosenkranz et al, 1964) and a G-trisomic nonmongoloid (Sparkes et al, 1966). One XYY male had a 21-trisomic offspring and a daughter with primary amenorrhea (Sandberg et al, 1961). A second XYY male fathered a child with multiple malformations (Wilton and Lever, 1967) but we cannot say whether the child's condition stemmed from its father's chromosomal anomaly.

2. Familial Interchange (Translocation)

Chromosomal interchange (translocation) most often occurs between two acrocentric chromosomes; that is, within group D (D/D) or G (G/G), or between one chromosome in each group (D/G). In addition, there are rare instances of interchange between an acrocentric and parts of a non-acrocentric (A, B, C, E, F) chromosome or between parts of nonacrocentric chromosomes.

Balanced translocation (interchange heterozygosity) consists of 44 normal chromosomes and the interchange structure containing (most of) the genes of the two

fused chromosomes. Balanced translocation is usually not associated with phenotypic anomalies.

Unbalanced translocation consists of 45 normal chromosomes and the interchange structure. The interchange structure itself is made up of one of the two chromosomes involved in the interchange and parts of a third such chromosome. In these instances, one speaks of " partial trisomy ". In an unbalanced 21/21 translocation, for instance, there is one regular chromosome 21 and an interchange structure consisting of parts of the second chromosome 21 and parts of a third chromosome 21. Partial trisomy produces a clinical picture similar to that of true trisomy. There is no phenotypic difference, for example, between a G/G (21/21) or D/G interchange mongoloid and a 21-trisomic mongoloid.

We do not know the frequency of interchange heterozygosity in the general population. It can occur either as a sporadic mutation or as a familial, " hereditary " trait existing unnoticed through generations. Recognition may not come until the phenotypic anomalies of a child with the translocation in unbalanced form arouse suspicion of aneuploidy and warrant chromosomal analysis. Discovery of an unbalanced translocation in the proband would lead to chromosomal analysis of his parents and, perhaps, other family members.

Chromosomal analysis of families with familial interchange has revealed that, as a rule, the incidence of euploid individuals is higher than that of individuals with interchange heterozygosity, and that family members with unbalanced translocation (partial trisomy) are rarer than either. Gametes with a normal karyotype or balanced translocation thus seem to be at a selective advantage over aneuploid gametes.

The most frequent partial trisomy is translocation mongolism, which accounts for about 3.5% of all cases of mongolism and occurs in one in 20000 live births. G/G interchange mongolism is slightly more frequent than D/G interchange mongolism; other types of unbalanced interchanges leading to mongolism are rare (Richards et al, 1965). Over 90% of the cases of G/G interchange mongolism and 50% of the cases of D/G interchange mongolism are sporadic, and are born to euploid parents. The risk that the euploid parents of an interchange mongoloid child will have another such child cannot be predicted; it is probably no higher than that for euploid parents of a 21-trisomic mongoloid. The recurrence risk of interchange mongolism can be predicted if one of the parents carries a balanced translocation. Every pregnancy of a female who carries a balanced D/G (15/21) or G/G (21/22) translocation has a chance of about 20% of ending in the delivery of a mongoloid child. Each impregnation by a male with either of these balanced translocations has a chance of slightly below 20% of ending in the birth of a mongoloid. Any male or female who carries a balanced G/G (21/21) translocation has a 100% chance of having an interchange mongoloid child.

The segregation pattern of a gametic stem cell with balanced 21/21 translocation gives rise to 2 gametes, one with the 21/21 translocation and the other with no chromosome 21. Fertilization of the former gamete leads to partial trisomy 21 (mongolism); fertilization of the latter leads to a nonviable monosomy 21 which will be

aborted. Abortions are more frequent in families in which one parent carries interchange heterozygosity than in the random population; this is in keeping with the high wastage of aneuploid zygotes in general.

Mongolism due to familial interchanges between chromosome 21 and a nonacrocentric chromosome is rare, and exact figures as to its recurrence risk are not yet available. We can assume the risk to be substantial if one parent carries the translocation in balanced form.

Partial trisomy D_1 is rarer than partial trisomy G (interchange mongolism). As of Spring 1966, Hecht et al had collected 41 cases through personal observation, inquiry, and research of the literature. Since that time, a few more cases have been reported (Erkman et al, 1965; Hauschteck et al, 1966; Craig and Luzzatti, 1967). The data presently available indicate that about 10% of the offspring of persons with balanced D/D translocation have been aneuploid; this represents a major risk. It is interesting to note here that not all these aneuploid offspring have had partial trisomy D_1, a 21-trisomic child being observed in a few instances (Moorhead et al, 1961; Hamerton et al, 1963). Moreover, two families with balanced D/D translocation have been reported in which there was an increased incidence of mental retardation among the euploid offspring (Moorhead et al, 1961; Dekaban, 1966).

A number of families with interchange between nonacrocentric chromosomes have been described. Although it was rare that more than one case (the proband or index case) had the interchange in unbalanced form, this does not preclude an increased risk of having more than one such child. Walzer et al (1966), for example, reported a large kindred with an A(3)/B translocation distributed over four generations. Most of the members had a normal karyotype; a few had the translocation in balanced form; and only one (the index case) had the translocation in unbalanced form. This latter individual showed severe, multiple malformations. At least 6 other cases of multiple malformations occurred in the same family (chromosomal analyses were not performed on these persons), and a number of abortions were also recorded.

Laurent and Robert (1966) reported an interesting observation of three children with " cat cry " syndrome in a sibship of 7. The karyotypes of all three revealed deletion of parts of the short arm of chromosome 5. The phenotypically normal mother had the same deletion, but the missing fragment was translocated to the long arm of a C chromosome, thus giving her a eusomic complement. A fourth child of that family had part of the short arm of chromosome 5 in triplicate, having 46 chromosomes plus the extra segment translocated to the C chromosome. An observation similar to that of Laurent was made by De Capoa et al (1967).

Balanced interchanges appear to affect the segregation pattern inducing nondisjunction of chromosomes other than those involved in the interchange. Trisomy 21 occurring in families with familial D/D interchange has been mentioned (Moorhead et al, 1961; Hamerton et al, 1963). Lejeune et al (1963) described a family with a balanced 2/22 interchange in 7 members of three generations. One of these persons had a child with monosomy X. Until greater knowledge is gained, it cannot be said whether these findings are coincidental. Whatever the final answer, it is

unlikely to essentially modify our eugenic advice to parents with a balanced translocation; we consider that such persons have a major risk of having aneuploid offspring.

3. Familial (Fraternal) Agglomerations of Aneuploidy with Euploid Parents

It is not too unusual to find two or, less frequently, more aneuploid individuals, whose parents have euploid chromosomal complements, in the same family. Such agglomerations can be divided into two groups: (1) agglomerations of different aneuploidies in a sibship or wider kindred; and (2) agglomerations of the same aneuploidy in a sibship or wider kindred.

Considering the high frequency of aneuploidies in the general population, it is not unreasonable to assume that some familial agglomerations of aneuploidy are coincidental. This is particularly true of agglomerations of different aneuploidies, but it can also be said of most familial agglomerations of the same aneuploidy (statistical proof for this statement will be presented elsewhere). It should be remembered, however, that there are rare instances of multiple familial aneuploidies of the same type, born to euploid parents, which may not be coincidental. The causative mechanisms of such situations are poorly understood; and, thus, predications as to the recurrence risk of a given aneuploidy for a given parent are not always possible. We can, however, make a few general statements.

Euploid parents who have a near relative (first cousin, nephew, uncle) with aneuploidy do not usually have a greater chance of having an aneuploid child than does any other couple of similar age.

Euploid parents who have one aneuploid child have a slightly higher chance of having a second child with the same aneuploidy, but this increased risk of not of such a magnitude that it should influence their family planning. This statement can also apply to euploid parents who have one aneuploid child and a relative (first cousin, etc) with the same aneuploidy.

Euploid parents who have 2 children with the same aneuploidy are presumed to have a major risk of having more children with that aneuploidy. We studied 11 families in which the euploid parents had more than one 21-trisomic offspring; 9 of these couples had two 21-trisomic offspring, and two couples (18%) had three 21-trisomic offspring. From this observation, we concluded that parents with two aneuploid children should be advised against having further children.

In some families in which aneuploidy occurred, chromosomes exhibiting structural anomalies were found in various euploid family members, notably a parent of the aneuploid individual. Several of these " marker " chromosomes have been described: macrochromosomes (Wolf et al, 1964), chromosomes with giant satellites (Cooper and Hirschhorn, 1962), and elongated Y chromosomes (Dekaban et al, 1963; Bishop et al, 1962). Structural anomalies of the Y chromosome are found in 3% of the male population, Beer et al (1967) attributing no definite pathogenetic consequences to them. The incidence of most other marker chromosomes in the general

population is not known. It has been proposed that a marker chromosome has an untoward effect on meiosis I, causing nondisjunction and aneuploidy, but a causal relationship between marker chromosomes and aneuploidy has not been established. We do not, therefore, become greatly concerned when a marker chromosome occurs in an otherwise normal karyotype.

4. Familial Mosaicism

Approximately 20 families with chromosomal mosaicism in two or three generations have been reported. Familial mosaicism varies widely in type and distribution. The mosaicisms can consist of autosomes alone, of sex chromosomes alone (Rosenkranz, 1965), or of both autosomes and sex chromosomes. In addition, the mosaic pattern can be the same in all family members involved, or various persons can show various patterns. We observed one family (Zellweger and Abbo, 1965) in which the proband's father and grandmother had the same mosaicism (one normal clone and a second clone with D/D interchange heterozygosity); the proband, a mongoloid girl, had 7 different clones; her phenotypically normal brother had an XO/XY mosaicism. Gedda et al (1967) reported a family in which both parents were mosaics. The father had a 46/47 (normal/trisomy A) chromosomal complement, the mother a 45/46 (the aneuploid clone missing an A chromosome). Their two living children had all three clones: 45/46/47 (monosomy A/normal/trisomy A).

Mosaicism is caused by postzygotic mitotic error; in other words, it arises after segregation of the chromosomes and formation of the gamete has occurred. It would therefore appear that, in general, mosaicisms could not originate from genetic errors and gametopathies. On the other hand, the occurrence of identical or different mosaicisms in a family, transmitted by either parent and involving members of two or three generations, does suggest a genetic factor, possibly a gene promoting mitotic nondisjunction. Because families with proven familial mosaicism have a definitely increased tendency to produce mongoloid or malformed children, they should receive eugenic counseling. The nature of such counseling would depend on the severity of the clinical condition caused by the mosaicism.

Summary

Chromosomal aneuploidy in individuals is very frequent, and is generally a sporadic occurrence. Some aneuploidies seem to be familial, however; that is, parents may have more than one aneuploid child, or they may come from families in which an agglomeration of aneuploidies is distributed over several generations. Since, in such instances, parents often seek eugenic counsel to learn their chances of having aneuploid children, four types of familial aneuploidy and their recurrence risks are

described. Special emphasis is given to the more important types of familial interchange, for which the recurrence risks can be calculated with fair accuracy. Familial mosaicism, a rare and puzzling genetic entity with which aneuploidy seems definitely correlated, is discussed.

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RIASSUNTO

L'aneuploidia cromosomica è molto frequente a livello individuale e generalmente ricorre in maniera sporadica. Tuttavia alcuni casi di aneuploidia sembrano essere familiari; esistono cioè individui che possono avere più di un figlio aneuploide, oppure provenire da famiglie in cui l'aneuploidia si presenta in più generazioni. Poiché in tali circostanze i genitori ricorrono spesso al consultorio eugenico per informarsi sulle probabilità di avere bambini aneuploidi, è stato possibile descrivere quattro tipi di aneuploidia familiare con i rispettivi rischi di ricorrenza. Vengono particolarmente considerati i principali tipi di interscambio familiare, per cui il rischio di ricorrenza può esssere calcolato con una certa precisione. Viene infine discussso il mosaicismo familiare — rara ed enigmatica entità genetica — con cui l'aneuploidia appare chiaramente correlata.

RÉSUMÉ

L'aneuploïdie chromosomique est bien fréquente chez les individus, mais généralement sporadique. Toutefois, des cas peuvent être familiaux; c'est-à-dire des individus peuvent avoir plus d'un enfant aneuploïde, ou bien être déscendus de familles où l'aneuploïdie se répète dans plusieurs générations. Dans ces cas, les parents s'adressent généralement à l'eugéniste pour connaître leur probabilité d'avoir un enfant aneuploïde. Il a été donc possible de décrire quatre cas d'aneuploïdie familiale avec les probabilités respectives. Spécialement considérés ont été les principaux types d'interchange familial, pour lesquels la probabilité peut être calculée avec une certaine précision. Le mosaïcisme familial est une rare et bizarre entité génétique avec laquelle l'aneuploïdie paraît clairement corrélée.

ZUSAMMENFASSUNG

Die Chromosomen-Aneuploidie tritt sehr häufig bei einzelnen Individuen und im allgemeinen sporadisch auf. Es scheint aber auch familiäre Fälle zu geben, d. h. Menschen, die mehr als ein aneuploides Kind haben oder aus Familien stammen, in denen die Aneuploidie in mehreren Generationen vorkommt. Unter diesen Umständen wenden sich Eltern oft an die eugenische Beratungsstelle, um zu erfahren, ob sie etwa aneuploide Kinder haben könnten. Verf. waren daher in der Lage, vier Typen von familiärer Aneuploidie zu beschreiben und die Möglichkeit ihres Wiederauftretens zu erörtern. Insbesondere betrachten Verf. die Haupttypen der familiären Translokation, für die sich die Eventualität des Wiederauftretens mit einer gewissen Präzision errechnen lässt. Zuletzt erörtern sie den familiären Mosaizismus, eine seltene und rätselhafte genetische Gegebenheit, welche deutlich mit der Aneuploidie verbunden zu sein scheint.

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