well be that, in this family, 18q— is unable to segregate properly during gametogenesis and early postzygotic mitosis, leading to an unbalanced state and +18q—.

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References


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Trisomy 21 with 47,+18 lymphocyte cell line: double mitotic nondisjunction

SUMMARY A patient with Down's syndrome was found to have 47,XX,+18/47,XX,+21 mosaicism. Chromosome 18 trisomy was found only in 18% of lymphocytes and not in skin fibroblasts. A likely interpretation is double nondisjunction in a single lymphocyte precursor of a trisomy 21 embryo. A brief review of other cases of mitotic multiple nondisjunction and double aneuploid mosaicism is presented.

Chromosomal mosaicism occurs in a small percentage of patients with Down's syndrome. The vast majority of these mosaics have a normal cell line in addition to the trisomy 21 cell line. This report describes the first reported instance, to our knowledge, of an unusual type of double trisomy mosaicism in lymphocytes involving chromosomes 18 and 21.

Case report

The proposita was referred for chromosome analysis at age 20 years because of numerous signs of trisomy 21. Her facial appearance was typical of Down's syndrome, with a flat nasal bridge, oblique palpebral fissures, and epicanthal folds. There was a high arched palate and a furred tongue. The patient was 140 cm tall (less than 3rd centile), obese (weight 50.5 kg), and her head circumference was 50.5 cm (less than 2nd centile). Her hands were broad and short with bilateral simian lines and laterally displaced axial triradii. Her fingers, wrists, and elbows were hyperextensible. There was muscle hypotonia, and her co-ordination was poor. No focal deficits were noted on neurological examination. Her electroencephalogram was interpreted as moderately abnormal because of excessive posterior slowing and had a background alpha rhythm of 8 to 9 Hz moderate voltage activity.

Psychometric examination indicated the patient to be mildly retarded (WAIS: verbal IQ, 64; performance IQ, 63; full scale IQ, 61). Academic skills assessed by PIAT were as follows: mathematics, 1.4 grade equivalent; reading recognition, 3.9 grade equivalent; and general information, 3.2 grade equivalent. In her subjective evaluation she showed a strong tendency towards inappropriate responses and fantasy activities.

The proposita was the 3rd child of unrelated parents. Her mother and father were aged 45 years and 52 years, respectively, at the time of her birth. Her sibs were normal and there was no family history of mental retardation.

CHROMOSOME STUDIES

Of a total of 100 cultured lymphocytes analysed from two blood samples, 82 cells were 47,XX,+21 and 18 were 47,XX,+18. Giemsa banded E and G groups are
shown in the Fig. Examination of 100 cultured skin fibroblasts revealed only trisomy 21.

The patient's parents are deceased; there is no record of chromosome analysis being performed on them.

Discussion

Double trisomy, with or without mosaicism, has been reported in numerous instances. The majority of these cases has either full double trisomy (resulting from 2 nondisjunctions in gametogenesis or a single nondisjunction in a trisomic zygote) or, less often, mosaicism based on a single centromere missegregation in a trisomic zygote (Ebbin et al., 1972; Wilson et al., 1974). The same chromosomes are usually involved that are most often found in the single trisomies. A single postzygotic nondisjunction of a sex chromosome can also give rise to double aneuploidy with multiple cell lines, exemplified by such trisomy/monosomy mosaicism as XO/XXX, XO/XY/XXX, and XO/XX/XXX (Hamerton, 1971), or even double monosomy mosaicism (Weber et al., 1971).

We feel that the most probable events leading to the present instance of 'double' trisomy mosaicism are chromosome 18 nondisjunction and chromosome 21 anaphase lag (or nondisjunction) in a haematopoietic precursor of a trisomy 21 embryo. This seems likely because of the mother's advanced age at pregnancy, because trisomy 21 is much more prevalent in the patient's blood and is the only abnormality detected in skin, and because no normal or doubly trisomic cells were seen among 200 metaphases. Thus, two mitotic missegregations are probable. Since the trisomy 21 cell line is much more widely distributed, the patient has typical Down's syndrome. The report of Marks et al. (1967) describes a very similar case involving chromosomes 18 and 21, but only leucocyte chromosomes were analysed. Reports by Zellweger and Abbo (1965) and Warren and Keith (1971) describe similar situations involving D and E group chromosomes.

The Table lists cases of double aneuploid mosaicism where more than one mitotic nondisjunction and/or anaphase lag is the most likely explanation for the observed relatively complex mosaics. In addition, single aneuploid mosaics have been reported where two missegregations are required (Ribas-Mundo and Prats, 1965). Thus, it seems clear that multiple mitotic segregational errors occurring early in embryogenesis, while rare, should be expected from time to time, as should full double trisomies resulting from two segregational errors in gametogenesis. The separation of such sporadic occurrences from familial instances (discussed below) is not possible unless multiple cases are found in one family.

The genetic control over disjunction has been reviewed by Hamerton (1971) and is well known in Drosophila and in some plant species. In man, meiotic nondisjunction occurs in some families at an increased rate, as evidenced by the increase in risk of recurrence for trisomy (Mikkelsen and Stene, 1970), and by the much more frequent occurrence of double trisomies than is predicted by chance (Hamerton et al., 1965).

Multiple errors in gametogenesis are best exemplified by multisomy X and Y cases; in fact, pentasomy X has been reported (Mulchay and Stevens, 1975), probably resulting from successive oogenetic nondisjunction at both meioses (Race and Sanger, 1969).
In addition, mosaicism in man is familial in a number of instances, as reviewed by Hsu et al. (1970) for 10 families, and reported more recently by Zdansky et al. (1971), Siegelman (1972), Shih et al. (1974), and DeBault and Halmi (1975). It is probable that apparent instances of increased nondisjunction in humans have various causes, including dominant and recessive inheritance of factors affecting normal disjunction. These causes encompass mutant genes, chromosome structural variants, and environmental agents and, except for a few chromosome translocations, remain unidentified. For counselling, no increase in risk can be related in cases of sporadic mitotic double aneuploidy. Where multiple mitotic nondisjunctions have apparently occurred in a trisomic zygote the recurrence risk is for practical purposes the same as that for the primary trisomy.

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References

Case reports

Table: Cases of double aneuploid mosaicism requiring more than one unequal mitotic segregation

<table>
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<th>Report</th>
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<th>Probable explanation</th>
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</thead>
<tbody>
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<td>45, X/46, XY/48, XXXY</td>
<td>Nondisjunction and anaphase lag in XXY zygote</td>
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<tr>
<td>Baikie et al. (1965)</td>
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<td>Nondisjunction and/or anaphase lag in doubly trisomic zygote*</td>
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<td>Nondisjunction and/or anaphase lag in doubly trisomic zygote</td>
</tr>
<tr>
<td></td>
<td>(Case 3) 47, XY, +D/47, XY, +E (skin)</td>
<td>Nondisjunction and anaphase lag in trisomic zygote</td>
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<tr>
<td>Marks et al. (1967)</td>
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</tr>
<tr>
<td>Garson et al. (1969)</td>
<td>47, XX, +D/47, XX, +18/48, XX, +D, +E (blood)</td>
<td>Nondisjunction and/or anaphase lag in doubly trisomic zygote*</td>
</tr>
<tr>
<td>Porter et al. (1969)</td>
<td>47, XY, +D/47, XY + G/48, XY, +D, +G (blood)</td>
<td>Nondisjunction and/or anaphase lag in doubly trisomic zygote*</td>
</tr>
<tr>
<td>Warren and Keith (1971)</td>
<td>47, XY, +D/47, XY, +E</td>
<td>Two nondisjunctions at 2 cell stage of euploid zygote or nondisjunction and anaphase lag in trisomic zygote</td>
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<tr>
<td>Cohen and Davidson (1972)</td>
<td>47, XX, +21 (skin)</td>
<td>Nondisjunction (2) or anaphase lag (2) in lymphocyte precursor; trisomic zygote</td>
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<tr>
<td></td>
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<td>Weber et al. (1973)</td>
<td>47, XX, +21 (skin)</td>
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<tr>
<td></td>
<td>47, XX, +21/47, XX, +mar (blood)</td>
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</tr>
<tr>
<td>Schinzel et al. (1974)</td>
<td>45, X/47, XY, +18 (blood and skin)</td>
<td>Nondisjunction and anaphase lag in lymphocyte precursor: trisomic zygote</td>
</tr>
<tr>
<td>Gafter et al. (1976)</td>
<td>45, X/46, XX/47, XXX/47, XX, +8</td>
<td>Two nondisjunctions in euploid embryo</td>
</tr>
<tr>
<td>Present case</td>
<td>47, XX, +21 (skin)</td>
<td>Nondisjunction and anaphase lag in lymphocyte precursor: trisomic zygote</td>
</tr>
</tbody>
</table>

* Explained also by nondisjunction and lag in a trisomic zygote.


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The phenotype $A_eB$: a probable result of chimerism

**SUMMARY** An apparently normal healthy adult with the blood group phenotype $A_eB$ is described. The unusual ABO group is apparently the result of chimerism, the proportion of the minor population of cells being so small as to be only detectable by absorption and elution techniques.

**Case report**

The propositus was an apparently normal healthy blood donor, aged 24 years. During routine testing his red cells grouped as B, but no anti-A was detected in his serum. He had a brother and sister still living and also had a stillborn twin, sex unknown. His karyotype was 46,XY and all cells analysed showed a normal male pattern. His white cells typed as HLA A11, AW30: BW21, BW40.

**Serological findings**

Standard blood grouping methods were used throughout. Elution was carried out by the Landsteiner-Miller technique (as described by Dunsford and Bowley, 1967). In the ABO absorption and elution experiments, 0.5 ml packed cells were incubated with 2 ml anti-A for 2 hours at 4°C and the antibody was eluted into 1 ml physiological saline. In the anti-Fy* absorption and elution experiments, 4 ml packed cells were incubated with 8 ml anti-Fy* for 2 hours at 37°C and the antibody eluted into 1 ml antibody-free serum.

**Results**

The blood groups of the propositus and his family are as follows:

- **Propositus**, $A_eB$, Rh CcDeE, M, S+s-, P1+, Lu(a-), K-, Le(a-b+), Fy(a+b), Jk(a-b-).
- **Father**, $A_eB$, Rh CcDeE, M, S+s-, P1-, Lu(a-), K-, Le(a-b+), Fy(a+b), Jk(a-b-).
- **Mother**, $A_1$, Rh CcDeE, M, S+s-, P1+, Lu(a-), K-, Le(a-b+), Fy(a+b), Jk(a-b-).
- **Brother**, $B$, Rh ccDeEe, M, S+s-, P1+, Lu(a-), K-, Le(a-b+), Fy(a+b), Jk(a-b-).
- **Sister**, $A_1$, Rh CcDeEe, M, S+s-, P1+, Lu(a-), K-, Le(a-b+), Fy(a+b), Jk(a-b-).

The red cells of the propositus were not agglutinated by 10 different anti-A reagents or with a high titre anti-A+B that had been absorbed for anti-B. However, anti-A could be eluted from his red cells after they had been sensitised with anti-A. No anti-A was detected in his serum; however, on 2 occasions a weak anti-A, active at 4°C was found in his serum. He was a secretor of B and H substances, but not of A substance. His plasma contained B and H transferases within the normal range, but no A transferase was detected. The H antigen strength was similar to that of normal group B cells.

The blood groups of the family show that the only other antigen the propositus lacked, but his stillborn twin might have possessed, was Fy*. In view of this,
Trisomy 21 with 47,+18 lymphocyte cell line: double mitotic nondisjunction.
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