Down's Syndrome and Acute Leukaemia: A Cytogenetic Study

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The incidence of acute leukaemia in children with Down's syndrome is substantially greater than it is in normal children (Stewart, Webb, and Hewitt, 1958; Holland, Doll, and Carter, 1962), and the leukaemia complicating Down's syndrome is more often of myeloblastic type than is the case in childhood leukaemia generally (Boggs, Wintrobe, and Cartwright, 1962; Warkany, Schubert, and Thompson, 1963; Conen and Erkman, 1966). These indications that there may be fundamental differences between the leukaemias arising in association with trisomy 21 and those found in normal children have not been reflected in differences in the acquired cytogenetic abnormalities reported to date (Conen and Erkman, 1966). However, the combination of the two diseases is still rare and chromosome studies on further cases are required to evaluate fully the pattern of karyotypic abnormalities which may be present.

This report describes studies performed on a 3-year-old girl with acute leukaemia complicating Down's syndrome.

Case Report

A female child, aged 3 years, was admitted to hospital with a history of upper respiratory tract infections for several weeks and a recurrent rash on the legs and trunk for one month. Her birthweight had been 3060 g. after a normal pregnancy and delivery. At the time of her birth her mother was 21 years old and her father 24 years old. The parents and two younger sibs were in good health; there was no family history of Down's syndrome nor of leukaemia.

On examination the patient showed features typical of Down's syndrome. In addition, there was moderate skin and conjunctival pallor and a purpuric rash on the trunk. The liver was palpable 4 cm. below the right costal margin; the spleen was not palpable. There was no enlargement of the superficial lymph nodes. The haemoglobin value was 6.5 g./100 ml. and the white blood cell count was 10,200/cu. mm., with 38% myeloblasts, 3% myelocytes, 25% neutrophils, 7% mature basophils, and 27% lymphocytes. The platelet count was 23,000/cu. mm. A diagnosis of acute myeloblastic leukaemia was established by bone-marrow aspiration before treatment. Numerous myeloblasts and abnormal promyelocytes with basophilic granulation were present. The differential cell count showed 34% myeloblasts, 8% promyelocytes, 3% myelocytes, 3.5% metamyelocytes, 7.5% band forms, 4.5% segmented neutrophils, 2% basophils, 17% lymphocytes, 0.5% plasma cells, and 20% normoblasts.

The patient was transfused and given 6-mercaptopurine and prednisone, but remission of the leukaemia was not induced and she died four weeks later.

Chromosome Studies. Chromosome preparations were obtained from the bone-marrow aspirate by a modification of the method of Tjio and Whang (1962). Two aneuploid cell lines were present and only one cell with a normal chromosome number was counted (Table). The major line had 49 chromosomes (Fig.) with 6 small acrocentric chromosomes and 17 chromosomes in group C (49,XX,C+,G+,G+). The minor line had 47 chromosomes with one small acrocentric chromosome in addition to the female chromosome complement (47,XX,G+).

Discussion

The leukaemia in our patient was of myeloblastic cell type with basophilic granulation unusually prominent in the leukaemic cells. The cytogenetic studies revealed a minor cell line with 47 chromosomes interpreted as being non-leukaemic and showing constitutional trisomy 21, while the cells with 49 chromosomes presumably represent a clone of leukaemic cells. The additional chromosomes in the C and G groups have presumably arisen by non-disjunction during division of a precursor cell.

**TABLE**

<table>
<thead>
<tr>
<th>CHROMOSOME COUNTS ON BONE-MARROW</th>
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<tbody>
<tr>
<td><strong>Chromosome Counts</strong></td>
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<tr>
<td>------------------------</td>
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<tr>
<td><strong>No. of cells</strong></td>
</tr>
<tr>
<td>1</td>
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<td>11</td>
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<td>41</td>
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The earlier cytogenetic studies of acute leukaemia in children with Down's syndrome did not reveal any chromosome abnormalities other than those known to be associated with the primary condition (Sandberg et al., 1961; Tough et al., 1961; Wald et al., 1961; German, DeMayo, and Bearn, 1962; Thompson, Bell, and Little, 1963). Methods of preparation involving preliminary culture were used in most of these studies so that the leukaemic cells may not have been represented in the final metaphase preparations. More recent investigations using direct marrow methods suggest that acquired chromosome abnormalities are common in the acute leukaemia accompanying Down's syndrome (Ross and Atkins, 1962; Lejeune et al., 1963; Mercer, Keller, and Lonsdale, 1963; Warkany et al., 1963; Honda et al., 1964; Kiossoglou et al., 1964; Reisman, Mitani, and Zuelzer, 1964; Conen and Erkman, 1966). The abnormal cell lines shown have usually possessed 48 or 49 chromosomes with trisomy 21 and additional chromosomes most commonly of either group C or G, and occasionally of other groups. Similar varied and apparently non-specific abnormalities have been described in the largely lymphoblastic acute leukaemias occurring in children without Down's syndrome, again with frequent occurrence in groups C and G. The C group is numerically large, but the frequent occurrence of abnormalities in this group is said to be more than would be expected if these arose at random (Sandberg, 1968).

The comparison of cytogenetic findings in leukaemias arising in children with or without Down's syndrome is at present limited by the variable incidence of the chromosome abnormalities reported in different series as well as by the rarity of the combination of leukaemia and Down's syndrome and consequent lack of studies in this group.

**Summary**

Cytogenetic studies on bone-marrow cells from a 3-year-old girl with acute myeloblastic leukaemia complicating Down's syndrome showed two cell lines. One cell line showed trisomy 21 only, while the other, assumed to represent a clone of leukaemic cells, had a consistent chromosome number of 49 and a karyotype 49,XX,C+G+G+.
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