Chromosome Abnormalities in Down’s Syndrome Patients With Acute Leukemia

By Yasuhiko Kaneko, Janet D. Rowley, Daina Variokois, Robert R. Chilcote, John W. Moohr, and Daksha Patel

Chromosome and cytologic studies were performed on three Down’s syndrome (DS) patients with acute nonlymphocytic leukemia (ANLL). All three patients had an aneuploid clone in their leukemic cells: 50,XX,+6,+19,+21,+22, 48,XX,+8,+21, and 47,XY,+8,-21,+dic(21;21)(p13;p11). Every patient appeared to have acute undifferentiated leukemia when the blast cells were examined with Wright-Giemsa stain; cytochemistry studies, however, showed that the leukemic blasts were in an early stage of myeloid differentiation.

It is generally accepted that children with DS are at greater risk of acute leukemia (AL) than those without DS. Although DS patients were thought to have primarily acute myeloblastic leukemia (AML), Rosner and Lee provided evidence that the morphological types of AL in DS children were similar to those in leukemic children in general. The chromosome abnormalities in the leukemic cells of DS patients were considered to be similar to those found in the leukemic cells of other patients. Most patients, however, were reported before the advent of banding methods; banding has been used to identify abnormalities in only four of these patients. It is now apparent that some types of acute leukemia are associated with specific chromosome changes; for example, acute promyelocytic leukemia is associated with a 15;17 translocation. Here we describe chromosome abnormalities in three DS children with AL. Our findings and a review of data on 40 other cases suggest that certain karyotypic patterns in the leukemic cells of some DS children may be associated with a specific morphological type of AL.

MATERIALS AND METHODS

Cytology and Cytochemistry

Bone marrow (BM) and peripheral blood (PB) were stained with Wright-Giemsa. The cytochemical reactions included peroxidase, periodic acid Schiff (PAS), alpha naphthyl acetate esterase (ANAE) with and without NaF inhibition, naphthol AS-D chloroacetate esterase (NASDCA), and acid phosphatase (ACP).

Immunologic Studies

Immunologic markers on leukemic cells in peripheral blood and/or bone marrow were evaluated; these included E-rosettes, EAC-rosettes, and surface immunoglobulin (SIg). Leukemic cells in the peripheral blood of patient no. 2 were examined for the presence of the common-ALL antigen.

Chromosome Studies

Chromosomes of all three patients were studied in PB cells cultured for 24 hr without phytohemagglutinin (PHA). Bone marrow cells of patient no. 1 that were prepared with a direct technique and PB cells of patient no. 3 that were cultured for 96 hr with PHA were also studied. The cells were analyzed with regular Giemsa staining and Q-banding methods. To examine cells from patient no. 3, we also used silver staining and C-banding.

CASE REPORTS

Patient no. 1

A 34-mo-old black girl was admitted to the University of Chicago Hospitals and Clinics (UCHC) on April 2, 1980, with fever, lassitude, and pallor. The patient had typical features of DS when she was born. At the time of her birth, her mother was 24 and her father was 28 yr old. The mother was addicted to methadone and marijuana in the prenatal period. The patient’s elder brother and younger sister were in good health; there was no family history of DS or of leukemia. The patient was diagnosed as having patent ductus arteriosus (PDA), a cleft mitral valve; ligation of the PDA was performed 15 days after birth. At 17 mo of age, the patient had pneumococcal bacteremia with arthritis of the right knee. She was treated with penicillin and had a prompt clinical response.

On admission, her conjunctivae were extremely pale, and several small lymph nodes were palpated in the cervical, axillary, and inguinal regions. The spleen was palpated 4 cm below the left costal margin, and the liver was 7 cm below the right costal margin. Her hemoglobin was 3.9 g/dl, the white blood cell count was 66,400/μl with 70% undifferentiated blasts, 18% segmented neutrophils, and 6% monocytes, and the platelet count was 12,000/μl. The BM smear showed hypercellularity with 55.0% undifferentiated blasts, 12.0% mature granulocytes, 2.0% myelocytes, 2.0% myelocytes, 12.0% mature granulocytes, 11.5%...
lymphocytes, and 6.0% normoblasts. Samples of BM and PB were obtained for chromosome and cytochemical studies. Radiologic and laboratory examinations revealed that she had congestive heart failure, dehydration, and acute renal failure. Despite intensive supportive therapy, she died 7 days after admission. No antileukemic drugs were administered.

**Patient no. 2**

A 23-mo-old black girl was admitted to UCHC on May 15, 1980, with fever and diarrhea. The patient had typical features of DS when she was born. At the time of her birth, both her mother and her father were 35 yr old; her parents, elder brother, and sister were in good health. When she was 13 mo of age, surgical correction of the arteriovenous canal was performed. At 15 mo, she had anemia, thrombocytopenia, and hemoglobinuria. A BM aspirate revealed erythroid hyperplasia with megaloblastic changes and about 10% myeloblasts. She was treated with prednisone for 3 wk, but the anemia and thrombocytopenia persisted.

On admission, her spleen was palpated 6 cm below the left costal margin, and the liver was palpated 7 cm below the right costal margin. No systemic lymphadenopathy was found. Her hemoglobin was 6.8 g/dl, the white blood cell count was 34,200/μl with 64% undifferentiated blasts, 14% segmented neutrophils, 20% lymphocytes, and 2% monocytes, and the platelet count was 8,000/μl. The BM aspirate showed hypercellularity with 63.5% undifferentiated blasts, 7.0% promyelocytes, 1.0% myelocytes, 6.5% lymphocytes, and 11.5% normoblasts. A sample of PB was obtained for chromosome and cytochemical studies. The patient did not respond to treatment with systemic vincristine, prednisone, and L-asparaginase, nor to intrathecal methotrexate injection. She subsequently was treated with adriamycin and cytosine arabinoside. She developed pancytopenia and died of sepsis on July 2, 1980.

**Patient no. 3**

The patient was a 40-mo-old white boy with the clinical features of DS. He was noted to have pancytopenia with a small percentage of blasts in his PB when he was 18 mo old. A BM aspiration was obtained for chromosome and cytochemical studies at this time. He was given cyclophosphamide, vincristine, cytosine arabinoside, and prednisone and had a prompt response. He currently has normal white blood cell counts, with no blasts in the PB after the second course of therapy. Details of the clinical features will be reported elsewhere.

**RESULTS**

**Cytology, Cytochemistry, and Immunologic Studies**

The results of morphological and cytochemical studies of leukemic cells in the three patients are summarized in Table 1.

**Patient no. 1**

The biopsy and aspirate contained up to 50% blasts (Fig. 1). The cells were large, with fine chromatin, and often contained several large nucleoli. Cells with a similar appearance were seen in the PB smears. The peroxidase reaction was negative, and only two blasts in the entire aspirate showed a weak reaction with naphthol ASD chloroacetate esterase (NASDCA). The alpha naphthyl acetate esterase (ANAE) reaction was diffusely positive, as is seen in some myelogenous leukemias, especially in the myelomonocytic leukemias. The acid phosphatase (ACP) was positive in almost all of the blasts. At autopsy, leukemic infiltrates were seen in the BM, spleen, lymph nodes, lungs, and kidneys. A terminal nodule in the kidney contained a few primitive cells that showed a positive reaction with NASDCA. None of the blasts in the PB and the BM formed E or EAC rosettes, and none were S Ig-positive. This case was diagnosed as acute leukemia with possible tendency toward myeloid differentiation.

<table>
<thead>
<tr>
<th>Table 1. Morphological and Cytochemical Findings in Leukemic Cells of Three Patients With Down’s Syndrome (DS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
</tr>
<tr>
<td><strong>Patient no. 1 PB</strong> (BM) Undifferentiated; Decreased Cytoplasm</td>
</tr>
<tr>
<td>Peroxidase</td>
</tr>
<tr>
<td>Periodic Acid Schiff</td>
</tr>
<tr>
<td>Alpha naphthyl butyrate</td>
</tr>
<tr>
<td>Alpha naphthyl acetate esterase</td>
</tr>
<tr>
<td>Alpha naphthyl acetate esterase with NaF</td>
</tr>
<tr>
<td>Naphthol AS-D chloroacetate esterase</td>
</tr>
<tr>
<td>Acid phosphatase</td>
</tr>
</tbody>
</table>

Scale: 0 to ++ ++ ; PB, peripheral blood; BM, bone marrow.
LEUKEMIA CHROMOSOMES IN DOWN'S SYNDROME

Fig. 1. (A) A large number of blasts in the bone marrow aspirate of patient no. 1 have a very fine chromatin structure and several large nucleoli. Some cells contain a moderate amount of cytoplasm. (B) Peripheral blood smear of the same patient likewise shows very immature cells, some of which resemble myeloblasts (Wright-Giemsa x1104).

Patient no. 2

The BM biopsy and aspirate contained approximately 60% immature cells that had scanty cytoplasm and no evidence of differentiation (Fig. 2). The peroxidase reaction was negative, but ACP was positive in approximately 70% of the blasts. The reaction product was granular and diffusely distributed throughout the cytoplasm; this result is seen in primitive cells, but can also be observed in myeloblasts. The periodic acid Schiff reaction (PAS) showed both diffuse and coarse granularity. The ANAE reaction was weak in this case, however; it also showed a diffuse pattern in several blasts. None of the blasts in the PB formed E or EAC rosettes, none were SIg-positive, and none were positive for the common-ALL antigen. This case was very difficult to subclassify and was therefore called acute leukemia, probably myelogenous.

Patient no. 3

The PB smear contained approximately 40% immature cells that had scanty cytoplasm, primitive nuclei, and multiple nucleoli, most of them small. The cytchemical reaction was weakly positive with ANAE and strongly positive with ACP. Both of these reactions were seen in a single focus, as can be seen in lymphoid cells as well as myeloid precursors. PAS positivity was seen only in granular form. None of the blasts in the PB formed E or EAC rosettes. These findings are consistent with very immature cells, which have some tendency toward myeloid differentiation.

Chromosome Studies

The chromosome findings are summarized in Table 2.

Patient no. 1

Eight of 15 banded cells from PB and 4 of 5 from BM had the same karyotype, 50,XX,+6,+19,+21,+22 (Fig. 3). Four banded cells from PB were 47,XX,+21. The former cells appeared to be leukemic, whereas the latter cells had the constitutional karyotype expected in a patient with DS. A cell with 46 chromosomes had a normal female karyotype. It was unclear whether this was a broken cell.

Patient no. 2

Three of 20 banded cells from PB had the karyotype 48,XX,+8,+21; 11 others had 47,XX,+21. One of the remaining 6 banded cells, which showed random loss of chromosomes due to cell breakage, had an extra chromosome no. 8. The cells with 48 chromosomes
Table 2. Chromosomal Findings in the Three DS Patients With Acute Leukemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of Chromosomes</th>
<th>Percentage of Abnormal Cells†</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 45</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>15(4)</td>
<td>1(1)*</td>
<td>3(2)*</td>
</tr>
<tr>
<td>Patient 1</td>
<td>BM (direct)</td>
<td>1(1)</td>
<td>6(0)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>PB (- PHA)</td>
<td>2(2)*</td>
<td>6(4)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>PB (- PHA)</td>
<td>6(4)*</td>
<td>8(2)*</td>
</tr>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>PB (+ PHA)</td>
<td>6(1)*</td>
<td>19(9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Number of metaphases analyzed with Q banding.
*Random loss of chromosomes due to cell breakage.
†Cells with abnormalities in addition to DS abnormality. Percentage of abnormal cells was calculated on the basis of banding of cells.
‡One of 2 cells had an extra chromosome No. 8.

This patient appeared to be leukemic, and those with 47 may have been nonleukemic cells with the expected constitutional karyotype.

Patient no. 3

Eight of 15 banded cells from PB cultured without PHA had 47 chromosomes, including an extra chromosome no. 8, one normal chromosome no. 21, and an abnormal chromosome that appeared to be dicentric, composed of two chromosomes no. 21. This rearranged chromosome appeared to include a short arm of chromosome no. 21, a part of which was positive in silver staining, between the two centromeres; two centromeric regions were stained with the C-banding method. The karyotype was 47,XY,+8,+21,+dic(21;21)(p13;p11) (Fig. 4). The remaining seven cells, which showed random loss of chromosomes due to cell breakage, also had an extra no. 8, loss of one no. 21, and a dic(21;21) chromosome.

This patient was considered to have DS with a chromosome rearrangement in his constitutionally abnormal cells. Such an abnormality is usually caused by a Robertsonian translocation between two chromosomes no. 21, or by an isochromosome for the long arm of chromosome no. 21. The probable mechanism of chromosome rearrangement is, however, breakage of one chromosome no. 21 at band p13, breakage of the other no. 21 at band p11, and reunion of the chromatids. We are aware of one report on a patient with DS who had this rearrangement.34 Our patient is the only one with translocation trisomy 21 among 43 DS patients with AL who are summarized in Table 4.

DISCUSSION

Fraumeni et al. have reported that the median age of non-DS children with AL is about 3 yr.35 Whereas acute lymphoblastic leukemia (ALL) predominated

Fig. 3. Q-banded chromosomes of a cell from peripheral blood of patient no. 1. Arrows show extra chromosomes nos. 6, 19, 21, and 22. Karyotype is 50,XX, +6, +19, +21, +22.

Fig. 4. Q-banded chromosomes of a cell from peripheral blood of patient no. 3. Arrows show an extra no. 8 and a dicentric chromosome composed of two chromosomes no. 21. The short arm of a chromosome no. 21 is retained between two centromeres. The karyotype is 47,XY, +8, –21, + dic(21;21) (p13;p11).
between the ages of 1 and 5 yr, AML predominated below the age of 1 yr and after age 9. On the whole, ALL was more common than any other type of leukemia among non-DS children. The morphological classification of 38 DS children whose chromosomes in leukemic cells were studied, and that of 1187 non-DS children with leukemia, are summarized in Table 3. The distribution of leukemic cell types in the 38 DS children reviewed here, which showed a predominance of acute nonlymphocytic leukemia (ANLL) and only a small number of cases of ALL, is in striking contrast to the distribution in non-DS children, although the number of DS patients is relatively small. The median age in 35 of the 38 DS patients whose ages were known was 2 yr, and only three patients were less than 1 yr old. The explanation for the difference between this result and that of Rosner and Lee, which indicated that the morphological types of AL were similar in DS and non-DS children, is unclear. Twenty-six of the 38 DS patients in our review were included in that of Rosner and Lee.

Sixteen DS patients with AL were reported to have the karyotype 47,XX,+21 or 47,XY,+21, which was not considered abnormal. These patients had leukemias of various hematologic types (Table 4). The chromosomes of only one of these were studied with banding. Each of the three patients whom we studied, however, had a clonal chromosome abnormality. These patients, together with those previously reported to have chromosome abnormalities, provide karyotypes on 27 DS patients with leukemia (Table 4). Thus, chromosome abnormalities were found in about 63% of the DS patients with AL; this is similar to the incidence in other patients with AL.

### Table 3. Morphological Classification for 38 DS Children Whose Chromosomes Were Studied and That in 1187 Non-DS Children Reported by Fraumeni et al.

<table>
<thead>
<tr>
<th></th>
<th>AML*</th>
<th>AMOL†</th>
<th>ALL</th>
<th>AUL‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS children (38)</td>
<td>25</td>
<td>1</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Non-DS children (1187)</td>
<td>281</td>
<td>91</td>
<td>523</td>
<td>292</td>
</tr>
</tbody>
</table>

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### Table 4. Chromosomes and Morphological Classification of Leukemic Cells in DS Patients

<table>
<thead>
<tr>
<th>Classification</th>
<th>AML</th>
<th>EL</th>
<th>ALL</th>
<th>ASL*</th>
<th>AUL</th>
<th>Classification Not Given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only +21</td>
<td>Propp et al., Conen and Erkman (cases 3, 4, 7), Reisman et al. (case 13), Okada et al.</td>
<td>Hagemeyer et al. (case 14)</td>
<td>Lampart, Hellriegel et al. (case 4)</td>
<td>Conen and Erkman (cases 5, 6), Hellriegel (case 3)</td>
<td>Tough et al. (cases 1, 3, 4, 5)</td>
<td></td>
</tr>
<tr>
<td>+C(B)</td>
<td>Warkany et al., Honda et al., Reisman et al. (case 14), present patients 2+ and 3¶</td>
<td>Hellriegel et al. (case 5)§</td>
<td>Johnston§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+F(19), +G(22), +other abnormalities</td>
<td>DeMayo et al., Kiosoglu et al., Petit et al., Conen and Erkman (case 1), present patient 2¶</td>
<td>Juberg and Jones</td>
<td>Lejune et al. (leukoblast), Berger et al. (hemoblast)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other abnormalities</td>
<td>Mercer et al., Schleiermacher et al., Ross and Atkins, Buchanan and Becroft, Reithore et al., Vincent et al., Benedict et al. (AMMOL)</td>
<td>Hagemeyer et al. (case 26)</td>
<td>Hellriegel et al. (case 1)</td>
<td>Reisman et al. (case 15), Hellriegel et al. (case 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodiploidy</td>
<td>Crisalli et al.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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*ASL, acute stem cell leukemia; AUL, acute undifferentiated leukemia; AMMOL, acute myelomonocytic leukemia.
†Karyotypes were studied with banding.
‡Patients were cited from two different articles.
§Patients had two related clones, one of which was +C.
Of the 27 DS children with chromosome abnormalities, 3 had ALL, 2 had acute stem cell leukemia (ASL), 19 had ANLL, and 2 others were described as having “hemoblasts” or “leukoblasts.”

The distribution of the modal chromosome number in 19 DS patients with ANLL and 38 non-DS ANLL children with an abnormal karyotype reported in the literature were summarized in Table 5. The distribution pattern in the two groups is quite different. None of these DS patients with ANLL had a modal number that was hypodiploid or pseudodiploid. Nine of the 19 had an extra chromosome in addition to trisomy no. 21, and the remainder had modal numbers ranging from 49 to 59. In contrast, pseudodiploidy is most frequent (47%) in non-DS childhood ANLL. Half of the DS patients had 2 or more extra abnormal chromosomes, which were seen in only 8% of non-DS children.

We also compared the pattern of extra chromosomes in DS ANLL children with that in non-DS ANLL children. Among the 19 DS children, 15 had extra C chromosomes (78.9%), 7 had extra Fs (36.8%), and 10 had extra Gs (52.6%). In contrast, of 38 non-DS children, 6 had extra Cs (15.8%), 6 had extra Fs (15.8%), and none had extra Gs. Thus, the incidence of extra C, F, and/or G chromosomes, particularly C and G chromosomes, is higher in the DS children than in the non-DS children. The karyotypes of only 5 of the 19 DS children were studied with banding. An extra chromosome no. 8 was seen in 2 of them, and an extra no. 19 in 2, an extra no. 21 in 2, and an extra nos. 6, 15, 18, and 22 each in one patient.

On the other hand, among 38 non-DS children, an extra chromosome no. 8 was seen in 5 of them, an extra no. 19 in 6, an extra Y in 2, and an extra nos. 1, 6, 13, 15, and 18 each in one patient. The high incidence of hyperdiploidy with the frequent occurrence of extra C, F, and/or G chromosomes suggests that certain chromosomes in leukemic cells of DS ANLL children may be particularly susceptible to nondisjunction, although selection may also play a role.

It would be interesting to determine whether certain karyotypic abnormalities in DS children are associated with a specific type of leukemia, as is the case in some other leukemias. Our patient no. 1 had the karyotype 50,XX,+6,+19,+21,+22. Seven other patients were reported to have similar karyotypes characterized by hyperdiploidy with 3 and more extra chromosomes, two of which were a no. 19 and a no. 22 (the patient of Berger et al.) or an F and a G (in six patients). On the basis of morphological and immunologic studies, the leukemic cells in our patient no. 1 were thought to be undifferentiated; however, cytochemical findings indicated that they were early myeloid cells. The presence of primitive cells that may be of myeloid origin in patients who had +F and +G has been reported by Berger et al. and Lejeune et al. In three other patients with this karyotype, the diagnosis of AML is uncertain because of the lack of cytologic data supporting that diagnosis. The patient of Juberg and Jones had erythroleukemia (EL), which terminated in AML. Thus, the +19,+22 chromosome abnormality may be associated with AL in an early stage of myeloid differentiation.

Our patients nos. 2 and 3, with an extra no. 8 chromosome as determined with banding, had several cytologic and clinical features in common, including a preleukemic stage 8–12 mo prior to the development of leukemia. Neither patient responded to vincristine and prednisone, which were used for treatment of ALL patients. The leukemic cells of both patients were very immature, and cytochemical study suggested that the blasts were probably in early myeloid differentiation. These cells could not be differentiated from the blasts in our patient no. 1 with +19,+22.

A gain of no. 8 without other abnormalities is frequently seen in various forms of ANLL. A simple gain of no. 8 has, however, not been reported in ALL except in one non-DS ALL patient; further analysis, however, disclosed abnormalities in addition to trisomy no. 8. The ALL patient of Morse et al. had two different clones initially, one of which was 47,XX,+8; these cells were present during remission and therefore may not have been leukemic. Thus far, these findings indicate that a simple trisomy no. 8 in leukemic cells is related to myeloid differentiation. This is compatible with the diagnosis of ANLL in

Table 5. Distribution of Modal Chromosome Numbers in 19 DS ANLL Children With an Abnormal Karyotype and That in 38 non-DS ANLL Children With an Abnormal Karyotype

<table>
<thead>
<tr>
<th>Modal Chromosome Number</th>
<th>DS children (19)</th>
<th>Non-DS children (38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>46</td>
<td></td>
<td>18†</td>
</tr>
<tr>
<td>47</td>
<td>9*</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>49</td>
<td>3</td>
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</tr>
<tr>
<td>50</td>
<td>2</td>
<td>1</td>
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<tr>
<td>51</td>
<td>1</td>
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<tr>
<td>52.6%</td>
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<tr>
<td>53</td>
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<td></td>
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<tr>
<td>59</td>
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</tbody>
</table>

*Patient no. 3 with a dic(21;21)(p13;p11) constitutional abnormality is classified as having 48 chromosomes.
†One patient with a t(13;14) constitutional abnormality is classified as having 46 chromosomes.
patients nos. 2 and 3. Three other patients with a simple + C had AML;10,18 one had thrombocytopenia 8 mo prior to the development of leukemia and was described as having primitive myeloid cells.19

Thus, the modal chromosome number in DS patients with ANLL is hyperdiploid, with gains particularly of C, F, and/or G chromosomes. The abnormalities of +8 and of +19, +22 in DS children may be associated with AL in an early stage of myeloid differentiation. The combination of chromosome studies with banding techniques and cytologic studies that include cytochemistry and immunologic markers will clarify whether children with DS have an increased incidence of AL in an early stage of myeloid differentiation. These studies will also establish whether particular subgroups of this type of leukemia are associated with a specific chromosome abnormality.

ACKNOWLEDGMENT

The authors thank Nicole Raymond for photography and Karen Gordon and Fay Yates for secretarial assistance.

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Chromosome abnormalities in Down's syndrome patients with acute leukemia

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