Transient Leukemoid Reaction and Trisomy 21 Mosaicism in a Phenotypically Normal Newborn

By Garrett M. Brodeur, Gary V. Dahl, Dorothy L. Williams, Robert E. Tipton, and David K. Kalwinsky

Transient leukemoid reactions that resemble acute leukemia have been well described for infants with trisomy 21 (Down syndrome). We report a phenotypically normal 3-day-old boy with hepatosplenomegaly, leukocytosis, and circulating myeloblasts. On chromosome analysis, trisomy 21 was found in all blood and bone marrow cells. However, only 4% of cultured skin fibroblasts were trisomic and the other 96% were normal, thus indicating mosaicism. Without treatment, the leukocyte count gradually returned to normal and the organomegaly diminished. Subsequently, chromosome analysis of blood and bone marrow disclosed a predominance of cells with a normal karyotype. These findings suggest that mosaicism could be responsible for the transient leukemoid reactions in some newborns—i.e., the trisomic cells may temporarily gain a proliferative advantage over the normal cells, perhaps by inhibiting their growth. Serial cytogenetic studies, as well as chromosome analysis of more than one tissue, may help to distinguish transient leukemoid reactions from acute leukemia in infants.

ACUTE leukemia occurs with increased frequency in newborns with Down syndrome. In contrast to that of later childhood, the predominant type of leukemia in infancy is myeloblastic. Conditions that appear identical to acute myeloblastic leukemia, but spontaneously resolve, are not unusual in infants with Down syndrome. While some consider these conditions to be acute leukemia that remits without treatment, others contend that they are transient leukemoid reactions. The mechanism responsible for spontaneous resolution is unclear, but may be related to an inherent abnormality in some patients with Down syndrome, since it is exceedingly rare in normal newborns. We present a phenotypically normal infant with trisomy 21 mosaicism who had a transient leukemoid reaction that resembled acute myeloblastic leukemia. Serial cytogenetic studies of several types of cells provided useful information about the spontaneous resolution of this child's disease.

MATERIALS AND METHODS

Cytogenetic studies of blood were done with a modification of the technique of Moorhead et al. Cultures of blood lymphocytes were incubated overnight without phytohemagglutinin (PHA) and for 72 hr with PHA stimulation. Bone marrow studies were done according to a modification of the technique of Tjio and Whang. Fibroblasts were grown from a skin biopsy specimen and harvested for cytogenetic analysis after 33–51 days in culture. A modification of the trypsin-Giemsa technique of Seabright was used for the chromosome banding of all preparations.

CASE REPORT

A 3-day-old white boy was referred to St. Jude Children's Research Hospital (SJCRH) for evaluation of acute myeloblastic leukemia. His mother was a 24-year-old white woman (gravida V, para IV, aborta O), and the pregnancy, labor, and delivery were uncomplicated. There was no blood group incompatibility or evidence of congenital infection. A complete blood count was done on his second day of life when excessive bleeding developed after circumcision. The leukocyte count was \(160 \times 10^9/liter\) with 60% blasts that resembled myeloblasts. The patient was then referred to SJCRH for further evaluation.

On admission to SJCRH, he had a normal appearance and was in no acute distress. Abnormal physical findings included an enlarged liver, palpable 4 cm below the right costal margin, and an enlarged spleen, palpable 5 cm below the left costal margin. An erythematous papular rash on the face, chest, and lower extremities was consistent with erythema toxicum. Laboratory data included a hemoglobin of 15.9 g/dl, and a leukocyte count of \(136 \times 10^9/liter\) with 19% neutrophils, 3% lymphocytes, 8% eosinophils, and 70% myeloblasts. The platelet count was \(242 \times 10^9/liter\) and the reticulocyte count was 3%. The bone marrow aspirate was hypercellular with 50% replacement by primitive cells that resembled myeloblasts and reacted with peroxidase, Sudan Black, and specific esterase stains. These clinical and cytologic findings were consistent with a diagnosis of acute myeloblastic leukemia.

Since newborns with acute leukemia frequently have Down syndrome, he was examined carefully for the characteristic features. The facial appearance, hands, feet, and dermatoglyphics were all normal. Radiographs were also normal except that the acetabular angle was 17\(^\circ\)—2 standard deviations below the mean value for newborns. Chromosome analysis disclosed trisomy 21 in all cells from the bone marrow and in all cells from blood incubated with and without PHA. Five days later, a skin biopsy was done and the patient's fibroblasts were cultured for later chromosome analysis.

Although he was phenotypically normal, the cytogenetic findings suggested that the patient had Down syndrome. Since leukemic conditions sometimes resolve spontaneously in these patients, no chemotherapy was given. Anemia and thrombocytopenia developed during the first month. Transfusions with packed red cells were required, but other complications, such as hemorrhage or infection, did not develop. Within 2 mo, the blood counts had returned to

From the Divisions of Hematology-Oncology and Pathology, St. Jude Children's Research Hospital, and the Department of Pediatrics, Section of Medical Genetics, University of Tennessee Center for Health Sciences, Memphis, Tenn.

Supported in part by Clinical Cancer Education Grant CA-23944, Cancer Center Support (CORE) Grant CA-21765, the Leukemia Program Project Grant CA-20180, a grant from the National Foundation, March of Dimes, and by ALSAC.

Submitted October 16, 1979; accepted December 19, 1979.

Address reprint requests to Garrett M. Brodeur, M.D., Division of Hematology-Oncology, St. Jude Children's Research Hospital, 332 North Lauderdale, P.O. Box 318, Memphis, Tenn. 38101.

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0006-4971/80/5504-0024$01.00/0

Blood, Vol. 55, No. 4 (April), 1980

691
normal and the organomegaly had diminished. Based on the cyto-
genetic study of cultured fibroblasts that were obtained earlier, the
child had mosaicism for trisomy 21 (47 trisomic and 96 normal
cells).

By the time he was 3 mo old, the organomegaly had almost
disappeared. The hemoglobin at that time was 9.4 g/dl and the
leukocyte count was 8800 × 10^9/liter with 50% neutrophils, 40%
lymphocytes, 7% monocytes, 2% eosinophils, 1% basophils, and no
blasts. The platelet count was 406 × 10^9/liter. After 72-hr PHA
stimulation, 76% of blood lymphocytes had a normal karyotype, and
24% had the 47,XY,+21 karyotype. Only 34 bone marrow cells
were satisfactory for analysis, and all had a normal karyotype
(Table 1). At 9 mo of age, he appeared to be healthy and developing
normally. At the parents’ request, chromosome analyses of blood
and bone marrow were not done.

<table>
<thead>
<tr>
<th>Patient Age (days)</th>
<th>Tissue Sampled</th>
<th>Cells Counted</th>
<th>Percent of Cells Counted</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Blood</td>
<td>50</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>8 Blood</td>
<td>50</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>100 Blood</td>
<td>75</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>100 Marrow</td>
<td>34</td>
<td>9</td>
<td>100</td>
</tr>
</tbody>
</table>

*Not applicable.

Table 1. Cytogenetic Data

DISCUSSION

The transient leukemic reaction or “transient acute leukemia” in patients with Down syndrome is a
well recognized but poorly understood phenomenon. In
a review of 56 newborns with Down syndrome who had
the clinical and hematologic features of acute leukemia,2 the hematologic disorder resolved “spontaneously
” in 21. Resolution also occurred in 4 children with
Down syndrome who developed the leukemoid condition when they were 1 mo to 3 yr old. The mechanism
of this transient leukemoid reaction is not understood,
but it may indicate ineffective regulation of myelo-
poiesis due to delayed maturation of the myeloid and
other bone marrow elements.2,3 Also, some of these
children may have a physiologic stress produced by
associated conditions, such as blood group incompati-
bility, infection, or heart disease, that may stimulate
an overreaction of the myeloid elements in the bone
marrow.

In the English literature there are nine case reports
of cytogenetic studies in newborns with Down
syndrome who had spontaneous resolution of a condi-
tion indistinguishable from acute leukemia.4-12 Six of
these nine patients had a 47,+G karyotype and were
still free of disease 1.5–4 yr later. Another died when
he was 8 mo old and had no evidence of leukemia at
autopsy. The last two patients developed leukemia
again when they were about 2 yr old. At birth, one

patient had a small percentage of bone marrow cells
with an abnormal karyotype (48,XY,+21,+C).8 This
clone disappeared spontaneously but reappeared when
fulminant acute leukemia developed. The other was a
2-yr-old who had an abnormal clone (59,+4C,+3D,+E,+2F,+3G) at age 2 in addition to the
trisomy 21 karyotype; cytogenetic studies were not
done during the neonatal period.9 There is only one
report of transient spontaneous remission of acute
leukemia in a phenotypically normal newborn, and
this patient had a normal karyotype.13

In our patient, all of the cells from blood samples
incubated with PHA had the 47,XY,+21 karyotype,
although only 70% were myeloblasts. This finding was
puzzling, since the PHA should have stimulated the
proliferation of thymus-derived lymphocytes, and
some normal karyotypes should have been found.
Similarly, trisomy 21 was present in all cells from the
bone marrow when only 50% of it had been replaced
by myeloblasts. The absence of normal karyotypes
may indicate that the proliferation of trisomic cells
suppressed production of the cytogenetically normal
cells. Within 3 mo, this apparent proliferative advan-
tage was lost. Cells with a normal karyotype became
dominant, and myeloblasts disappeared from the
blood. Also, none of the trisomic cells persisted in the
marrow, although the percentage of marrow blasts
was still slightly increased (9%).

In about half of the cases of acute myeloblastic
leukemia, the malignant cells have an abnormal
karyotype, and gain, loss, or rearrangement of chro-
mosome 21 occurs with increased frequency.14 At first
it was not clear whether the blood and marrow cells
with trisomy 21 in our patient represented a malignant
clone or his “normal” somatic cells. However, later
studies of skin fibroblasts indicated that the child had
mosaicism for trisomy 21. It is likely that this child
had a leukemoid reaction involving the trisomic cells
that subsequently were replaced by cells with a normal
karyotype. Mosaicism for trisomy 21 may be the basis
for the transient leukemoid reaction in some newborns.
This may also apply to newborns who are phenotypi-
cally normal, as was the case for our patient.

Serial cytogenetic analysis should help to distin-
guish between congenital acute leukemia and transient
leukemoid reactions in newborns. Further, any
newborn suspected of having leukemia should have
cytogenetic analysis of blood and bone marrow. Irre-
spective of the phenotype, findings of trisomy 21
should warrant chromosome analysis of skin fibro-
blasts to check for mosaicism. These patients should
not be given chemotherapy unless their disease
progresses despite supportive treatment. Patients with
LEUKEMOID REACTION TRISOMY 21 MOSAICISM


a normal karyotype and those with abnormal karyotypes other than trisomy 21 probably should be treated, since the likelihood of spontaneous resolution is remote.13

ACKNOWLEDGMENT

We are grateful to Dr. Alvin M. Mauer for helpful suggestions and to Jane Seifert for reviewing this manuscript.

REFERENCES

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