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Two Chromosome Aberrations in the Child of a Woman With Systemic Lupus Erythematosus Treated With Azathioprine and Prednisone

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A boy with microcephaly, unusual facial features, micropenis, and growth retardation was born to a 30-year-old woman who took azathioprine and prednisone before and during pregnancy for systemic lupus erythematosus. The child has two apparently de novo chromosomal abnormalities: an apparently balanced translocation between chromosomes 6 and 14 and an interstitial deletion of chromosome 7. The karyotype is 46,XY,del(7)(q21);t(6;14)(q21;q12). Use of azathioprine and prednisone in pregnancy has been associated with intrauterine growth retardation, congenital malformations, and transient chromosome breaks in the blood of newborns. To our knowledge, this is the first report of de novo constitutional chromosome abnormalities in such an infant. We suggest that the assessment of infants born to parents treated with azathioprine should include a chromosome study, even if the infants seem to be normal.

Key words: azathioprine, balanced translocation (6,14), chromosome 7, deletion 7q, maternal systemic lupus erythematosus, multiple de novo chromosome abnormalities.

INTRODUCTION

Azathioprine and prednisone are immunosuppressive agents, commonly used together to prevent renal homograft rejection and to treat autoimmune diseases such as systemic lupus erythematosus (SLE). Prednisone is teratogenic in rodents, inducing mostly cleft palate; in humans, use of the drug during pregnancy has been associated with low birth weight of infants [International Agency for Research on Cancer, 1981a].

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Azathioprine causes cleft palate, skeletal malformations, and other abnormalities in mice and rabbits; it is mutagenic in bacteria, yeast, Drosophila, and mice [International Agency for Research on Cancer, 1981b]. In humans, there have been reports of congenital anomalies and low birth weight in infants of women treated with azathioprine and prednisone [Penn et al, 1980]. Azathioprine is also associated with transient chromosome breakage and increased sister chromatid exchange in lymphocytes of patients and newborns exposed in utero [International Agency for Research on Cancer, 1981b].

We describe an infant with multiple congenital anomalies and an apparently balanced translocation between the long arms of chromosomes 6 and 14 as well as an interstitial deletion of most of chromosome band 7q21. Both parents had normal chromosomes. The infant's mother took azathioprine and prednisone before conception and during pregnancy to control her SLE.

CLINICAL REPORT

A 6-month-old male infant was referred to Johns Hopkins Hospital for evaluation of failure to thrive. He was the 2,000-gm, 43.5-cm product of a 34-week gestation to a 30-year-old, gravida 1 black woman. The parents were nonconsanguineous, and the family history was unremarkable. His mother had a 14-year history of SLE with heliotropic rash, hemolytic anemia, and autoimmune hepatitis. She was being treated with azathioprine (100 mg/day) and prednisone (30 mg/day) at the time of conception. When the pregnancy was confirmed during the 10th week of gestation, prednisone was stopped and azathioprine was reduced to 50 mg/day. At 30 weeks azathioprine was increased to 100 mg/day due to recurrence of hemolytic anemia. Since the anemia had not improved by the 32nd gestational week, azathioprine was increased to 150 mg/day and prednisone was restarted at 30 mg/day. A normal spontaneous vaginal delivery at 34 weeks followed spontaneous onset of labor. Apgar scores were 6 at 1 minute and 9 at 5 minutes. A nuchal cord and meconium staining were present at birth. Head circumference was 28 cm (50th centile for 30 weeks gestation). Abnormal face and a small penis were noted. The newborn course was complicated by 1) Coomb's positive hemolytic anemia; 2) hyperbilirubinemia; 3) abdominal distension with guaiac-positive stools, from which enteropathic E coli was cultured; 4) a seizure associated with transient hypocalcemia; 5) late metabolic acidosis of prematurity; 6) inadequate growth despite an intake up to 190 calories/kg/day and correction of the acidosis. After discharge the infant had chronic diarrhea and continued to have inadequate weight gain despite demand feeding with Prosobee® at an intake of up to 32 oz/day.

At 6 months the infant's length and head circumference were appropriate for a 1-month-old male, and weight was appropriate for 39 weeks gestation. He had an asymmetric, unusual face, with right side larger than left, epicanthal folds, and relatively short palpebral fissues, anteverted nares, a tented upper lip, and large, prominent, pointed auricles with simple helices and anteversion and retroflexion on the right side (Fig. 1). His muscle tone was good despite a markedly decreased muscle mass. Stretched penile length measured 3 cm (1–2 S.D. below the mean for age). No ophthalmologic, neurological, cardiac, or skeletal abnormalities were found. Six ossification centers were seen on hemiskeletal survey (1–2 S.D. below the mean for age). His psychomotor development was appropriate for 3 months of age. A barium

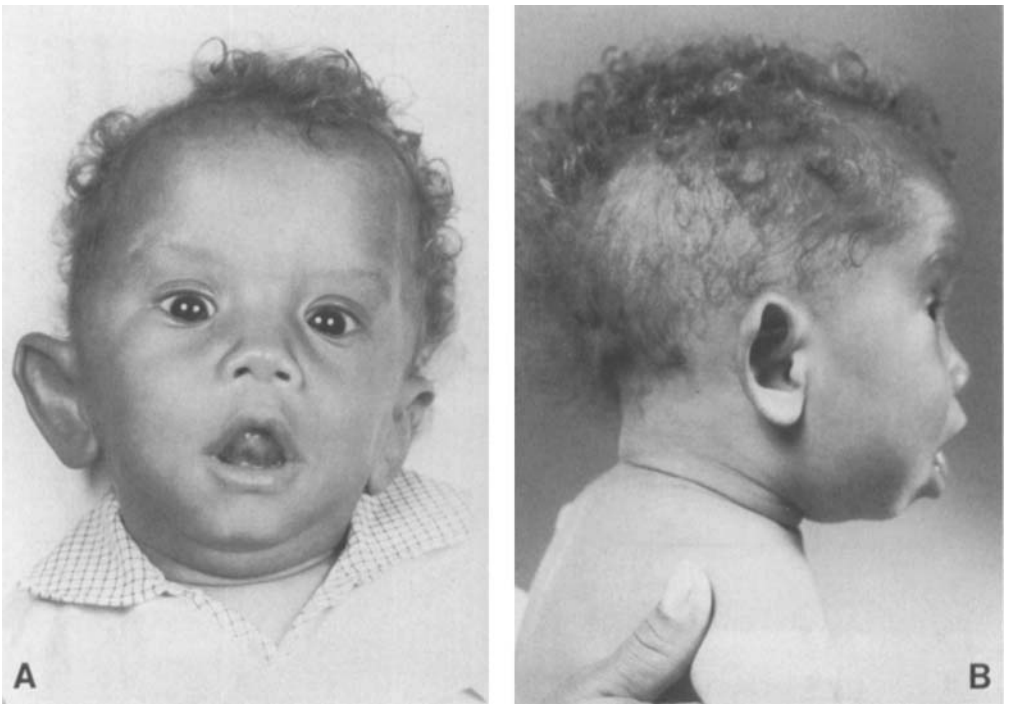


Fig. 1A,B. The proband at six months of age.

enema showed significant narrowing of the sigmoid colon with proximal dilatation. A colonic stricture was surgically removed.

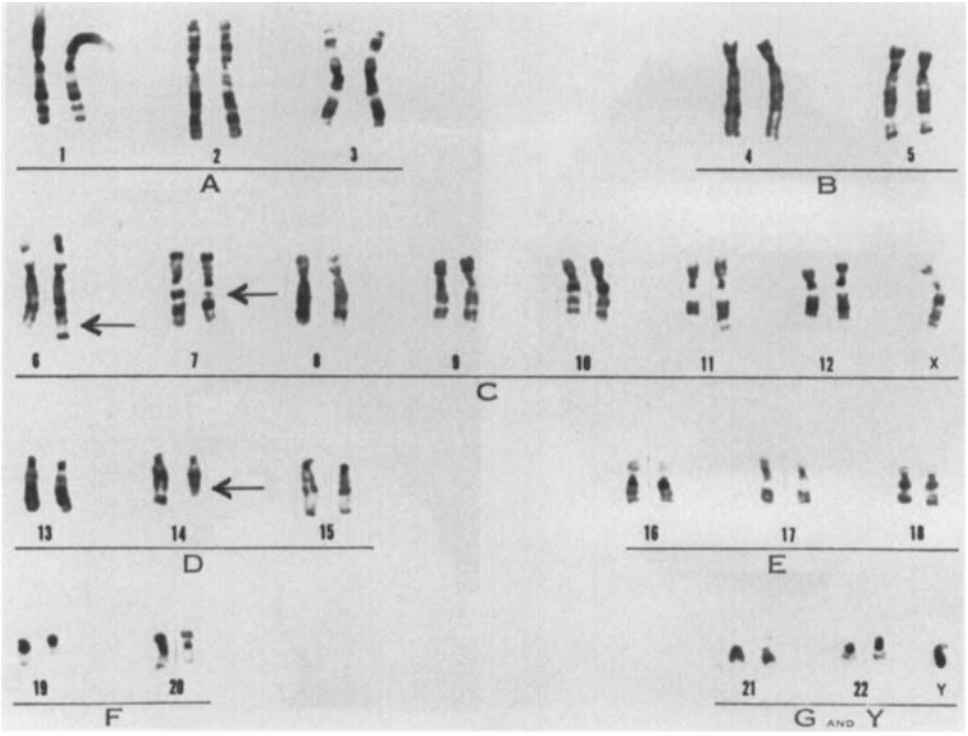
At 14 months of age, length and head circumference were appropriate for 5 months of age, and weight for 3 months. His penile size had not changed during the previous 8 months. Serum thyroxine, growth hormone, and testosterone measurements were normal. Development was at the 11-month level.

The child did not resemble his parents.

CYTOGENETIC STUDIES

Cytogenetic analysis of 25 peripheral blood lymphocytes, using Giemsa (G) and reverse (RBA) banding showed, in every cell, a translocation involving the long arms of chromosomes 6 and 14, with breakpoints at 6q21 and 14q12. In addition, an interstitial deletion of most of band 7q21 was seen in every cell, with probable breakpoints at q21.1 and q21.3. (Due to banding symmetry in the region of the deletion, however, breakpoints within q21.1 and at q22 cannot be ruled out). The karyotype (Fig. 2) is 46,XY,del(7)(q21);t(6;14)(q21;q12).

Both parents had normal chromosomes. Chromosome breakage was assessed in the mother, who was taking 50 mg/day of azathioprine plus prednisone. No breaks or gaps were seen in 20 cells; however, one cell had a reciprocal translocation between chromosomes 3 and 12. The sister chromatid exchange rate was not significantly



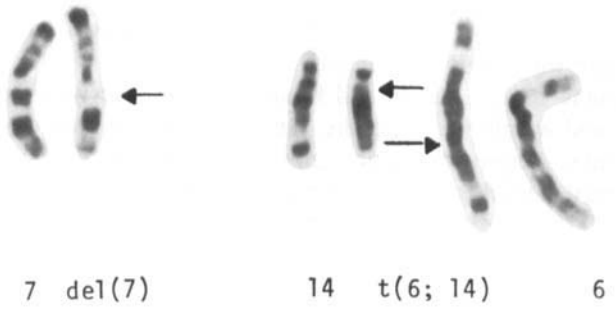


Fig. 2. A) G-banded Karyotype of proband. B) Partial karyotype of proband showing chromosome abnormalities. Arrows indicate interstitial deletion of most of band 7q21 and reciprocal translocation between long arms of chromosomes 6 and 14.

increased over that of a normal control (6.7 vs 5.3 exchanges/cell for mother and control, respectively; ten cells of each were examined). Due to poor growth of the maternal culture, additional cells were not available for analysis.

A comparison of the number 14 chromosomes of the parents and child was made, using G and RBA banding, in an attempt to trace the source of the child's translocated chromosome 14. However, polymorphisms were uninformative.

DISCUSSION

The phenotypic abnormalities of our propositus have a number of possible causes. First, the deletion of most of band 7q21 makes the child monosomic for this region. Interstitial deletions of the long arm of chromosome 7 were recently reviewed [Gibson et al, 1982]. All patients had developmental retardation; several shared manifestations with our patient, although none was identical. Microcephaly was found in three of seven patients. One patient [Gibson et al, 1982] had a wide nasal bridge, anteverted nares, and a small phallus in addition to several other facial and somatic abnormalities. Another infant [Ayraud et al, 1976] had "leprechaun facies" and numerous other anomalies and a larger del(7q) than did our patient. The authors concluded that interstitial deletions of 7q21 do not result in a consistently recognizable syndrome. Additional case reports and more detailed cytogenetic mapping will be helpful in correlating phenotype with deletions in this region of chromosome 7.

A second possible cause of phenotypic abnormalities in our proband is his translocation between 6q21 and 14q12. Although the translocation is reciprocal and there is no apparent duplication or deletion of chromosome material, there may nevertheless be loss of from one to thousands of nucleotide pairs at a breakpoint which would be cytologically undetectable.

Other factors that may also contribute to the patient's abnormal phenotype are his continuous intrauterine exposure to both the maternal disease and the drugs. Maternal lupus has been associated with an increased frequency of spontaneous abortions and intrauterine growth retardation, but not with congenital malformations [Estes and Larsen 1965; Zurier et al, 1978; Devoe and Taylor 1979]. Prednisone and azathioprine have both been associated with intrauterine growth retardation. Parental use of azathioprine in conjunction with prednisone has also been implicated in an increased frequency of congenital malformations. In one study of six pregnancies during which both drugs were administered for SLE, four resulted in term, small-for-gestational age infants and two in abortion [Sharon et al, 1974]. Another study assessed 44 infants born to women with renal transplants treated with prednisone and azathioprine during pregnancy [Penn et al, 1980]. Four (9%) had major congenital anomalies: pulmonary stenosis, a deformed hand, and bilateral inguinal hernias. Twenty infants (45%) were premature, and six (14%) were small for gestational age. The same study assessed 60 infants born to men with renal transplants who received both drugs prior to conception. Two (3%) had multiple congenital anomalies. Results of chromosome studies, if done, were not reported.

There are numerous reports of increased chromosome breakage in bone marrow and peripheral lymphocytes of patients treated with azathioprine and in lymphocytes of infants born to mothers who received this drug during pregnancy [van Went 1979; International Agency for Research on Cancer, 1981b]. However, there appears to be no documentation of infants with constitutional chromosome rearrangements. Possibly such de novo abnormalities would be found if the assessment of infants born to parents on drug therapy included banded chromsome analysis. Chromosome breaks often result in deletions and structural rearrangements [Therman, 1980]; azathioprine-induced breaks in germ cells prior to conception could produce a child with translocations and deletions such as our propositus.

Multiple de novo structural abnormalities in one individual are rare, although such cases have been reported [Simoni et al, 1979; Stoll et al, 1979]. None was found

in 4,765 babies screened by band-stained cytogenetic methods in 2 studies of consecutive newborns [Lin et al, 1976; Buckton et al, 1980], giving a frequency of less than 0.0002.

Thus, our propositus' 2 chromosomal abnormalities may have been drug-induced rather than being a chance coincidence of two rare events. Cytogenetic study of a series of babies, even if their phenotype appears normal, would help to establish the risk of drug-induced chromosome changes in the offspring of patients on azathioprine and prednisone therapy.

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