We describe a male infant with unusual facial appearance, relative pancytopenia, bilateral simian creases, and an accessory nipple. Cytogenetic analysis showed deletion of the long arm of chromosome 11 [46,XY,del(11)(pter→q23.2:)]. Bone-marrow study showed a myelodysplastic change of hemopoietic cells compatible with peripheral blood findings. Pachygyria of the temporal and frontal lobes was demonstrated by magnetic resonance image (MRI) of the brain. We present our findings in order to contribute to the information on 11q23 deletion. Am. J. Med. Genet. 75:341–344, 1998.

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KEY WORDS: Jacobsen syndrome; del(11)(q23); myelodysplastic syndrome; pachygyria

INTRODUCTION

Jacobsen et al. [1973] first described a multiple congenital anomalies/mental retardation (MCA/MR) patient with a partial deletion of the long arm of chromosome 11. Since then, several reports of this genetic syndrome have been published [Schinzel et al., 1977; Felding and Mitelman, 1979; Küster et al., 1985; Palka et al., 1986; Ishida et al., 1992]. In most reported cases, the breakpoints were found at 11q23 [Küster et al., 1985]. The most common characteristics of this syndrome are mental retardation (100%), high-arched palate (100%), “carp mouth” (95%), broad and/or flat nasal bridge (90%), micrognathia (90%), trigonocephaly (85%), hypertelorism (80%), epicanthal folds (60%), prenatals and postnatal growth retardation (50–60%), ptosis (50%), congenital heart anomalies (50%), and thrombocytopenia (50%). The association has been named Jacobsen syndrome [Schinzel et al., 1977].

Herein we present a patient with Jacobsen syndrome, associated with a myelodysplastic change of hemopoietic cells.

CASE REPORT

A 6-month-old Chinese boy was referred due to developmental delay. He was the second child of a 30-year-old healthy mother. The pregnancy had been uneventful, no medication or X-ray exposure had been noted, and no familial history suggesting a chromosomal abnormality could be detected. He was delivered vaginally normally at 40 weeks’ gestation, and birth weight was 2,370 g. Anemia (Hb, 9.0 g/dl) and thrombocytopenia (platelet count, 70 × 10^9/l) were noted after birth, but brain, renal, and abdominal ultrasonography showed no evidence of bleeding. At age 6 months, weight was 6,495 g (10–25th centile), length 67 cm (50–75th centile), and head circumference 43 cm (25–50th centile). Clinical findings included bilateral ptosis, abnormal eyelash arrangement (absence of eyelash in the inner one-third portion), lagophthalmos, small carp mouth (Fig. 1A), low-set and deformed ears (Fig. 1B), right accessory nipple over the anterior axillary line and the second intercostal space, bilateral simian creases (Fig. 1C), clinodactyly of all fingers, trigonocephaly, and micrognathia (Fig. 1D). Neurological development was compatible with age 5 months. Brain MRI showed decreased sulcation and enlarged gyri at both the frontal and temporal areas (Fig. 2), and slight delay of myelination. Echocardiography revealed a normal heart.

Peripheral blood count documented pancytopenia (white cell count 3.9 × 10^9/l, hemoglobin 9.2 g/dl, platelet count 69 × 10^9/l, and reticulocyte count 1.5%), with the differential count as follows: segment form, 31%; eosinophil, 2%; basophil, 3%; monocyte, 5%; and lymphocyte, 59%. Blood smear showed many giant platelets and target cells. The target cells were due to thalassemia trait with evidence of microcytosis of red cells (MCV, 77 mm^3), and the results of hemoglobin electrophoresis showed HbF 4.6%, HbA2 3.3%, and HbA 92.1%. While a bone-marrow aspiration indicated normocellularity, with the differential count comprising 6.4% myeloblast, 12% promyelocyte, 8.2% myelocyte, 5.6% metamyelocyte, 1.4% band form, 0.6% segment form, 3.2% monocyte, 3.2% eosinophil, 24.4% lymphocyte, 0.2% plasma cell, 28.8% proerythroblasts and nor-
moblast, and 6.0% reticulum cell. Megakaryocytic changes included small forms, increased nucleus-to-cytoplasm ratio, decreased nuclear lobulation, multiple small separated nuclei, and mononuclear, bizarre appearance. Myeloid abnormalities included nuclear cytoplasmic asynchrony, hypogranularity, and poor maturation. The number of erythroblasts was markedly reduced. Iron staining showed decreased iron store in bone-marrow cells. Chromosome analysis was performed on bone-marrow cells after a 1-day culture without any stimulants and on 3-day cultured peripheral blood lymphocytes with phytohemagglutinin. All metaphase cells analyzed with G-banding and high-resolution G-banding showed a terminal deletion of the long arm of chromosome 11 [del(11)(pter→q23.2:)] (Fig. 3). Chromosome analysis of the parents was refused.

**DISCUSSION**

Jacobsen syndrome is caused by distal 11q deletion. Patients with the syndrome lose portions of chromosome bands distal to 11q23, q24, and/or q25 [Penny et al., 1995]. Terminal deletions extending proximal to 11q23 generally have not been observed. An exception was an infant who was a mosaic for 46,XY/46,XY,del(11)(pter→q21:) and had holoprosencephaly, cyclopia, and arrhinencephaly [Helmuth et al., 1989]. Terminal deletion extending proximal to 11q23 may be lethal, and this exceptional case survived to 35 weeks of life because of his mosaic status. The deletion in Jacobsen syndrome patients resulted from a de novo terminal deletion, unbalanced segregation of balanced translocations in parents [Jacobsen et al., 1973], de novo translocations [Van Hemel et al., 1992], or other chromosomal rearrangements, such as a ring chromosome 11 [Palka et al., 1986; Penny et al., 1995].

The clinical manifestations of a qter→q23 deletion are nonspecific, and may be observed in many other syndromes. Nevertheless, Jacobsen syndrome is recognizable by prenatal and postnatal growth retardation, trigonocephaly, abnormal eyelash arrangement, epicanthal folds, ptosis, “carp mouth” high-arched palate, retrogrenathia, low-set and malformed ears, cardiac anomalies, mental retardation, and thrombocytopenia or pancytopenia [Penny et al., 1995]. Approximately 25% of patients die before age 2 years, mainly of cardiac defects. Life expectancy for this syndrome remains unknown [Penny et al., 1995]. Our patient showed the following anomalies of Jacobsen syndrome: ptosis, “carp-shaped” mouth, trigonocephaly, and relative pancytopenia. Clinical manifestations found in some cases of del(11)(q23) but not observed in our patient include...

Fig. 1. Patient shows bilateral ptosis, abnormal eyelash arrangement (absence of eyelashes in inner one-third portion), small “carp mouth” (A), low-set and deformed ear (B), simian crease (C), and trigonocephaly and micrognathia (D).
malformations of the heart, intestine, kidney, and genitalia.

The bone-marrow findings in our patient were compatible with myelodysplastic syndrome (MDS). MDS may progress to cytopenia and a propensity in some cases for transformation into acute myelogenous leukemia. MDS seems to evolve in a multistep process, in which sequential mutational events (chromosomal and/or molecular) occur, into genetically unstable clones, such as monosomy 7 or 5, trisomy 18, and deletion 5q, 11q, and 18q [Sokal et al., 1980; Nowell, 1982; Musi-lova et al., 1989]. As the 11q deletions frequently occur at bands q22–q23, the loss of gene(s) that is localized within the overlapping region, rather than alternations of base sequences, could be due to molecular events implicated in the evolution of myelodysplastic clones.

Fig. 2. Brain MRI at age 5 months shows pachygyria of the frontal area (arrow in A), and of the temporal area (arrow in B).

Fig. 3. Karyotype of the patient, showing del(11)(pter→q23.2):.
Although deletions and/or rearrangements involving 11q23 in childhood leukemia/MDS occur usually de novo in a single hematopoietic stem cell, the deletion in our patient was of germline origin. To our knowledge, there has no report of association of Jacobsen syndrome with MDS. The pancytopenia and myelodysplastic change of hemopoietic cells in our patient could be explained by 11q23 deletion. The study of childhood MDS by Bader-Meunier et al. [1996] demonstrated that some congenital anomalies, such as Down syndrome, Shwachman disease, Dubowitz syndrome, Pearson disease, and neurofibromatosis with MDS, can exhibit particular anomalies and offer a chance of spontaneous remission without mention of Jacobsen syndrome. In addition, many infantile leukemias associated with chromosomal rearrangements involving 11q23 have a poor prognosis [Felix et al., 1995].

The cause of mental retardation in Jacobsen syndrome remains unknown. In our patient, pachygyria of the temporal and frontal lobes was shown by brain MRI. Although his neurologic development has been within normal limits, mental deficiency is evident in pachygyria infants [Kuzniecky et al., 1989].

REFERENCES


