Clinical Report

Primary Immunodeficiency in Combination With Transverse Upper Limb Defect and Anal Atresia in a 34-Year-Old Patient With Jacobsen Syndrome

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We describe a 34-year-old male patient with Jacobsen syndrome associated with a broad spectrum of anomalies and an increased susceptibility to infections. Features commonly seen in Jacobsen syndrome were short stature, mental retardation, congenital heart disease, cryptorchidism, strabismus, distal hypospadia glandis, and mild thrombocytopenia. Chromosome analysis disclosed a mosaic 46,XY,del(11)(q24.1)/46,XY karyotype with a very low percentage of normal cells. In addition, transverse upper limb defect, imperforate anus, and hearing impairment were noted. Cellular anomalies include functional impairment and deficiency of T-helper cells, and a low serum immunoglobulin M (IgM)-level. The presence of a transverse limb defect and primary immunodeficiency has not been reported previously in Jacobsen syndrome.

FAMILY HISTORY

This patient was born in 1969 as the 5th child of unrelated German parents. His mother was 37-years-old and his father was 39 at the time of delivery. One of his brothers had an isolated atrial septal defect (ASD). Parents and siblings are of normal intelligence and normal phenotype. There is no family history of diabetes or unusual predisposition to clotting abnormalities.

PRE- AND PERI-NATAL HISTORY

The pregnancy and birth were uneventful. His birth weight was 2,750 g (3rd centile), length was 51 cm (25th centile), occipitofrontal head circumference (OFC) was 35 cm (25th centile). A terminal transverse defect of the right arm, anal atresia, hypospadia glandis, and undescended testicles were noted at birth. At 2 days of life, the membranous atresia of the anus was corrected surgically. At the same time an enlargement of the heart was noticed on a preoperative X-ray of the lungs. However, the diagnosis of a ventriculo-septal defect (VSD) of the heart was not noted at the time.

DEVELOPMENT IN CHILDHOOD AND ADULTHOOD

The mother noticed mild speech developmental delay in relation to her older children, whereas walking without support was within normal range. Mild hearing impairment and mental retardation were noted in early childhood, and he received special schooling. The patient never learned to write and read properly, or to
do simple arithmetic calculations. At the age of about 5 years, a VSD of the heart was diagnosed by echocardiography. During childhood, there was an increased incidence of viral and bacterial infections. At the age of 2 years, a severe varicella-zoster-infection occurred with prolonged illness. A second varicella-zoster-infection was diagnosed when the patient was 19-years-old. At the age of 10, orchidopexy was carried out. At the age of 26 the VSD was corrected surgically. He had episodic urinary incontinence and permanent impotence. He experienced episodes of severe eczema on the capillitium and trunk with superinfections and ulcerations at age 32. He lives with his parents and works at a handicap workshop.

**PHYSICAL EXAMINATION**

At the age of 34 years, his height was 155 cm (−3.4 SD), weight 60 kg (50th centile), OFC 52 cm (−3.5 SD) (Fig. 1). He had coarse hair, a high frontal hairline, a wide flat nasal bridge, thin upper lip- and a high-arched palate. Neuroophthalmological examination revealed a left-sided nonparalytic strabismus as well as limitation of horizontal and vertical gaze movements of his right eye (Fig. 2). He had amblyopia, corneal hypesthesia, and pigment epithelium defects of the iris. The ears were normal. His short neck displayed bilateral hypotrophy of the sternomastoid muscles. His muscle stretch reflexes were very brisk, but plantar responses were downgoing. There was complete absence of the right hand and wrist with a hypoplastic forearm which showed four rudimentary cutaneous finger-like “stubs” distally (Fig. 3). There were no signs of pectoralis and/or nipple anomalies. A mild thoraco-lumbar scoliosis was noted. He had hypospadia glandis, without other genital abnormalities. The patient had a normal beard and pubic hair pattern. Skin exam revealed there were multiple ulcerations with pustules and surrounding inflammation, scarring, and erythematous lichenification. On initial exam, his body temperature was 39°C.

A CT-scan of the skull revealed no abnormalities of the brain. Audiological examination demonstrated bilateral symmetrical sensorineural hearing impairment. Radiological examination of the right arm revealed short and dysplastic bones of the radius and ulna, with lack of any carpal hand bones (Fig. 4). Additional radiologic investigations displayed a mild thoraco-lumbar scoliosis and a normal number and shape of the vertebrae. Thoracic X-ray and CT-scan revealed some enlargement of the heart, no vascular abnormalities, and a normal, symmetrical appearance of pectoralis muscles. Echocardiography did not show any signs of a re-shunt from the corrected VSD and was without any other associated heart or vascular defects. In particular, no abnormalities of the proximal aorta and great vessels could be determined. Sonography of the abdominal organs including kidneys was completely normal. Gastrografin swallow test demonstrated no tracheoesophageal fistula. Dental examination revealed hypoplasia of two teeth (18, 28) and aplasia of two teeth (38, 48) (specified according to the Fédération Dentaire Internationale, FDI). Microbiological examination of the skin ulcerations showed *Streptococci A*, and an examination for fungi was negative.

Conventional cytogenetic studies were performed on phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes and long-term cultured skin fibroblasts. Partly due to low mitotic indices, several lymphocyte analyses only had a resolution of 300–400 bands per haploid genome only. A final lymphocyte chromosome analysis by GTG banding reached a resolution of 400–500 bands per haploid genome. The resolution of the fibroblast chromosome analysis was approximately 400 bands per haploid genome. While no aberrations were detected in the first blood lymphocyte analyses, the final analysis with the higher resolution demonstrated a terminal deletion in 11q in 17 of 18 cells (Fig. 5). Karyotype was determined to be mos
46,XY,del(11)(q24.1)[17]/46,XY[1]. The deletion was confirmed in all skin fibroblast metaphases.

To exclude a microdeletion of the DiGeorge syndrome/Velocardiofacial syndrome critical region in 22q11.2, a fluorescence in situ hybridization (FISH) using a Tuple1 probe (Vysis, Downers Grove, UK) was performed on skin fibroblast metaphases according to manufacturer’s instructions. To exclude an interstitial as opposed to a terminal deletion of distal 11q, a two color FISH using chromosome 11 subtelomeric probes [Knight et al., 2000] was performed on lymphocyte metaphases. PAC 770G7 was used for terminal 11q24.3 and PAC 44H16 as a control probe in 11p15.5. Probe DNA isolation and labeling as well as hybridization were performed as described elsewhere [Engels et al., 2002]. Hybridizations were analyzed on an Axioplan 2 imaging fluorescence microscope (Zeiss, Jena, Germany) equipped with a Sensys CCD camera (Photometrics, Tucson, Arizona) and a Cytovision workstation (Applied Imaging, Newcastle upon Tyne, UK). For the Tuple1 probe, a deletion was excluded in 12 metaphases analyzed. The chromosome 11 specific two color FISH gave the following results: while four out of 25 metaphases gave a normal signal pattern with signals in both subtelomeric regions of both chromosome 11 homologues, a deletion of the signals of PAC 770G7 in 11q24.3 was demonstrated in the remaining 21 metaphases (Fig. 6), which confirmed a terminal deletion 11q as a mosaic pattern. The proband’s karyotype is mos 46,XY,del(11)(q24.1)[17]/46,XY[1].ish11q24.5(770G7-)[21]/(770G7x2)[4].

Neither the patient’s parents nor siblings were available for chromosomal analysis.
LABORATORY FINDINGS

Analysis of the white blood cells showed a marked T-helper cell deficiency of over 50% (196 CD3⁺CD4⁺ T-cells/mm³ blood) compared to normal cell numbers (400–1,800 CD3⁺CD4⁺ T-cells/mm³ blood). The platelet count was between 100 and 110 × 10⁹/L (normal values 140–450 × 10⁹/L). The serum level of immunoglobulin M (IgM) was 35 mg/dl (normal values 60–263 mg/dl). The serum parathormone was normal, and a 24 hr urinary specimen showed normal values of calcium and phosphate. HIV 1/2, immunoglobulin G (IgG), and IgM was negative. Granulocyte function (phagocytic uptake and respiratory burst activity) was normal. Natural killer (NK) cells were present in relative normal numbers (17% CD3⁻CD56⁻CD16⁺ NK cells, normal values from 10 to 20%). Spontaneous NK cell-mediated cytotoxicity of K562 target cells and antibody-dependent-cellular-cytotoxicity (ADCC) of rabbit Ig-coated Raji cells was normal (data not shown). T-cell stimulatory function (phagocytic uptake and respiratory burst activity) was normal. Natural killer (NK) cells were present in relative normal numbers (17% CD3⁻CD56⁻CD16⁺ NK cells, normal values from 10 to 20%). Spontaneous NK cell-mediated cytotoxicity of K562 target cells and antibody-dependent-cellular-cytotoxicity (ADCC) of rabbit Ig-coated Raji cells was normal (data not shown). T-cell stimulatory function (phagocytic uptake and respiratory burst activity) was normal. Natural killer (NK) cells were present in relative normal numbers (17% CD3⁻CD56⁻CD16⁺ NK cells, normal values from 10 to 20%). Spontaneous NK cell-mediated cytotoxicity of K562 target cells and antibody-dependent-cellular-cytotoxicity (ADCC) of rabbit Ig-coated Raji cells was normal (data not shown). T-cell stimulatory capacity (vitro towards the mitogen PHA was reduced to about 50% of the normal value of immunocompetent persons. In an allogeic mixed lymphocyte reaction (MLR), T-cells responded poorly to major histocompatibility-complex (MHC) -nonidentical dendritic cells (Fig. 7). T-cells of healthy persons responded well to dendritic cells of the patient. MHC class-I expression on lymphocytes and MHC class-II expression on monocytes and PHA-activated T-cells was normal.

Skin tests for delayed type hypersensitivity reactions were negative.

DISCUSSION

This is a 34-year-old patient with an unusual and complex phenotype resulting from 11q⁻ mosaicism, probably of de novo origin. His karyotype was mos 46,XY,del(11)(q24.1)[17]/46,XY[1]. FISH analysis using a probe in the subtelomeric region of 11q confirmed the presence of a terminal deletion in the majority of metaphases, which corresponded to the diagnosis of Jacobsen syndrome [Michaelis et al., 1998; Tunnallcliffe et al., 1999].

There is a high expression variability of the phenotype in Jacobsen syndrome [Pivnick et al., 1996], and the severity of clinical abnormalities in these patients is not correlated with the extent of the deletion. It has been suggested that the presence of the 11q⁻ phenotype depends on the loss of genetic material between band 11q24.1 and the terminal end of the long arm of chromosome 11 [O’Hare et al., 1984]. Fryns et al. [1986] identified the crucial band for this syndrome as 11q24.1 and showed that a very distal 11q24.2 deletion resulted in a different phenotype. The most frequent cytogenetic breakpoint observed in 11q deletion syndrome is in 11q23.3, a folate-sensitive fragile site [Nancarrow et al., 1994]. It has been suggested that fragile sites may predispose to chromosome breakage in vivo [Glover and Stein, 1988]. Of the reported cases with Jacobsen
syndrome, the majority are terminal deletions, most of the remaining cases are interstitial deletions.

The most consistent findings associated with deletions of 11q23→qter include psychomotor and growth retardation, trigonocephaly, hypertelorism, low-set ears, cardiac defects, digit anomalies, and thrombocytopenia or pancytopenia [Cousineau et al., 1983]. This patient exhibits short stature, mild mental retardation, a wide nasal bridge, cardiac defect, upper transverse limb defect, mild thrombocytopenia, and a primary immunodeficiency. Trigonocephaly was absent, even though it is reported in 80–95% of patients with 11q deletion [Lewanda et al., 1995]. It was assumed that an 8 cM region distal to11q23.3 or possibly proximal to 11q24.1 could play a role in craniostenosis and may lead to trigonocephaly [Penny et al., 1995]. Absence of trigonocephaly in this patient suggests the deletion may be located distally from that region.

Characteristic digit anomalies in distal 11q patients are cutaneous syndactyly, clinodactyly, short fingers, and toe abnormalities. An associated transverse upper limb defect has never been reported in Jacobsen syndrome. The etiology of digit anomalies in Jacobsen syndrome are unknown. The patient’s complete absence of the right hand and wrist with a hypoplastic forearm and four rudimentary cutaneous finger-like “stubs” could represent an extensive reduction defect. Isolated terminal transverse limb defects have been described as a result of an interruption of the early embryonic blood supply in the subclavian arteries, the vertebral arteries and their branches [Bavinck and Weaver, 1986]. Possible causes for the reduction of blood flow in the subclavian arteries have been suggested, among them are thrombi, blood vessel edema, hemorrhage, amniotic bands and others [Al-Sannah, 2000; Hunter, 2000]. The thrombocytopenia commonly seen in Jacobsen syndrome and also in this patient could lead to hemorrhage followed by vascular disruption and transverse limb defects. In addition, at least theoretically, in this patient, one can not exclude immunologic dysfunctions with inflammatory mechanisms in the early embryonic circulation leading to localized hypoxemia and ischemia followed by disruption of blood vessels as a cause of his transverse terminal limb defect. Finally, there is an association with limb defects and congenital heart disease, although echocardiography revealed no additional vascular or heart defects [Rosano et al., 2000].

Although recurrent infections such as upper respiratory airway infections in Jacobsen syndrome have been described [Ono et al., 1996], these manifestations are rather common in childhood. However, the patient’s increased susceptibility towards herpes viruses and bacterial infections after childhood assumes both cellular and humoral deficiencies. NK cells are able to lyse sensitized target cells (rabbit Ig coated Raji cells, a Burkitt’s lymphoma cell line) through the mechanism of ADCC and to kill K562 target cells (a chronic myelogenous leukemia cell line) naturally [Garcia-Penarrubia et al., 1989; Robertson and Ritz, 1990]. The NK cell number of this patient, relative to his PBMC and NK cell function, revealed normal results compared to an age-matched control (data not shown). The immunodeficiency in our patient focuses clearly towards a primary abnormal T-cell function. There is diminished, but not absent, lymphocyte response to mitogens, and a depressed proliferative response to allogeneic cells. Skin tests for delayed-type hypersensitivity were abnormal. The low serum IgM level found in our patient might be due to aberrant regulation of B cells by the deficient T-cells. This secondary humoral deficiency is a known phenomenon in DiGeorge syndrome, Wiskott–Aldrich syndrome, and other T-cell immunodeficiencies [Radford et al., 1986; Sleasman et al., 1990]. Interestingly, there is one report of a patient presenting with humoral immune deficiency (decreased serum IgM and IgA levels) in the 11q deletion syndrome [Sirvent et al., 1998]. It is not clear if this immune dysfunction is due to aberrant cellular mechanisms. Evaluation of the immune system should be undertaken in all patients with multiple abnormalities and recurrent infections to help to delineate syndromes, allowing for better patient care and family counselling. In this patient, the incapacity to eliminate bacterial and viral antigens may play an important role in the persistence of eczema.

Many syndromes are associated with hearing impairment. In patients with chromosomal 11 deletions, sensorineural deafness has been occasionally reported [Ho et al., 1987; Megarbane et al., 2002]. Other groups report normal hearing with difficulties in processing auditory informations that lead to speech delay as a manifestation of 11q deletion [Muleh and Jenkyn, 1977]. Generally, improved techniques for auditory assessment of infants and young children may account for increased reports of hearing impairment with malformations [Hall et al., 1995]. This could also apply to this case, since hearing impairment was mild and had not been previously determined in this patient.

Anal atresia is often accompanied by other birth defects (57%) of which 7% have chromosomal abnormalities [Harris et al., 1995]. In Jacobsen syndrome, anal atresia has been reported only once, which emphasizes the variability of chromosomal material that can be affected in this condition [Leege et al., 1999].

In summary, this case broadens the wide range of abnormalities seen in Jacobsen syndrome to include severe upper transverse limb defect, primary immunodeficiency, and imperforate anus.

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