

Another Patient with Chromosome 18 Deletion Syndrome and Juvenile Rheumatoid Arthritis

PAUL ROSEN, ROBERT J. HOPKIN, DAVID N. GLASS, and T. BRENT GRAHAM

ABSTRACT. Previously, 4 children with deletion of the long arm of chromosome 18 and chronic arthritis were reported. We present an 8-year-old girl with arthritis, atrial septal defect, external auditory canal atresia, and developmental delay. She is the fifth child reported with 18q- syndrome and juvenile rheumatoid arthritis. Evidence is mounting that genetic loci on chromosome 18 may play a role in the expression of complex autoimmune diseases. Idiopathic arthritis should be considered as a potential additional feature in 18q- syndrome. (J Rheumatol 2004;31:998-1000)

Key Indexing Terms:

CHROMOSOME DELETION

JUVENILE RHEUMATOID ARTHRITIS

Autoimmune disorders, including autoimmune endocrinopathies and arthritis, have been described in patients with chromosome 18 abnormalities. The association may represent chance or effects of specific genetic loci. We report a child with 18q- syndrome and juvenile rheumatoid arthritis (JRA). This is the fifth report of a child with deletion of the long arm of chromosome 18 and chronic arthritis.

CASE REPORT

An 8-year-old Caucasian girl was referred to the pediatric rheumatology clinic for evaluation of joint swelling. Four months prior, the patient had fallen and twisted her left knee while playing soccer. She developed a limp the following day. The parents observed swelling in both knees. One month later, she developed swelling over the right sternoclavicular joint. Plain radiographs of the clavicle were normal. She was evaluated by the orthopedic service and referred to rheumatology.

The patient was born full term to a 30-year-old gravida 3, para 3 woman and her 29-year-old husband. Prenatal ultrasonography was normal. No other prenatal testing was done. Birth weight was 7 pounds. There were no perinatal problems.

The medical history was remarkable for atrial septal defect and bilateral aural atresia.

At age one year, a heart murmur was detected. Secundum atrial septal defect (ASD) was diagnosed by echocardiography. At age 21 months, the patient successfully underwent surgical repair of the ASD. Repeat echocar-

diography at age 4 years demonstrated ASD patch closure and mild tricuspid insufficiency. At age 5 years, she underwent surgical repair of a left aural atresia. The right external auditory canal was also atretic. She wore a hearing aid for the right ear.

Her growth had been below normal since age 9 months. She had been in speech therapy since infancy. She began walking at age 17 months. She used 2-3 word sentences by age 2 years. She was in the age appropriate grade at school. Her parents felt that she had to work harder than other children to keep up with her schoolwork. The family described her as uncoordinated.

The family history included 2 healthy siblings. The mother had mitral valve prolapse. There was no history of arthritis, progressive joint disease, or autoimmune disorders.

On physical examination, the height (118 cm) and weight (18.4 kg) were below the 5th centile. Head circumference (49.5 cm) was at the 5th centile. The ear canals were narrow. There were mildly prominent nasal pyramids and hypoplastic *alae nasi*. The mouth was broad with a thin upper lip and short philtrum (Figure 1). Speech was hypernasal. The right sternoclavicular joint was swollen and tender. The chest wall showed healed surgical scars. The cardiac examination revealed a soft 2/6 systolic murmur in the supine position over the left second intercostal space. She was a normal Tanner stage I female. There were large effusions in both knees. The fingers were long and thin. The fingers, wrists, elbows, hips, and back were hypermobile. Slit lamp examination and fundoscopic examinations were normal. Laboratory studies showed normal complete blood count, urinalysis, and thyroid function. Sedimentation rate was 75 mm/h (< 10 normal). Rheumatoid factor was negative. Antinuclear antibody (ANA) was positive at a titer of 1:1280 in a diffuse pattern. Albumin, serum IgA, and serum IgM were all normal. Serum IgG was elevated at 1310 mg/dl (608-1229). Calcium was normal. C3 was elevated at 183 mg/dl (71-150). C4 was elevated at 46 mg/dl (11.8-39). C-reactive protein was elevated at 2.5 mg/dl (< 0.8 normal). Lyme IgG and IgM Western blot strips were non-reactive.

Plain radiographs of the knees showed effusions. On magnetic resonance imaging, there was increased T2 weighted signal in the soft tissues anterior to the sternoclavicular joint consistent with synovitis.

The patient was referred to the genetics service for suspected chromosome 22q11.2 deletion syndrome. FISH study for 22q11.2 deletion was negative. Chromosomal analysis revealed a terminal deletion of the distal portion of the q arm on chromosome 18. The break point was at q22 (Figure 2). HLA typing revealed the presence of alleles DRB1* 11 and 15.

The patient was treated with naproxen. Arthritis in the knees and sternoclavicular joint completely resolved within 5 months.

From the William S. Rowe Division of Rheumatology and the Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine; Cincinnati, OH; and the Division of Rheumatology, Children's Hospital of Pittsburgh, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

P. Rosen, MD, MPH, Assistant Professor of Pediatrics, Division of Rheumatology, Children's Hospital of Pittsburgh; R.J. Hopkin, MD, Assistant Professor of Pediatrics, Division of Genetics; D.N. Glass, MD, Professor of Pediatrics, Division Director of Rheumatology; T.B. Graham, MD, Assistant Professor of Pediatrics, Division of Rheumatology, Cincinnati Children's Hospital Medical Center.

Address reprint requests to Dr. P. Rosen, MD, Children's Hospital of Pittsburgh, Division of Rheumatology, 3705 Fifth Ave., Pittsburgh, PA, USA, 15213-2583. E-mail: Paul.Rosen@chp.edu

Submitted June 10, 2003; revision accepted December 12, 2003.

DISCUSSION

Long arm 18 deletion syndrome (18q- syndrome) was first reported by de Grouchy, *et al* in 1964¹. The syndrome has since been well described as a distinct recognizable entity². Some of the most common features and less common abnormalities of the syndrome are listed in Table 1.

Our patient had many of the features associated with 18q- syndrome. These include cardiac defect, atresia of the auditory canal, growth delay, developmental delay, and poor coordination. The unique feature in our patient was the presence of arthritis. She had the DRB1*11 allele, which has been associated with JRA³.

Chromosome 18 abnormalities have been reported in individuals with hypothyroidism, hypoparathyroidism, growth hormone deficiency, and insulin dependent diabetes mellitus (IDDM)⁴⁻⁷. Reports of chromosome 18 anomaly and autoimmune disease may represent chance associations or true genetic linkages⁴. Given the number of patients reported with 18q deletion (approximately 100) the incidence of reported autoimmune disease appears to be increased over the general population.

There have been reports of 4 patients with 18q deletions and JRA⁸⁻¹⁰. In addition, Curran and Al-Salihi, *et al* reported a patient with contractures of the knees starting at age 14 months, but in whom arthritis was not clearly documented¹¹. Ruvalcaba reported a patient with bilateral recurrent effusions in the knees who was IgA deficient, but a diagnosis of JRA was not established¹². Finally there is a recent report of linkage to chromosome 18q12-q21 with increased risk for a variety of autoimmune disorders¹³.

Patients with chromosome 18 anomalies have been reported to have normal, decreased, and elevated serum IgA levels. It has been suggested that genetic loci for IgA deficiency are related to chromosome 18^{14,15}. Two of 6 patients



Figure 1. 8-year-old girl with atrial septal defect, bilateral aural atresia, and arthritis. Note the hypoplastic *alae nasi*, broad mouth, and short philtrum.



Figure 2. Partial karyotype with ideogram showing the patient's normal and deleted copies of chromosome 18.

Table 1. Features of deletion 18q syndrome^{2,16}.

Common Features	
	Growth deficiency
	Mental deficiency (IQ 40-85), conductive deafness, seizures
	Microcephaly, carp-shaped mouth
	Narrow or atretic external auditory canals
	High-frequency whorl digital pattern
	Foot anomalies
	Cardiac defect
Additional Features	
	Inner epicanthal folds, slanted palpebral fissures, ocular hypertelorism, cataract
	Atretic middle ear
	Cleft palate, cleft lip
	Horseshoe kidney
	Eczema
	IgA deficiency
	Olfactory and optic nerve hypertrophy
	Behavioral problems, autism, cerebellar hypoplasia

with a ring-18 chromosome were reported to be IgA deficient¹⁴. IgA deficiency was detected in 2 of 6 patients with a chromosome 18 long arm deletion¹⁶. Thus, 4 of 12 patients with IgA deficiency and chromosome 18 anomaly suggest the association may not be due to chance when the incidence of IgA deficiency in the general population is 1/700¹⁷.

There is an association of IgA deficiency with JRA^{18,19}. In JRA patients, the incidence of IgA deficiency was found to be 8%¹⁸. The frequency of IgA deficiency was higher when only patients with pauciarticular disease were considered. The frequency of IgA deficiency was 33% in JRA patients with involvement of just one joint¹⁹. The relationship between IgA deficiency and JRA in patients with 18q deletions is not clear, but both IgA deficiency and JRA appear to be increased in this population.

Arthritis has been described in other chromosomal

anomaly syndromes. A well-described example is the association of arthritis with chromosome 22q11.2 deletion (DiGeorge anomalad/velocardiofacial syndrome/conotruncal anomaly face syndrome). The characteristic phenotype includes anomalies of the parathyroid, thymus, face, palate, and heart²⁰. The resulting phenotype may include hypocalcemia, immunodeficiency, and conotruncal cardiac abnormalities. The phenotype may also include polyarticular arthritis. Other chromosomal anomalies that have autoimmune and inflammatory arthritis as an associated finding include trisomy 21 and Turner syndrome^{21,22}.

We report another patient with 18q- syndrome and JRA. This, the fifth such patient, lends support to the idea that idiopathic arthritis should be considered as an additional feature of 18q- syndrome. Our case also supports the idea that genetic loci on chromosome 18 may play a role in the expression of complex autoimmune diseases.

REFERENCES

- de Grouchy J, Royer P, Salmon C, Lamy M. Deletion partielle du bras long du chromosome 18. *Path Biol (Paris)* 1964;12:579-82.
- Jones KL. Smith's recognizable patterns of human malformation 5th edition. Philadelphia: WB Saunders; 1997:66.
- Melin-Aldana H, Giannini EH, Taylor J, et al. Human leukocyte antigen DRB1*1104 in the chronic iridocyclitis of pauciarticular juvenile rheumatoid arthritis. *J Pediatr* 1992;121:56-60.
- Dacou-Voutetakis C, Sertedaki A, Maniatis-Christidis M, et al. Insulin dependent diabetes mellitus (IDDM) and autoimmune thyroiditis in a boy with a ring chromosome 18: additional evidence of autoimmunity or IDDM gene(s) on chromosome 18. *J Med Genet* 1999;36:156-8.
- Gordon MF, Bressman S, Brin MF, et al. Dystonia in a patient with deletion of 18q. *Mov Disord* 1995;10:496-9.
- Faed MJ, Whyte R, Paterson CR, McCathie M, Robertson J. Deletion of the long arms of chromosome 18 (46,XX, 18q-) associated with absence of IgA and hypothyroidism in an adult. *J Med Genet* 1972;9:102-5.
- Ghidoni PD, Hale DE, Cody JD, et al. Growth hormone deficiency associated in the 18q deletion syndrome. *Am J Med Genet* 1997;69:7-12.
- Petty RE, Malleson P, Kalousek, DK. Chronic arthritis in two children with partial deletion of chromosome 18. *J Rheumatol* 1987;14:586-7.
- Hansen US, Herlin T. Chronic arthritis in a boy with 18q- syndrome. *J Rheumatol* 1994;21:1958-9.
- Daentl DL. Birth defects. In: Bergsma D, editor. First conference on the clinical delineation of birth defects, Part V. Phynotypic aspects of chromosomal aberrations. New York: The National Foundation-March of Dimes; 1969:5:87.
- Curran JP, Al-Salihi FL, Allderdice PW. Partial deletion of the long arm of chromosome-18. *Pediatrics* 1970;46:721-9.
- Ruvalcaba RHA, Thuline HC. IgA absence associated with short arm deletion of chromosome no. 18. *J Pediatr* 1969;74:964-5.
- Merriman TR, Cordell HJ, Eaves IA, et al. Suggestive evidence for association of human chromosome 18q12-21 and its orthologue on rat and mouse chromosome 18 with several autoimmune diseases. *Diabetes* 2001;50:184-94.
- Finley SC, Finley WH, Noto TA, et al. IgA absence associated with a ring-18 chromosome. *Lancet* 1968;1:1095-6.
- Feingold M, Schwartz RS, Atkins L, et al. IgA deficiency associated with partial deletion of chromosome 18 [abstract]. *J Clin Invest* 1968;47:34a.
- Finley SC, Cooper MD, Finley WH, Uchida IA, Noto TA, Roddam RF. Immunological profile in a chromosome 18 deletion syndrome with IgA deficiency. *J Med Genet* 1969;6:388-93.
- Bachmann R. Studies on the serum γ A-globulin level. The frequency of A- γ A-globulinemia. *Scan J Clin Lab Invest* 1965;17:316-20.
- Cassidy JT and Burt TA. Isolated IgA deficiency in juvenile rheumatoid arthritis [abstract]. *Arthritis Rheum* 1967;10 Suppl:272.
- Barkley DO, Hohermuth HJ, Howard A, et al. IgA deficiency in juvenile chronic polyarthritis. *J Rheumatol* 1979;6:219-24.
- Sullivan KE, McDonald-McGinn DM, Driscoll DA, et al. Juvenile rheumatoid arthritis-like polyarthritis in chromosome 22q11.2 deletion syndrome (DiGeorge anomalad/velocardiofacial syndrome/conotruncal anomaly face syndrome). *Arthritis Rheum* 1997;40:430-6.
- Olson JC, Bender JC, Levinson JE, Oestreich A, Lovell DJ. Arthropathy of Down's syndrome. *Pediatrics* 1990;86:931-6.
- Zulian F, Schumacher HR, Calore A, Goldsmith DP, Athreya BH. Juvenile arthritis in Turner syndrome: a multicenter study. *Clin Exp Rheumatol* 1998;16:489-94.
- Glass DN, Litvin D, Wallace K, et al. Early onset pauciarticular juvenile rheumatoid arthritis (JRA) associated with HLA DR5, iritis, and antinuclear antibody. *J Clin Invest* 1980;66:426-9.