Case Report

Chronic Arthritis Associated with Chromosome Deletion 22q11.2 Syndrome

PIRKKO PELKONEN, PEKKA LAHDENNE, RISTO LANTTO, and VISA HONKANEN

ABSTRACT. We describe 3 children with chromosome deletion 22q11.2 and chronic arthritis. The onset of arthritis occurred between the ages of 8 and 17 months. The disease course has been polyarticular in all 3. Neither iridocyclitis nor antinuclear antibody positivity was present. On the basis of the findings in these 3 patients and 9 reported in the literature, chronic arthritis in the 22q11.2 deletion syndrome seems to be characterized by very early onset and severe polyarticular course. Based on our findings the prevalence of chronic arthritis in patients with del 22q11.2 is estimated to be 25-fold compared to that in the general population. (J Rheumatol 2002;29:2648–50)

Key Indexing Terms:
CHROMOSOME DELETION CATCH 22 JUVENILE ARTHRITIS

Recently, chronic arthritis has been described in association with the deletion of chromosome 22q11[1-3]. The phenotype of the deletion is variable, but most cases of DiGeorge anomalad and velocardiofacial syndrome have this deletion. The acronym CATCH 22 refers to some of the principal features of the phenotype: cardiac anomalies, abnormal facies, thymic aplasia or hypoplasia (sometimes manifesting as an immune deficiency), cleft palate, and hypocalcemia[4]. More than half of patients have language related learning difficulties[5]. Altogether 9 patients with del 22q11.2 and arthritis have been reported[1-3,6]. We describe 3 new patients with this association and review the rheumatological findings of the patients reported previously.

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In the 3 patients, a microdeletion of chromosome 22 was verified by the fluorescent *in situ* hybridization (FISH) test at the ages of 8 months, 2 days, and 6 months, respectively. The FISH test was negative in the parents of Patients 1 and 2; the parents of Patient 3 have not been tested. The findings related to the del 22q11.2 syndrome in each patient are given in Table 1. For evaluation of immune deficiency, mitogen responses (Patients 1, 2, and 3) and lymphocyte subsets (Patients 1 and 2) were studied, and serum immunoglobulin concentrations were followed sequentially.

Rheumatological findings. Onset of arthritis was at the age of 8 months (Patient 1), 13 months (Patient 2), and 17 months (Patient 3). Pertinent rheumatological findings in our 3 patients and in the 9 patients reported so far are given in Table 2. We also studied patients' synovial fluid in samples taken in association with intraarticular injections, but found the cell counts were not different from those seen in patients with juvenile idiopathic arthritis (JIA) in general: in knee joint aspirates obtained from the 3 patients the white blood cell counts were 11.1×10^{12}/l (58% mononuclear cells, Patient 1), 6.96×10^{12}/l (51% mononuclear, Patient 2), and 10.2×10^{12}/l (42% mononuclear, Patient 3).

DISCUSSION

The clinical features of arthritis associated with del 22q11.2, summarized in Table 2, are based on findings in 12 patients. The disease set in very early, before 6 years of age in 10/12 patients, and 6/12 had onset in infancy. This contrasts with patients with JIA, in whom onset before the age of 6 years occurs in about 40%[7]. All the patients have shown a polyarticular course, whereas in a 10 year followup study nearly 50% of patients with juvenile rheumatoid arthritis/JIA remained oligoarticular[8]. Iridocyclitis complicates the course of one in 6 patients with JIA[9], but so far no patient in the small group with del 22q11.2 has been reported to have iridocyclitis. Four of the patients have shown antinuclear antibody positivity and one has been rheumatoid factor positive; these data correspond to those in the JIA population in general.

In a cohort of 80 patients with del 22q11.2, Sullivan, *et al* found the frequency of polyarthritis to be 50-fold compared with that in the general population[2]. Our 3 patients represent all the cases with del 22q11.2 and chronic arthritis known to pediatric rheumatologists in Finland, with a population of around one million children under 16 years of age and with a prevalence of JIA of 1:1250[10]. We sent an inquiry to the 7 laboratories using the FISH technique to find del 22q11.2 in this country. During the 6 year period 1994–99, the number of new diagnoses of the 22q11.2 deletion in children below 16 years of age was 98. This gives the estimated prevalence of 2 cases of chronic arthritis in 100 children with del 22q11.2 syndrome (about 1:50). In one of our patients, the diagnosis of del 22q11.2 syndrome was made prior to the study period. Thus, the prevalence of chronic arthritis in

From the Hospital for Children and Adolescents, Helsinki University Central Hospital, Helsinki; Department of Pediatrics, Oulu University Hospital, Oulu; and the Rheumatism Foundation Hospital, Heinola, Finland.

P. Pelkonen, MD, PhD; P. Lahdenne, MD, PhD, Helsinki University Central Hospital; R. Lantto, MD, Oulu University Hospital; V. Honkanen, MD, PhD, Rheumatism Foundation Hospital.

Address reprint requests to Dr. V. Honkanen, Rheumatism Foundation Hospital, FIN-18120 Heinola, Finland. E-mail: visa.honkanen@reuma.fi

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Table 1. Features of CATCH 22 in the 3 patients with arthritis.

Finding	Patient 1	Patient 2	Patient 3
Cardiac abnormality	VSD	IIA type B, ASD sec., PDA, ARSA	VSD
Thymus	Not found at operation	Not seen in radiograph	Not seen in radiograph
Immunodeficiency			
T cells subsets	Normal	Transiently abnormal	Not studied
* cd4/cd8	*2.0	*0.9	
* cd4	*0.94 × 10^9/l	* 0.360 × 10^9/l	
T cell stimulation tests	Normal	Transiently abnormal	Normal
Immunoglobulins	Normal	IgA deficiency	Normal
Hypocalcemia	Yes	Yes	Yes
Dysmorphic features			
Ears	Low-set	Low-set, circular	Circular,
Eyes	Downward slanting	Short palpebral fissures, telcanthus	telecanthus
Nose			
Mouth	High arched palate		High arched palate
Voice	Hypernasal speech		
Growth: height; weight	–1.2 SD; + 23%	–2 SD; –10%	–3.3 SD; –6%
Motor development	Slow	Slow	Slow
Additional features	Talipes equinovarus, transient myositis		Vitiligo, hypothyroidism

VSD: ventricular septal defect; IAA: interrupted aortic arch; ASD: atrial septal defect; PDA: patent ductus arteriosus; ARSA: aberrant right subclavian artery.

Table 2. Characteristics of chronic arthritis in patients of the present series and those reported previously.

	The present series			Rasmussen[1]		Sullivan[2]			Verloes[3]			DiRocco[6]
	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3	Patient 1
Age at onset of arthritis	8 mo	12 mo	17 mo	7 yrs	5 yrs	5 yrs	19 mo	17 mo	3 yrs	3 yrs	1 yr	4 yrs
Sex	M	F	F	F	F	F	M	M	F	M	F	F
Course type of arthritis	Poly	Poly	Poly	Poly	Poly	Poly	Poly	Poly	Poly	Poly	Poly	Poly
Antinuclear antibodies	Neg	Neg	Neg	Pos	Pos	Neg	Pos	Pos	Neg	Neg	Neg	Neg
Rheumatoid factor	Neg	Neg	Neg	Pos	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
Iridocyclitis	No	No	No	No	No	No data	No data	No data	No data	No data	No data	No
Family history of arthritis	No	No	Father	Mother?	Grandmother	No data	No data	No	No	No	No data	No data

children with the deletion is about 25-fold that in the general population. Admittedly, the phenotypic variation of the 22q11.2 deletion, which may leave some cases undiagnosed, limits the accuracy of this estimate. The median age at diagnosis of del 22q11.2 was 4 years. The number of live births during the same 6 year period was 363,032. As the majority of the tests are made in early childhood, a prevalence of 1:3700 in Finnish children can be estimated, which corresponds closely to the reported 1:4000 prevalence of 22q11.2 deletion in the general population[11].

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