Case Report

Juvenile Idiopathic Polyarticular Arthritis and IgA Deficiency in the 22q11 Deletion Syndrome

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ABSTRACT. Five patients with the 22q11 deletion syndrome (velocardiofacial syndrome) developed chronic inflammatory polyarticular arthritis. These new cases add to 8 previously reported and confirm the association. The arthritis in all cases was moderate to severe, but at least partially responsive to methotrexate and/or corticosteroids, and was clinically indistinguishable from juvenile idiopathic arthritis (JIA). Analysis of the total 13 patients indicates that 2 are rheumatoid factor positive, 6 are antinuclear antibody positive, 5 have subtle T cell deficiencies, and 6 have hypergammaglobulinemia. Of particular interest is the occurrence of IgA deficiency in 4 patients, including 2 from our own series. Although IgA deficiency is seen in both JIA (2–4%) and 22q11 deletion syndrome (2–4%), the prevalence of low IgA in this series (31%) is much greater than expected. This phenomenon and the true association of inflammatory arthritis and a chromosome deletion disorder provides further evidence of important genetic factors in the pathogenesis of JIA. (J Rheumatol 2001; 28:2326–34)

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We describe 5 children with 22q11 deletion syndrome who developed moderate to severe chronic polyarticular arthritis. Monoallelic deletion at the DiGeorge region (DGR) chromosomal site (22q11.1–11.3) is associated with a spectrum of clinical disorders and variable phenotype[1-6]. This includes variable features encompassing what have variously been described as DiGeorge syndrome, velocardiofacial syndrome (VCFS), and the conotruncal anomaly face syndrome. The expanded syndrome is the commonest of the chromosomal deletion disorders, occurring with an estimated frequency of one in 2000 to 4000 births[7,8]. The clinical manifestations include facial and pharyngeal malformations, cardiac outflow tract abnormalities, hypoparathyroidism, increased susceptibility to infection, and a variable T cell immunodeficiency[9,10].

Recently, 3 separate groups[11-13] have reported the development of an inflammatory arthritis similar to juvenile idiopathic arthritis (JIA) in a total of 8 patients with 22q11 deletion. We report 5 new cases and review the clinical and immunological profiles of all 13 patients now described with 22q11 deletion and arthritis. We discuss potential genetic factors that may predispose them to the development of chronic arthritis. Of particular interest is the occurrence of selective IgA deficiency in 4 of the 13 patients with arthritis and the 22q11 deletion.

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CASE REPORTS

Case 1. Patient 1 is an 18-year-old white female. She was a full term delivery with birth weight 2500 g. Her facies were noted to be mildly dysmorphic with hypertelorism and mild maxillary hypoplasia. At 24 h of age she was noted to be jittery and hypocalcemic and a cardiac murmur was noted. The hypocalcemia resolved rapidly and no further specific investigations were performed. She remained well until 5 months of age when she became cyanotic. Cardiac catheterization disclosed a complex outflow tract defect with an overriding aortic arch and pulmonary artery stenosis. Over the next 12 months she became progressively more cyanotic with recurrent respiratory infections, and at l8 months of age a complex right-to-left shunting procedure was performed. Postoperatively her oxygen saturation improved but she had recurrent respiratory infections, associated with poor growth. She had significantly delayed speech, and her speech was hypernasal in quality. At 6 years, an abnormal palate, bifid uvula, and bilateral middle ear disease were identified. A diagnosis of vocal dyspraxia and velopharyngeal insufficiency was made and a pharyngoplasty was performed.

At age 6, she developed intermittent swelling of the left knee lasting for several weeks, which was attributed to recurrent trauma. Cyanosis related to her cardiac disease became increasingly severe over the next 10 years and total corrective surgery was undertaken when she was 17 years old. On admission to the cardiothoracic unit prior to surgery she was complaining of a painful and swollen left knee, and was referred to the pediatric rheuma-

tology team. Examination disclosed a left knee effusion with a 25° flexion deformity and marked muscle atrophy. She also had moderate synovitis of the right knee, right elbow and multiple metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal (MTP) joints, which had previously been undetected, although somewhat symptomatic to the patient. Her dysmorphic facies and hypernasal speech were also noted.

Abnormal laboratory tests included erythrocyte sedimentation rate (ESR) 76 mm/h, C-reactive protein 3.9 mg/l, rheumatoid factor (RF) titer 1:1280, borderline phytohemagglutination stimulation test, and slightly low CD3, CD4 and CD8 levels. Antinuclear antibody (ANA) was negative. Fluorescent *in situ* hybridization (FISH) analysis was requested on the basis of her history and current clinical findings and confirmed the suspicions of deletion at the 22q11 locus. Other laboratory tests are summarized in Table 1. Radiographs showed periarticular osteopenia of affected joints; there was osteopenia of the cervical spine with fusion of the posterior elements of C2 and C3.

Treatment included intraarticular steroids and serial casting of the left knee, intravenous steroids and oral MTX, with significant improvement both clinically and functionally.

Case 2. Patient 2 is a 13-year-old white female born at 36 weeks' gestation with a birth weight of 3200 g. No morphologic abnormalities were noted at birth. Shortly after birth a cardiac murmur was noted and a ventricular septal defect and a patent ductus arteriosus were discovered. Cardiac surgery was performed at 6 weeks of age, complicated by postoperative airway obstruction due to subglottic stenosis. She required a tracheostomy until 3 years of age. Over the following years she had recurrent respiratory infections with a poor growth pattern. Post-decannulation it was noted that she had severely delayed speech and that her speech was hypernasal in quality. There was also a history of occasional nasal regurgitation of food. A diagnosis of velopharyngeal insufficiency as the cause of her abnormal speech pattern was made. Mildly dysmorphic facial features were first noted when she was 5 years of age. These included hypertelorism and a small, triangular face.

At age 11 she developed persistent swelling of the knees with abnormal gait. Her pediatrician made a diagnosis of JIA and she was given nonsteroidal antiinflammatory drugs (NSAID). Because of an incomplete response she was referred to the pediatric rheumatology service at 12 years of age. Examination revealed active inflammatory synovitis of many joints including hips, knees, ankles, and small joints of hands and feet. ESR was 5 mm/h, ANA was positive, titer 1:80, RF negative. There was CD4+ T cell lymphopenia and hypergammaglobulinemia. FISH analysis performed due to the constellation of symptoms and signs revealed a monoallelic deletion at the 22q11.2 locus. Radiographs disclosed moderate osteopenia with joint space narrowing of multiple joints. Other results are shown in Table 1.

She was initially treated with hydroxychloroquine, with only partial response. Treatment with oral MTX was commenced at 13 years of age, with considerable, sustained improvement.

Case 3. Patient 3 is a 4-year-old white male born at term with birth weight 3990 g. At 5 days of age he became cyanotic, and cardiac catheterization disclosed a ventricular septal defect and aortic insufficiency. Corrective cardiac surgery was performed at 6 days of age. He had postoperative hypocalcemia, which gradually improved over 48 h. At 2 years of age he was noted to have delayed speech with a hypernasal speech pattern. A diagnosis of submucous cleft palate was made, and corrective palatal surgery was performed. He was then noted to be dysmorphic, with a facies thought to be characteristic of the velocardiofacial syndrome. The diagnosis was established by FISH analysis, which confirmed 22q11.2 deletion.

At 3 years he developed pain and swelling of the small joints of the hands, wrists, knees, and ankles over a period of 3 months. Clinical examination revealed pallor secondary to anemia, obvious synovitis of multiple joints including fingers, wrists, elbows, neck, knees and ankles, with marked restriction of movement.

Laboratory findings (Table 1) included hemoglobin 9.9 g/dl, normal ESR and CRP. Serum immunoglobulins showed IgG of 15.8 g/l, IgM 0.3 g/l, and IgA 0.09 g/l. IgG subclasses and vaccine antibody titers were normal. The CD4 count was 540 cells/µl.

A diagnosis of JIA was made and treatment commenced with intravenous methylprednisolone pulses and oral MTX. Intensive physiotherapy was provided. Over the following 12 months he made considerable improvement, with control of his inflammatory arthritis and improvement in his functional abilities.

Case 4. Patient 4 is a 22-year-old white female. She was born by normal vaginal delivery with birth weight 3420 g. A cardiac murmur was detected at the routine postnatal examination. Echocardiography revealed a ventricular septal defect and pulmonary stenosis for which corrective surgery was eventually performed at 4 years of age.

She developed swollen knees at 18 months of age. Her pediatrician made a diagnosis of JIA and she was initially treated with NSAID and later

Table 1. Clinical rheumatological and laboratory characteristics of 5 patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	F	F	M	F	F
Age at onset of arthritis, yrs	4	11	3	1.5	5
ILAR classification of arthritis	Polyarticular RF +	Polyarticular RF –	Polyarticular RF –	Extended oligoarticular	Polyarticular RF +
Systemic features	No	No	No	No	No
Destructive joint changes	Yes	Yes	No	Yes	Yes
ANA	Neg	Speckled 1:80	Speckled 1:80	1:80	Neg
Rheumatoid factor	Pos 1:1280	Neg	Neg	Neg	Neg
ESR at onset arthritis mm/h	76	5	4	12	9
IgA, g/l (n: 0.4–2)	2.69	1.36	0.09	< 0.2	1.26
IgM, g/l (n: 0.5–2)	1.11	32.07	0.3	1.90	0.52
IgG, g/l (n: 4.9–15)	14.1	17.7	15.88	20.1	14.49
CD3, cells/µl*	804	**444**	**855**	ND	395
CD4, cells/µl*	540	**312**	**213**	ND	484
CD8, cells/µl*	288	**120**	**162**	ND	**21**
PHA SI (n > 100)	94.7	501.4	81.3	ND	Normal

* Normal ranges for T cell subsets age-dependent: values in bold indicate value below 5th centile for age.
ILAR: International League Against Rheumatism; PHA SI: phytohemagglutinin stimulation index; ANA: antinuclear antibody; ND: not done.

Table 2. Summary of 13 children with 22q11 deletion syndrome and chronic arthritis.

Case	Author	Age of Onset/Sex	Subtype of Arthritis (ILAR)	Other Clinical Features	ANA	RF	Partial IgA Deficiency	Other Immune Tests
1	Present series (UK)	5 F	Polyarticular, RF+	VPI, CHD, deafness	–	+	–	IgG 14.1* IgM 1.11 IgA 2.69 CD3 804** CD4 540 CD8 288 **PHA decreased**
2	Present series (UK)	11 F	Extended oligoarticular	VPI, subglottic stenosis, CHD osteopenia, short stature	+	–	–	IgG 17.7 IgM 32.07 IgA 1.36 **CD3 444** **CD4 312** **CD8 120** PHA: normal
3	Present series (UK)	3 M	Polyarticular	VPI, cleft palate, CHD, hypocalcemia, developmental delay	+	–	+	IgG 15.88 IgM 0.3 **IgA 0.09** **CD3 855** **CD4 213** **CD8 162** **PHA decreased**
4	Present series (UK)	1 F	Extended oligoarticular	VPI, developmental delay, complex CHD	+	–	+	IgG 20.1 IgM 1.9 **IgA < 0.2** T cells and PHA: ND
5	Present series (UCLA)	5 F	Extended oligoarticular	CHD, renal agenesis, thrombocytopenia	–	–	–	IgG 12.5 IgM 0.65 IgA 1.16 CD3 395 CD4 484 **CD8 21** PHA: ND
6	Rasmussen[12]	7 F	Polyarticular, RF+	VPI, CHD, scoliosis, Arnold-Chiari malformation	+	+	–	IgG, A, M: normal T cells: normal
7	Rasmussen[12]	5 F	Extended oligoarticular	VPI, subglottic stenosis, sleep apnea	–	–	–	IgG 23.82 IgM, IgA: N T cells: N
8	Sullivan[11]	5 F	Polyarticular	VPI, CHD, auricular anomalies	–	–	+	IgG 15.8 IgM 1.0 **IgA < 0.06** CD3 884 CD4 665 **CD8 150** **PHA decreased**
9	Sullivan[11]	1 M	Extended oligoarticular	Cleft palate, CHD, recurrent infections	+	–	–	IgG 10.7 IgM 1.37 IgA 1.37 CD3 1183 CD4 573 CD8 475 **PHA decreased**
10	Sullivan[11]	1 M	Polyarticular	CHD, osteoporosis, kypho-scoliosis, recurrent infections	+	–	+	IgG 25.77 IgM 10.5 **IgA < 0.08** CD3 3523 CD4 1394 CD8 1802 PHA: N

Table 2. Continued.

Case	Author	Age of Onset/Sex	Subtype of Arthritis (ILAR)	Other Clinical Features	ANA	RF	Partial IgA Deficiency	Other Immune Tests
11	Verloes[13]	4 F	Extended oligoarticular	VPI, GER, myopathic facies	–	–	–	Elevated IgG IgA, IgM and T cells: ND
12	Verloes[13]	3 M	Polyarticular	VPI, CHD, GER, osteopenia	–	–	–	Igs G, A, M: N T cells: ND
13	Verloes[13]	1 F	Polyarticular	VPI, CHD, deafness	–	–	–	Igs G, A, M: N T cells: N

* g/l; ** cells/µl.
Normal values: IgA 4–20 g/l; IgG 4.9–16.1 g/l; IgM 5–20 g/l; normal ranges for T cell subsets age-dependent: values in bold indicate value below 5th centile for age.
VPI: velopharyngeal insufficiency; CHD: congenital heart disease; GER: gastroesophageal reflux; ND: not done; N: normal.

with oral corticosteroids. Other problems included moderate learning difficulties with significant speech and language delay. The arthritis became progressively more severe and subsequently extended to involve most of her joints. She had raised acute phase reactants. IgA was extremely low (< 0.2 g/l), but precise IgA quantification was not performed and it was therefore not possible to determine whether she had a true or partial IgA deficiency. Her ANA was weakly positive and RF was negative. Radiographs showed destructive joint changes. Despite treatment early in the disease with oral steroids and later with oral MTX with some partial improvement, progressive disease led to several surgical interventions, including MTP resection and soft tissue releases of the hip joints.

At the last examination there was ongoing active polyarticular synovitis despite ongoing treatment with MTX, corticosteroids, and NSAID.

The underlying diagnosis of 22q11 deletion syndrome was only considered when she was seen at followup in the rheumatology clinic by one of the authors (KJM) at age 21 years and was noted to have hypernasal speech. The history was reviewed, and FISH analysis confirmed the suspicion of a deletion at the 22q11.2 locus.

Case 5. Patient 5 is a 12-year-old Hispanic female born at term with birth weight 2296 g. At birth she was jaundiced, hypocalcemic, tachypneic, and cyanotic. Cardiac evaluation revealed a tetralogy of Fallot. At 3 months, she had a Blalock-Taussig shunt inserted, which was revised at 22 months of age. Corrective surgery was performed at 4.5 years. The postoperative course was complicated by epistaxis and diffuse encephalitis.

At age 5 she was noted to have a fixed facial expression, contractures of the fingers, a high pitched voice, muscle weakness, and difficulty ambulating. Muscle enzymes, nerve conduction studies, and muscle biopsy showed no evidence of myopathy.

At 10 years of age she was referred to the genetics team, who noted mild learning difficulties, height and weight below the 5th percentile, flexion deformities of her hands and knees, scoliosis, tapered extremities, and overlapping toes. ESR was 9 mm/h and ANA and RF were both negative. FISH analysis revealed a microdeletion at the 22q11 locus. Other results are summarized in Tables 1 and 2.

At 12 years of age she was referred to the rheumatology team, who noted flexion deformities of the hands and knees, subluxation of the 2nd to 5th MTP joints, and bilateral hallux valgus. Radiographs showed multiple flexion deformities and severe periarticular osteopenia. Treatment was initiated with regular naproxen, oral MTX, and physiotherapy. There was some clinical improvement, with less pain and improved mobility within 3 months.

DISCUSSION

Prior to referral to the pediatric rheumatology service only 2 of our patients (Cases 3 and 5) had been diagnosed as having a 22q11.2 deletion, at 2 and 10 years of age, respectively. In the remaining cases the diagnosis was neither suspected nor established by FISH testing until many years after birth (18, 12, and 22 years of age for Cases 1, 2, 4, respectively). All patients had congenital heart disease, abnormal facies, poor growth, early onset of respiratory infections, and learning problems, characteristic of other children with 22q11 deletion syndromes. In all cases, the arthritis was polyarticular and moderately severe, necessitating steroid and/or MTX therapy. Patient 1 had a positive test for RF and Patients 2, 3, and 4 had positive test for ANA. Patients 3 and 4 had low IgA, Patients 2, 3 and 5 had decreased T cells. Patient 3 had reduced mitogen response to phytohemagglutinin (PHA).

Other clinical features in some patients included osteoporosis, deafness, learning difficulties, and hypocalcemia (Table 3). In none of the 5 cases was there a family history suggestive of 22q11 deletion syndrome in the parents.

These 5 cases resemble the other 8 cases of inflammatory arthritis reported in the 22q11 deletion syndrome (Table 3). In all 13 cases there was either a polyarticular onset or a rapid evolution to a polyarticular form, phenotypically identical to JIA. The onset was predominantly early (i.e., before 6 years of age in 11 of 13) and in 4 it was before the age of 2 years. In 9 patients the arthritis was considered severe, necessitating treatment with steroids or MTX.

Six of the 13 patients had positive ANA, and 2 were RF positive, one of whom was also positive for ANA. Four patients had low IgA, 3 of whom were ANA positive. Six patients had hypergammaglobulinemia (IgG > l5 g/l). One or more abnormalities of T cell number or function could be detected in 7 of the 13 patients including decreased PHA proliferation (4 of 6 tested), low CD4 counts (4 of 9), and elevated CD8 count in one patient.

There was no apparent relationship of these laboratory abnormalities to the age of onset, initial pattern, or severity of arthritis. Indeed, Patient 7 (Table 2), with no immunological abnormalities, had severe destructive disease. All the patients with IgA deficiency had recurrent respiratory infec-

Table 3. HLA haplotypes in 13 patients with 22q11 deletion syndrome and chronic arthritis.

Case	ILAR Classification of Arthritis	A	B	C	DRB1	DPB1	DQB1
1	EO	—	—	—	**0101**/1201	—	
2	EO	—	—	—	**0101**/0201	—	—
3	P	—	—	—	**0401/1103**	—	—
4	EO	—	—	—	—	—	—
5	EO	2/2	18/35	—	1101/**0802**	—	0301/0402
6	P	—	—	—	—	—	—
7	EO	—	—	—	—	—	—
8	P	2/3	7/44	—	**1103**/1302	0301/0102	0301/0604
9	EO	2/28	51/70	5/7	**0101/0801**	0201/0201	0501/0402
10	P	1/2	8/38	7/7	**1301/0101**	0201/0301	0603/0603
11	EO	3/9	3/5	7/7	**0101**/1101	—	0201/0301
12	P	1/2	8/44	5/7	**0401**/1701	—	0601/0601
13	P	2/3	13/62	6/6	**1301/1301**	—	—

ILAR: International League Against Rheumatism; EO: extended oligoarticular onset; P: polyarticular onset. Values printed in bold type: haplotypes indicate a recognized association between this haplotype and JIA.

tions, but this was also seen to some degree in the group with normal IgA (data not shown). No patient had uveitis, nor were there other family members with inflammatory arthritis or related conditions.

Prior to l996, the association between inflammatory arthritis and DiGeorge syndrome (DGS) or the velocardiofacial syndrome (VCFS) was unrecognized, despite frequent publication of the wide range of clinical manifestations of these syndromes. However, with the recognition that some forms of VCFS may have relatively subtle or late-presenting manifestations and the increased availability of FISH analysis, many more children with cardiac, pharyngeal, and facial abnormalities are being recognized as having the underlying 22q11.2 deletion. For these reasons we believe it is likely that JIA-type inflammatory arthritis has gone unrecognized in this syndrome until recently. Late referrals to pediatric rheumatology units and lack of recognition of joint inflammation are still commonplace, as was the case in several of the patients we report.

Given the incidence of JIA of roughly 1:10,000[14], and of 22q11.2 deletion 1:2000–4000, one would expect the 2 conditions to coexist very rarely indeed. Our report adds to the previous reports[11-13], in particular that of Sullivan, *et al*, who reported JIA in 4 of 80 patients with VCFS[11], and more recently in 6 of a further 250 (K.E. Sullivan, personal communication), and indicates a marked increase in frequency of JIA in 22q11.2 deletion.

The association, although largely with a polyarticular disease course, is not with one particular form of JIA but includes both oligoarticular and polyarticular onset JIA and patients with and without RF. This implies that the chromosome deletion may provide a permissive role in the development of JIA generally, rather than encode for one particular subtype.

Table 4. IgA deficiency, 22q11 deletion, and arthritis.

	All Patients	Low IgA	Normal IgA
Number of patients (%)	13	4	9
Mean age of onset of arthritis, yrs	3.9 (median 4)	2.5 (median 2)	4.6 (median 4)
Oligoarticular onset pattern (first 6 mo of disease)	6/13 (46)	1/4 (25)	6/9 (67)
Polyarticular onset pattern (first 6 mo of disease)	7/13 (54)	3/4 (75)	3/9 (33)
RF positive	2/13 (15)	0/4 (0)	2/9 (22)
ANA positive	6/12 (50)*	3/4 (75)	3/9 (33)
Elevated IgG (> 1500 mg/ml)	6/12 (50)	4/4 (100)	2/9 (22)
Low CD4 cells (< 500/µ)	2/12 (16)	0/3* (0)	2/7 (29)

* Results unavailable for Patient 4.

Table 5. Chromosomal abnormalities associated with inflammatory arthritis.

Chromosomal Abnormality	Details of Arthritis
2p terminal deletion	2 patients: one with polyarticular flexion deformities, one with flexion deformities of fingers[47,48]
Trisomy 5q, terminal 2p deletion	Polyarthritis refractory to treatment, anterior uveitis[49]
18p deletion	2 patients: "JIA-like"[50]
18q partial deletion	2 "JIA-like"[51]
18q deletion	Ankylosis of knees[52]
Trisomy 21	Polyarthritis[53,54]
45, XO — Turner syndrome	"JIA-like." Polyarticular and oligoarticular presentations. 20 patients described to date[55]
Klinefelter syndrome (47, XXY)	Rheumatoid arthritis[56]

Table 6. Other autoimmune conditions associated with defined chromosomal abnormalities.

Chromosomal Abnormality	Autoimmune Condition
2p deletion/trisomy 5q	Lupus nephritis[57]
4/5 balanced translocation	Periarteritis nodosa[58]
Trisomy 21	Celiac disease[59]
	Scleroderma (1 case)[52]
	Autoimmune thyroid disease[60]
22 Ph1 (Phil)	Ankylosing spondylitis, rheumatoid arthritis[61]
XXY — Klinefelter	Sjögren's, Raynaud's, scleroderma[62,63]
XO — Turner	Crohn's disease, thyroiditis, insulin dependent diabetes mellitus[64–77]
Mosaicism XXXXX/XXXX/XXX/XX/XO	Sjögren's syndrome[78]

At least partial HLA typing was available for 4 of our patients and thus has been reported now in 10 of 13 overall (Table 3). Insufficient data were available on Class I typing or DP or DQ alleles for meaningful analysis. There are numerous HLA associations with the different subtypes of JIA and many of these are found in this population. All patients had at least one risk allele and many had 2. This included DRB1*0101 or *0401 in 7 cases (risk factors for polyarticular course of disease), but also DRB1*0801/2 and *1103 and *1301 in 6 cases, risk factors for oligoarticular or more restricted disease.

To summarize, no single associated HLA allele was found in these patients with VCFS and JIA. The distribution of the alleles fitted generally with the different forms of JIA that seem to be associated. This lends further support to the contention that the inflammatory polyarthritis in this syndrome is truly JIA and not simply arthritis as part of the syndrome.

There is controversy regarding the precise definition of IgA deficiency. In this study a widely accepted cutoff level of 0.15 g/l was employed[15]. The occurrence of true IgA deficiency in 3 patients and at least partial deficiency in a fourth is of interest. Of the total group of 13, those 4 patients with low IgA tended to be younger at presentation of arthritis (Table 4), although the limited numbers in each group preclude constructive statistical comparison. Three of 4 were ANA positive, none was RF positive. Due to limited clinical information available on the previously reported cases, it is not known whether patients with low IgA had an altered disease severity, although overall they tended more frequently to have polyarticular onset disease.

Sullivan, *et al*[10] reported initially that 4 of their 32 VCFS patients (12%) had selective IgA deficiency. In a further study of 250 VCFS patients, 7 (2.8%) had selective IgA deficiency (K.E. Sullivan, personal communication). Children with JIA have an increased incidence of selective IgA deficiency, usually 2 to 4%[17,18]. This is in contrast to the incidence of IgA deficiency in the general population of roughly 0.25%[19-21]. Although it is therefore not unexpected that patients with 22q11 deletion and JIA may have IgA deficiency, the frequency of 31% (4/13) is above that which would be expected by chance. The IgA deficiency, the pharyngeal and swallowing abnormalities, and the cardiac problems all predispose these patients to recurrent infections. This may provide a potential mechanism for the increased incidence of inflammatory arthritis in 22q11 deletion syndrome. Various infectious agents have been implicated in the development of reactive arthritis, and several groups have speculated that persistence of an infectious agent or some component antigen within the synovium may lead to chronic inflammatory arthritis[22-26]. The low T cell numbers in some patients and the decreased PHA proliferative responses may further predispose to chronic viral or mycoplasma infections that may be subclinical. In general, however, the B and T cell abnormalities in these patients were much less severe than those observed in patients with primary immunodeficiencies such as cross-linked agammaglobulinemia, common variable immunodeficiency, and immunodeficiency with hyper-IgM. Although associations between the various humoral immunodeficiencies and inflammatory arthritis have been well documented, arthritis is still rare in these conditions. There was also no history of infection immediately preceding the onset of arthritis in any patient, although several reported a history of recurrent infections.

A further possible explanation is that 22q11 deletion and the associated IgA deficiency predispose patients to autoimmune diseases. IgA deficiency has been described in numerous patients with autoimmune syndromes including dermatomyositis, autoimmune hemolytic anemia, and autoimmune endocrinopathies[27-30]. Similarly, patients with 22q11 deletion have been reported with autoimmune hemolytic anemia, immune thrombocytopenia, and thyroiditis[31,32].

Alternatively, the 22q11 deletion syndromes may conceivably be associated with immune dysregulation that in turn leads to autoimmunity. While most of these patients have apparently clinically insignificant T cell abnormalities, they all may have had a significant thymic defect during embryogenesis (and in the case of DiGeorge syndrome, extending into postnatal life), with the result that a critical regulatory T cell subpopulation may be defective or missing and/or clones of autoreactive T or B cells are not eliminated during immune development.

A number of candidate genes at the 22q11.2 locus have been identified, but in each case further investigation found no evidence of an etiological role[33-36].

More recently the focus of interest has shifted to the TBX1 gene, which maps to the center of the DiGeorge region. TBX1 is a member of a phylogenetically conserved family of genes that share a common DNA binding domain, the T-Box. T-Box genes are transcription factors involved in the regulation of developmental processes. Mouse TBX1 (which shares 98% amino acid identity with human TBX1) has been shown to be expressed during early embryogenesis in the pharyngeal arches pouches, otic vesicle, and vertebral column[37]. Studies employing genetic manipulation techniques in mice have shown TBX1 to be critical in the regulation of development of structures affected in 22q11 deletion syndrome, including thymic development, in a dose dependent manner[38-40]. We postulate that hemideletion of this gene could result in premature thymic apoptosis and a consequent qualitative defect in immunological tolerance and thus a predisposition to autoimmunity. Consistent with this is evidence of T cell dysfunction in 5 of the 13 patients. Further detailed analysis of thymic function may reveal more widespread abnormalities.

An alternative explanation is a common genetic constitution linking these disorders. Genetic factors predisposing to the development of arthritis do exist, exemplified by families with more than one affected person, an increased frequency of JIA in siblings and twins, and the presence of particular HLA haplotypes like those present in some of the patients in this series[41]. It must be emphasized, however, that HLA associations are felt to explain only a fraction of the genetic risk in JIA[42,43]. Polymorphisms of other immune response genes such as cytokine genes have been identified that appear to affect disease course or severity in JIA[44-46].

An association between inflammatory arthritis in childhood and a number of chromosomal disorders has been reported (Table 5)[47-56], as have other autoimmune conditions[52,57-78] (Table 6). It is possible that in patients with 22q11 deletion syndrome, who thus have an automatically dominant set of genes on the nondeleted chromosome, a particular polymorphism is effectively uncovered in the absence of the second allele. This polymorphism may affect both the chance of developing JIA and/or the disease course and severity.

The occurrence of polyarticular arthritis in these 13 patients implies interplay between hereditary factors (thymic abnormality, partial IgA deficiency, HLA phenotype) and possible environmental factors (such as the antigenic excess as a result of increased infections) leading to the development of chronic arthritis.

Clinicians involved in the management of children (and adults, since many children with 22q11 deletion will survive well into adulthood) with arthritis or 22q11 deletion syndrome should be aware of the association between these conditions in order that potentially treatable co-pathology is not overlooked. Further, investigation of the precise nature and actions of the genes at the 22q11 locus may provide general insight into the pathogenesis of both JIA and other autoimmune conditions.

REFERENCES

1. Driscoll DA, Salvin J, Sellinger B, et al. Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: Implications for genetic counselling and prenatal diagnosis. J Med Genet 1993;30:813-7.
2. De La Chapelle A, Herva R, Koivisto M, et al. A deletion in chromosome 22 can cause DiGeorge syndrome. Hum Genet 1981;57:253-6.
3. Goodship J, Cross I, Scambler P, et al. Monozygotic twins with chromosome 22q11 deletion and discordant phenotype. J Med Genet 1995;32:746-8.
4. Kelley RI, Zackai EH, Emmanuel BS, et al. The association of the DiGeorge anomalad with partial deletion of chromosome 22. J Pediatr 1982;101:197-200.
5. Shprintzen RJ, Goldberg RB, Young D, et al. The velocardiofacial syndrome: A clinical and genetic analysis. Pediatrics 1981; 67:167-72.
6. Hong R. The DiGeorge anomaly (Catch 22, DiGeorge/ Velocardiofacial syndrome). Semin Hematol 1998;35:282-90.
7. Wilson DI, Cross IE, Wren C, et al. Minimum prevalence of chromosome 22q11 deletions [abstract]. Am J Hum Genet 1994;55:A169
8. Tezenus du Montcel S, Mendizabai H, Ayme S, et al. Prevalence of 22q11 microdeletion [letter]. J Med Genet 1996;33:719.
9. Conley ME, Beckwith JB, Mancer JFK, et al. The spectrum of the DiGeorge syndrome. J Pediatr 1979;94:883-90.
10. Sullivan KE, Jawad AF, Randall P, et al. Lack of correlation between impaired T cell production, immunodeficiency and other phenotypic features in chromosome 22q11.2 deletion syndromes. Clin Immunol Immunopathol 1998;86:141-6.
11. 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;40:439-6.
12. Rasmussen SA, Williams CA, Ayoub EM, et al. Juvenile rheumatoid arthritis in velocardiofacial syndrome: coincidence or unusual complication? Am J Med Genet 1996;64:546-50.
13. Verloes A, Curry C, Jamar M, et al. Juvenile rheumatoid arthritis and del (22q11) syndrome: A non-random association. J Med Genet 1998;35:943-7.
14. Kunnano I, Kallio P, Pelkonen P. Incidence of arthritis in urban Finnish children. Arthritis Rheum 1986;29:1232-8.
15. Roberts RL, Stiehm ER. Antibody (B cell) immunodeficiencies. In: Parslow TG, Stites DP, Terr AI, et al, editors. Medical immunology. New York: Lange-McGraw Hill; 2001:299-312.

16. Smith CA, Driscoll DA, Emanuel BS, McDonald-McGinn DM, Zackai EH, Sullivan KE. Increased prevalence of immunoglobulin a deficiency in patients with the chromosome 22q11.2 deletion syndrome (Digeorge syndrome/velocardiofacial syndrome). Clin Diagn Lab Immunol 1998;5:415-7.
17. Cassidy JT, Petty RE, Sullivan DB. Abnormalities in the distribution of serum immunoglobulin concentrations in juvenile rheumatoid arthritis. J Clin Invest 1973;52:1931-6.
18. Barkley DO, Hohermuth HJ, Howard A, Webster DB, Ansell BM. IgA deficiency in juvenile chronic polyarthritis. J Rheumatol 1979;6:219-24.
19. Holt PDJ, Tandy NP, Anstee DJ. Screening of blood donors for IgA deficiency: a study of the donor population of Southwest England. J Clin Pathol 1977;30:1007-10.
20. Ropars C, Muller A, Paint N, Beige D, Avenard G. Large-scale detection of IgA deficient blood donors. J Immunol 1982;54:183-9.
21. Wells JV, McNally MP, King MA. Selective IgA deficiency in Australian blood donors. Aust NZ J Med 1980;10:410-3.
22. Battafarano DF, Combs JA, Enzenauer RJ, Fitzpatrick JE. Chronic septic arthritis caused by Borrelia burgdorferi. Clin Orthop 1993;297:238-41.
23. Washburn LR, Cole BC, Ward JR. Chronic arthritis of rabbits induced by mycoplasmas. III. Induction with nonviable mycoplasma arthritidis antigens. Arthritis Rheum 1982;25:937-46.
24. Huppertz HI. How could infectious agents hide in synovial cells? Possible mechanisms of persistent viral infection in a model for the etiopathogenesis of chronic arthritis. Rheumatol Int 1994;14:71-5.
25. Inman RD, Chiu B. Synoviocyte-packaged Chlamydia trachomatis induces a chronic aseptic arthritis. J Clin Invest 1998;102:1776-82.
26. Wuorela M, Granfors K. Infectious agents as triggers of reactive arthritis. Am J Med Sci 1998;316:264-70.
27. Liblau RS, Bach JF. Selective IgA deficiency and autoimmunity. Int Arch Allergy Immunol 1992;99:16-27.
28. Kornstad L, Nordhagen R. Immunodeficiency and autoimmunity. Selective IgA deficiency in thyroid autoimmunity. Int Arch Allergy Appl Immunol 1974;47:942-5.
29. Luster MI, Leslie GA, Cole RK. Selective IgA deficiency in chickens with spontaneous autoimmune thyroiditis. Nature 1976;263:331.
30. St. Euer A, McCrea DJ, Colaco CB. Primary Sjogren's syndrome, ulcerative colitis and selective IgA deficiency. Postgrad Med J 1996;72:499-500.
31. DePiero AD, Lourie EM, Berman BW, Robin NH, Zinn AB, Hostoffer RW. Current immune cytopenias in two patients with DiGeorge/velocardiofacial syndrome. J Pediatr 1997;131:484-6.
32. Kawamura T, Nimura I, Hanafusa M, et al. DiGeorge syndrome with Graves' disease: a case report. Endocr J 2000;47:91-5.
33. Yamagishi H, Garg V, Matsuoka R, Thomas T, Srivastava D. A molecular pathway revealing a genetic basis for human cardiac and craniofacial defects. Science 1999;283:1158-61.
34. Funke B, Puech A, Saint-Jore B, et al. Isolation and characterisation of a human gene containing a nuclear localisation signal from the critical region for velocardiofacial syndrome on 22q11. Genomics 1998;53:146-54.
35. Roberts C, Daw SC, Halford S, Scambler PJ. Cloning and developmental expression analysis of chick hira (chira), a candidate gene for DiGeorge syndrome. Hum Mol Genet 1997;6:237-45.
36. Sirotkin H, Morrow B, Saint-Jore B, et al. Identification, characterisation, and precise mapping of a human gene encoding a novel membrane-spanning protein from the 22q11 region deleted in velocardiofacial syndrome. Genomics 1997;42:245-51.
37. Chieffo C, Garvey N, Gong W, et al. Isolation and characterisation of a gene from the DiGeorge chromosomal region homologous to the mouse Tbx1 gene. Genomics 1997;43:267-77.
38. Merscher, Funke B, Epstein JA, et al. TBX1 is responsible for cardiovascular defects in velocardiofacial/DiGeorge syndrome. Cell 2001;104:619-29.
39. Jerome LA, Pappaiannou VE. DiGeorge syndrome phenotype in mice mutant for the T-Box gene, Tbx1. Nature Genetics 2001:27:286-91.
40. Lindsay E, Vitelli F, Su H, et al. Tbx1 haploinsufficiency in the DiGeorge syndrome region causes aortic arch defects in mice [letter]. Nature 2001;410:97-101.
41. Moroldo MB, Tague BL, Shear ES, Glass DN, Giannini EH. Juvenile rheumatoid arthritis in affected sibpairs. Arthritis Rheum 1997;40:1962-6.
42. Glass DN, Giannini EH. Juvenile rheumatoid arthritis as a complex genetic trait. Arthritis Rheum 1999;42:2261-8.
43. Murray K, Thompson SD, Glass DN. Pathogenesis of juvenile chronic arthritis: genetic and environmental factors. Arch Dis Child 1997;77:530-4.
44. Date Y, Seki N, Kamizono S, et al. Identification of a genetic risk factor for systemic juvenile rheumatoid arthritis in the 5′-flanking region of the TNF alpha gene and HLA genes. Arthritis Rheum 1999;42:2577-82.
45. Crawley E, Kay R, Sillibourne J, et al. Polymorphic haplotypes of the interleukin-10 5′ flanking region determine variable interleukin-10 transcription and are associated with particular phenotypes of juvenile rheumatoid arthritis. Arthritis Rheum 1999;42:1101-8.
46. Fishman D, Faulds G, Jeffery R, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 1998;102:1369-76.
47. Schinzel A. Catalogue of unbalanced chromosome aberrations in man. New York: de Gruyter; 1983:101-7, 228-38.
48. Neidlich J, Zackai E, Aronson M, Emmanuel BS. Deletion of 2p: a cytogenetic and clinical update. Am J Med Genet 1987;27:707-10.
49. Kung Ihnat DH, McIlvain-Simpson G, Conard K, Scott CI, Singsen BH. Inflammatory arthropathies in children with chromosomal abnormalities. J Rheumatol 1992;20:742-5.
50. Ruvalcaba RHA, Thuline HC. IgA absence associated with short arm deletion of chromosome 18. J Paediatr 1969;74:964-5.
51. Petty RE, Malleson P, Kalousek DK. Chronic arthritis in two children with partial deletion of chromosome 18. J Rheumatol 1987;14:586-7.
52. Curran JP, al-Salihi FL, Allderdice PW. Partial deletion of the long arm of chromosome E-18. Pediatrics 1970;46:721-9.
53. Olsen JC, Bender JC, Levinson JE, Oestreich A, Lovell DJ. Arthropathy of Down's syndrome. Pediatrics 1990;86:931-6.
54. Yancey CL, Zmijewski C, Athreya BH, Doughty R. Arthropathy of Down's syndrome. Arthritis Rheum 1984;27:929-34.
55. Balestrazzi P, Ferraccioli GF, Ambanelli U, Giovannelli G. Juvenile rheumatoid arthritis in Turner's syndrome. Clin Exp Rheumatol 1986;4:61-2.
56. Kobayashi S, Yamamoto S, Tanaka M, et al. Klinefelter's syndrome and rheumatoid arthritis: Report of a case and review of the literature. Clin Rheumatol 1994;13:500-3.
57. Kiss P, Osztovics M. Familial translocation, t(2;5) (p23;q31): followup after 15 years [letter]. Clin Genet 1975;8:112-6.
58. Buchanan JG, Scott PJ, McLachlan EM, Smith F, Richmond DE, North JDK. A chromosome translocation in association with periarteritis nodosa and macroglobulinaemia. Am J Med 1967;42:1003-10.
59. Walker-Smith JA. Celiac disease and Down syndrome [letter; comment]. J Pediatrics 2000;137:743-4.
60. Karlsson B, Gustafsson J, Hedov G. Thyroid dysfunction in Down syndrome: relation to age and thyroid autoimmunity. Arch Dis Child 1998;79:242-5.
61. Heath CW, Moloney WC. The Philadelphia chromosome in an

unusual case of myeloproliferative disease. Blood 1965;26:471-8.
62. Kobayashi S, Shimamoto T, Taniguchi O, et al. Klinefelter's syndrome associated with progressive systemic sclerosis: report of a case and review of the literature. Clin Rheumatol 1991;10:84-6.
63. Tsung SH, Heckman MG. Klinefelter syndrome, immunological disorders and malignant neoplasm. Arch Pathol Lab Med 1974;98:351-4.
64. Weinrieb IJ, Fineman RM, Spiro HM. Turner syndrome and inflammatory bowel disease. N Engl J Med 1976;294:1221-2.
65. Keating JP, Ternberg JL, Packman R. Association of Crohn's disease and Turner syndrome. J Paediatr 1978;92:160-1.
66. Price WH. A high incidence of chronic inflammatory bowel disease in patients with Turner syndrome. J Med Genet 1979;16:263-6.
67. Arulanantham K, Kramer MS, Gryboski JD. The association of inflammatory bowel disease and X chromosomal abnormality. Pediatrics 1980;66:63-7.
68. Kohler JA, Grant DB. Crohn's disease in Turner's syndrome. BMJ (Clin Res Ed) 1981;282:950.
69. Nishimura H, Kino M, Kubo S, Kawamura K. Hashimoto's thyroiditis and ulcerative colitis in a patient with Turner's syndrome [letter]. JAMA 1985;254:357.
70. de Kerdanet M, Lucas J, Lemee F, Lecornu M. Turner's syndrome with X-isochromosome and Hashimoto's thyroiditis. Clin Endocrinol 1994;41:673-6.
71. Bright GM, Blizzard RM, Kaiser DL, Clarke WL. Organ specific autoantibodies in children with common endocrine diseases. J Pediatr 1982;100:8-14.
72. Williams ED, Engel E, Forbes AP. Thyroiditis and gonadal dysgenesis. N Engl J Med 1964;270:805-10.
73. Pai GS, Leach DC, Weiss L, Wolf C, Van Dyke DL. Thyroid abnormalities in 20 children with Turner syndrome. J Pediatr 1977;91:267-9.
74. Ivarsson SA, Ericsson UB, Nilsson KO, et al. Thyroid autoantibodies, Turner's syndrome and growth hormone therapy. Acta Paediatr 1995;84:63-5.
75. Fleming S, Cowell C, Bailey J, Burrow GN. Hashimoto's disease in Turner's syndrome. Clin Invest Med 1988;11:243-6.
76. Franzese A, De Filippo G, Argenziano A, Salerno MC. Turner syndrome and insulin-dependent diabetes mellitus. Arch Pediatr 1994;1:727-9.
77. Kumon Y, Hisatake K, Suehiro T, Sumiyoshi R, Hashimoto K. Insulin resistance in a patient with diabetes mellitus associated with Turner's syndrome. Intern Med 1994;33:560-3.
78. Miyakawa H, Iyonaga K, Arima S, et al. A superfemale with primary Sjogren's syndrome which involved systemic organs. J Intern Med 1997;242:261-5.