

Juvenile idiopathic arthritis-type disease associated with chromosomal aberrations

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ABSTRACT

The association of certain chromosome aberrations with arthropathy has been previously described, but there is a limited number of reports in the literature. Two children are described, one with 18q- syndrome and another with supernumary marker chromosome 15, both presenting with juvenile idiopathic arthritis-type disease, aggressive progression and moderate response to inflammatory, corticosteroid and immunosuppressive treatment.

Introduction

Association of certain chromosome aberrations with arthropathy has been previously reported, however the literature on this subject is limited (1). Inflammatory arthropathy has been described in association with chromosomal abnormalities, such as Down syndrome (1), Turner syndrome (2) and in 4% of patients with 22q11- deletion syndrome (3). 18q- syndrome is a well-defined rare chromosome aberration and there are five reports in the literature associating this abnormality with arthritis (4-7).

In the present report, two girls with different chromosomal abnormalities and juvenile idiopathic arthritis-type disease are described.

Case reports

Case A

Patient A is a 12-year-old girl, born after an uneventful pregnancy and normal delivery. She was the first child of non consanguineous, phenotypically normal parents.

Microcephaly, hypertelorism, small and slightly upslanting fissures, flat nasal bridge, long philtrum, small chin and dysmorphic ears were noted soon after birth. A proportionally abnormally small 5th finger and abnormal dermatoglyphics were also present; nipples were widely spaced; hypotonia with poor feeding was evident at the age of 3 months (Fig. 1).

At the age of 15 months, she was first admitted to hospital because of failure to thrive. Laboratory workup revealed IgA deficiency, IgG and IgM immunoglobulins within normal range and normal lymphocyte subpopulations. In

a 2-D echocardiogram, a large atrium secundum defect was found, which was surgically repaired. At that time, a cytogenetic analysis was performed which showed a normal 46, XX karyotype.

At 5 years of age, the patient was readmitted because of monoarthritis of her left knee. She had soft tissue swelling, synovitis and effusion. At this age, she had normal weight (25th PC), short stature (<5th PC) and microcephaly (<5th PC). She had good gross, but poor fine motor skills and borderline intelligence. In the following six months arthritis of both ankles was noted with marked swelling, as well as arthritis of the small joints of her hands and feet with synovitis and limitation of movements. She was treated with naproxen. At this time she also complained of fatigue and morning stiffness. Karyotype analysis was repeated and telomere screening by



Fig. 1. Dysmorphic features and arthritis of knees and feet in patient A.

Competing interests: none declared.

fluorescent in situ hybridization (FISH) using telomere probes (Chromoprobe Multiprobe®, Cytocell technologies) revealed a deletion of the telomere of one chromosome 18q (Fig. 2).

During the following four years flexion contractures of her fingers gradually developed (Fig. 3) and arthritis of both her wrists with marked synovitis was added. Methotrexate once weekly (15mg/kg/week) and small doses of prednisolone in alternate regime were prescribed.

Laboratory studies at the age of 5 showed normal blood count, slightly elevated ESR (40mmHg) and negative antibodies against an extended number of bacteria and viruses. During follow-up, ESR remained elevated, while immunoglobulin IgG and IgM levels were increased for her age (IgG = 2130mg/dl, IgM = 97mg/dl). IgA titers have been constantly below 5mg/dl, a finding suggesting IgA deficiency. C3 and C4 were within normal limits. Antinuclear antibodies (ANA) were not detected and rheumatoid factor was negative. Antithyroid antibodies TGHA were detected (783 iu/ml) for the first time when she was 9 years old but thyroid function was normal. Slit lamp examination was normal. Radiographs showed effusions of her knees. A synovial biopsy was not performed as the parents refused to give an informed consent.

At the age of 12, when the patient was re-evaluated, magnetic resonance imaging showed increased fluid in the left hip but fluid analysis was not performed as the parents refused to give an informed consent.

Case B

Patient B is a nine-year-old girl, the second child of phenotypically normal non-consanguineous parents, born after an uneventful pregnancy. Soon after birth slight dysmorphic features were noticed, including bilateral blepharoptosis, small nose, long philtrum, large low set ears and increased joint mobility (Fig 3). There was a 2nd – 3rd toe overlap in both feet. Her development, regarding motor and cognitive skills, was delayed. She sat at the age of 8 months and walked at the age of 2 years. Her gait was unsteady, but neu-

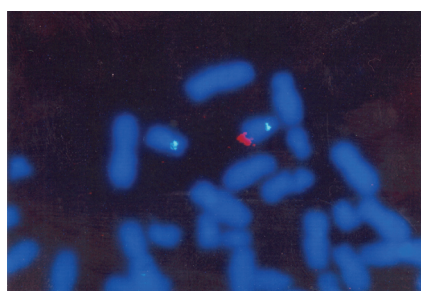


Fig. 2. FISH analysis of metaphase spreads from patient A showing deletion (only one signal) of the telomere of chromosome 18.



Fig. 3. Arthritis of the knees in patient B.

rological examination did not reveal ataxia or clonus and reflexes were normal. Behavioral problems, such as hyperactivity, aggressiveness and autistic features were soon evident. Failure to thrive and frequent infections were additional problems. Cytogenetic inves-

tigation revealed a 47, XX+marker karyotype. FISH using a chromosome 15 whole paint probe (CAMBIO) and the SNRPN gene probe (ONCOR) demonstrated that the marker was derived from chromosome 15 and did not contain the SNRPN region (Fig 4). Parental karyotypes were normal. Molecular analysis using dinucleotide repeat polymorphisms within the PWS/AS critical region (D15S11, D15S113, GABRB3, D15S10, D15S97, D15S543, D15S87, CYP19) showed normal biparental inheritance.

She was first examined by a rheumatologist at the age of 7 years, because she developed afternoon low grade fever of more than one month's duration, prominent morning stiffness and arthritis of the small joints of her hands. Clinical examination revealed enlargement of her knees with mild soft tissue swelling, marked synovitis and limitation of the extension. Deformities of her fingers and toes were also detected (Fig 3). Increased values of serum reacting protein and erythrocyte sedimentation rate were found, while blood count, titers of immunoglobulins, rheumatoid factor and anti-nuclear antibodies (ANA) were negative. Lymphocyte subpopulations were also normal. She

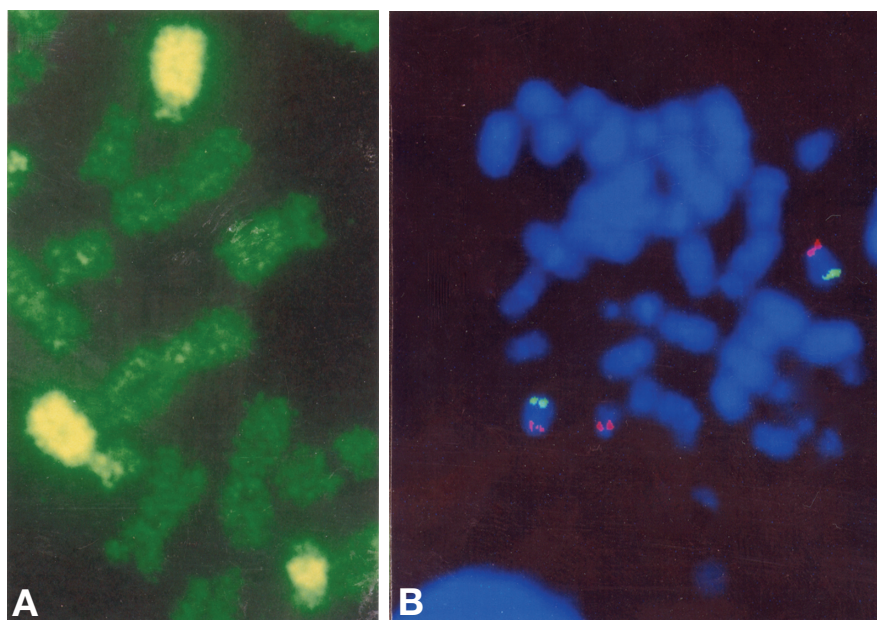


Fig. 4. FISH analysis with chromosome 15 whole paint probe and (left) the SNRPN gene probe in combination with chromosome 15 centromere probe (red signal) showed that the marker chromosome was derived from chromosome 15 (3 green signals) and did not contain the SNRPN region (2 red signals)

Table I. Literature reports of patients with 18q- syndrome and arthritis and comparison with patient A.

Report	Sex /age of onset	Type of arthritis	Additional symptoms	Laboratory investigation	Chromosome aberration
Petty <i>et al.</i> (1987)	♂ / 11 y	Warm, painful, intraarticular fluid, decreased mobility (knees, ankles)	–	IgA deficiency, RF (+), ANA (–)	Ring (18) (p11.3-23)
	♂ / 5.5 y	Intermittent pain, swollen, warm, morning stiffness (knees, right wrist)	Rash	↓ IgG, IgM, ANA (–)	Del (18) (q21.2-22)
Hansen <i>et al.</i> (1994)	♂ / 4 y	Sudden onset, tenderness, flexion contractures, chronic swelling (knees, left ankle)	Uveitis	↑ IgG, IgM, ANA(–), RF(–) x-rays (+): subchondral erosions	Del (18) (q22-qter)
Rosen <i>et al.</i> (2004)	♂ / 8 y	Onset after trauma, effusions (knees)	–	↑ ESR, C3, IgG, IgM RF(–), ANA (+), MRI (+)	Del (18) (q22-qter)
Patient A	♂ / 5 y	Polyarthritis of the ankles, wrists, knees, small joints and hips	–	↑ ESR, IgG, IgM, IgA deficiency RF(–), ANA (–), MRI (+)	Telomere del 18q

was treated with NSAIDs and prednisolone 2mg/kg/day and although the fever subsided completely, arthritis displayed limited response. During the next two years many exacerbations of her arthritis were noted, involving both knees and the inter-phalangeal joints of her fingers and toes. A combination of naproxen and methotrexate was prescribed, but behavioral problems did not permit compliance to the therapy.

Discussion

We have described two patients with abnormalities of chromosomes 18 and 15 in combination with juvenile idiopathic arthritis-type disease at the age of 5 and 7 years respectively, which progressed to multiple deformities.

The diagnosis of rheumatoid disease in our patients has been a subject of debate, as juvenile idiopathic arthritis (JIA) is an exclusion diagnosis. In particular, the debate has been focused towards two diagnostic directions, syndromic arthropathy and juvenile idiopathic arthritis. The presence of severe synovitis, in combination with pain and increased ESR during the relapse phase of the disease in patient A and the low grade fever and increased ESR at the disease onset in patient B, outline the inflammatory element of the arthritis. In addition, the onset of arthritis during childhood and not at birth, as well as the development of contractures, strongly indicate the diagnosis of JIA-type arthritis and not of syndromic arthropathy.

Patient A had all features of 18q- syndrome, IgA deficiency and chronic

arthritis (Table I) (4). The 18q22→18qter chromosomal region has been previously reported to be associated with IgA deficiency and autoimmunity, in particular autoimmune endocrinopathies and juvenile idiopathic arthritis (9). Furthermore, IgA deficiency has been associated with autoimmune disease and JIA. (10). To the best of our knowledge, five patients with JIA-type arthritis and 18q- syndrome have been previously reported (Table I) (4–7).

Linkage analysis studies in families with rheumatoid arthritis showed that both HLA and non-HLA genes may be involved in disease susceptibility (11–14). Meta-analysis data of chromosome 18q demonstrated the presence of a number of SNPs located on non-encoding and regulatory regions of the genome that are strongly associated with rheumatoid arthritis (15, 16). Reports of additional cases, however, is required to confirm these findings. It is interesting that the deletion detected in our patient was restricted to the subtelomeric region, implying that genes implicated in IgA synthesis regulation and juvenile idiopathic arthritis are located within this region.

Patient B is the first reported case associating a partial trisomy of chromosome 15 with inflammatory arthropathy. *De novo* structural imbalances of chromosome 15 are usually associated with a variety of phenotypic features, such as mental retardation, convulsions Prader-Willi/Angelman syndrome, infertility and congenital heart defects (17). Additionally, the presence of

potential autism susceptibility genes in the 15q11-q13 region is reported (18). There is also one report identifying a structural alteration of chromosome 15 in the synovial fibroblasts of a patient with arthritis (19).

In conclusion, the two cases described in this study suggest that chromosomal regions 18q and 15q may contain non-HLA susceptibility loci involved in chronic inflammatory arthritis and provide a basis for carrying out targeted linkage analysis and candidate gene studies in patients with juvenile rheumatoid arthritis.

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