Case Report

Juvenile Rheumatoid Arthritis-like Polyarthritis in Nijmegen Breakage Syndrome

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ABSTRACT. Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disease (8q21) from the family of the genetically determined chromosomal instability syndromes. The disorder is characterized by microcephaly, growth retardation, immunodeficiency, and high incidence of cancer. Several noninflammatory anomalies of the musculoskeletal system have been described in patients with this syndrome. We describe an Argentinian girl with all the clinical, immunological, and cytogenic characteristics described for NBS plus a juvenile rheumatoid arthritis-like syndrome. To our knowledge this is the first report of a patient with the NBS who presented with a symmetric chronic polyarthritis resembling JRA. (J Rheumatol 2001;28:2548–50)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS NIJMEGEN BREAKAGE SYNDROME
GENETIC DISEASE IMMUNODEFICIENCY POLYARTHRITIS

The Nijmegen breakage syndrome (NBS) chromosomal instability syndrome, previously classified as ataxia telangiectasia (AT) variant, shares most of its immunological and cytogenetic characteristics with AT, even though they map in 2 different loci[1]. The AT gene maps on chromosome 11q22, encoding for ATM protein[2], while NBS gene has recently been localized on chromosome 8q21, encoding for a novel protein designated nibrin[3]. Both AT-mutated and nibrin have been functionally related with cell cycle control and double strand DNA repair[2–4]. The most common shared features of these syndromes are lymphopenia, IgA, IgG2 and IgG4 deficiency, impaired antibody response, specific rearrangements involving chromosomes 7 and 14, and lymphoid cancer predisposition[1]. In particular, patients with NBS show microcephaly, peculiar bird-like face, growth retardation, and mild to moderate mental retardation. As well, several noninflammatory anomalies of the musculoskeletal system have been described in patients with this syndrome[5-8]. We describe an Argentinian girl with all the clinical, immunological, and cytogenic characteristics described for NBS plus a juvenile rheumatoid arthritis-like syndrome.

CASE REPORT

An Argentinian girl was the first daughter of a young, nonconsanguineous Argentinian couple (paternal grandfather was Hungarian). Since the age of 6 years, she had repeated episodes of pneumonia and diarrhea. She was referred to our center in May 1995 because of recurrent respiratory tract infections. At first visit (age 13 yrs, 5 mo) her clinical examination showed a mentally retarded patient with short stature (height 127.5 cm), microcephaly (cephalic perimeter 44.5 cm), mongoloid oblicuity of palpebral fissures, cafe au lait spots, ephelides, Tanner I, and multiple signs of chronic, active polyarthritis (Figure 1). She also exhibited signs of chronic hypoxemia, such as clubbed nails. Routine analysis at admission showed pulse oximetry 94%; hemoglobin 15.5 g/dl; white blood cell count 15.5×10^9/l, 86% polymorphonuclear, 12% lymphocytes, 1% monocytes, 1% eosinophils; platelet count 411×10^9/l; erythrocyte sedimentation rate 2 mm/h. NBS was suspected, and further investigations gave the following results: low serum IgG and IgA levels (IgG 117 mg/dl, IgA < 6 mg/dl), normal IgM (70 mg/dl); negative antinuclear antibody, negative rheumatoid factor; elevated C3 and normal C4 levels (> 150, 29 mg/dl, respectively); absent response to 23 serotype pneumococcal vaccine (prestimulation < 4 mg/l, poststimulation 6 mg/l; protection level 200 mg/l); normal response to tetanus toxoid (prestimulation: negative, poststimulation: 1/512); normal lymphocyte phenotype (total lymphocytes 1.86×10^9/l, CD3 57%, CD4 39%, CD8 18%, CD16/56 36%, CD19 6%, CD3/DR 25%); below normal lymphocyte proliferation to mitogens (phytohemaglutinin 64,970 cpm, normal range 93,235–188,129; pokeweed mitogen 43,209 cpm, normal 46,050–113,202; concanavalin A 73,390 cpm, normal 82,153–188,027; CD3 50,990 cpm, normal 85,038–176,294); normal alpha-fetoprotein levels (< 3 ng/ml). Chromosome analysis: 46xx, the basic karyotype was normal, but 40% of the 40 metaphases analyzed showed rearrangements involving chromosomes 7 and 14 with breakpoints at 7p13, 7q34, 14q11, and 14q32 (Figure 2).

Her rheumatological findings were symmetric polyarthritis affecting both large and small joints [elbows, wrists, hips, knees, ankles, metacarpophalangeals (MCP), proximal interphalangeals (PIP), metatarsophalangeals (MTP)]. These joints were swollen (swelling did not appear to be due to effusion but to synovial hypertrophy), tender, and showed stress pain as well as increased temperature. Also, limitation of range of motion of neck, shoulders, elbows, wrists, hips, knees, ankles, and subtalar joints was evident. She also exhibited palmar tenosynovitis. She complained of morning stiffness lasting about 2 hours.

Plain radiographs showed signs consistent with chronic arthritis (Figures 3 and 4).

Treatment and outcome. Nonsteroidal antiinflammatory drug (NSAID) therapy (ibuprofen 30 mg/kg/day) was started promptly during her first admission,

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Figure 1. A. Note the patient's short stature. Wrist and knee swelling are also observable. B. Her bird-like appearance.

Figure 2. G-banded metaphase showing translocation t (7;14) (q34;q11) (arrow).

with a favorable response. After 2 weeks of therapy, her joint swelling, tenderness, and morning stiffness disappeared, while the aforementioned limitations persisted. Replacement intravenous gammaglobulin (IVGG) 500 mg/kg/mo was initiated after her immunological evaluation was finished, 3 weeks after admission. She was then discharged with identical medical prescription. She was lost to followup for nearly one year. When she returned to our hospital, she showed a clinically worse condition. She had not received NSAID regularly and IVGG had not been administered at all. She described marked morning stiffness, and on examination she had symmetric active polyarthritis involving elbows, wrists, MCP, PIP, hips, knees, ankles, and MTP; bilateral palmar flexor tenosynovitis; and range of motion that was limited on elbows, wrists, hips, and knees. IVGG (500 mg/kg/mo) and NSAID (ibuprofen 30 mg/kg/day) were reintroduced. Low dose short course oral steroids were prescribed (prednisone 0.5 mg/kg/day for 7 days). After one week of therapy, she experienced a striking clinical improvement with no morning stiffness and almost no active arthritis. She was discharged and has not returned to our center since June 1996.

DISCUSSION

This is the first report of a patient with NBS syndrome who presented with a rheumatic disease indistinguishable from JRA. As in other immunodeficiencies, it is possible that predisposition to infections, potentiation of the virulence of biologic agents, and perpetuation of inflammation could lead to the development of autoimmunity and chronic arthritis. Immunological abnormalities such as defective surveillance or misdirection of immunological responses have also been related to the pathogenesis of autoimmune disease[9]. The occurrence of chronic polyarthritis similar to JRA in other primary immunodeficiencies, such as X-linked agammaglobulinemia, IgA deficiency, and common variable immunodeficiency, is well known[10]. Recently, 3 patients with DiGeorge syndrome and JRA-like polyarthritis were described[11].

On the other hand, certain congenital diseases with a probable or definite genetic disorder and no immunodeficiency, such as Fabry's disease, neonatal onset multisystemic inflammatory disease (NOMID), or trisomy 11, present with musculoskeletal features that resemble JRA[12].

Notwithstanding the reported musculoskeletal abnormalities in NBS (clinodactyly, polydactyly, wide gap I/II toes, and syndactyly II/III toes), no inflammatory manifestations have been previously described in association with this syndrome[7,8]. Our patient clearly showed signs of joint inflammation — swelling, increased local temperature, tenderness, and pain on motion. Moreover, her relapsing-remitting course suggested a chronic inflammatory condition. Although we did not obtain a synovial sample for pathological analysis, the physical findings supported the inflammatory character of her disease.

She improved clinically after receiving NSAID and IVGG on both visits to our center. Replacement therapy with IVGG was administered twice, once in each hospitalization. Immunomodulatory treatment for JRA with 2 g/kg/dose IVGG was not indicated in this patient[13]. Even though sustained replacement IVGG treatment has been described to improve inflammatory joint involvement in predominantly antibody deficiencies[10], we believe her response was mainly due to the NSAID, rather than to IVGG — she experienced clinical improvement of her joint involvement before IVGG was initiated and after NSAID were started. None the less, we cannot exclude the possibility of an infectious trigger in the onset of this patient's arthritis. Mycoplasma infections have been related to chronic arthritis in certain predominantly antibody immunodeficiencies[10]. This infection was not investigated in this patient.

Unfortunately, none of the treatments prescribed was sustained for a length of time sufficient to evaluate longterm outcome.

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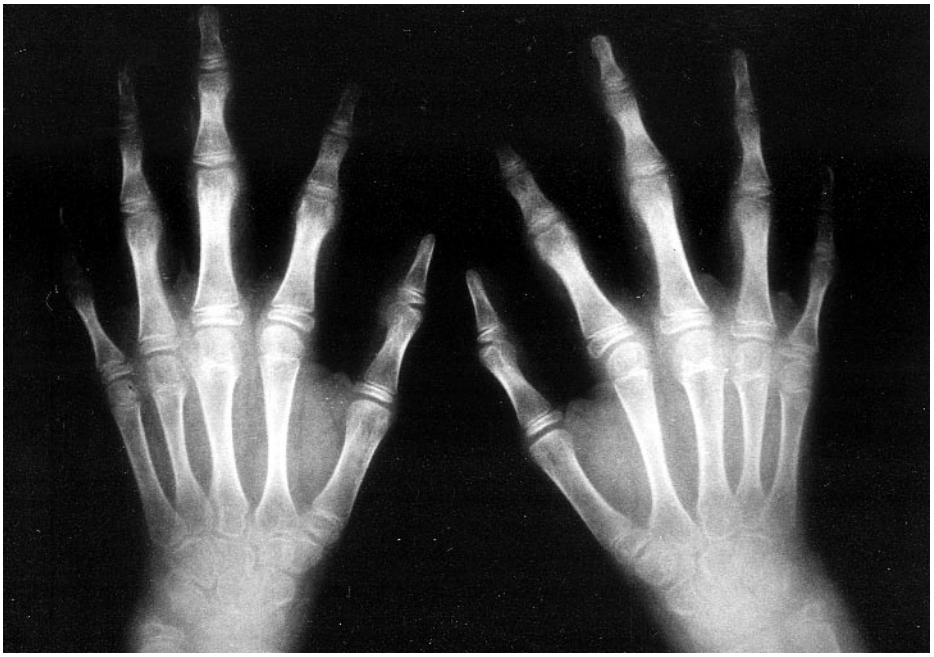

Figure 3. Plain radiographs of the wrist showing osteopenia in juxtaarticular bone of carpi and thinned cortical in tubular bones.

Figure 4. Plain radiographs of the hips showing narrowing of hip joint space, subchondral pseudocystic lesions in femoral heads and acetabuli, and osteosclerosis in both acetabuli.

We have reported the occurrence of chronic polyarthritis in a patient with Nijmegen breakage syndrome, a genetic disorder comprising immunodeficiency. This newly described association should be added to the list of primary immunodeficiencies that may present with chronic arthritis mimicking JRA.

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