BTK Gene Mutation in Two Non-Identical Twins with X-Linked Agammaglobulinemia Associated with Polyarticular Juvenile Idiopathic Arthritis

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X-linked agammaglobulinemia is a genetic disorder of B cell maturation caused by a variety of mutations in the gene encoding Bruton tyrosine kinase (*BTK*). XLA affects only males and results in profound humoral immunodeficiency. The incidence of XLA is around 1:200,000 in newborns. XLA is characterized by recurrent bacterial infections due to low levels or absence of serum immunoglobulin isotypes [1,2]. The early administration of high dose intravenous immunoglobulin may prevent these infections [3].

Among patients with XLA 20% may have arthritis, primarily septic arthritis, and association with rheumatoid arthritis or juvenile idiopathic arthritis may also occur [1,2,4,5]. We present here a pair of non-identical twins who each had a mutation in the *BTK* gene. Both siblings presented with polyarticular juvenile idiopathic arthritis.

PATIENT DESCRIPTIONS

We report two 27 year old non-identical twin boys with XLA associated with seronegative, polyarticular JIA. The twins were born in 1981 and the diagnosis of XLA was established according to standard criteria in 1986 [2]. Their treatment consisted of monthly 400 mg/kg hIVIG.

The first boy originally presented to our rheumatology clinic with recurrent bilateral knee synovitis. He had a medical history of recurrent sinopulmonary infections, and pulmonary segmentectomy was performed due to pulmonary abscess. Serum IgA and IgM levels were below the detection limit (IgG 5.73 g/L, IgA < 0.06 g/L, IgM < 0.05 g/L) and a profound deficiency in circulating $CD19^+$ B cells (0.02%, normal range 5-15%) was observed.

At first presentation, joint radiography could not demonstrate joint erosions. Synovial fluid cultures were negative, excluding septic arthritis. Synovial crystals could not be identified. Serological tests for several viruses and bacteria were also negative. The patients were negative for antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide and HLA-B27. hIVIG substitution did not affect the synovitis: articular symptoms worsened involving both wrists, metacarpophalangeal and proxymal interphalangeal joints. The patient also developed subcutaneous nodules. Radiological progression was observed after one year in the metacarpophalangeal joints. Erythrocyte sedimentation rate was 1 mm/hr due to the lack of B cell products, while C-reactive protein was elevated (9.4 mg/L, normal range < 5 mg/L). Thus, the patient had seronegative, polyarticular JIA associated with humoral immunodeficiency. Considering severe profound polyarthritis in this patient adequately substituted with hIVIG, naproxen, then sulfasalazine therapy was initiated at a dose of 30 mg/kg, which soon resulted in clinical improvement and remission.

In the second boy, XLA was also diagnosed in 1986 after recurrent sinopulmonary infections and pneumonia. hIVIG therapy was administered at a monthly dose of 400 mg/kg.

In June 2000 the patient presented to our rheumatology clinic with recurrent bilateral knee and right hip synovitis. Rheumatoid factor, anti-CCP, antinuclear antibody and HLA-B27 were negative. Radiography showed no erosions. We observed significant $CD19^+$ B cell deficiency (0.02%) with very low serum IgG (5.63 g/L), IgA (< 0.06 g/L) and IgM (< 0.05 g/L).

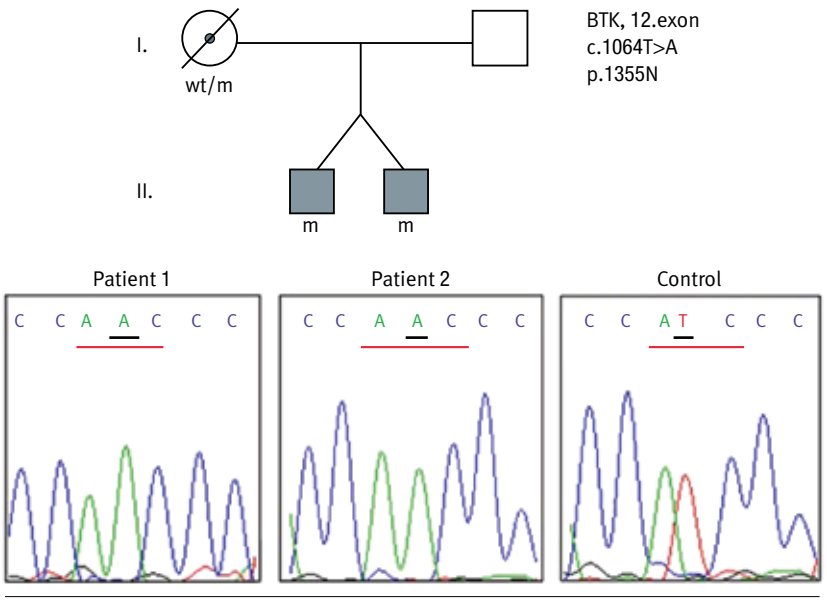
Upon naproxen therapy, synovitis progressed and a classical rheumatoid nodule developed over the elbow. In March 2005, leukocytoclastic vasculitis confirmed by histology developed on the forearm skin. Vasculitis subsided upon corticosteroid therapy. The patient was diagnosed with seronegative polyarticular JIA and 30 mg/kg sulfasalazine was introduced. Peripheral magnetic resonance imaging revealed small erosions in the os capitatum.

In 2006, we wished to confirm XLA by genetic analysis in the twins. Therefore, genomic DNA was extracted from blood leukocytes (GenElute Blood Genomic DNA Kit, Sigma, USA). Exons 1 to 19 and the flanking intron regions of the *BTK* gene were amplified from gDNA by polymerase chain reaction. Amplicons were

XLA = X-linked agammaglobulinemia
JIA = juvenile idiopathic arthritis
hIVIG = high dose intravenous immunoglobulin
anti-CCP = anti-cyclic citrullinated peptide

sequenced using the Big Dye Terminator sequencing kit (Applied Biosystems, USA). Capillary sequence analysis was performed in a blinded fashion with respect to the clinical diagnosis. Sequence variations are described in relation to reference sequences, GenBank accession no. NM_000061 for *BTK* cDNA, where the c.1 position represents A of the ATG translation initiation start site. A mutation (T→A) in exon 12 at position 1064 was identified resulting in an Ile→Asn amino acid change at position 355 in the BTK protein identified by PCR. All the other exons were found to be intact. A normal control was also genotyped. Thus, XLA could be genetically confirmed in these siblings based on the mutation in exon 12 of the *BTK* gene [Figure].

Pedigree and automated sequencing profiles of genomic DNA. Missense mutation (c.1064T>A; p.I355S) in *BTK* was found in both patients



COMMENT

We describe two cases of XLA associated with polyarticular JIA and nodules in non-identical twins. The definitive diagnosis of JIA was established in both cases by clinical and laboratory assessments. XLA was confirmed by recurrent infections, very low B cell numbers and later by the mutation in the *BTK* gene [1,2].

We present for the first time the association of XLA confirmed by molecular genetic analysis with polyarticular JIA in twins. In addition, although the reported XLA-associated cases were relatively mild and responded well to treatment with non-steroidal anti-inflammatory drugs, our twins needed disease-modifying anti-rheumatic drug therapy despite XLA.

PCR = polymerase chain reaction

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"At least one way of measuring the freedom of any society is the amount of comedy that is permitted, and clearly a healthy society permits more satirical comment than a repressive one, so that if comedy is to function in some way as a safety release then it must obviously deal with these taboo areas. This is part of the responsibility we accord our licensed jesters, that nothing be excused the searching light of comedy. If anything can survive the probe of humor it is clearly of value, and conversely all groups who claim immunity from laughter are claiming special privileges which should not be granted"

Eric Idle (b. 1943), English comedian, actor, author, singer, writer, and comedic composer who wrote and performed as a member of the popular British comedy group *Monty Python*

"I have never met a man so ignorant that I couldn't learn something from him"

Galileo Galilei (1564-1642), Italian physicist and astronomer