

JOINT DISEASE IN CHILDREN WITH X-LINKED AGAMMAGLOBULINEMIA

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ABSTRACT

Patients with X-linked agammaglobulinemia (XLA) are prone to recurrent bacterial infections due to low levels of immunoglobulins. Clinical symptoms include recurrent bacterial otitis media, bronchitis, pneumonia, meningitis, skin infection and arthritis. In the majority of cases arthritis can be shown to be caused by infection, but also aseptic arthritis and autoimmune diseases may be present. Monoarthritis and oligoarthritis is usual pattern, although polyarthritis may occur. We present diagnostic and therapeutic problems in two cases with agammaglobulinemia and arthritis.

Key words: agammaglobulinemia, arthritis, children

INTRODUCTION

X-Linked agammaglobulinemia (XLA) or Bruton agammaglobulinemia is inherited immunodeficiency disease caused by mutations in the gene coding for Bruton tyrosine kinase (BTK). The disease was first elucidated by Bruton in 1952, for whom the gene is named. BTK is critical to the maturation of B cells. The BTK gene defect has been mapped to the long arm of the X chromosome at band Xq21.3 to Xq22.

Patients with XLA are prone to recurrent bacterial infections due to low levels of immunoglobulins. Diagnosis is based on the evaluation of immunoglobulin levels with immunoglobulin G (IgG) <2g/l, absence of immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin E (IgE) and B lymphocytes in peripheral blood.

Joint complaints are relatively common symptoms noted by these patients. [1-6] The prevalence of arthritis in hypogammaglobulinemia ranges from 10-30%. [6, 7]

In this paper we present two patients with agammaglobulinemia and arthritis.

CASE REPORTS

• Case 1

This patient was admitted to our clinic for first time when he was 7 years old. His older brother died from chronic lung disease and sepsis. The child had history of repeatedly

treated upper and lower respiratory tract infections which had tendency to prolong and often were resistant to applied treatment. At admission he had pneumonia and painful swelling with mild redness and restricted motions of the right knee which lasted for 3 months and therapy with antibiotics and non-steroid anti-inflammatory drugs was not effective.

The performed examination revealed the following results: haemoglobin 9,3 g/dl, erythrocytes $3,2 \times 10^6/\mu\text{l}$, leucocytes $10,3 \times 10^3/\mu\text{l}$, platelets $230 \times 10^3/\mu\text{l}$, elevated erythrocyte sedimentation rate 95/120, antistreptolysin titre negative, antinuclear antibody negative, rheuma factor negative, lupus cells absent, Mantoux test 10/ 5mm. Immunoglobulin levels were evaluated and the results were: IgA and IgM – undetected levels, IgG 0,89 g/l. Investigation of lymphocyte subpopulations revealed absence of B lymphocytes CD19 and CD20 markers, and genetic analysis find mutation of the BTK gene Aspartic acid 579 Asparagine (Guanine 1867 Adenine). On the base of these findings we considered congenital immune defect – XLA. X-rays of the lungs showed collapses of lingula, left-side pleural adhesions and calcificates in the mediastinal lymph nodes – changes suggestive for tuberculosis (Figure 1, 2).

Fig. 1. Case 1. X-rays of the lungs.



Fig. 2. Case 1. X-rays of the lungs.



X-rays of the knee showed oedema of the soft tissue of the joint with no visible changes in the bones building the knee joint (Figure 3). Biopsy of the synovial membrane showed non-specific infiltration with lymphocytes, chronic hyperplastic synovitis without evidence of specific inflammation. Culture of synovial fluid was negative. Culture of sputum was negative for *Mycobacterium tuberculosis*. The child received three-week course of antibiotics without effect. Later we started tuberculostatic therapy for 6 months and regular monthly substitution with intravenous immunoglobulins (IVG).

Figure 3. Case 1. X- rays of the right knee.



The inflammation of the joint resolved after two months and since then the child had no longer any symptoms of arthritis. X-rays on the knee after therapy revealed normal bones and joint structures.

• Case 2

This patient had suffered from respiratory infections since age of 3 years. His immunoglobulin levels were evaluated for the first time at the age of 6, and the initial levels were IgA 0,01g/l, IgG 1,24g/l, IgM 0,05g/l with lack of B Lymphocytes, and mutation of BTK gene Tryptophan 634 Stop (Guanin 2033-Adenin). Diagnosis of XLA was confirmed and we started monthly substitution of IVG.

At the age of 10 years he had inflammation of his right ankle joint with mild fever, pain and swelling, white blood cells $6,4 \times 10^3/\mu\text{L}$ and low erythrocytes sedimentation rate 10/25. X-rays of the affected joint showed mild swelling of the joint soft tissue. Examination of the synovial fluid for bacteria was negative and for *Mycoplasma* was not performed.

Since we considered bacterial arthritis, we administered antibiotics with wide spectrum intravenously within ten days, but symptoms of arthritis such as redness and pain returned three to four days after cessation of therapy. Because of this we administered second 10-days course of antibiotics with mild effect. Based on the data from literature that mycoplasma arthritis is common in patients with XLA, we started therapy with Doxycyclin for two months, followed by good effect and the inflammation resolved without joint damage.

DISCUSSION

The reported cases are examples of diagnostic and therapeutic problems regarding origin of arthritis in children with HLA.

In case 1, septic arthritis was discussed as diagnostic possibility. Regarding to septic arthritis in patients with HLA, the most frequent pathogens are *Mycoplasma* species and *Ureaplasma* species.[14-18, 25] Nearly 40% of cases with septic arthritis and HLA are caused by these pathogens. The differential diagnosis of arthritis in patients with agammaglobulinemia should strictly exclude *Mycoplasma* infection by culture on special media or longer anaerobic culture, and molecular methods for *Mycoplasma*.

Staphylococcus aureus, *Streptococcus pneumoniae* and *Haemophilus influenzae* also can cause septic arthritis in hypogammaglobulinemia. [4, 8-12] Bacterial arthritis is usually more acute and painful than other unless treated with antibiotics, and rare in patients received IVG.

In case 1 synovial fluid was negative for bacteria and was not tested for *Mycoplasma*. The child received three-week course of antibiotics without effect.

While septic arthritis due to atypical organisms is common, aseptic arthritis has also been reported.[1, 19, 20]

Chronic arthritis in such patients is usually without erosions and responds well to gamma globulin replacement therapy, which is distinct from classic rheumatoid arthritis and may be classified as a reactive arthritis.¹

Juvenile chronic arthritis (JCA) was also considered.[1, 3, 7, 8, 21-24] But in reported case were manifested only mild joint complaints limited to the right knee joint without other JCA symptoms, and X-rays was not characteristic for prolonged rheumatoid process.

In case 1 we also suspected tuberculosis which can be found often in children with hypogammaglobulinemia.¹³ This suspicion was made on the base of X-rays of the lungs, positive Mantoux test and socio-epidemiological data, despite negative both synovial and sputum culture for *Mycobacterium tuberculosis*, and lack of specific lesions in synovial biopsy. We started with six-month triple tuberculostatic therapy which included Rifampicin, and also IVG substitution. After the therapy there was significant improvement of pulmonary findings as well as complete regression of the knee arthritis. Good response may be due to effective tuberculostatic therapy, but also if the arthritis was of aseptic origin, gammaglobulin therapy solved the problem. *Mycoplasma hominis* has also moderate susceptibility to Rifampicin, and the arthritis, in case it was not tuberculosis, could be improved by tuberculostatic therapy.

In Case 2 we faced relapsing arthritis with poor response to cephalosporins and macrolides in child already received IVG. Bacterial culture from synovial fluid was negative and cultures for mycoplasma were not performed. Therefore we started empiric treatment for *Mycoplasma* with Doxycycline for two months. Since the diagnosis of *Mycoplasma* infections is difficult and time-requiring, tetracycline treatment should be administered to patients with hypogammaglobulinemia demonstrating arthritis, pleuritis, or meningitis that may be caused by *Mycoplasma* infection.

Tetracyclines are the first choice for treatment of infections caused by *Mycoplasma hominis*. [26]

CONCLUSIONS

Reported cases are examples of diagnostic problems regarding to the origin of arthritis in the course of agammaglobulinemia. Arthritis is one of relatively frequent symptoms found in patients with hypogammaglobulinemia. Majority of arthritis are caused by microorganisms but also aseptic arthritis and JCA may be present. Sophisticated laboratory tests are necessary for differential diagnosis of arthritis.

If such tests are not performed, empiric treatment based on the data from the literature as a guideline should be implemented.

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