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Case Report

Bruton's X-Linked Agammaglobulinemia Presenting as Chronic Monoarticular Arthritis

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Abstract

Bruton's X-Linked Agammaglobulinemia (XLA) is an X linked recessive primary immune deficiency disorder characterized by recurrent bacterial infections and failure to generate immunoglobulins of all isotypes due to the absence or profoundly decreased mature B cells and plasma cells, secondary to mutations in the Bruton's tyrosine kinase (Btk) gene. The coexistence of chronic monoarticular arthritis in a patient with Bruton's XLA has been described an uncommon presentation. We describe a 5 year-old boy with XLA and chronic monoarticular arthritis.

Introduction

The adaptive immune response consists of humoral immunity mediated by B lymphocytes and cellular immunity maintained by T lymphocytes. Agammaglobulinemia was the first primary immunodeficiency to be described. In 1952, Colonel Ogden Bruton noted the absence of the "gammaglobulin" fraction on protein electrophoresis in a boy with recurrent bacterial sinopulmonary infections[1]. Bruton's X-linked agammaglobulinemia (XLA) is a humoral immunodeficiency disease caused by a mutation in the Bruton tyrosine kinase (BTK) gene at Xq21.3, resulting in defective B cell differentiation and a decrease in all serum immunoglobulins[2]. The prevalence of XLA has been estimated at 1 case per 250,000 males in the United States. B-cell deficiencies or dysfunction lead to increased susceptibility to infection, especially with encapsulated pyogenic organisms, such as *Streptococcus pneumoniae, Haemophilus influenzae*, and *Pseudomonas* species. Pneumonia, sinusitis, meningitis, and bacterial diarrhea are common, as is an increased susceptibility to enteroviral infections[3]. The recurrent bacterial infections typical of XLA begin after 6 months of age when the maternally acquired transplacental antibody levels decrease and the infant is unable to synthesize antibodies normally. Chronic arthritis is an uncommon presentation of the XLA. We describe a 5 year old boy with Bruton's X-linked agammaglobulinemia presenting with chronic monoarticular arthritis.

The Case

A five year old boy presented with a history of pain and swelling of right knee joint for past one year, which had not improved with multiple doses of intravenous antimicrobials and a nine month course of anti-tubercular drugs. He had a history of recurrent pneumonia since six months of age which required hospitalization. He also had a history of chronic ear discharge, recurrent soft tissue infections and recurrent diarrhoea. He also had received six months course of anti tubercular drugs for pulmonary tuberculosis at the age of one year in view of recurrent lower respiratory infection. He was a product of non-consanguineous parents and had four sibling, three elder healthy sisters and one youngest brother. The youngest brother died due to pneumonia at the age one year, who also had history of recurrent pneumonia.

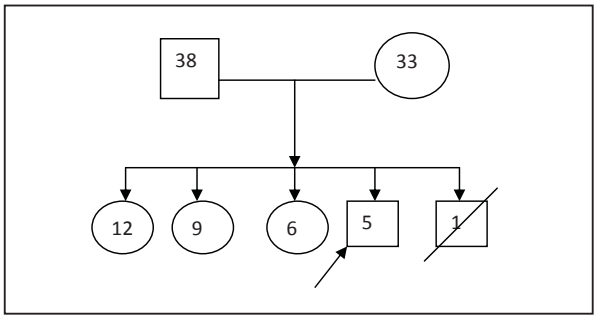

Fig 1: Showing pedigree chart of the family.

On admission he was afebrile, and malnourished. He had mild pallor, pulse rate 98 per minute, respiratory rate of 32 per minute, weight 10 kg (less than 3rd centile), length 96 cm (less than 3rd centile), and multiple healed scars of boils all over body. Tonsils were atrophic and not even single lymph node was palpable in spite of recent abscess in the neck Figure 2. Right knee joint was swollen, and mildly tender. Cardiovascular and central nervous system examination were normal. Respiratory examination revealed bilateral crepts on inframammary and infrascapular areas. Liver was palpable 2 cm below right costal margin. Ophthalmological (Slit lamp and Fundus) examination was normal. On the basis of clinical history and examination findings, differential diagnosis were

1. Bruton's agammaglobulinemia,
2. Common variable immunodeficiency,
3. Secondary Immunodeficiency disorder (HIV Infections),
4. Hyper IgM syndrome and
5. Oligoarticular Juvenile Rheumatoid arthritis.

On laboratory workup, initial investigation findings (Table 1), which ruled out Secondary Immunodeficiency disorder (HIV Infections). Specific laboratory workup findings are shown in Table 2.

Table1: Showing Initial Investigation findings:

Investigation	Value
Hemoglobin	9.2 gm/dl
Total Leukocytes Count	6,200/ µl
Differential leukocytes count	P69 L28 E2 M1
Platelets count	320000 / µl
Rheumatoid Factor	Negative
C-reactive Protein	Positive (1.5 mg/dl)
Anti nuclear antibody (ELISA)	negative
Blood Urea	26 mg/dl
Serum Creatinine	0.6 mg/dl
SGPT	22U/L
Na +/ K+/ Ca++	138/4.6/ 8.2
HIV1 & HIV2	Negative

Chest X-ray PA view findings were suggestive of right mid zone patchy consolidation & early bronchiectatic changes (Figure 2). Mantoux test and three consecutive days early morning gastric aspirates for Acid Fast Bacilli (AFB) were negative. Stool routine and microscopic examination showed cyst of Giardia Lambia. Laboratory evaluation of the synovial fluid revealed synovial fluid WBC 110 cells/mm3, India ink stain for Cryptococcus, Fungal stain, gram stain and AFB Stain were negative. Synovial fluid culture was sterile.

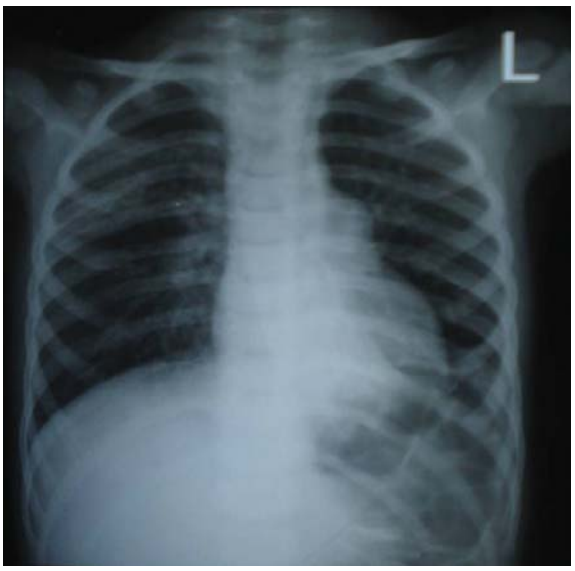

Fig 2: Chest X-ray PA view showing Right mid zone patchy consolidation & early Bronchiectatic changes.

Table 2: Immunoglobulin and Immunophenotype Profile (SRL Ranbaxy Laboratories) of the patient.

Investigations	Value
IgG	60 mg/dl (Normal- 350 mg/ dl- 1.2 gm/dl)
IgA	5 mg/dl (Normal- 17 mg/ dl- 318 mg/dl)
IgM	26mg/dl (Normal- 30 mg/ dl- 265 mg/dl)
IgE	0 (Normal 1.7 IU/ml- 58.4 IU/ml)
CD3	93% (Normal 55-82 %)
CD19	0.06 % (Normal- 09-29%)
Btk protein expression in monocytes	Absent

Patient was diagnosed as Bruton's Agammaglobulinemia with Chronic monoarticular arthritis and Giardiasis, and was managed with broad spectrum intra venous (IV) antimicrobials, IV Immunoglobulin replacement therapy @ 500mg/ kg, 7 days course of metronidazole for giardiasis and Nutritional suppliments. Patient was discharged on Co-Trimoxazole prophylaxis and nutritional supplements with advice of monthly IV Immunoglobulin replacement therapy @ 400mg/kg/month and regular follow up. On follow-up, right knee joint pain and swelling gradually subsided and there was no recurrent Sino-pulmonary and soft tissue infection. Over six months of follow up patient was doing well and gained two kg weight, but unfortunately patient was lost to follow up for past seven months.

Table 3: Difference between XLA and CVID

	Bruton's X-Linked Agammaglobulinemia (XLA)	CVID
Age of onset	Usually by 9–18 months	Usually 2nd – 4th decade
Family History of immunodeficiency	Usually +ve	Variable
Inheritance	X-linked recessive	Variable
Lymph Nodes	Absent (Non Palpable)	Normal / Enlarged
Tonsils	Absent / Atrophic tonsils	Normal tonsils
$CD19^+$ B cell numbers	Markedly decreased/absent	Normal/low
$CD3^+$ T cell numbers	Normal	Variable
Specific Antibody titers	Absent	Decreased/absent
Mutations reported	Btk	TACI, ICOS, BAFF-R, $CD19^+$
Common Complications	Infections	Infections
	Allergy/Atopy	Allergy/Atopy
	Autoimmunity	Autoimmunity
	Malignancy	Malignancy
Treatment	IV Immunoglobulin (IV IG)	IV Immunoglobulin (IV IG)

Table 4: Difference between XLA and Hyper IgM Syndrome

	Bruton's X-Linked Agammaglobulinemia(XLA)	Hyper IgM syndrome
Age of onset	Usually by 9–18 months	Usually 1-2 year
Family History of immunodeficiency	Usually +ve	Variable
Inheritance	X-linked recessive	Variable
Lymph Nodes	Absent (Non Palpable)	Non Palpable
Tonsils	Absent / Atrophic tonsils	Small tonsils
Neutrophil count	Normal	Decreased
$CD19^+$ B cell numbers	Markedly decreased/absent	Normal
$CD3^+$ T cell numbers	Normal	Normal
IgM	Decreased	Normal/Elevated
IgG & IgA	Markedly decreased	Markedly Decreased
Mutation	Btk gene	CD 40 Ligand
Clinical Presentation	Recurrent pyogenic infections	Recurrent Pyogenic Infections
	Autoimmunity	Autoimmunity
	Malignancy	Malignancy
Treatment	IV Immunoglobulin (IVIG)	IVIG, G-CSF, Stem cell Transplant

Discussion

Our case was a definite case of Bruton's X–linked agammaglobulinemia (XLA), based on standard criteria described below[4].

Diagnostic Criteria

Definitive: A male patient with less than 2% CD19 B cells and at least one of the following findings is present.

1. Mutation in BTK gene.
2. Absence of BTK mRNA on northern blot analysis of neutrophils or monocytes.
3. Absence of BTK protein in monocytes or platelets.
4. Maternal cousins, uncles, or nephews with less than 2% CD19 B cells.

Probable: A male patient with less than 2% CD19 B cells in whom all of the following findings are present:

1. Recurrent bacterial infections in the first 5 years of life.
2. Serum IgG, IgM, and IgA more than 2 SD below normal for the patient's age.
3. Absent isohemagglutinins and/or poor response to vaccines.
4. Other causes of hypogammaglobulinemia have been excluded.

Possible: A male patient with less than 2% CD19 B cells in whom other causes of hypogammaglobulinemia have been excluded and at least one of the following findings is present:

1. Recurrent bacterial infections in the first 5 years of life.
2. Serum IgG, IgM, and IgA more than 2 SD below normal for the age.
3. Absence of isohemagglutinins.

Knowledge of the key characteristics of Bruton's X-linked Agammaglobulinemia (XLA) and Common variable immunodeficiency (CVID) may assist in the differentiation of these two clinically similar diseases (Table 3). XLA and CVID are both humoral immunodeficiencies that can manifest similar clinical presentations in male child[5].

Bruton's X-Linked Agammaglobulinemia(XLA) can be differentiated with Hyper IgM syndrome as shown in Table 4[6].

Oligo-articular Juvenile Rheumatoid arthritis (JRA) describes the involvement of 4 or fewer joints and affects an estimated 40-60% of children with JRA. At least two distinct subgroups have been identified: Early childhood onset (frequently associated with positive anti-nuclear antibodies and iridocyclitis) and late childhood onset.

Early childhood onset Oligo-articular JRA affects predominantly girls under the age of 6 years. More common in Caucasian children, it accounts for about 30-40% of patients with JRA. About 50% have monoarticular arthritis. Large joints of the lower extremities are most often involved, including knees and ankles, occasionally elbows. This subtype is associated with positive ANAs (anti-nuclear antibodies) and chronic iridocyclitis.

The late childhood onset Oligo-articular JRA is associated with HLA B27 and development of enthesitis and sacroiliitis. It affects approximately 10-15% of children with JRA. There is a male predominance with the age of onset usually after 8 years of age. A family history of spondyloarthropathy such as ankylosing spondylitis, Reiter's disease, inflammatory bowel disease with spondylitis, psoriatic arthritis, and acute iridocyclitis is often obtained.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are important initial agents in the treatment of JRA. Methotrexate is an effective agent in children with severe JRA and is frequently used to treat children who have failed to respond to NSAIDs. (Sulfasalazine may be effective in treatment of JRA, although drug toxicity may be a problem[7,8].

This case was a five year old male child with only one joint involvement, normal ophthalmological (Slit lamp and fundus) examination, negative anti-nuclear antibodies (ANAs), Negative rheumatoid factor (RF) and no significant response to non steroidal anti-inflammatory drugs. Thus in this case Oligo-articular JRA was excluded.

This case presented predominantly as chronic monoarticular arthritis which is an uncommon manifestation of XLA. In different studies arthritis was reported as predominant manifestation in 11% to 20% of XLA[9,10].

Although most children with XLA develop recurrent bacterial respiratory tract infections during infancy, 20% are diagnosed in children aged 3-5 years, reflecting the widespread use of antibiotics. Unfortunately, permanent damage to the lungs with bronchiectasis may have already occurred[11] as in our case, which was diagnosed at 5 years of age, already had bronchiectasis.

This case also had chronic diarrhea caused by *Giardia lambia*. XLA patients often suffer chronic enteroviral infections, persistent rotaviral infection, chronic diarrhea by *Giardia lamblia*, and other persistent infections as a result of incomplete eradication of antigen due to humoral immunodeficiency[12].

Early IVGG replacement therapy decreased the rates of admission and morbidity for chronic complications, such as bronchiectasis and chronic lung disease, and prevented fatal complications like meningoencephalitis[13]. Lederman HM et al, in a large series reported that appropriate IV immunoglobulin replacement therapy should be started at six to eight weeks of age because around 25% of the XLA patients show clinical symptoms before 4 months of age[9].

After the infant period, more than three occurrences of otitis media and sinusitis, the absence of tonsils, and the presence of scanty cervical lymph nodes are indications to check serum immunoglobulin levels. If the levels of more than two types of immunoglobulin are decreased, XLA should be suspected[13]. XLA is a well-known immunodeficiency disease for which early diagnosis and proper management is possible with high index of suspicion.

Vaccinations

Live vaccine (especially oral polio vaccine in developing countries) should be avoided, and only the inactivated vaccine should be used. This is because even the weaker virus in the orally administered vaccine may give rise to a polio infection in an individual with X-linked agammaglobulinemia. Further, no live oral polio vaccine should be administered to close household contacts, as the virus is secreted through the feces for some time after vaccination, and there is a risk that it will spread[14].

Killed vaccines can be safely given, but they often have little or no effect, since the antibodies in the immunoglobulin infusions administered to the child deactivate the vaccine before it can trigger an immune response[14].

Fortunately, this case didn't have any negative consequences due to the live vaccines they received as standard care and during pulse polio immunization program prior to diagnosis. This phenomenon might be explained by the fact that T cell function in XLA is not impaired, so partial immune defence mechanisms can compensate for impaired humoral immunity[15].

Conclusion

Bruton's X-linked agammaglobulinemia (XLA) is a well-known immunodeficiency disease for which early diagnosis and proper management is possible if physicians have a high index of suspicion for this disease. Uncommonly XLA can manifest with varied phenotypes like chronic arthritis. Early IV IgG replacement therapy decreased the rates of admission and morbidity for chronic complications (13). Live vaccine (especially oral polio Vaccine) shoud be avoided, and only the inactivated vaccine should be used.

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