CASE REPORT

A Case of Bruton's Disease with Normal Immunoglobulin G Level

Soheila Alyasin[1], Farhad Abolnezhadian[1*], Amir Rezaei[2]

[1]Clinical Immunology and Allergy, [2]Pediatric Intensive Care, Department of Pediatrics, Division of Immunology and Allergy, Namazi Hospital, Shiraz University of Medical Science, Shiraz, Iran

INTRODUCTION

X-linked agamaglobulinemia (XLA) or Bruton's disease is a genetic disease resulting from a mutation in the Bruton's tyrosine kinase (Btk) gene. This mutation leads to B cell arrest during differentiation (1). This disease was first described by Ogden Bruton in 1952 (2). Approximately 85% of the affected subjects are male (3). This disorder is inherited as an X-linked recessive trait. Carrier females have no symptoms but have a 50% chance for transmission of the disorder to each of their sons. It is now possible to determine if the fetus of a carrier mother has XLA (4).

The prevalence of the disease ranges from 1 in 10,000 to 1 in 50,000 (1). Half of the affected individuals are diagnosed during the first year of life and more than 90% of them are diagnosed up to fifth year (3). Diagnosis of the disease is suggested by lymphoid hypoplasia (minimal or no tonsillar tissue and no palpable lymph node) and total immunoglobulins level less than 100 mg/dl. Isohemagglutinins and antibodies to antigens given during routine immunization are abnormally low in this disorder as well. Flow cytometry is an important test for this diagnosis (5).

Patients with XLA are protected for the first few months of life by maternal antibody and therefore do not typically present clinically with infection until after 6 months of age, when the maternally-derived antibody level decreases significantly. After diagnosis, treatment includes replacement of intravenous immunoglobulin (IVIG), which significantly reduces the risk of infection (6). The most common organisms affecting these patients are *Haemophilus influenza*, *Streptococcus pneumonia* and *Staphylococcus aureus* (3).

Based on our knowledge, 4 cases of XLA patients with normal IgG levels (above 500 mg/dl) and 5 cases of XLA subjects with near normal IgG levels (400-500 mg/dl) have been reported in the world (7). Here, we report a case of Bruton's disease as the fifth case with normal serum IgG level.

*Corresponding author: Dr. Farhad Abolnezhadian, Allergy and Immunology Ward, Namazi Medical Center, Shiraz, Iran, Tell: (+) 98 711 612 54 48-49, Fax: (+) 98 711 647 43 26, e-mail: abolnezhadian@yahoo.com

CASE REPORT

The patient is a 20-year-old male subject with history of several infections. He had small tonsils on physical examination with normal vital signs. He had normal growth during childhood and received routine immunization without any post-vaccination problems. His parents were not relatives but two of his maternal uncles had died at childhood with unknown febrile disease.

He had several episodes of severe infections during childhood such that he was affected with pneumonia at age 6 years and received antibiotic therapy but developed bilateral maxillary sinusitis 2 months thereafter which was confirmed by paranasal sinuses CT scanning. No document of immunoglobulin level or flow cytometry is available from that time. He was symptom free from 6th year up to 15th year of life while was under treatment with regular weekly subcutaneous immunoglobulin and then monthly IVIG meanwhile.

He developed severe pneumonia at age 15 years and therefore was admitted. Chest CT scanning revealed subsegmental atelectasis of both lung fields specially near the dome of diaphragm predominantly at left side. He had the following laboratory test results at that time:

WBC= 6800/mm^3 with 33% lymphocyte; CD_3= 83% (52-78), CD_4= 54% (25-48), CD_8= 42% (9-35), CD_4:CD_8=1.29 (0.9-3.4), CD_{16}/CD_{56}=14% (6-27), CD_{19}= 0 (8-24); IgG= 15.6 g/l (6.5-13.5), IgA= 0.3 g/l (0.86-3.2), IgM= 0.26 g/l (0.35-2.75).

Considering the normal levels of immunoglobulins the patient did not receive IVIG at that admission and the immunoglobulins levels were checked again 2 and 4 months later which were within normal limits and therefore IVIG was not given at all. Antitetanus antibody was checked which was below 0.1 IU/ml (reference value >0.1).

He was admitted again due to left elbow cellulitis with positive culture for *Staphylococcus aureus* and received antibiotic therapy when he was 16 years old. Immunoglobulins levels were also within normal limits; however, the patient was given IVIG in that time and one month later but not thereafter. He then developed left leg cellulitis at 18 years old which was treated by antibiotic administration but did not receive IVIG. At 19 years old he was admitted and treated for pneumonia. He had empyema and large loculated pleural effusion with collapsed consolidation in left side on chest sonography. He underwent left lung abscess surgery together with antibiotic therapy and IVIG administration. Laboratory tests were as follows:

WBC= 7700/ mm^3 (lymphocyte 47%); CD_3= 89% (55-83), CD_4= 47% (28-57), CD_8= 33% (10-39), CD_4:CD_8=1.42 (0.9-3.6), CD_{16}=11% (10.1-20.9), CD_{19} = 0 (6-19); IgG= 6.77 g/l (6.5-13.5), IgG_1= 447.8 mg/dl, IgG_2= 143.6 mg/dl, IgA< 0.37 g/l (0.86-3.2), IgM< 0.25 g/l (0.35-2.75).

Three months later serum immunoglobulins levels were within normal limits and isohemagglutinin test result was as follows: blood group, B negative; IgM anti A (RT and 4°C) = 1:2 (positive >1:8). The patient did not receive monthly IVIG during this period of time as well but we decided to give him monthly IVIG despite normal IgG levels due to the history of recurrent severe infections. He was symptom-free at last visit. He underwent an injection of 23-valent pneumococcal vaccine which resulted in significantly impaired response. At last flowcytometry, we also checked the expression of CD_{20} on PBMCs which was zero as well.

DISCUSSION

Our patient was asymptomatic until 6 years of age except for some episodes of common respiratory diseases but no document exist in this regard. At 6 years of age following severe pneumonia he was given prophylactic immunoglobulin regularly up to 15 years of age. He was problem-free over this period of time until he developed severe pneumonia leading to hospital admission at 15 years of age. He was not given IVIG thereafter due to normal levels of IgG; however he had some episodes of severe infections up to 20 years of age. He had fragmentary follow-up visits in immunology and allergy service and had normal levels of IgG on each time.

Serum level of IgG is usually less than 200 mg/dl (2 g/l) and serum concentration of IgM and IgA is generally below 20 mg/dl (0.2 g/l) in patients with XLA (5). Serum IgG levels as high as 200-300 mg/dl have also been reported in some cases of XLA (3). Our patient had serum IgG levels of at least 500 mg/dl each time but developed severe infections despite normal IgG levels. Approximately 10-12% of immunodeficient patients with serum concentration of immunoglobulin higher than expected are not recognized up to after 5 years of age (5). Our patient is also a case with normal IgG level and was diagnosed as XLA at 6th year of life.

XLA may have atypical presentation. Sigmon *et al*. (7) reported 2 cases of XLA diagnosed late in life including a 64 years old male with IgG level of 360 mg/dl (565-1765) and a 46 years old male with IgG level of 260 mg/dl (565-1765). Then they reviewed the literature and found 16 cases of adult presentation of the disease which were mostly diagnosed during evaluation for recurrent pneumonia, sinusitis and otitis media and subsequently by Btk mutation in adulthood. Five patients had diagnosis of common variable immunodeficiency but then were classified as atypical variants of XLA. These patients age ranged from 21 to 60 years and had IgG levels ranging between 20 and 773 mg/dl. Many of these patients had mild or subclinical symptoms prior to diagnosis which may partially be due to the low to normal levels of IgG. Our patient had similarly normal IgG levels which explain his late presentation of the disease.

The essential question in XLA patients with near normal and normal IgG levels is about the source of immunoglobulin production. Considering the 23 days half-life of human IgG (3) and its daily clearance of 1.47 μg/min (0.85-2.44) (8), it is needed to be supplied by a production site in the body rather than the administered IVIG. There may be some memory B cells in this group of XLA patients that produce IgG but cannot be detected in peripheral blood or the produced IgG may be nonfunctional. We checked CD20 as another marker of B cell at last follow-up which was zero confirming that the patient has no B cell. Considering that the level of antitetanus and antipneumococcal antibodies were below normal in our patient despite receiving the vaccines, it is in favor of impaired producing specific antibody which suggests B cell deficiency.

Affected males have normal number of pre-B cells in the bone marrow (9). It has been shown that pro-B and pre-B1 cells comprise more than 80% of the bone marrow B cell population in patients with XLA compared to less than 20% in normal individuals (10). It seems that pre-B cells of the bone marrow are the source of immunoglobulins in these patients which may be nonfunctional.

The diagnosis of XLA is made based on the following criteria: (5)

Definitive XLA

Male patient with less than 2% $CD19^+$ B cells and at least one of the following findings:

1-Mutation in Btk
2-Absent Btk mRNA on Northern blot analysis of neutrophils or monocytes
3-Absent Btk protein in monocytes or platelets
4-Maternal cousins, uncles or nephews with less than 2% $CD19^+$ B cells

Probable XLA

Male patient with less than 2% $CD19^+$ B cells and all of the following findings:

1-Onset of recurrent bacterial infections in the first year of life
2-Serum IgG, IgM, IgA more than 2 standard deviation below normal for age
3-Absent Isohemagglutinins and/or poor response to vaccines
4-Exclusion of other causes for hypogamaglobulinemia

Possible XLA

Male patient with less than 2% $CD19^+$ B cells without any other causes of hypogamaglobulinemia together with at least one of the following findings:

1-Onset of recurrent bacterial infections in the first 5 year of life
2-Serum IgG, IgM, IgA more than 2 standard deviation below normal for age
3-Absent Isohemagglutinins

Some authors however, believe that identifying the Btk gene mutation is not absolutely necessary for the diagnosis of XLA (11). In the study performed by Wang *et al*., (12) this mutation was not identified in 4 of the 16 patients with XLA. Although we do not have the result of genetic analysis in our patient, the history of recurrent pneumonias requiring hospital admission, lung abscess formation, recurrent cellulites, bilateral sinusitis, absent CD19 and CD20 B cells, absent palpable lymph nodes and hypoplastic tonsils are in favor of the diagnosis of XLA.

In summary we recommend that XLA patients should receive IVIG on a regular monthly basis despite normal levels of serum IgG.

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