

X-linked Agammaglobulinemia – Is it Really Rare?

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Received date: January 12, 2018; Accepted date: February 05, 2018; Published date: February 23, 2018

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Abstract

Background: X-Linked Agammaglobulinemia is a disease of the immune system in which there is defective development of the B lymphocytes due to which the production of gammaglobulins is markedly reduced; which results in immunodeficiency and high vulnerability to contract fatal infections. This is the reason for which a patient with XLA presents with history of recurrent infections. XLA is known to be caused due to a mutation in the Btk gene. Btk gene mutation observed on gene mapping markedly reduced levels of B lymphocytes and immunoglobulins; are the confirmatory laboratory findings for the diagnosis of XLA. As there is immunodeficiency in the patient, this condition is treated with intravenous immunoglobulin therapy. In this article, two cases with XLA have been described. Over a period of one month, two cases of XLA were admitted at the hospital. This is to pay attention to the fact that XLA is a rare condition, accounting to 1 in 200,000 live births. In view of its rarity, the two cases have been reported ahead in the article.

Methods: Two patients who were a known case of X-Linked Agammaglobulinemia were reviewed in detail. Their records were reviewed and appropriate clinical data collected. The serum levels of immunoglobulins and B lymphocytes of these patients were thoroughly evaluated. BTK gene screening was also analysed to confirm the diagnosis of XLA.

Results: Two patients who were previously diagnosed with XLA came to our hospital with complaints of recurrent respiratory tract infections. One patient, a 12 years old boy admitted with complaints of cough with expectoration and fever, was found to have low levels of B lymphocytes, IgM and IgA. His mother and elder brother were already diagnosed with XLA. The second patient, a 10 years old boy who got admitted at the hospital with fever and cough, has low levels of B lymphocytes, IgM and IgA. Genescreening showed BTK gene mutation. His mother is a known case of XLA confirmed with BTK genemutation on screening.

Conclusion: The two cases mentioned above represent X-Linked Agammaglobulinemia, which is a rare disease with an occurrence rate of 1 in 200,000 live births. These two cases were reported at our hospital within duration of two weeks. Paying attention to the fact of the rarity of this condition, the admission of two patients with a rare disease as XLA, within such a short duration of time, claims the consideration of these cases to be reported. Implications on detecting female carriers in the family, counselling of the family members, and early diagnosis and treatment of affected males in the family; are all important aspects associated with the diagnosis of XLA in a patient.

Keywords: BTK gene; XLA; Rare disease; Immune disorder; Infections

Introduction

X-linked agammaglobulinemia (XLA) is categorized as one of the primary immunodeficiency diseases which are characterized by a defect in the development of B lymphocytes, extreme hypogammaglobulinemia, and marked deficiency in the formation of the antibodies and their functions [1-3]. A mutation in the gene for B-lymphocyte tyrosine kinase, known as the Btk Gene, is the cause of this disease [1-6]. Patients affected by this disease are highly susceptible to infections, especially caused by Haemophilus influenzae, Pneumococcus, Giardia lamblia and Enteroviruses [4-10]. Colonel Ogden Bruton identified the first XLA patient in 1952 [11]. Many children with XLA are now expected to reach adult life. For this reason, such cases should be carefully followed-up till adulthood and

even later, which makes it necessary for the physicians to keep a close look-up at pediatric patients diagnosed with XLA. In a study of 201 patients, it was found that 43% of patients were 18 years old and more [10]. In the same study, only 3 patients died during a prospective follow-up period of four and a half years [10]. Out of these three patients, 2 died due to iatrogenic causes [10].

Earlier, gammaglobulin was the only replacement therapy available which was to be given by the intramuscular route and hence, the dose was limited. Later on, intravenous route of gammaglobulin was developed which could be given in larger dose and could sustain higher levels of IgG in the serum [12]. In recent times, XLA has become to be diagnosed earlier in life [10] which allows to initiate treatment earlier and, to pay more attention to the diagnosis and treatment of associated infections.

Case Presentation

Two patients who are a known case of X-Linked Agammaglobulinemia were reviewed in detail. Their records were reviewed, detailed family history noted and appropriate clinical data collected. A thorough evaluation of levels of immunoglobulins and B lymphocytes in the serum of these patients was performed. BTK gene screening was also analysed to confirm the diagnosis of XLA. A review of literature in which other cases of XLA have been reported is also mentioned, by PubMed and other online search of literature.

Case I

A 12 years old boy came to the hospital with chief complaints of cough with expectoration and fever since 2 weeks; Azithromycin and Antipyretics were started but no improvement was observed. On investigations, the CRP level and White Blood Cell count was high. Chest X-ray showed bronchial pneumonia. Treatment was started with Erythromycin and Ceftizoxime Sodium, as well as Bromhexine and Antipyretics. Cough and fever reduced but not completely subsided. The patient was admitted at a hospital with the diagnosis of left sided pneumonia and pleural effusion 4 years ago, for which he was treated with antibiotics. The patient gives a history of recurrent respiratory tract infections. On further investigations, it was noticed that the levels of immunoglobulin were reduced. IgG – 1.33 g/L, IgA – less than 0.22 g/L, IgM – less than 0.159 g/L. T lymphocytes – 88.79%, NK cells – 6.35%, B-lymphocytes – 1.60% (markedly reduced). There is a positive family history of the mother being diagnosed to have X-linked agammaglobulinemia, as well as his elder brother. Based on the decreased levels of immunoglobulins and the positive family history, the diagnosis was confirmed to be X-linked agammaglobulinemia. The patient has been on regular intravenous immunoglobulin infusion, 12.5g, since 2013. During his stay at the hospital this time, he was treated with intravenous antibiotics (cephalosporins), monthly dose of intravenous immunoglobulin, and the necessary supportive measures (Table 1).

Immunoglobulin	Serum Levels (Case 1)	Normal Range (12-13 yrs.)
IgG	1.33 g/L (<i>reduced</i>)	7.59-15.49 g/L
IgA	Less than 0.22 g/L (<i>reduced</i>)	3.58- 5.80 g/L
IgM	Less than 0.159 g/L (<i>reduced</i>)	2.39- 3.50 g/L

Table 1: Serum levels (case 1 vs. normal).

Case II

A 10 years old boy came to the hospital with complains of cough and fever since 1 week, for which he was on treatment with Cefuroxime sodium, Bomhexine and aerosol inhalation. The fever and cough subsided after a while, nevertheless recurred again with paroxysmal coughing and expectoration followed by dyspnoea. The patient was admitted at a hospital and started on antimicrobial treatment. CT scans of the chest; showed Bronchpneumonia. On investigations, the CRP level -24mg/L (increased) and WBC count – $18.58 \times 10^9/L$ (increased), the absolute values of lymphocyte – $5.59 \times 10^9/L$, monocyte - $1.13 \times 10^9/L$, and neutrophil- $11.71 \times 10^9 /L$, were increased; Suppressor T cell – 42.79% (increased), B lymphocytes – 0.09% (decreased), CD4+/CD8+ ratio – 0.85 (decreased). IgG- 0.02

g/L, IgA - less than 0.25, IgM- less than 0.17 g/L. Gene screening confirmed X-linked agammaglobulinemia.

BTK, exon along and its surrounding intron EXON 6 frameshift leads to an early termination of the amino acid encoding. On auscultation of the lungs, rales were heard bilaterally. The patient has a history of recurrent respiratory tract infections. He was diagnosed to have bronchopneumonia in 2014. On investigations, he was diagnosed with XLA for which he was started on IVIG 400 mg/kg/day for 3 days. He was also diagnosed to have acute bronchitis for which he was treated with cephalosporin and anti tussive agents. The patient has a history of delayed growth and development as compared to children of the corresponding age. There is a positive family history of the mother being diagnosed to have X-linked agammaglobulinemia with the BTK gene frameshift mutation. Based on the BTK gene mutation and reduced immunoglobulin levels in this patient, and a positive family history, the diagnosis was confirmed to be X-Linked Agammaglobulinemia. This patient was being treated with intravenous cefazolin sodium, budesonide and terbutaline suspension, ipratropium inhalation, and other necessary supportive measures (Table 2).

Immunoglobulin	Serum levels (Case 2)	Normal Range (10 -11 yrs.)
IgG	0.02 g/L	6.98 – 15.60 g/L
IgA	Less than 0.25 g/L	2.04 – 5.30 g/L
IgM	Less than 0.17 g/L	2.08 – 3.10 g/L

Table 2: Serum levels (case 2 vs. normal).

Discussion

X-Linked Agammaglobulinemia (XLA) is a rare genetic disorder in which mature B cells are not generated, which is manifested by a complete lack of or very low levels of gammaglobulins in the blood stream [13]. The B cells normally produce antibodies which are needed to defend the body from infections by maintaining a humoral immune response. Such patients are vulnerable to develop fatal infections. This condition is more common in the males, and has an occurrence rate of 1 in 200,000 live births [14], and with a frequency of 1 in 100,000 newborn males [15]. The occurrence of a mutation at the Bruton's Tyrosine Kinase (Btk) gene results in inhibition in the development of B cell at the stage when the pre-B cell matures to immature B cell, and hence, results in decreased production of immunoglobulin in the serum. In particular, the Btk gene is responsible for a signalling effect on the B cell receptor which mediates the development and maturation of B cell. Patients affected by this condition, usually, present with recurrent infections, especially with extracellular, encapsulated bacteria; and in early childhood [16].

Criteria for diagnosis

A patient to be diagnosed with XLA needs to fulfill one or more of these criteria [17]:

- Btk gene mutation and/or defective expression of Btk protein.
- A positive family history – either Btk gene mutation or defective expression of Btk protein, or very low levels of B lymphocytes in their blood and reduced levels of gammaglobulins.
- Very low levels of B lymphocytes in the patient's blood and reduced levels of gammaglobulins.

In our study of the above mentioned two cases, both the kids presented with respiratory tract infections.

They had been having recurrent episodes of such infections, for which they were on antibiotics required at every episode of such infections. It was observed that there was a positive family history of the Btk gene mutation and, reduced levels of B lymphocytes and gammaglobulins; which fulfils the above mentioned diagnostic criteria for XLA. Hence, these patients were started on intravenous Immunoglobulin therapy, 400-500 mg/kg given once in a month, following which they showed an improvement in the IgG levels in the blood, and treatment of associated infections with appropriate antibiotics. The prognosis is good as long as the immunoglobulin therapy is on, which maintains the serum immunoglobulin levels and thus, infections can be prevented. The cause of death in a patient with XLA is usually severe infections.

We also review below other cases which were reported with the diagnosis of XLA in pediatric patients. These cases were detected using PubMed and general online search of the world literature. A case of a 12 year old boy with XLA and Enthesitis- related arthritis was reported in which it was suggested that there could be a possible link between immune deficiency, immune dysregulation, and rheumatic illness [18]. A case of 22 months old boy was diagnosed with XLA which was initially masked by normal levels of immunoglobulin. Strong suspicion and careful clinical evaluation showed markedly reduced levels of B lymphocytes and gene mapping showed BTK gene mutation which confirmed the diagnosis of XLA. This case highlighted the fact that XLA may show variability in phenotypic presentation and disunity between routine immunologic investigations and severe disease in XLA, hence, necessitating clinical skills to make the diagnosis [19]. A case study of 10 years old boy diagnosed with XLA, which focuses on the fact that a diagnosis of immune defect should be considered in any patient who gives a history of recurrent infections, and the immunological investigation should be carefully evaluated [20]. Another case report is a very rare co-incidence of XLA with Secondary hemophagocytic syndrome without a history of bacterial infections, which was a challenging case to treat. Treatment was provided with intravenous antibiotics and intravenous immunoglobulin [21].

Conclusion

Hence, the two cases reported are to emphasize on the fact that any case with history of recurrent infections should click a picture in the mind of the physician to consider immune deficiency diseases like XLA, which, though rare, can be the root cause. The diagnosis of XLA and its proper treatment will have better prognosis for the child to reach adulthood and, excel in future and become a productive member in the society.

Conflict of Interest

None declared.

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