Unmasking Bruton's Agammaglobulinemia: A Pediatric Case Report

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Abstract

Bruton's Agammaglobulinemia, also known as X-linked agammaglobulinemia (XLA), is a rare primary immunodeficiency disorder caused by mutations in the Bruton's tyrosine kinase (BTK) gene. This genetic defect prevents the production of mature B lymphocytes, leading to a significant decrease in antibody production which mediates the humoral immunity. These patients are also especially susceptible to recurrent bacterial infections which are often life threatening, especially during early childhood, and have a higher risk of autoimmune diseases and cancers. Early diagnosis and proper management can significantly enhance patient outcome. This paper discusses a case of Bruton's agammaglobulinemia discussing its clinical features, diagnostic approach, and current treatment options.

Keywords: X-Linked Agammaglobulinemia; Bruton's Agammaglobulinemia; Primary Immunodeficiency.

Introduction

Bruton's Agammaglobulinemia (BA), first identified by Dr. Ogden Bruton in 1952, is a disorder due to X-linked recessive inheritance which is characterized by the presence of absent or markedly reduced serum immunoglobulins (Ig) in the blood. This is one of the most common primary immunodeficiencies found among males with an estimated incidence of 1 in 2,50,000 live births. The condition is due to mutations in the gene BTK, located on the X chromosome, which encodes Bruton's tyrosine kinase, a protein important for the development and maturation of B cells.

Patients with BA commonly suffer from repeated episodes of bacterial infections, often life threatening, due to encapsulated pathogens like Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis mainly affecting the respiratory tract and the ears. The diagnosis of BA is often difficult at early stages because many symptoms overlap with other immunodeficiencies and the clinician often consider it as an isolated single episode of an infection. However, once diagnosed, the condition is managed with regular immunoglobulin replacement therapy and antimicrobial prophylaxis to minimize the frequency and severity of infections.

Case Report

A 10 year old boy was referred to our hospital with recurrent episodes of respiratory tract infections and seizures. On complete workup of the case, child presented with similar history from the age of 3 months requiring multiple hospitalizations and intravenous antibiotics to control fatal infections, including otitis media, sinusitis, meningitis and pneumonia. His medical history was notable for poor weight gain, delayed

developmental milestones, and a family history of similar complaints in maternal relatives. He had received multiple courses of antibiotics, but the infections would resolve only temporarily and recur shortly thereafter.

Upon presentation, physical examination revealed a generally healthy child with stable vitals. On laboratory evaluation, his complete blood count was normal. NCCT – Head revealed findings suggestive of post-meningitic sequelae. However, serum immunoglobulin levels were markedly reduced with serum IgG, IgM and IgA less than 75mg/dL, 25mg/dL and 10mg/dL respectively. Additionally, flow cytometry of peripheral blood confirmed the diagnosis, revealing absolute B-Lymphopenia(nil) and monocytopenia(162cells/mm^3) with altered CD4:CD8 ratio with increased absolute T cells(4990cells/mm^3) suggestive of primary immunodeficiency disease.

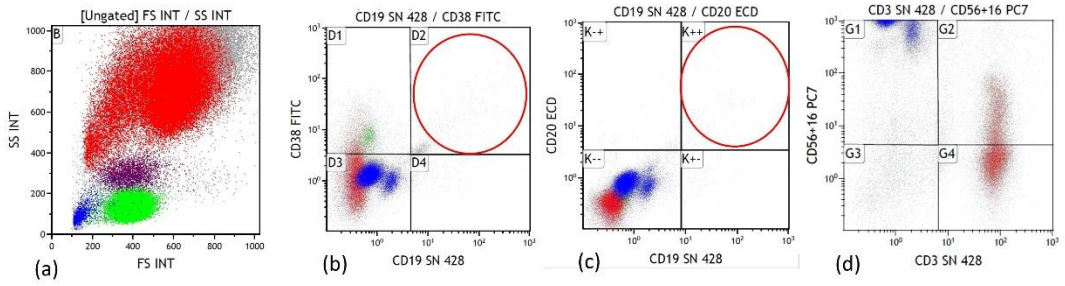

Fig (a) showing the scatter plot, with (b) and (c) revealing absolute B lymphopenia and (d) showing presence of T cells

Figure 1: (a) showing scatter plot, with (b) and (c) revealing absolute B lymphopenia and (d) showing presence of T cells.

Given the family history, clinical presentation and laboratory findings, a diagnosis of Bruton's agammaglobulinemia was rendered. The child was immediately started on intravenous immunoglobulin(IVIG) replacement therapy and antibiotics for prophylaxis against bacterial infections. IVIG was started at a dose of 01gm/kg weekly for the initial 03 months and there after tapered the dose to 0.5 gm/kg in every three weeks, when serum immunoglobulin levels were more than 500 mg/dL. Now the child in on 0.25 gm/kg IVIG, every 4 weeks and is maintaining a steady immunoglobulin level for last 6 months. Regular follow-up visits are advised with a special focus on monitoring immunoglobulin levels, assessing for any emerging infections, and adjusting his treatment plan as and when needed.

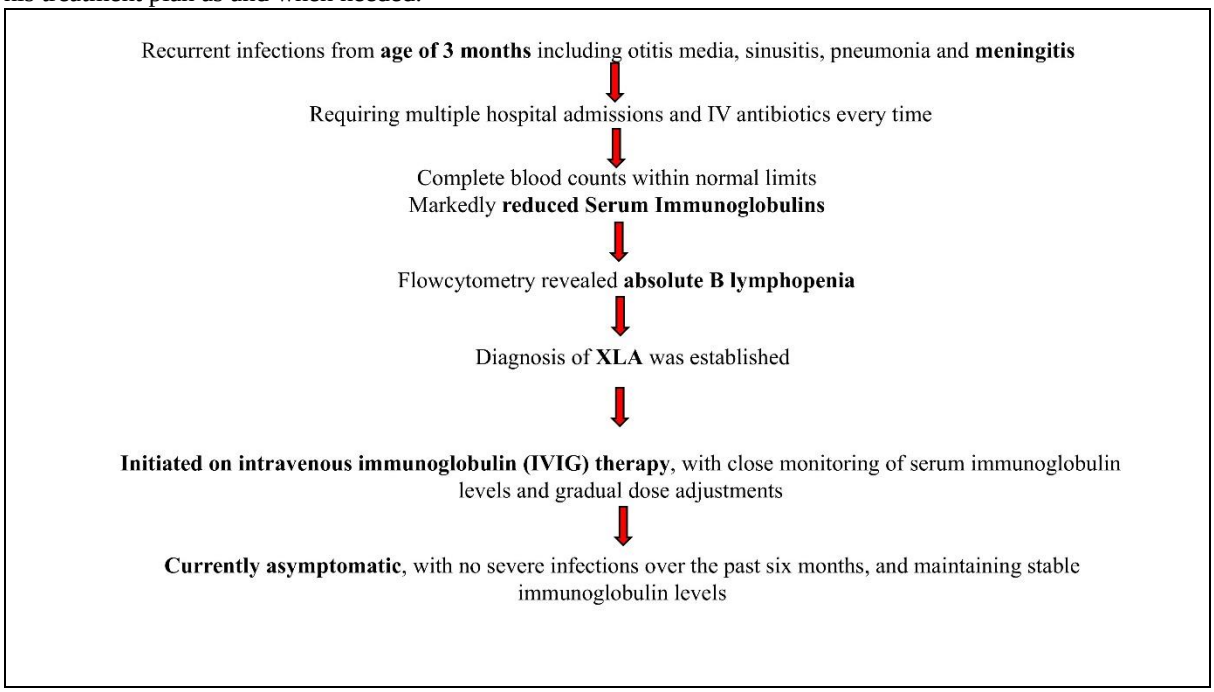

Figure 2: Flowchart summarizing the clinical course of the present case of XLA.

Discussion

Bruton's agammaglobulinemia results from mutations in the BTK gene. The mutant form of the BTK gene does not produce its protein; thereby stopping this signalling cascade at the stage where differentiation of pre-B cells to mature B cells happens. This implies that there are very few circulating mature B cells and a grossly impaired humoral immune response in XLA patients. The absence of functional B cells prevents the production of sufficient amounts of antibodies (immunoglobulins). This deficiency in antibody production makes patients with XLA extremely susceptible to infections, especially bacterial infections which are often fatal.

The symptoms usually begin after age of 6 months, since the maternal antibodies start decline from then. Early manifestations include recurrent respiratory infections, otitis media, and gastroenteritis. Failure to thrive and chronic diarrhoea may also occur. But this case stands out with presence of recurrent CNS infections, presented as multiple episodes of seizures.

The diagnosis is often missed as it gives a normal hemogram and peripheral smear picture most of the time. An important component of the diagnostic workup is the determination of serum immunoglobulin levels. In BA, these are usually low or absent, confirming the failure of the immune system to produce antibodies as in the present case. In patients with XLA, B cells are significantly reduced or absent, which is a key diagnostic indicator.

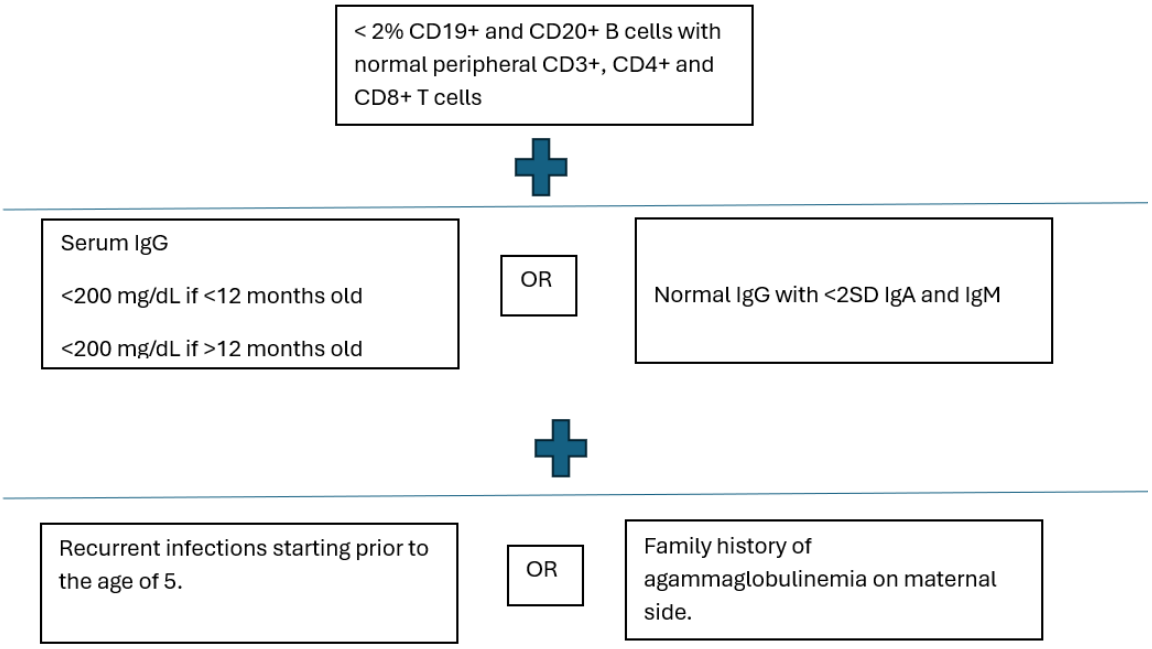

Figure 3: Diagnostic guide for XLA based on B-cell immunophenotyping, immunoglobulin levels, and clinical or family history.

The present case met all the previously outlined diagnostic criteria. There was a marked reduction in CD19 and CD20 positive B lymphocytes, indicating impaired B cell function. Additionally, the patient showed decreased serum immunoglobulin levels, consistent with an underlying immunodeficiency. This was further supported by a clinical history of recurrent infections and a notable family history of similar immune-related conditions.

Transient hypogammaglobulinemia of infancy can mimic early XLA but typically resolves spontaneously and is characterized by delayed IgG production rather than permanent B-cell absence. Furthermore, disorders like common variable immunodeficiency (CVID), severe combined immunodeficiency (SCID), and hyper-IgM syndromes may also present with recurrent infections and low immunoglobulins in early life, warranting careful evaluation of B- and T-cell subsets and immunoglobulin profiles to ensure accurate diagnosis. The isolated B lymphopenia as revealed by flowcytometry rules out the above possibilities along with the serum immunoglobulin levels.

Genetic testing for mutations in the BTK gene is the gold standard for diagnosis, but could not be done in the present case due to lack of resources. However, when the facility is not available, the flowcytometry findings along with immunoglobulin levels are fair enough indication to start patient on treatment according to ESID guidelines.

The mainstay of treatment for XLA is immunoglobulin replacement therapy (IVIG). This helps to recover the antibody levels and thus provide a form of passive immunity, protecting the patient against fatal infections. In the present case, child maintains a steady level of serum immunoglobulin on gradual titration of IVIG doses. Antibiotic prophylaxis is also essential in the prevention of infections, especially those caused by encapsulated bacteria for which broad spectrum antibiotics are given in our case.

With patients with XLA living longer, there is a growing interest in the possibility of stem cell or gene therapy as a curative treatment. Bone marrow transplants from matched donors can restore B cell function in some patients, for those who do not respond well to immunoglobulin therapy.

Patients with XLA, if managed well, can lead a fairly normal life but have to be kept under long-term immunoglobulin therapy and regular follow up for infections.

Conclusion

Bruton's agammaglobulinemia is a rare and severe disorders of immune deficiency characterized by inadequate development of B cells there by resulting in a significant decline in production of immunoglobulins, which mediates humoral immunity. It should be suspected in any paediatric case presenting with recurrent infection in early ages of childhood. The ongoing advancements in gene and stem cell therapies gives hope for potential cures in the future. This case report underscores the necessity of considering Bruton's agammaglobulinemia in children with recurrent infections.

Disclosure

The authors declared no conflicts of interest. Written consent was obtained from the patient/kin of the patient.

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