Case Report

X-linked agammaglobulinemia presenting as recurrent otitis media in a young child: A case report of a pathogenic BTK variant

Mirunaliny Murugesan [1]*, Velvizhi E [2], Thilagavathy M [3], Karthikeyan S[4]

[1]Consultant Biochemist, Kauvery Hospital, Trichy, Tamil Nadu
[2]Consultant Biochemist, Kauvery Hospital, Trichy, Tamil Nadu
[3]Consultant Microbiologist, Kauvery Hospital, Trichy, Tamil Nadu
[4]Consultant Paediatric Pulmonologist, Kauvery Hospital, Trichy, Tamil Nadu
*Correspondence

Abstract

Background: X-Linked Agammaglobulinemia (XLA), also known as Bruton agammaglobulinemia, is a rare inherited primary immunodeficiency caused by pathogenic variants in the Bruton Tyrosine Kinase (BTK) gene. Defects in BTK impair B-cell maturation, resulting in profound hypogammaglobulinemia and increased susceptibility to recurrent bacterial infections, particularly involving the respiratory tract, ears, and paranasal sinuses. Early diagnosis is essential to prevent long-term complications and to initiate appropriate immunoglobulin replacement therapy.

Case Presentation: A 3-year-old boy presented with recurrent ear discharge for five months and persistent rhinitis. Clinical examination revealed bilateral acute suppurative otitis media and absent tonsillar tissue. Immunological investigations demonstrated markedly reduced serum immunoglobulin levels, suggestive of a primary antibody deficiency. To establish the molecular diagnosis, targeted next-generation sequencing identified a hemizygous pathogenic nonsense variant in exon 16 of the BTK gene, c.1573C>T (p.Arg525Ter). Based on the clinical, immunological, and genetic findings, a diagnosis of X-linked agammaglobulinemia was confirmed.

Conclusion: This case highlights the importance of considering primary immunodeficiency disorders in children presenting with recurrent infections, especially recurrent otitis media and upper respiratory tract infections. Comprehensive immunological evaluation, complemented by molecular genetic testing, is important for establishing the diagnosis and enabling timely management."

Keywords: X-linked agammaglobulinemia (XLA); Bruton's tyrosine kinase (BTK); Primary antibody deficiency; Recurrent otitis media; Hypogammaglobulinemia; Next-generation sequencing

1. Introduction

Primary immunodeficiency disorders constitute a heterogeneous group of inherited diseases characterized by defects in the development, function, or regulation of the immune system. Among these disorders, X-linked agammaglobulinemia (XLA; OMIM #300755) is one of the well-characterized forms of primary antibody deficiency. First described by Ogden Bruton in 1952, XLA results from pathogenic variants in the Bruton tyrosine kinase (BTK) gene located on chromosome Xq21.3–Xq22.[1,2] The BTK gene encodes

Bruton tyrosine kinase, a cytoplasmic signalling molecule that plays a crucial role in B-cell receptor signaling and normal B-cell maturation.[2]

Deficiency of functional BTK protein leads to arrest of B-cell differentiation at the pre-B-cell stage in the bone marrow. Consequently, affected individuals have markedly reduced or absent mature circulating B lymphocytes and profoundly decreased serum immunoglobulin levels. [2, 3] This immunological defect predisposes patients to recurrent bacterial infections involving the respiratory tract, middle ear, paranasal sinuses, and gastrointestinal tract. Clinical manifestations usually become evident after the decline of maternally acquired immunoglobulins during infancy. [3, 4]

"XLA is a rare inherited primary antibody deficiency predominantly affecting males."[3,5] Advances in molecular diagnostic techniques, particularly next-generation sequencing (NGS), have significantly improved the identification of pathogenic BTK variants and facilitated earlier diagnosis.[3,5] Early recognition and prompt initiation of immunoglobulin replacement therapy are essential to reduce morbidity, prevent complications, and improve long-term clinical outcomes.[4,5]

2. Case Presentation

A 3-year-old boy born to a non-consanguineous marriage presented to our hospital with recurrent ear discharge for the past five months. He also had a history of recurrent rhinitis. The antenatal and perinatal periods were uneventful.

On clinical examination, the child was diagnosed with bilateral acute suppurative otitis media. The tonsils were markedly hypoplastic/not clinically appreciable, and there was no peripheral lymphadenopathy. The recurrent infections and absence of lymphoid tissue raised suspicion of an underlying primary immunodeficiency disorder.

3. Laboratory Investigations On Presentation

Test	Result	Reference Range
Hemoglobin	10.2 g/dL	10–13.2 g/dL
Total Leukocyte Count	4,500 cells/mm³	4,920–11,800 cells/mm³
Platelet Count	347,000 cells/mm³	203,000–431,000 cells/mm³
Serum IgG	<270 mg/dl	316–1148 mg/dL
Serum IgA	<40 mg/dl	70–400 mg/dL
Serum IgM	<25 mg/dl	39–151 mg/dL

Immunological evaluation revealed markedly reduced concentrations of all major immunoglobulin classes, consistent with severe hypogammaglobulinemia and supportive of a primary antibody deficiency.

4. Genetic Findings

Genetic analysis identified a hemizygous nonsense variant in exon 16 of the BTK gene (chrX: g.101354688G>A; depth 60×), resulting in a premature termination codon at amino acid position 525 (c.1573C>T; p.Arg525Ter; ENST00000308731.8).

This variant has previously been reported in patients with X-linked agammaglobulinemic and is classified as pathogenic in the ClinVar database. The variant was absent from population databases including the 1000 Genomes Project, gnomAD, TOPMed, and internal reference datasets. Furthermore, the affected amino acid residue is highly conserved across species, supporting its pathogenic role.

Mutations in the BTK gene are responsible for X-linked agammaglobulinemia (XLA; OMIM #300755), a primary immunodeficiency characterized by defective B-cell maturation and severely impaired immunoglobulin production. BTK is essential for B-cell receptor signalling and normal B-cell development. Loss of functional BTK protein results in arrest of B-cell differentiation at the pre-B-cell stage, leading to markedly reduced or absent mature B lymphocytes and profound hypogammaglobulinemia. XLA accounts for approximately 85–90% of all cases of agammaglobulinemia.

Based on the clinical presentation, immunological findings, and identification of a pathogenic hemizygous nonsense variant in the BTK gene, a definitive diagnosis of X-linked agammaglobulinemia (Bruton's agammaglobulinemia) was established.

5. Discussion

Role of BTK in B-cell Development: X-linked agammaglobulinemia (XLA) is caused by pathogenic variants in the BTK gene, which encodes Bruton tyrosine kinase, an essential molecule for B-cell maturation. Defective BTK

function arrests B-cell development at the pre-B-cell stage, resulting in markedly reduced circulating B cells and profound hypogammaglobulinemia. [2, 3]

Clinical Presentation and Diagnostic Findings: Patients with XLA typically present during infancy after the decline of maternally derived immunoglobulins. Recurrent bacterial infections of the respiratory tract and middle ear are common manifestations. In the present case, recurrent ear discharge and persistent rhinitis were the initial symptoms. The clinically non appreciable tonsillar tissue and markedly reduced serum IgG, IgA, and IgM levels provided important clues to an underlying humoral immunodeficiency. [3–5]

Molecular Diagnosis: Targeted next-generation sequencing identified a hemizygous pathogenic nonsense variant in the BTK gene, c.1573C>T (p.Arg525Ter), confirming the diagnosis of XLA. Molecular testing is valuable for differentiating XLA from other primary antibody deficiencies and for guiding genetic counselling. [3, 5]

Clinical Significance and Management: Early diagnosis and initiation of immunoglobulin replacement therapy are essential to reduce infections and prevent long-term complications such as bronchiectasis and chronic lung disease.[4,5] This case highlights the importance of combining clinical findings, immunoglobulin profiling, and molecular genetic testing for accurate diagnosis and timely management of XLA. [1, 4, 5]

Treatment and follow-up: The patient is receiving monthly intravenous immunoglobulin (IVIG) replacement therapy and was treated with ceftriaxone for infection. The patient has also been advised to undergo bone marrow transplantation as part of further management. Continued IVIG replacement, prompt treatment of infections, and regular follow-up are essential to reduce infectious complications and monitor for long-term sequelae.[5]

6. Conclusion

This case emphasizes the importance of considering X-linked agammaglobulinemia in young male children presenting with recurrent sino-otologic infections and profound hypogammaglobulinemia. The markedly hypoplastic or clinically non-appreciable tonsils, together with profound hypogammaglobulinemia, provided important clinical clues, while molecular identification of the pathogenic BTK variant (c.1573C>T; p.Arg525Ter) established the definitive diagnosis. Early recognition and genetic confirmation are crucial for timely initiation of immunoglobulin replacement therapy, prevention of irreversible complications, and improved long-term clinical outcomes.

References

[1] Bruton OC. Agammaglobulinemia. Pediatrics. 1952;9(6):722-728.

[2] Tsukada S, Saffran DC, Rawlings DJ, et al. Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. Cell. 1993;72(2):279-290.

[3] Conley ME, Dobbs AK, Farmer DM, et al. Primary B cell immunodeficiencies: comparisons and contrasts. Annu Rev Immunol. 2009;27:199-227.

[4] Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136(5):1186-1205.e1-78.

[5] Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2022 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42 (7):1473-1507.