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Samreen Kulsom Zaidi

Aga Khan University

Sonia Qureshi

Aga Khan University, sonia.queshi@aku.edu

Farah Naz Qamar

Aga Khan University, farah.qamar@aku.edu

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X-linked agammaglobulinemia — first case with Bruton tyrosine kinase mutation from Pakistan

Samreen Kulsom Zaidi, Sonia Qureshi, Farah Naz Qamar

Abstract

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency with more than 600 mutations in Bruton tyrosine kinase (Btk) gene which are responsible for early-onset agammaglobulinemia and repeated infections. Herein we present a case of a 3-year-old boy with history of repeated diarrhoea and an episode of meningoencephalitis with hemiplegia. The workup showed extremely low levels of immunoglobulin with low CD+19 cells. Genetic analysis showed Btk mutation 18 c.1883delCp.T628fs. To the best of our knowledge this is the first report of a case of XLA confirmed by molecular technique from Pakistan.

Keywords: Bruton type agammaglobulinemia, Bruton tyrosine Kinase mutation, Whole exome sequencing, Diarrhoea.

Introduction

X-linked agammaglobulinemia (XLA) / hypogammaglobulinemia, also known as Bruton's agammaglobulinemia is a prototype of humoral immunodeficiency first described by Bruton in 1952.¹ It is an uncommon congenital disease and is the major primary immunodeficiency recognised in childhood. As an x-linked recessive disorder, the incidence rate of XLA is around 0.5/100,000.² XLA is caused by mutations in the Bruton tyrosine kinase (Btk) gene. Patients classically show less than 2% of the peripheral B cells and decreased levels of all immunoglobulins³ that influence the affected patients to repeated, severe bacterial infections, principally invasive extracellular pyogenic organisms.⁴ The most common presenting problems are bronchiectasis, recurrent pneumonia and recurrent upper respiratory tract infections, including sinusitis, otitis media and pharyngitis. Btk mutation also plays a key role in signal transduction of pre-B-cell receptor (BCR). In one case report, it was noted that XLA is also associated with precursor B-cell acute lymphoblastic leukaemia, which is the most common malignancy in children.⁵ XLA is caused

by 600 different mutations in the Bruton tyrosine kinase (Btk) gene. The Btk gene is mapped on X chromosome at Xq21.3-Xq22. It has five domains (PH, TH, SH3, SH2, and TK) and XLA is caused by mutation in all these five structural domains.⁶ Herein, we report a case of a child with repeated diarrhoea since the age of eighteen months and diagnosed to have XLA with Btk mutation on gene sequencing.

Case Report

A 3-year-old boy presented to the Emergency Department at Aga Khan University Hospital in the month of January 2013 with complaints of diarrhoea and fever for 3 days. The child had a significant past history with recurrent diarrhoea since the age of eighteen months. For this complaint, he was treated by multiple doctors with oral and intravenous antibiotics and usually got relief for few days before becoming symptomatic again. One year prior to presenting at our department, he had been hospitalised for one month due to meningoencephalitis which resulted in right-sided hemiplegia. He was treated with intravenous antibiotics and physiotherapy. Family history was also remarkable. He was born to consanguineous parents and has three sisters and two brothers, alive. One brother was treated for tuberculosis (TB). Two elder brothers had died in infancy, one due to diarrhoea and the other due to pneumonia.

On examination his height and weight were below the fifth percentile, was moderately dehydrated, and was also anaemic. No lymphadenopathy or enlarged tonsils were noted. Systemic examination showed protuberant abdomen with no visceromegaly. He had decreased power and tone in the right upper and lower limbs. Laboratory investigations showed normal absolute neutrophil count and absolute lymphocyte count, and hypokalaemia with normal renal function. He was also screened for TB due to its endemicity in our region and history of contact but the result was negative. Due to history of repeated infections and family history of male deaths, there was a strong suspicion of immunodeficiency. Evaluation showed markedly low immunoglobulins: IgG: <0.7, IgM: <0.08, and IgA: <0.15. Flow cytometry showed undetectable levels of CD+19 B

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Department of Paediatrics and Child Health, The Aga Khan University Hospital, Karachi, Pakistan.

Correspondence: Farah Naz Qamar. Email: farah.qamar@aku.edu

cells. Whole genome sequencing showed Btk mutation with a frame shift deletion 18 c.1883delCp.T628fs.

The child improved on supportive care and antibiotics. Currently he is on regular intravenous immunoglobulins (IVIG) replacement and follow-up.

Discussion

XLA is a primary immunodeficiency which is caused by 600 different mutations in the Btk gene. Even though most of the clinical symptoms develop in childhood, certain cases may remain undiagnosed or misdiagnosed as common immunodeficiency, selective IgG or IgA deficiency as they only show mild hypogammaglobulinemia and lack recurrent infections in childhood. In early 1993, germline mutation of Btk gene was identified as a cause of XLA. These mutations cause defects in early B cell development.⁶

The Btk gene is found at Xq21.3-Xq22 and encompasses 37.5 kb that contain 19 exons. Btk belongs to a group of related cytoplasmic tyrosine kinases, known as the Btk/Tec family, and comprises of five different structural domains, which contain the N-terminus, pleckstrin homology (PH) domain, Tec homology (TH) domain, SRC homology 3 (SH3) domain, SH2 domain, and the catalytic kinase (SH1) domain.^{7,8} Mutations in any domain of the Btk can induce dysfunction of the Btk protein, block the development of pre-B cells from naive B cells and reduce the lifespan of mature B lymphocytes.^{9,10} The deficiency of B lymphocytes and plasmocytes in the peripheral blood can decrease the synthesis of different immunoglobulins, reduce precise responses to several antigens, and hence eventually induce immunodeficiency.¹¹

Flow cytometric analysis using the anti-Btk antibody is a commanding diagnostic tool for screening XLA patients to measure Btk expression in peripheral monocytes. It is used for subsequent genetic counselling, carrier detection and prenatal diagnosis.¹² It is available at some reference laboratories and efforts should be made to collaborate with these reference laboratories to aid in patient counselling as well as identify the spectrum of primary immunodeficiency in our population. We have done this with the help of "The Jeffrey Modell Foundation" Immunology Division, Boston Children's Hospital.

Existing treatment options for XLA includes lifelong prophylactic therapy with IVIG that repairs some of the missing antibodies, suitable antibiotics for prevention of acute and chronic infections, nutritional rehabilitation and immunisation. If the disease is diagnosed early, patients can have a good quality of life. In order to

decrease the recurrences, number of hospital admissions and severity of infections, early treatment with immunoglobulin replacement therapy is important.¹³ Live viral vaccines should be avoided. Former reports propose that high dose IVIG replacement therapy (>400 mg/kg every 3 weeks) is more effective than low-dose (<200mg/kg) in patients with XLA.¹⁴ In our patient we have given immunoglobulins every 3-4 weeks. His serum IgG levels were also monitored and sustained above 5 g/L. These therapies are effective; nevertheless they are costly and non-curative. There is no definitive cure for XLA, yet the likelihood of using gene-corrected haematopoietic stem cells to complement the immune defects in mouse models has been studied. It may be hopeful to initiate stem cell-based therapy for XLA using gene-corrected autologous haematopoietic stem cells.¹⁵

Conclusion

Flow cytometric assessment of Btk expression in monocytes may set up a speedy and sensitive approach for recognition of XLA patients and female carriers, and support the clinicians to execute IVIG replacement therapy in an appropriate manner which might considerably decline the incidence of complications and the death rate.

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Competing Interests: All the authors declare that they have no competing interests.

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