International Journal of Contemporary Pediatrics
Myathari R et al. Int J Contemp Pediatr. 2021 Dec;8(12):1980-1983
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20214539

Case Report

X-linked agammaglobulinemia rare disease with a rarer presentation

Ramakrishna Myathari*, Anand Gupta

Department of Pediatrics, Sarvodaya Hospital, Faridabad, Haryana, India

Received: 29 September 2021
Revised: 15 November 2021
Accepted: 17 November 2021

***Correspondence:**
Dr. Ramakrishna Myathari,
E-mail: ramakrishnamyathari@gmail.com

ABSTRACT

X-linked agammaglobulinemia (XLA) is a rare disorder, characterized by absence of mature B cells leading to severe antibodies deficiency. This translates to recurrent sinopulmonary infections in affected children. The most common age group of presentation is 6 months to 2 years. Being an X-linked recessive disorder males are affected, females are carriers. Intravenous immunoglobulins and antibiotics remains the corner stone of treatment. Here in, we report a case of 11-year-old male having recurrent episodes of fever with one episode of hospitalization 3 years back. Child was treated at healthcare facility elsewhere for recurrent fever. He presented to our institute with signs and symptoms suggestive of meningitis, investigated, had culture proven Staphylococcus aureus meningitis with a low Absolute Lymphocyte Count (ALC). On further work up found to have low serum immunoglobulins (IgG, IgM, IgA) and Flowcytometry showing absence of B cells (CD19/CD20). Child was diagnosed to have XLA. This case highlights the importance of having strong clinical suspicion of XLA, despite not having recurrent sinopulmonary infections.

Keywords: X-linked agammaglobulinemia, Bruton's disease, Meningitis

INTRODUCTION

X-linked agammaglobulinemia (XLA) is a rare inherited disorder resulting from a mutation in the Bruton tyrosine kinase (BTK) gene that encodes an essential protein involved in B cell mutation. In particular, it promotes pre-B cell expansion at the pre-B_1 to pre B_2 stage.[1] This leads to profound defect in B-lymphocytes development, resulting in antibodies formation defect, and recurrent infections.[3]

BTK is an enzyme that is encoded by BTK gene its deficiency leads to Bruton disorder, because BTK is critical in the maturation of pre-B cells to mature B cells.[4] Peripheral blood report of the patient shows significant reduction in level of B Lymphocytes (<1% of normal).[5] Plasma cells all Immunoglobulins (Ig) isotypes, result of BTK gene mutation on X-chromosome.[5-8] This disorder usually manifests in infants as soon as the protective effect of maternal antibodies wanes. These patients then become susceptible to recurrent infections (predominantly pulmonary); most common age group of presentation is 6 months to 2 years.[3,9,10]

Our index case was 11 years old, presented with acute bacterial meningitis, had history of recurrent episode of fever, though pulmonary system was spared till date.

CASE REPORT

A 11 years male presented to us with history of fever, irritability, photophobia. Examination revealed clinical signs of meningitis, other relevant finding revealed absent tonsillar tissue, his height/weight was less than 3rd centile as per WHO standards.

Investigations

CSF analysis revealed picture of bacterial meningitis, culture grew Staphylococcus aureus, blood counts

showed polymorphonuclear leucocytosis, leucopenia, hypogammaglobulinemia, C-reactive protein-304, HIV report non-reactive (Table 1). Child was managed with intravenous antibiotics as per culture sensitivity report, steroids were given as per treatment protocol. On probing, there was history of sibling death (maternal aunt son). Possibility of XLA considered in view of hypogammaglobulinemia/absent tonsillar tissue, leucopenia.

Further investigation showed low serum immunoglobulins (IgA, IgG, IgM) as per age and sex, flow cytometry showed absence of circulating B cells. Diagnosis of XLA was established in this child (Table 2).

Table 1: Initial Investigation findings.

Investigation	Value
HB	11.1 g/dl
TLC	31.5×103/µl
DLC	
Neutrophils	90.60%
Lymphocytes	1.90%
Eosinophil	0.00%
Monocytes	7.40%
Basophils	0.10%
HCT	31.50%
RBC	4.35×106/µ1
MCV	72.4 fl
MCH	25.5 pg
MCHC	35.2 g/dl
RDW-SD	39.1 fl
RDW-CV	14.80%
Platelets	408×103/µ1
Absolute neutrophil count	28.5×103/µ1
Absolute lymphocytes count	0.61×103/µ1
Absolute eosinophil count	0.00×103/µ1
Absolute monocytes count	2.32×103/µ1
Absolute basophils count	0.03×103/µ1
HIV (ELISA)	Non-reactive
CRP	360.8 mg/l
CSF-culture report	Staphylococcus aureus spp cultured

Table 2: Serum immunoglobulin profile.

Immunoglobulin	Values (mg/dl)
IgG	444
IgM	<21
IgA	<33

Table 3: Flow cytometry.

Cells		Values
B-lymphocytes	CD 19 (total B-cells)	0.08%
	Absolute CD-19	1/µl
T-lymphocytes	CD3 (total T-cells)	93.13%
	Absolute CD-3	1233/µl
	CD4 (helper T-cells)	49.28%
	Absolute CD-4	653/µl
	CD-8 (suppressor T-cells)	21.20%
	Absolute CD-8	282/µl
	CD4/CD8	2.3
Natural killer cells	CD3-CD (16+56)	5.91%
	Absolute CD3-CD (16+56)	78/µl
CD-20 (B-cell marker)	CD2O (total B-cells)	0.08%
	Absolute CD2O	1/µl

DISCUSSION

Index case was diagnosed as XLA as per these criteria laid. One or more of the following criteria: (a) BTK gene mutation and/or defective expression of BTK protein; (b) a positive family history- either BTK gene mutation or very low levels of B-lymphocytes in their blood and reduced levels of gamma-globulins; and (c) very low level of B-lymphocytes in the patient's blood and reduced levels of gamma-globulins.

XLA and CVID (Common variable immunodeficiency) both are primary immunodeficiency disorders. Clinical presentation of XLA is similar to that of CVID. To distinguish between XLA and CVID, flow cytometry plays an important part. Absence of circulating B cells distinguishes XLA from CVID (Table 4).

Other primary immunodeficiency disorder mimicking XLA (notably hyper IgM syndrome) can be distinguished as shown in (Table 5). Patients with XLA are particularly suspectable to respiratory infection, mostly due to encapsulated pyogenic bacteria and bowel infections caused by Salmonella, Yersinia, Campylobacter, Giardia.[11-13] Index case is a late diagnosed one, presented to us at uncommon age of 11 years. Presentation was that of acute bacterial meningitis. As per best of our knowledge a very smaller number of individuals presented with ALA around at this age but they had history of sinopulmonary infections which is not in our case.

Case report of Zuzana et al on XLA caused by new mutation in BTK gene, showed delayed diagnosis of ALA at the age of 10 years. According to the documentation this child underwent several bacterial pneumonias, sinusitis. A case report of Zoha et al on novel BTK mutation in X-linked agammaglobulinemia report of 17-years-old male. In above case they have been diagnosed in late ages but they also had study of recurrent sinopulmonary infections which was not seen in our case. This being an uncommon infection in such age group, high index of suspicion was kept and subsequent workup established the diagnosis.

It is to be noted that usual age of presentation of XLA is 6 months to 2 years, clinical manifestation being recurrent sinopulmonary infections, requiring frequent hospitalizations. Our case had none such history. It emphasizes the fact that children presenting with severe life-threatening infections, should be evaluated carefully for immunodeficiency disorders.

Table 4: Difference between XLA and CVID.

Parameters	XLA	CVID
Age of onset	6 months- 2 years	At any age
Inheritance	X-linked recessive	Variable
Lymph nodes	Absent	Normal
Tonsils	Absent	Normal
Family H/O immunodeficiency	Present	Variable
CD_{19}^{+} B cells	Marked reduced/absent	Normal/low
CD_{3}^{+} T cells	Normal	Variable
Mutation	BTK	TACI, ICOS, CD19+

Table 5: Difference XLA and hyper IgM syndrome.

Parameters	XLA	Hyper IgM syndrome
Age of onset	6 months-2 years	Usually 1-2 yrs.
Family H/O immunodeficiency	Present	Variable
Inheritance	X-linked recessive	Variable
Lymphnodes/tonsils	Absent	Small
CD_{19}^{+} B cells	Marked reduced/absent	Normal
CD_{3}^{+} T cells	Normal	Normal
IgM	Decreased	Increased/normal
Mutation	BTK	CD40 ligand

CONCLUSION

Early diagnosis and timely intervention results in improved growth, fewer infections and normal life in such difficult cases. Whereas, delay in identifying such disorders may lead to serious sequelae including death. Therefore, it is of utmost importance that clinician should be aware of disease and high index of suspicion should be kept in such cases.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Vetrie D, Vořechovský I, Sideras P, Holland J, Davies A, Flinter F, et al. The gene involved in X-linked agammaglobulinaemia is a member of the Src family of protein-tyrosine kinases. J Immunol. 2012;188(7):2948-55.
2. Conley ME. Early defects in B cell development. Curr Opin Allergy Clin Immunol. 2002;2(6):517-22.
3. Sullivan KE, Rebecca H. Primary Defects of Antibody Production. Nelson Text book of pediatrics. 20th ed. Netherland: Elsevier; 2016: 1107.
4. Vetrie D, Vorechovský I, Sideras P, Holland J, Davies A, Flinter F, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature. 1993;361(6409):226-33.
5. Ochs HD, Smith CI. X-linked agammaglobulinemia. A clinical and molecular analysis. Medicine. 1996;75(6):287-99.
6. Dan L, Anthony F, Dennis K, Stephen H, Jameson J, Joseph L. Harrison's Principles of Internal Medicine. 20th ed. New York: McGraw Hill; 2011.
7. Chun JK, Lee TJ, Song JW, Linton JA, Kim DS. Analysis of clinical presentations of Bruton disease: a review of 20 years of accumulated data from pediatric patients at Severance Hospital. Yonsei Med J. 2008;49(1):28-36.
8. Melo KM, Dantas E, Pinto MI, Neto A, Gonzalez IG, Mallozi MC, et al. Primary Immunodeficiency May Be Misdiagnosed as Cow's Milk Allergy: Seven Cases Referred to a Tertiary Pediatric Hospital. ISRN Pediatr. 2013;2013:470286.
9. Plebani A, Soresina A, Rondelli R, Amato GM, Azzari C, Cardinale F, et al. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. Clin Immunol. 2002;104(3):221-30.
10. Conley ME, Howard V. Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. J Pediatr. 2002;141:566-71.
11. Liu Y, Wu Y, Lam KT, Lee PP, Tu W, Lau YL. Dendritic and T cell response to influenza is normal in the patients with X-linked agammaglobulinemia. J Clin Immunol. 2012;32(3):421-9.
12. Chear CT, Gill HK, Ramly NH, Dhaliwal JS, Bujang N, Ripen AM, et al. A novel Bruton's tyrosine kinase gene (BTK) invariant splice site mutation in a Malaysian family with X-linked agammaglobulinemia. Asian Pac J Allergy Immunol. 2013;31(4):320-4.
13. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. Medicine (Baltimore). 1985;64(3):145-56.

Cite this article as: Myathari R, Gupta A. X-linked agammaglobulinemia rare disease with a rarer presentation. Int J Contemp Pediatr 2021;8:1980-3.