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REVIEW ARTICLE

X-linked Agammaglobulinemia

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Abstract X-linked agammaglobulinemia (XLA) is one of the commonest primary immune deficiencies encountered in pediatric clinical practice. In adults, common variable immunodeficiency (CVID) is the most common primary immunodeficiency disease (PID). It is an X-linked disorder characterized by increased susceptibility to encapsulated bacteria, severe hypergammaglobulinemia and absent circulating B cells in the peripheral blood. Replacement immunoglobulin therapy is the main cornerstone of treatment. Aggressive management of intercurrent infections and prophylactic antimicrobials are needed. This review attempts to highlight varied clinical manifestations and management of XLA, especially in the context of developing country.

Keywords Brutons disease · Immunoglobulins · Antibody deficiency · Hypogammaglobulinemia

Introduction

Primary antibody deficiencies are the most common type of pediatric primary immune deficiency diseases. X-linked agammaglobulinemia (XLA) is a prototype disease of this group of disorders. It is characterized by increased susceptibility to infection with severe hypogammaglobulinemia and absent circulating B cells in peripheral blood. XLA was also the first primary immune deficiency disease for which genetic cause was identified.

Colonel Ogden Bruton in 1952 described an eight-year-old male with recurrent pneumococcal sepsis and complete absence of gamma globulin [1]. He also demonstrated the child to be free of infection following monthly supplementation of subcutaneous human gamma globulins. He postulated it to be an acquired condition in which the patient's antibody mechanism is altered and hence was unable to synthesize antibody to a specific organism. However, in early 1993 a molecular defect was identified by two different groups [2, 3] and the gene was named after Colonel Bruton.

An accurate estimate of the incidence or prevalence of XLA is difficult to obtain, essentially because it is an uncommon disease and large population screening data is unavailable. According to the results of US registry, the incidence of XLA is estimated to be 1 in 190,000 male births or 1 in 379,000 live births [4]. However, this may be an underestimated figure and many ethnic differences exist [4].

Genetics

XLA is caused by a mutation in the Bruton tyrosine kinase (*BTK*) gene, located on the long arm of X-chromosome. Btk is a member of the Tec family of nonreceptor tyrosine kinases, which are signal transduction molecules. BTK is critical in the maturation of Pre-B cells to mature B cells [3]. Its major role is in promoting pre-B cell expansion at the preB1 to preB2 stage [5]. As a result of the mutation in *BTK* gene, there is a failure of B cell development and affected patients have significantly reduced levels (<1 %) of mature B lymphocytes in their peripheral blood circulation. They fail to generate plasma cells and consequently have markedly low levels of all classes of

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immunoglobulins with virtually no humoral responses [6]. It also results in reduced size of lymph nodes and tonsils, which are highly populated by B cells. However, T cell number and function is preserved.

XLA is inherited in X-linked manner, and *BTK* is the only known gene to cause it. Most of the mutations in *BTK* gene are familial with mothers of the affected individuals being healthy carriers. However, 15–20 % mutations are known to occur de novo. Around 50 % patients have a family history of previously affected family member [4]. Agammaglobulinemia due to *BTK* mutation has been described in a female due to skewed X-chromosome inactivation [7]. Sequence analysis of *BTK* gene detects 90 % of mutations. Approximately 70 % mutations are single base pair changes resulting in amino acid substitution, premature stop codons or splice defects. The remaining 22 % are insertions, deletions or small rearrangements [8].

Clinical Manifestations

Children with XLA become symptomatic by 6–12 mo of age, once the passively transferred protective maternal IgG fade. Most patients present with recurrent infections, and more than 50 % children have had serious infections by 2 y of life [8–10]. There are rare reports of individual patients with well documented XLA, who did not have sufficient clinical symptoms to be diagnosed with agammaglobulinemia until well into adult life. This is attributed to early and frequent treatment of infections with antimicrobials. Though some children may be identified early due to a positive family history, unfortunately even in countries with a high index of suspicion for PIDs, two-thirds of patients with a positive family history are not diagnosed at or soon after birth. Most children are diagnosed after having presented with clinical symptoms [10]. The clinical manifestations encountered in these children are summarized in Table 1.

Infections

Recurrent bacterial upper and lower respiratory tract infections are the most common manifestation of XLA. Typically, XLA patients suffer from recurrent sino-pulmonary infections like otitis media, sinusitis, bronchitis, pneumonia and gastrointestinal infections, however, the frequency of these manifestations is variable [8–10]. The infections are usually caused by encapsulated pyogenic bacteria, namely *Streptococcus pneumoniae*, *Hemophilus influenzae* type B, *Streptococcus pyogenes*, and Pseudomonas species [11]. Septicemia, pyogenic meningitis, osteomyelitis and septic arthritis are well described. On physical evaluation, there is evidence of growth failure. Signs of recurrent and chronic sino-pulmonary infections: postnasal discharge, tympanic membrane perforation, digital clubbing and bronchiectasis may be seen. Absent or atrophied tonsils and lymph nodes are often the most important clinical clue in clinching the diagnosis.

Mycoplasma infections cause respiratory, urogenital as well as joint infections. It is worth noting that Mycoplasma arthritis in patients with XLA may pose a clinical dilemma for treating physicians. The serology based tests are typically negative, and hence all attempts should be made to culture these organisms [12].

Infections of the gastrointestinal tract are frequent in XLA patients. *Giardia lamblia* is frequently isolated from stool samples from these patients, and sometimes its eradication may become difficult, resulting in chronic diarrhea and malabsorption. *Campylobacter jejuni* is also an unusual pathogen implicated in causing gastrointestinal manifestations as well as bacteremia and skin lesions [13, 14]. Recurrent conjunctivitis occurs in around 5–8 % patients [10].

Table 1 Clinical manifestations in patients with XLA

Clinical manifestation		Microorganisms
Infections	Sinopulmonary infections, Otitis media, Meningitis, Osteomyelitis, Septicemia	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Neisseria meningitidis*
	Arthritis	*Mycoplasma pneumoniae*
	Chronic diarrhea	*Campylobacter jejunii*, *Giardia lamblia*
	Meningoencephalitis	Enteroviruses
Autoimmune and Inflammation	Arthritis, Inflammatory bowel disease, Progressive encephalopathy	
Malignancy	Colorectal cancers, NonHodgkin lymphoma	
Associations	XLA and deafness-dystonia-optic neuropathy syndrome X-linked hypogammaglobulinemia and isolated growth hormone deficiency	
Others	Glomerulonephritis, Alopecia, Amyloidosis, von Recklinghausen disease	

Patients with XLA can handle most of the childhood viral infections well due to intact T cell function. However, they are susceptible to certain enteroviruses namely; Echovirus, Poliovirus and Coxsackie virus. Fatal, vaccine-associated polio virus infection, has been described in a child with XLA, who had received oral polio vaccine [15]. Enteroviral infections can cause chronic meningoencephalitis that can result in subtle neuroregression and later progress to full blown neurologic impairment and coma [16]. Enteroviral infection of muscle and skin may occasionally masquerade as dermatomyositis-like syndrome presenting with an erythematous rash and peripheral edema [17]. It may even cause chronic hepatitis manifesting with fever, rash and elevated hepatic enzymes [15].

Other uncommon manifestations include glomerulonephritis, alopecia, amyloidosis, and von Recklinghausen disease.

Many children (18 %) with XLA, especially in association with acute infection have neutropenia [18]. Other cytopenias have not been documented. The mechanism of neutropenia is unclear and has not been attributed to autoimmunity or involvement of BTK protein in neutrophl development.

Autoimmunity and Inflammation

Compared to other primary immune deficiency diseases, patients with XLA are considered to have a low risk of autoimmune or inflammatory disease. However, in a recent web-based patient survey, 69 % patients reported at least one and 53 % patients reported multiple inflammatory symptoms. However, only a total of 28 % patients were formally diagnosed to have an inflammatory disease [19]. The data suggested that a significant proportion of patients with XLA had symptoms of arthritis, inflammatory bowel disease or other inflammatory disorders and these symptoms were more common than in normal population.

A few recent studies have described progressive encephalopathy of unknown etiology in patients with XLA, even in those receiving a long-term replacement of immunoglobulins [20]. In early stages, subtle cognitive impairment occurs along with involvement of frontal lobe functions. Some patients also develop movement disorders. It is slowly progressive and eventually results in severe cognitive and physical disability and can even be fatal. Autoimmunity secondary to dysregulated immune responses is considered as a pathogenetic mechanism but has not yet been fully explained.

XLA and Deafness-Dystonia-Optic Neuropathy Syndrome

Large deletions in 3' end *BTK* and closely linked gene *TIMM8A* (also called *DDP*) are seen in approximately 3 %–5 % of individuals [21, 22]. Patients with this contiguous gene deletion syndrome have XLA and deafness-dystonia-optic neuropathy syndrome (DDS or Mohr-Tranebjærg syndrome). The diagnosis of XLA usually precedes hearing loss and often the hearing loss is incorrectly initially attributed to recurrent otitis media.

X-linked Hypogammaglobulinemia and Isolated Growth Hormone Deficiency

X-linked hypogammaglobulinemia (XLH) and isolated growth hormone deficiency (GHD) was initially described in a family with four affected family members [23]. However, later both sporadic and familial cases were described [24, 25]. Clinical and immunological phenotype was similar to XLA and hence was considered to be an association of XLA. However, later it was also found that XLH/GHD patients from the family originally reported, expressed normal levels of Btk protein in peripheral blood mononuclear cells and no mutation could be identified on *BTK* gene sequencing. Moreover in several other cases, complete correlation of hypogammaglobulinemia and X-linked inheritance of growth hormone deficiency could not be established. Recently, it has been recognized as a separate entity with *MEF* as a candidate gene [26].

Laboratory Diagnosis

The hallmark of patients with XLA is a marked reduction in all isotypes of serum immunoglobulins and almost a complete absence of peripheral B cells, defined by less than 2 % B lymphocytes in the peripheral blood (Fig. 1). Serum levels of functional antibodies are also markedly reduced or undetectable. T cell number and function are normal [6, 9].

Bruton tyrosine kinase (Btk) protein expression on monocytes can also be ascertained by flow cytometry (Fig. 2). This is a simple and robust test that aids in diagnosis. However, it may be noted that a normal expression of Btk on monocytes does not rule out a diagnosis of X-linked agammaglobulinemia. Female carriers of a defective *BTK* gene can show a mosaic pattern of expression, with two distinct populations of cells showing different levels of expression of Btk. Once the clinical and laboratory findings sustain the diagnosis, molecular analysis of the *BTK* gene should be performed.

Once the mutation is defined, carrier and prenatal diagnosis can be performed where necessary. If *BTK* mutation analysis results are noncontributory, sequencing analysis of the other known uncommon genes causing antibody deficiencies can be undertaken like μ heavy chain, *Igα*, *Igβ*, *λ5*, *BLNK*.

Based on the criteria given by European Society of Primary Immunodeficiency, a **definitive diagnosis** of XLA is made when a male patient has hypogammaglobulinemia or agammaglobulinemia, CD19+ B cells (< 2 %) and either a male family member of maternal lineage is documented to also have agammaglobulinemia and <2 % CD19+ B cells or a

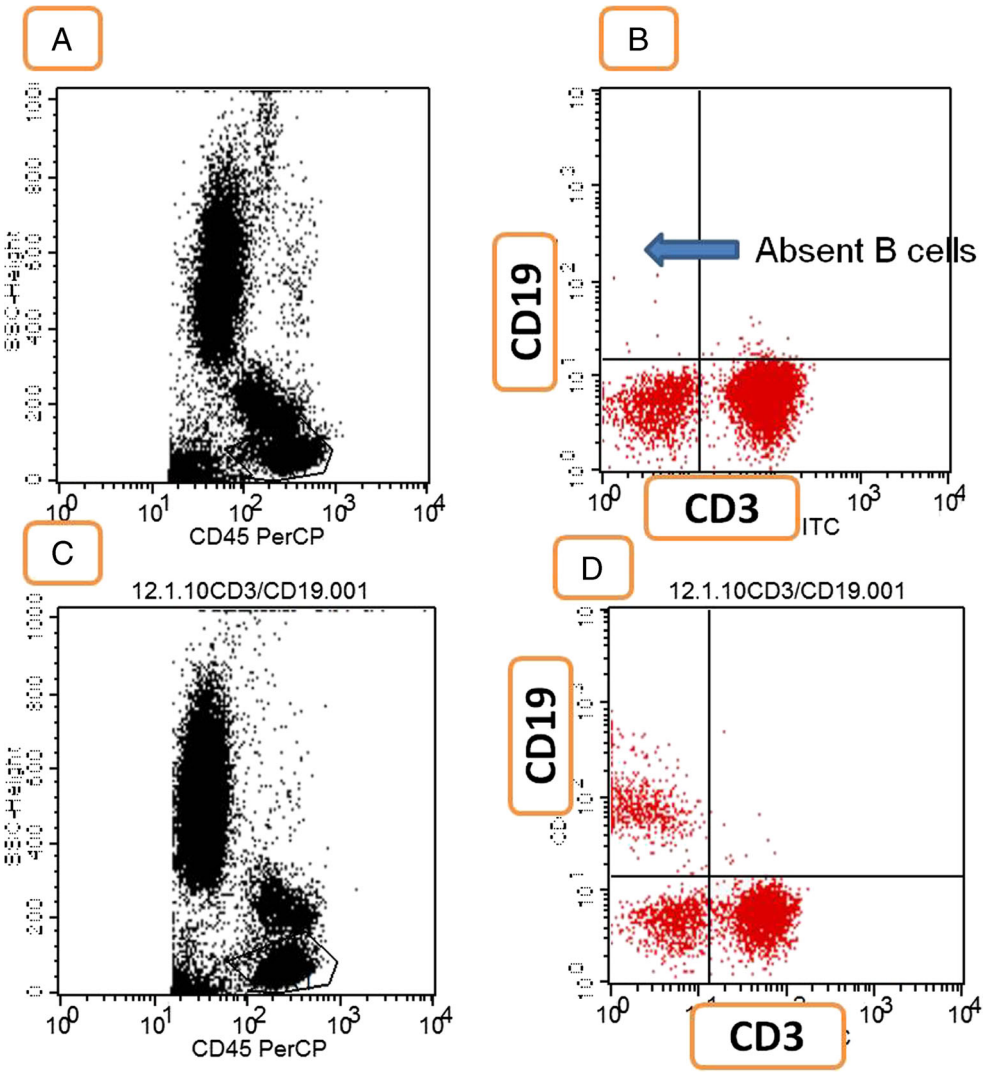

Fig. 1 Flow cytometry showing absence of B lymphocytes in peripheral blood in a young boy with X-linked agammaglobulinemia (A & B) and normal population of B lymphocytes in a healthy control (C & D)

confirmed [by deoxyribonucleic acid (DNA), messenger ribonucleic acid (mRNA), or protein analysis] defect in the *BTK* gene or Btk expression [27].

A **probable or possible diagnosis** based upon clinical history, quantitative serum immunoglobulin levels, and response to vaccines is made if these criteria are not met, but other causes of agammaglobulinemia/hypogammaglobulinemia are ruled out. Plasma cells are absent in the lymphoid tissue, bone marrow, and the lamina propria of the rectal mucosa.

Tests are being developed for screening of newborn babies for XLA and other B cell defects. Studies report immunoglobulin kappa-deleting recombination excision circles (KRECs

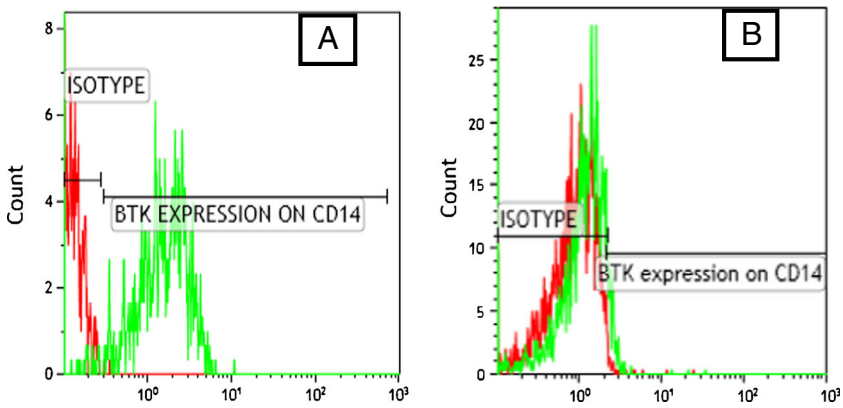

Fig. 2 Btk protein expression on monocytes: Estimation by flow-cytometery (**a**) normal expression of Btk protein indicated by shift to right after staining (**b**) absent Btk protein expression indicated by no shift to right after staining

assay) to be a useful screening tool for early B cell maturation defects. It is a similar to T-cell receptor excision circles (TRECs) used to screen for T cell defects. Dried blood spots are placed on newborn screening cards and polymerase chain reactions are performed to detect KRECs. KRECs are formed in the process of B cell maturation, during allelic exclusion and are not produced in patients with B cell maturation defects, such as XLA [28].

Treatment

Replacement of immunoglobulin is the cornerstone of treatment for patients with XLA. The development of safe and effective immunoglobulin formulations have altered the outcome and quality of life of these children. Most common forms of replacement therapy are either intravenous immunoglobulin (IGIV), subcutaneous immunoglobulin (SCIG) or enzyme facilitated subcutaneous immunoglobulin. However, the subcutaneous immunoglobulin is still not marketed in India.

A standard initial dose of IGIV for the treatment is 400 mg/kg (with a range of 300 to 600 mg/kg) every 3 to 4 wk. Subsequently, the dose must be optimized to maintain a "biological" trough value of the patient [29]. The goal of replacement therapy is to keep the patient free from infection and not to target for a particular IgG serum trough level.

A meta-analysis published in 2010, based on 17 clinical studies evaluated outcomes of IGIV replacement therapy and the relationship between serum IgG trough levels and occurrence of pneumonia in patients with XLA and common variable immunodeficiency (CVID). The study found an increase of 121 mg/dl in trough levels for every 100-mg/kg dose increase in IGIV. Overall, the study found that patients treated with IGIV therapy had a 27 % reduced risk of pneumonia for each 100 mg/kg increase of trough IgG serum level up to serum IgG level of 1000 mg/dl [30]. Unfortunately, this analysis did not provide information about the relationship between IGIV dosing and other types of infections.

A similar correlation between IgG serum trough levels and reduction in infection was reported by Lucas and collegues [31]. Patients with bronchiectasis or a disease-related phenotype (*e.g.*, enteropathy, lymphoproliferation, and autoimmunity) required higher doses of immunoglobulin replacement therapy. They also emphasized on individualizing the dose of therapeutic immunoglobulin to prevent breakthrough infections. However, little guidance is available in the current literature on initial treatment targets and escalation schedule.

On the other hand, Quinti and colleagues found that overall patients with pneumonia did not have significantly lower IgG trough levels than patients without pneumonia. However, persistently lower trough levels (*e.g.*, 400 mg/dl) in an individual predisposed and increased the risk of pneumonia [32].

Thus, the current evidence suggests that achieving an IgG trough level is important when using IGIV, at least for pneumonia, but the treatment of each patient must be individualized to achieve optimal care. Individualization of IgG replacement therapy in patients could be advanced by more information linking specific patient phenotypes to IgG levels and biomarkers of inflammation required to prevent infection [33].

Replacement IGIV therapy is extremely expensive and very difficult to sustain, especially in setting of developing countries like ours. In authors' study cohort of 10 children, even a lower trough levels were enough to keep the children infection free and ensure better growth, regular schooling and improved quality of life [34].

Patients with XLA also require aggressive antibiotic therapy for any documented and suspected infection. In some instances, prolonged antibiotic therapy may be indicated as treatment for ongoing pulmonary infections or chronic sinusitis. Cotrimoxazole at a dose of 5 mg/kg of single trimethoprim dose daily is used as prophylactic therapy. Finally, immunizations with live viral vaccines are held to be contraindicated. There are no data on the safety or efficacy of other vaccines in patients with XLA. Personal hygiene and precautions, such as handwashing and avoidance of respiratory droplets, must be advised. Finally, patients should avoid ingestion of untreated drinking water if possible.

Unlike other primary immune deficiencies, the use of hematopoietic stem cell transplant (HCT) in patients with XLA is not well studied and recommended. This is predominantly due to improved outcome with replacement immunoglobulin therapy. Even though, studies in murine models of B cell deficiency suggested that repair of *BTK* mutation even in a very small population of hematopoietic stem cells can lead to the recovery of B cell function in XLA patients [35, 36]. Howard et al. reported six patients with XLA, who underwent matched stem cell donor HCT without the use of conditioning or immune suppression [37]. Unfortunately, none of the patients showed any signs of engraftment or B cell reconstitution. Abu Arja et al. have recently reported a case of acute myeloid leukemia in a pediatric patient with XLA. Although, HCT was initiated to treat the patient's relapsed AML, it also completely corrected his XLA phenotype [38].

Hematopoietic stem cell gene therapy is a potential therapeutic approach for XLA. Retroviral vectors have previously been applied as gene therapy for various immunodeficiency diseases but are associated with an increase the risk of cancer due to random integration of the vector into chromosomes. Recently, adenovirus vectors are being developed and have been shown to have potentials to repair the *BTK* gene by homologous recombination and this could represent new promising therapy for XLA [39].

Prognosis

In the developed world, the overall prognosis for XLA has improved dramatically in the last 25 y due to early diagnosis, judicious use of antibiotics and regular replacement with safe and effective gammaglobulin preparations. Children with XLA are now surviving into adulthood [40, 41]. Even though, adults and children with XLA miss more days of school/work, and they are hospitalized more frequently than males in the general population, most of them lead productive and fulfilling lives despite these limitations [41]. Approximately, 10 % of individuals develop significant infections, chronic lung disease, or neurodegenerative disease despite appropriate therapy in addition to the side effects of monthly immunoglobulin infusions [42]. Malignancy have been reported in long-term survivors with XLA with an estimated 30-fold increase in the incidence of colorectal cancer [43].

In developing countries, however, the situation is not so promising. Many children die before the diagnosis is established and there are considerable delays in diagnosis. A significant proportion of children have permanent lung damage at the time of diagnosis. With no financial support from the Government sector, the parents and families struggle to provide optimal care. The treatment is expensive and beyond the reach of the average household. Mortality continues to be high. A committed effort on the part of parents, treating physicians and well as the Government is needed to improve the outcome of these children in developing countries.

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Compliance with Ethical Standards

Conflict of Interest None.

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References

1. Bruton OC. Agammaglobulinemia. Pediatrics. 1952;9:722–8.
2. Tsukada S, Saffran DC, Rawlings DJ, et al. Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. 1993. J Immunol. 2012;188:2936–47.
3. Vetrie D, Vorechovský I, Sideras P, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature. 1993;361:226–33.
4. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore). 2006;85:193–202.
5. Conley ME, Rohrer J, Rapalus L, Boylin EC, Minegishi Y. Defects in early B-cell development: comparing the consequences of abnormalities in pre-BCR signaling in the human and the mouse. Immunol Rev. 2000;178:75–90.
6. Ochs HD, Smith CI. X-linked agammaglobulinemia. A clinical and molecular analysis. Medicine (Baltimore). 1996;75(6):287–99.
7. Takada H, Kanegane H, Nomura A, et al. Female agammaglobulinemia due to the Bruton tyrosine kinase deficiency caused by extremely skewed X-chromosome inactivation. Blood. 2004;103:185–7.
8. Plebani A, Soresina A, Rondelli R, et al; Italian Pediatric Group for XLA-AIEOP. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. Clin Immunol. 2002;104:221–30.
9. Conley ME, Rohrer J, Minegishi Y. X-linked agammaglobulinemia. Clin Rev Allergy Immunol. 2000;19:183–204.
10. Conley ME, Howard V. Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. J Pediatr. 2002;141:566–71.
11. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. Medicine (Baltimore). 1985;64:145–56.
12. Roifman CM, Rao CP, Lederman HM, Lavi S, Quinn P, Gelfand EW. Increased susceptibility to mycoplasma infection in patients with hypogammaglobulinemia. Am J Med. 1986;80:590–4.
13. Chusid MJ, Coleman CM, Dunne WM. Chronic asymptomatic Campylobacter bacteremia in a boy with X-linked hypogammaglobulinemia. Pediatr Infect Dis J. 1987;6:943–4.
14. Kerstens PJ, Endtz HP, Meis JF, et al. Erysipelas-like skin lesions associated with Campylobacter jejuni septicemia in patients with hypogammaglobulinemia. Eur J Clin Microbiol Infect Dis. 1992;11:842–7.
15. Sarpong S, Skolnick HS, Ochs HD, Futatani T, Winkelstein JA. Survival of wild polio by a patient with XLA. Ann Allergy Asthma Immunol. 2002;88:59–60.
16. Halliday E, Winkelstein J, Webster ADB. Enteroviral infections in primary immunodeficiency (PID): a survey of morbidity and mortality. J Infect. 2003;46:1–8.
17. Rudge P, Webster AD, Revesz T, et al. Encephalomyelitis in primary hypogammaglobulinaemia. Brain J Neurol. 1996;119:1–15.
18. Jacobs ZD, Guajardo JR, Anderson KM. XLA-associated neutropenia treatment: a case report and review of the literature. J Pediatr Hematol Oncol. 2008;30:631–4.
19. Hernandez-Trujillo VP, Scalchunes C, Cunningham-Rundles C, et al. Autoimmunity and inflammation in X-linked agammaglobulinemia. J Clin Immunol. 2014;34:627–32.
20. Sag AT, Saka E, Ozgur TT, et al. Progressive neurodegenerative syndrome in a patient with X-linked agammaglobulinemia receiving intravenous immunoglobulin therapy. Cogn Behav Neurol. 2014;27:155–9.
21. Richter D, Conley ME, Rohrer J, et al. A contiguous deletion syndrome of X-linked agammaglobulinemia and sensorineural deafness. Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol. 2001;12:107–11.
22. Sedivá A, Smith CIE, Asplund AC, et al. Contiguous X-chromosome deletion syndrome encompassing the BTK, TIMM8A, TAF7L, and DRP2 genes. J Clin Immunol. 2007;27:640–6.
23. Fleisher TA, White RM, Broder S, et al. X-linked hypogammaglobulinemia and isolated growth hormone deficiency. N Engl J Med. 1980;302:1429–34.
24. Monafo V, Maghnie M, Terracciano L, Valtorta A, Massa M, Severi F. X-linked agammaglobulinemia and isolated growth hormone deficiency. Acta Paediatr Scand. 1991;80:563–6.
25. Duriez B, Duquesnoy P, Dastot F, Bougnères P, Amselem S, Goossens M. An exon-skipping mutation in the btk gene of a patient with X-linked agammaglobulinemia and isolated growth hormone deficiency. FEBS Lett. 1994;346:165–70.
26. Stewart DM, Tian L, Notarangelo LD, Nelson DL. X-linked hypogammaglobulinemia and isolated growth hormone deficiency: an update. Immunol Res. 2007;38:391–9.

27. ESID - European Society for Immunodeficiencies [Internet]. Available at: http://esid.org/Working-Parties/Registry/Diagnosis-criteria. Accessed on 16 Dec 2015.
28. Borte S, von Döbeln U, Fasth A, et al. Neonatal screening for severe primary immunodeficiency diseases using high-throughput triplex real-time PCR. Blood. 2012;119:2552–5.
29. Bonagura VR, Marchlewski R, Cox A, Rosenthal DW. Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. J Allergy Clin Immunol. 2008;122:210–2.
30. Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. Clin Immunol. 2010;137:21–30.
31. Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. J Allergy Clin Immunol. 2010;125:1354–60.e4.
32. Quinti I, Soresina A, Guerra A, et al. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. J Clin Immunol. 2011;31:315–22.
33. Milito C, Pulvirenti F, Pesce AM, et al. Adequate patient's outcome achieved with short immunoglobulin replacement intervals in severe antibody deficiencies. J Clin Immunol. 2014;34:813–9.
34. Singh S, Aulakh R, Bhalla AK, et al. Is Kawasaki disease incidence rising in Chandigarh, north India? Arch Dis Child. 2011;96:137–40.
35. Rohrer J, Conley ME. Correction of X-linked immunodeficient mice by competitive reconstitution with limiting numbers of normal bone marrow cells. Blood. 1999;94:3358–65.
36. Porpiglia AS, Rohrer J, Conley ME. Reconstitution of B cell function in murine models of immunodeficiency. Clin Immunol. 2003;107:90–7.
37. Howard V, Myers LA, Williams DA, et al. Stem cell transplants for patients with X-linked agammaglobulinemia. Clin Immunol. 2003;107:98–102.
38. Abu-Arja RF, Chernin LR, Abusin G, et al. Successful hematopoietic cell transplantation in a patient with X-linked agammaglobulinemia and acute myeloid leukemia. Pediatr Blood Cancer. 2015;62:1674–6.
39. Yamamoto H, Ishimura M, Ochiai M, et al. BTK gene targeting by homologous recombination using a helper-dependent adenovirus/adeno-associated virus hybrid vector. Gene Ther. 2015. doi:10.1038/gt.2015.91 Epub ahead of print.
40. Soresina A, Nacinovich R, Bomba M, et al; Italian Network for Primary Immunodeficiencies. The quality of life of children and adolescents with X-linked agammaglobulinemia. J Clin Immunol. 2009;29:501–7.
41. Howard V, Greene JM, Pahwa S, et al. The health status and quality of life of adults with X-linked agammaglobulinemia. Clin Immunol. 2006;118:201–8.
42. Mohammadzadeh I, Yeganeh M, Khaledi M, Salehiomran MR, Aghamohammadi A, Rezaei N. Debilitating progressive encephalitis in a patient with BTK deficiency. Acta Microbiol Immunol Hung. 2012;59:335–42.
43. van der Meer JW, Weening RS, Schellekens PT, van Munster IP, Nagengast FM. Colorectal cancer in patients with X-linked agammaglobulinaemia. Lancet. 1993;341:1439–40.