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X-LINKED AGAMMAGLOBULINEMIA

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B-lymphocyte development is essential for production of functional antibody and humoral immune responses. The mechanisms that regulate this process are complex and tightly regulated. Defects in nonredundant components of this pathway lead to a clinical and immunologic syndrome of congenital agammaglobulinemia with absence of B-cell development. X-linked agammaglobulinemia (XLA) was the first of these conditions to be described and is the most common cause of congenital agammaglobulinemia. In 1993, abnormalities in the Bruton's tyrosine kinase *(BTK)* gene were shown to be the cause of XLA. A considerable amount of research has since been dedicated to understanding the genetic basis and molecular pathogenesis of the disease.

Section snippets

HISTORY

XLA was the first human immunodeficiency described for which the underlying defect was clearly identifed. In 1952 Bruton reported the case of an 8-year-old boy who had suffered from recurrent

infections, including sepsis caused by pneumococcus of different serotypes. Subsequent analysis of serum by protein electrophoresis revealed a lack of gammaglobulin.[2] Realizing the association between the absence of gammaglobulin and recurrent infections, Bruton started gammaglobulin replacement therapy …

CLINICAL MANIFESTATIONS

The majority of affected boys are prone to recurrent bacterial infection with the peak incidence of onset at 6 months of age following the disappearance of maternal immunoglobulin.[40] A study of 96 North American patients found that symptoms appeared in 25% of the patients by the age of 4 months, 50% by 8 months, and 75% by 12 months.[40] In a British study of 44 patients, 40% of patients presented in the first year of life and 21% remained asymptomatic until 3 to 5 years of life.[31] In these two …

SPECTRUM OF INFECTIONS

Infections in XLA usually are caused by pyogenic bacteria with *Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae,* and *Pseudomonas* being the most common species[40] although many other types also have been reported.61, 70, 84 These reports were published before the introduction of the *H. influenzae B* vaccination programs, and although no recent studies have been published, it is likely that the spectrum of infection is now considerably different. Susceptibility to *Mycoplasma* …

XLA AND CANCER

Although certain primary immunodeficiencies can predispose to an increased incidence of tumors (ataxia–telangiectasia, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome), such a relationship is not obvious for XLA. Lederman and Winkelstein documented two patients in their study,[40] one with a B-cell lymphoma of the terminal ileum and the other with a reticulum cell sarcoma of the bowel. One patient with pituitary adenoma was reported by Hermaszewski and Webster.[31] Analysis of a …

MORTALITY

Smith and Witte[68] analyzed three major retrospective studies of patients with XLA and found 30 deaths recorded among 170 patients (17.6%). The major cause of death was viral infection and was predominantly caused by disseminated echoviral infection. The other major cause of death was cardiorespiratory failure from chronic pulmonary disease and cor pulmonale. Other causes of death included amyloidosis, septicemia with osteomyelitis, and inflammatory bowel disease. These data are based on …

HETEROGENEITY

Identification of *BTK* as the gene defective in XLA75, 77 allows unambiguous assignment of a molecular defect to individuals with abnormalities in antibody production. Although the majority of *BTK*-deficient patients display the classical immunophenotype of less than 1% peripheral B lymphocytes and virtual absence of all immunoglobulin isotypes, a significant number of atypical or “leaky” phenotypes have been identified, implying that XLA as a disease entity has considerable clinical and …

IMMUNOPATHOLOGY

The major immunologic abnormality in XLA is the lack of B lymphocytes in the peripheral blood and other organs and the consequent absence of immunoglobulin production. Physical examination of patients with XLA shows only rudimentary adenoidal and tonsillar tissue and peripheral lymphoid hypoplasia. Histologic analysis of secondary lymphoid tissue demonstrates lack of germinal center and follicle formation.[23] In the lamina propria of the gut, plasma cells typically are absent.

Examination of XLA …

MOLECULAR BASIS OF XLA

The genetic defect in XLA was identified in 1993 by two groups, one using a positional cloning approach[77] and the other searching for novel protein kinases expressed in B lymphocytes.[75] The gene was designated *BTK* and is located on the long arm of the X chromosome at Xq21.3. The human gene encompasses 37.5kb, is organized into 19 exons,25, 52, 60, 66 including a 5' untranslated region (exon 1), and encodes a 659 amino acid protein. *BTK* expression is primarily restricted to hematopoietic cells …

BTK FUNCTION AND ITS ROLE IN B-CELL DEVELOPMENT

Tyrosine kinases have been studied in many hematopoietic cell lineages and have been shown to act as signal transduction molecules mediating cell surface receptor activation events to downstream pathways. Cross-linking of a number of cell surface receptors, including interleukin-5 (IL-5), IL-6, CD38, FcRε, and most importantly surface IgM on B cells, results in the recruitment of cytosolic Btk to the plasma membrane and activation of Btk by tyrosine phosphorylation.[41] The process of Btk …

MUTATION ANALYSIS IN XLA

Identification of the *BTK* gene has led to research in mutational analysis by a number of groups worldwide. Over 500 unique mutations in *BTK* have been identified, and an international database of mutations and clinical information has been established (*BTK*base web page: http://www.uta.fi/laitokset/imt/bioinfo/*BTK*base ↗).78, 79, 81 Various different types of genetic abnormalities have been found in the *BTK* gene. One third of mutations are missense mutations, and these have been found predominantly …

ANIMAL MODELS

The consequence of mutations in *BTK* also have been studied in murine models of the disease. The X-linked immunodeficiency (xid) mouse has a single amino acid substitution (R28C) in the PH domain of Btk.55, 73 The immunophenotype of the xid mouse shows normal serum concentrations of IgG1, IgG2a and IgG2b but markedly reduced IgG3 and IgM concentrations. Mice also are unable to make antibody responses to T-cell–independent antigens but respond well to stimulation with T-cell–dependent antigens.[85] …

DIAGNOSIS

The diagnostic criteria for XLA agreed on by members of the Pan-American Group for Immunodeficiency (PAGID) and the European Society for Immundeficiency[8] (ESID) are listed as follows:

Definitive …

Male patient with CD19+ B cells less than 2% and at least one of the following:

- Mutation in *BTK* …
- Absent *BTK* mRNA or protein in peripheral blood mononuclear cells or neutrophils …
- Maternal family history of agammaglobulinemia and abnormal B-cell numbers …

…

Probable …

Male patient with CD19+ B cells less …

…

CLINICAL MANAGEMENT

The mainstay of treatment in XLA is immunglobulin replacement therapy. In most institutions, replacement is given on a regular basis through intravenous immunoglobulin (IVIG), but difficulty with venous access in young children and ease of administration has led to some centers adopting subcutaneous administration (SCIG) as an alternative approach. The use of IVIG replacement is now routine in most centers. Treatment aims to achieve serum IgG levels in the normal age-related range. For most …

GENE THERAPY

Gene therapy for XLA appears to be an attractive concept as only the B-cell lineage needs to be targeted. Because female carriers show nonrandom X-inactivation in B cells,6, 11 it would appear that there would be a survival advantage for corrected cells. Transgenic mice experiments have demonstrated the principle that *BTK* gene expression can overcome the B-cell developmental defects seen in *BTK* null mice.10, 43 In one strategy, a yeast artificial chromosome (YAC) transgenic mouse strain was …

SUMMARY

X-linked agammaglobulinemia remains the prototypic humoral immunodeficiency with absence of immunoglobulin production caused by an abnormality in B-cell development. Identification of *BTK* as the defective gene has led to a greater understanding of the molecular mechanisms involved in signaling downstream of B-cell surface receptors, although the pathogenesis of the arrest in B-cell development remains to be determined. Identification of *BTK* also has led to improved methods of diagnosis and …

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