Bruton's agammaglobulinemia

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Identity
Alias
X-linked agammaglobulinemia (XLA)

Inheritance
X-linked disorder occurring in males; frequency of XLA is about 0.3-0.6/10^5.

Clinics
Phenotype and clinics
Immunological deficiency, first described in 1952, manifest from late infancy and typically resulting in frequent bacterial infections commencing in the second half of the first year of life: tonsils and lymph nodes are very small; marked decrease of serum immunoglobulins of all isotypes (maternal IgG gives some protection in early infancy);

Neoplastic risk
Probably slight; in a 1963 paper, two patients with lymphoma were reported and reference was made to two adults with hypogammaglobulinemia who also had lymphomas; recent surveys of XLA patients do not reveal any cases of lymphoma; however, long-term vigilance needs to be maintained; at least seven cases of adenocarcinoma of the gastrointestinal tract in young adults with XLA have been reported; other malignancies have also been reported, but it is not clear whether they occur with an increased frequency;

Treatment
Vigorous antibiotic therapy and regular injections of immunoglobulin.

Prognosis
Good, on survival into early adulthood.

Other findings
Note
Absence of plasma cells in bone marrow and lymph nodes (the latter lack germinal centres) resulting in an almost complete lack of humoral immunity due to a failure of early B-lymphocyte development; normal myeloid and T-cell function: extremely deficient production of antibodies to all antigens.

Genes involved and proteins
BTK (Bruton’s tyrosine kinase)
Location: Xq21.3-Xq22
DNA/RNA
Description: Encoded in 19 exons spanning 37 kb.

Protein
Description: Btk is a 659 amino-acid cytoplasmic tyrosine kinase.
Expression: Is expressed at all except the terminally differentiated plasma cell stage of B-cell development.
Function: It is a member of a small family of src-related hematopoietic kinases and, like them, has several interaction domains that allow it to bind to other components of signal-transduction pathways; unlike other src family members, Btk family members have a pleckstrin homology (PH) domain which is followed by a proline rich region that binds to the SH3 region of several src family members.

Mutations
Germinal: Over 300 different mutations in Btk have been identified; only about 50% of patients with the clinical and laboratory findings of XLA have a family history of immunodeficiency; most of the remaining patients are the first manifestation of a new mutation in
Btk; most mutations are single base-pair substitutions that result in premature stop codons, splice defects, or amino-acid substitutions. 5-10% of patients with XLA have gross alterations in the BTK gene (usually deletions) detectable by Southern-blot analysis; most amino-acid substitutions in Btk render the protein unstable and markedly reduced or absent.

References


This article should be referenced as such: