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ORIGINAL ARTICLE

X-linked agammaglobulinemia: Experience in a Portuguese hospital☆,☆☆

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KEYWORDS
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Abstract
Introduction: X-linked agammaglobulinemia (XLA) is characterised by an arrest of B cell differentiation, leading to recurrent bacterial infections. Lifelong immunoglobulin replacement therapy (IRT) is indicated to prevent infections and their complications.
Materials and methods: A retrospective study of patients with XLA followed in a level three hospital was performed; data was collected retrospectively by review of clinical files.
Results: XLA was diagnosed in 9 children. One (11%) had a positive family history with a prenatal diagnosis. Infection was the clinical presentation in all the others (89%), at an average age of 13 months; diagnosis was established at a mean age of 3.4 years. Acute otitis media (7/9) and pneumonia (5/9) were the most frequently observed. Seven (78%) presented serum immunoglobulin G (IgG) levels below 200 mg/dL and all of them had $CD19^+$ B cells below 2%. Neutropenia was present at diagnosis in three patients (33%). Bruton tyrosine kinase (*BTK*) mutations were identified in all cases. Intravenous IRT was initiated, switched later to subcutaneous administration, in all. The mean time of follow-up was 10.7 years with cumulative time of 97 years. Eight children (89%) achieved IgG serum levels above 800 mg/dL. One presented lower values due to renal loss. No deaths occurred. After diagnosis the most frequent infections were acute otitis media (6/9). In spite of stable adequate IgG levels on IRT, two patients developed bronchiectasis.
Conclusions: XLA overall prognosis is good, as long as patients have an early and adequate treatment. However, bronchiectasis can occur even on adequate immunoglobulin replacement therapy.

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PALABRAS CLAVE
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Agammaglobulinemia ligada al cromosoma X: experiencia en un hospital portugués

Resumen
Introducción: La agammaglobulinemia ligada al cromosoma X (ALX) se caracteriza por la detención de la diferenciación celular de los linfocitos B, que da lugar a infecciones bacterianas recurrentes. La terapia de por vida de reemplazo de inmunoglobulina (TRI) está indicada para prevenir infecciones y sus complicaciones.
Material y métodos: Se hizo un estudio retrospectivo de pacientes con ALX en un hospital terciario. Los datos se revisaron retrospectivamente revisando historias clínicas.
Resultados: Se diagnosticó ALX en 9 niños. Uno de ellos (11%) tenía antecedentes familiares y había sido diagnosticado prenatalmente. El resto presentaron signos de infección (89%) a una edad media de 13 meses, siendo su edad media al diagnóstico de 3,4 años de edad. Las infecciones más frecuentes fueron otitis media aguda (7/9) y neumonía (5/9). Siete niños (78%) presentaron niveles séricos de inmunoglobulina G (IgG) inferiores a 200 mg/dL, y todos tenían niveles de células B $CD19^+$ B por debajo del 2%. Tres pacientes tuvieron neutropenia al diagnóstico (33%). En todos los casos se detectaron mutaciones en la tirosina cinasa de Bruton (*BTK*). También en todos se inició la TRI por la vía intravenosa, que luego continuó por la vía subcutánea. La duración media del seguimiento fue de 10,7 años, con un número total acumulado de 97 años. Ocho niños (89%) alcanzaron niveles séricos de IgG superiores a los 800 mg/dL. En un caso se observaron niveles más bajos por pérdida renal. No hubo ninguna defunción. El tipo de infección más frecuente tras el diagnóstico fue la otitis media aguda (6/9). A pesar de haberse conseguido niveles estables adecuados de IgG mediante la TRI, 2 pacientes desarrollaron bronquiectasias.
Conclusiones: En general, el pronóstico de la ALX es bueno siempre y cuando los pacientes reciban el tratamiento adecuado de manera precoz. Aún así, es posible que a pesar de ser tratados correctamente con TRI desarrollen bronquiectasias.

Introduction

X-linked agammaglobulinaemia (XLA [MIM 300755]) is a primary immunodeficiency characterised by the arrest of B cell differentiation,[1] leading to a considerably reduced B lymphocyte count and low serum immunoglobulin (Ig) levels that make patients more susceptible to recurrent and severe infections.[2] The infections usually start appearing between 3 and 6 months of age, when maternal IgG levels start to decline. If there is a family history of the disease, XLA may be suspected and diagnosed prenatally.[3] Respiratory tract infections by encapsulated bacteria, especially otitis, sinusitis, and pneumonia, are characteristic of XLA.[2,4,5] Most of these infections are caused by encapsulated pyogenic bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*).[2] The literature shows that the pathogens isolated most frequently from patients with septicaemia correspond to various *Pseudomonas* species.[2,6] Digestive tract infections by *Giardia lamblia* are also frequent.[2] Patients with XLA are particularly vulnerable to enteroviruses, especially polioviruses and coxsackieviruses. There have been reports of poliomyelitis caused by administration of the live attenuated vaccine, associated with high mortality rates.[2]

The estimated incidence of XLA ranges from 1:100,000 to 1:200,000 cases per live births.[2] The disease is caused by mutations in the *BTK* gene that encodes Bruton tyrosine kinase, located in the X chromosome (Xq21.3–Xq22).[7] The BTK protein is involved in every stage of the development of the B cell lineage and in the myeloid and erythroid precursors, and does not affect T lymphocytes or NK cells. Mutations in this protein cause defects in the early stages of B cell development, leading to a considerable reduction in B cell blood levels.[2] Over 800 different mutations have been described to date.[8] The detection of mutations in the *BTK* gene is a necessary criterion for the definitive diagnosis of XLA and for genetic counselling.[9]

Lifelong immunoglobulin replacement therapy (IRT) is indicated for patients with XLA. If the disease is diagnosed early, patients can have a good quality of life. Early treatment with IRT is essential to reduce the recurrence and severity of infections, the number of hospital admissions, and morbidity due to chronic complications of the disease.[2,10]

The purpose of this study was to learn the characteristics of patients with XLA followed up at the paediatric infectious diseases and immunodeficiencies unit of the department of paediatrics of a tertiary hospital in northern Portugal, analysing their clinical presentations and outcomes.

Materials and methods

Study design and protocol: we performed a descriptive retrospective study of the patients diagnosed with XLA and followed up at the paediatric infectious diseases and immunodeficiencies unit of the department of paediatrics of a tertiary hospital in northern Portugal between January