Abstract
In addition to the well-known X-linked form of agammaglobulinemia due to mutations in the gene coding for Bruton's tyrosine kinase (btk), autosomal recessive forms of agammaglobulinemia have been described. The different forms are all characterized by a complete lack of circulating mature B cells, resulting in agammaglobulinemia leading to particular susceptibility to bacterial infections of the respiratory and digestive tracts. Enteroviral meningo-encephalitis is a very severe and not infrequent complication. The only available treatment at present, is intravenous immunoglobulin replacement therapy. The incidence is very low, around 1/2,000,000 births. Four different molecular abnormalities have been reported, all resulting in defective signaling pathways of the pre-B-cell or the B-cell receptor.

Keywords
Autosomal recessive agammaglobulinemia, pre-B-cell receptor, B-cell receptor, membrane IgM.

Disease name
Autosomal recessive forms of agammaglobulinemia

Diagnostic criteria
In addition to the well-known form of X-linked agammaglobulinemia described by Bruton which is caused by mutations in the gene coding for a tyrosine kinase, btk (1,2), some patients clearly suffer from a disease inherited as an autosomal recessive trait.

The disease is characterized by the complete lack of circulating mature B cells (CD19⁺ IgM⁺) resulting from the early arrest of maturation of the B-cell lineage in the bone-marrows, at the level of pro-B or pre-B progenitors. This absence of circulating B cells in peripheral blood and therefore in secondary lymphoid organs results in the complete lack of secreted immunoglobulins. The serum levels of immunoglobulins have to be interpreted according to the patient's age. In some patients, a residual level of IgM can evoke a hyperimmunoglobulinemia (hyper-IgM) syndrome. The differential diagnosis also includes the common variable immunodeficiency but the complete absence of circulating B cells is characteristic of this agammaglobulinemia.

Clinical description
The clinical features are the same as those observed in the X-linked form.
Patients suffer from bacterial infections of the respiratory and digestive tracts, once begin after 6 months of life, when maternal IgG have disappeared. No opportunistic infections are noted, providing evidence of normal cellular immunity. A very severe and not infrequent complication can occur, i.e., meningoencephalitis due to enterovirus infection.

**Differential diagnosis**
The diagnosis of the X-linked form is easily excluded by the presence of the btk protein normally found by Western blotting of purified monocytes and by the normal sequence of the encoding gene btk.

**Incidence**
The incidence is low and has been estimated to be around 1/2000,000 births/years.

**Treatment**
As of diagnosis, all patients should given intravenous immunoglobulin replacement therapy (400-600 mg/kg/21 days), to achieve a residual IgG trough level > 8 g/l. This treatment usually leads to significant reduction of the severity and frequency of pulmonary bacterial infections but does not protect against enteroviral meningoencephalitis. For this complication, higher doses of intravenous immunoglobulins and/or intrathecal immunoglobulin administration are required. Nonetheless, the prognosis has been greatly improved by adequate intravenous immunoglobulin replacement therapy.

**Etiology**
The causes of the autosomal recessive forms of agammaglobulinemia are several. There can be a defect in the pre B-cell receptor which is constituted by the association of a « pseudo-light chain (V pre-B5) » and the heavy chain of the IgM (Cµ): a defect in either of the genes coding for these proteins chain results in the same defective signaling at the pro B-cell level due to the lack of membrane expression of the pre B-cell receptor (3,4).

Another defect involves the signaling protein Igα which is associated with the pre B-cell receptor and the mature B-cell receptor, membrane IgM: mutations in the gene encoding the Igα chain result in the arrest of maturation at the pro B-cell level due to the lack of activation of pre-B cells by the pre B-cell receptor (5).

Another defect has been described; it involves an adaptor protein (BLNK) which is strongly associated with the tyrosine kinase btk. Since btk, thus BLNK, is essentially required for activation through the B-cell receptor, the arrest of maturation occurs at the pre-B cell stage (6).

All these defects are characterized by a complete absence of circulating B cells, with the presence in the bone-marrow of immature B cells bearing the B cell specific marker CD19 but with no expression of the pre-B or B-cell receptor (absence of membrane IgM). The lack of mature B cells results in the complete absence of antibodies directed against vaccinal or infectious antigens.

**Prenatal diagnosis**
Because of the enteroviral meningoencephalitis complication, prenatal diagnosis has been set up and can be performed by genetic analysis looking for mutations. However, the frequency of each of the molecular defects leading to an autosomal recessive form of agammaglobulinemia is too low to be included in routine investigations. Nevertheless, aprenal diagnosis by counting circulating CD19⁺ B cells is available in all cases.

**Key words**
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**References**