JAK3 deficiency, (SCID T-B+)

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Creation Date: November 2001
Update: January 2005

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Abstract
JAK3 (Janus Kinase 3) deficiency is an autosomal recessive form of severe combined immune deficiency (SCID). It is characterized by lack of circulating T and NK (Natural Killer) cells and normal number of B lymphocytes. The disease is due to mutations in the JAK3 *gene encoding an intracellular tyrosine kinase that is physically and functionally coupled with several cytokine receptors. Identification of gene anomalies has allowed physicians to make the diagnosis (even prenatal), and may prompt novel forms of treatment based on gene therapy. Although a relatively low number of JAK3-deficient subjects have been diagnosed, JAK3 deficiency represents an important cause of autosomal recessive SCID in the United States and its prevalence in Europe appears to be even higher. However it is considered as a rare disease (incidence is between 1/100,000 and 1/1,000,000 live births). JAK3-deficient patients present with the classical clinical features of SCID in the first few months of life,* i.e. *chronic diarrhea, failure to thrive, recurrent respiratory infection and/or generalized infections from opportunistic pathogens, or signs of graft-versus-host reaction (skin rash, abnormalities of liver function, pancytopenia) from transplacental acquired maternal T cells. The treatment of choice for JAK3 deficiency is allogeneic bone marrow transplantation.**

Keywords
Severe Combined Immune Deficiency, lymphocytes, tyrosine kinase, cytokines, bone marrow transplantation, gene therapy.

Diagnosis criteria/definition
JAK3 deficiency is an autosomal recessive form of severe combined immune deficiency (SCID) (Pesu M *et al.*, 2005, O'Shea JJ *et al.*, 2004). It is characterized by lack of circulating T and NK (natural killer) lymphocytes with normal number of B cells (Notarangelo *et al.*, 2000). The disease is due to mutations in the *JAK3* gene that result in total absence or severe dysfunction of the intracellular tyrosine kinase JAK3. The latter is crucial for cytokine-mediated signaling in lymphocytes and other hematopoietic cells (Leonard *et al.* 1998).

Differential diagnosis

JAK3 deficiency is one of the many different forms of SCID in humans. While diagnosis of SCID is suggested by clinical findings (see below), a hint to better define the gene defect is provided by immunological analysis of lymphocyte subsets. In particular, JAK3 deficiency belongs to the [T-, B+, SCID], that also includes X-linked SCID, interleukin-7 receptor alpha IL-7RA deficiency, and other forms that remain still unknown (Buckley, 2004). Unlike defects in the *IL7RA* gene (in which normal number of NK cells are present), both X-linked SCID and JAK3 deficiencies are characterized by virtual absence of NK cells, and are therefore more properly defined as [T-, B+, NK-, SCID].

The immunological and clinical phenotype of JAK3 deficiency is virtually undistinguishable from that of X-linked SCID. This syndrome is due to mutations in the interleukin-2 receptor gamma IL2RG gene encoding for the common gamma chain (γc) shared by cytokine receptors for interleukin IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. In all these receptors, γc is physically and functionally coupled with JAK3, thus explaining phenotypic similarity of defects in these genes. Since X-linked SCID is the most common form of SCID in humans (about 30% of all cases), it appears necessary to exclude this disease before JAK3 deficiency is considered. Diagnosis of X-linked SCID is facilitated by occurrence in males, positive family history (with obvious X-linked inheritance), often associated with lack of surface membrane expression of the γc, as revealed by immunophenotyping of circulating lymphocytes. In contrast, JAK3 deficiency should be considered when immunologic diagnosis [T-, B+, NK-, SCID] is found in females, or whenever parental consanguinity is confirmed or suspected. Normal expression of γc in infants with [T- B+ NK- SCID] may also indicate a possible defect in JAK3. However, diagnosis of JAK3 deficiency can only be made with certainty when direct evidence of severe defects in JAK3 protein expression and/or function, or direct evidence of *JAK3* gene abnormalities are provided.

Prevalence

JAK3 deficiency was first suspected as a possible cause of SCID after the identification of X-linked SCID patients whose mutations of γcc was demonstrated to result in impaired interaction between γcc and JAK3 (Russell *et al.*, 1994). A series of patients affected by autosomal recessive T-B+ SCID were subsequently described (Macchi *et al.*, 1995; Russell *et al.*, 1995; Candotti *et al.*, 1997; Buckley *et al.*, 1997; Bozzi *et al.*, 1998; Schumacher *et al.*, 2000), thus identifying JAK3 deficiency as a new nosological entity with clinical features virtually undistinguishable from X-linked SCID. Although a relatively low number of JAK3-deficient subjects have been diagnosed, JAK3 deficiency represents an important cause of autosomal recessive SCID in the United States (Buckley, 2000), and its prevalence in Europe appears to be even higher (Notarangelo *et al.*, 2000). However it is considered as a rare disease (incidence is between 1/100.000 and 1/1.000.000 live births).

Clinical description

Typically, JAK3-deficient patients present with the classical clinical features of SCID during the first few months of life, *i.e.* chronic diarrhea, failure to thrive, recurrent respiratory infection and/or generalized infections from opportunistic pathogens, or signs of graft-versus-host reaction (skin rash, abnormalities of liver function, pancytopenia) from transplacental acquired maternal T cells.

Similarly to other SCID, JAK3 deficiency is a pediatric emergency and affected child will not survive beyond infancy in the absence of successful reconstitution of their immune system by allogeneic BMT (bone marrow transplantation).

Treatment

The treatment of choice for JAK3 deficiency is allogeneic BMT that has been demonstrated to be life-saving for affected patients. Although detailed information is available for only a limited number of BMTs performed on patients with established diagnosis of JAK3 deficiency, reconstitution of normal T cell numbers and function has been reported after both HLA-identical and haploidentical BMTs. Besides, similarly to other forms of [T-, B+, SCID], it appears that mismatched BMT are less likely to result in complete restoration of the B-cell compartment than transplantation from HLA-matched donors (Buckley *et al.*, 1999; Notarangelo et al, 2000). Competition between host and donor B cell progenitors, is thought to be responsible for the persistence of host-derived, nonfunctional B lymphocytes in JAK3-deficient patients after BMT.

The results of BMT performed in 14 JAK3-deficient patients showed excellent rates of engraftment and survival (Buckley, *et al.*, 1999; Notarangelo *et al.*, 2000). These rates are comparable to the general results obtained in larger series of [T-, B+, SCID] patients (Fischer *et al.*, 1990; Haddad *et al.*, 1998; Buckley, *et al.*, 1999). The absence of host NK cells in JAK3-deficient patients and other T-B+ SCID patients is likely to reduce the occurrence of graft failures (Haddad, *et al.*, 1998). In contrast to the uniform reconstitution of T-cell immunity observed in all

reported cases of JAK3 deficiency treated with BMT, 4 out of 12 JAK3-deficient patients who underwent haploidentical BMT were reported to have incomplete humoral immune reconstitution and therefore require continuous treatment with intravenous immune globulins. Hence, bone marrow transplantation is an effective means for reconstitution of T-cell immunity in JAK3 defect but is less successful for restoration of B-cell and NK cell functions. (Roberts JL et al., 2004). Post-BMT does not only occur in JAK3-deficient patients, but is common to [T-, B+, SCID] patients receiving haploidentical transplants (Haddad, et al., 1998; Buckley, et al., 1999) and constitutes an important prognostic factor as it may cause significant late morbidity in treated patients.

While waiting for BMT, patients with a putative diagnosis of SCID (possibly due to JAK3 deficiency) require careful prophylaxis of infections. This is based on environmental measures (isolation of SCID infants in laminar flow units or other protected environments), and prophylaxis drug such antibiotics combination: Trimethoprim-sulfamethoxazole (TMP-SMZ) (5 mg/Kg TMP, 25 mg/Kg SMZ three alternate days a week) to prevent *Pneumocystis carinii* pneumonia. Any potential infectious episode requires careful evaluation as well as prompt and aggressive treatment with antibiotics (or, if necessary, antifungal or antiviral drugs). Regular administration of intravenous immunoglobulins (400 mg/Kg/21 days) is necessary to provide adequate antibody supplementation.

Gene therapy is currently investigated as an alternative form of treatment for JAK3-deficient patients (Chinen J et al., 2004). Because of the clinical and biochemical similarities between JAK3 deficiency and X-linked SCID, genetic correction and engraftment of autologous hematopoietic stem cells is expected to result in reconstitution of immunity in JAK3-deficient patients hopefully reproducing the successful results obtained in X-linked SCID patients (Cavazzana-Calvo et al., 2000). Preclinical experiments in JAK3 knockout mice have demonstrated that retroviral-mediated *JAK3* gene transfer into hematopoietic stem cells is safe and leads to reconstitution of lymphoid development and specific immunity in treated mice (Bunting et al., 1998; Bunting et al., 1999), thus supporting the development of similar strategies for clinical applications in humans.

Since 2003, although gene therapy was highly successful in nine infants with X-linked SCID, the trials have been placed on hold due to the development of a leukemic process in two of the children because of insertional oncogenesis. (Hacein-Bey-Abina S et al, 2003, Chinen J et al., 2004)

Etiology

The JAK3 member of the Janus associated family of protein tyrosine kinases plays a crucial role in hematopoietic cytokine signaling (Leonard et al., 1998) and its deficiency in humans is usually associated with SCID. It is characterized by virtual absence of both T lymphocytes and NK cells and presence of significant numbers of nonfunctional B lymphocytes [T-B+ SCID] (Notarangelo et al., 2000). JAK3 is associated with the common γc of cytokine receptors (γc, the molecule mutated in X-linked SCID) and mediates the downstream signaling of cytokines of foremost importance such as interleukin IL-2, IL-4, IL-7, IL-9, and IL-15. In particular, JAK3 is activated upon cytokine binding to the specific cellular receptors, then it phosphorylates tyrosine residues of receptor chains which generate docking sites for Src homology 2 (SH2)-containing "signal transducers and activators of transcription" (STAT) proteins (Leonard et al., 1998). STAT are in turn phosphorylated before they dimerize and translocate to the nucleus where they bind to promoter sequences of cytokine-inducible genes mediating their transcription (Ihle, 1996).

JAK3 protein is organized into seven Janus homology (JH) domains; kinase activity (JH1) is mediated in the C terminal. Molecular analysis of patients with JAK3 deficiency has demonstrated that mutations can occur throughout the *JAK3* gene, with apparent clustering in the regions coding for the JH2 and JH3 domains of the JAK3 protein, but spanning from the proximal N-terminal portion of the molecule to the kinase domain located at the protein C-terminal (Notarangelo et al., 2000). Epstein-Barr virus transformed B-cell lines which originated from JAK3-deficient patients have constituted unique biological tools to study the effects of these mutations on the expression and function of the JAK3 protein. Lack of JAK3 expression leads to profound impairment of signaling through all cytokine receptors using c, thus duplicating the abnormalities caused by mutations of γc in X-linked SCID patients (Russell, et al., 1995; Candotti, et al., 1997; Taylor et al., 1997). Although in a number of cases residual expression of the mutant protein could be demonstrated, JAK3 function was found to be profoundly altered (Candotti, et al., 1997; Bozzi, et al., 1998; Notarangelo et al., 2000). Thus it provided important clues as to the JAK3 structure/function relationship. In particular, mutations in the JH2 pseudokinase domain were shown to directly interfere with the kinase activity of JAK3 (Chen et al., 2000), whereas mutations of the JH7 N-terminal domain abrogated JAK3 binding to γc (Cacalano et al., 1999). In both instances downstream cytokine signalling events are impaired, thus providing the biochemical

basis of the immune deficiency status (Chen, *et al.*, 2000; Cacalano, *et al.*, 1999). A mutation database for JAK3 deficiency has been set-up, and is available at the following address http://www.uta.fi/imt/bioinfo/JAK3base/ (Vihinen *et al*, 2000).

Classical mouse genetics experiments have corroborated the critical role of JAK3 in lymphocyte development through the generation of knockout mice that also showed profound immune deficiency with lack of CD8+ T lymphocytes and NK cells. Contrary to humans, JAK3 knockout animals may develop substantial number of CD4+ T lymphocytes which are, however, phenotypically and functionally abnormal, and with negligible numbers of B lymphocytes whose development seems blocked at the pro-B-cell stage (Thomis *et al.*, 1995; Nosaka *et al.*, 1995; Park *et al.*, 1995; Thomis *et al.*, 1997). The reasons for the differences in phenotype between JAK3-deficient mice and humans are not clear. However, the importance of IL-7 for B lymphopoiesis in mice has been evoked as a possible explanation for the differences in B-cell development, but not in humans (Thomis, *et al.*, 1995).

Diagnostic methods

JAK3-deficient patients may or may not be lymphopenic, but they generally present with low to undetectable numbers of T lymphocytes and NK cells, whereas absolute B cells counts are normal or increased [T-, B+, SCID]. Lymphocytes fail to proliferate although mitogenic stimulation and serum immune globulins are usually low, if not undetectable. Because of the similarities in the clinical and immunological phenotype, X-linked SCID, JAK3 and IL-7RA deficiencies should be included into the differential diagnosis of patients with [T-, B+, SCID]. Diagnosis of JAK3 deficiency should eventually be made following western blot analysis of JAK3 expression in patients' fresh lymphocytes or lymphoid cell lines and/or demonstration of JAK3 gene mutations. Since JAK3 deficiency has been demonstrated to be compatible with the presence of significant numbers of circulating, although poorly functioning, T lymphocytes (Brugnoni *et al.*, 1998), screening for JAK3 expression and/or mutations should probably also be considered in all non established cases of combined immune deficiency (CID) especially if presenting with high proportion of peripheral B lymphocytes.

Genetic counseling

JAK3 deficiency is inherited as a fully penetrant, autosomal recessive trait. Therefore, once the diagnosis has been firmly established in the index case, the risk of having affected child for parents who had a first chil with JAK3 deficiency can easily be estimated to be 1:4, regardless of fetal sex.

Antenatal diagnosis

Until recently, prenatal diagnosis of JAK3 deficiency could only be performed by analyzing the total number of lymphocytes, distribution of lymphocyte subsets, and in vitro response of fetal lymphocytes to mitogens, following fetal blood sampling at 19-21 weeks of gestation. Availability of the structure of the human *JAK3* gene now allows prenatal diagnosis based on DNA analysis of chorionic villus (Schumacher *et al.*, 1999).

Unresolved questions

Although most patients with JAK3 deficiency present with classical signs of SCID and although they have a characteristic immunological phenotype (*i.e.*, [T-, NK-, B+, SCID]), atypical presentations have been reported with post-natal development of substantial number of autologous T lymphocytes, and a prolonged survival, occasionally even in the absence of severe infections early in life (Brugnoni *et al.*, 1998). Consequently, the phenotypic spectrum of JAK3 deficiency is much broader than originally thought. While mutation analysis is a time-consuming and expensive strategy for diagnosis, analysis of protein expression has been possible only by Western-blotting so far. Development of diagnostic assay based on flow cytometry (by means of intracellular staining) might facilitate the diagnostic approach, at least for those cases (the majority, indeed) with reduced or absent protein expression.

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