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P14/LAMTOR2 Deficiency

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Definition

P14/LAMTOR2 deficiency is a very rare primary immunodeficiency syndrome due to a homozygous single point mutation in *p14* (also known as *LAMTOR2*) gene that causes reduction in the p14 protein expression, which is associated with severe congenital neutropenia and abnormal function of specialized lysosomes in cells of innate and adaptive immune system (Taub et al. 2012).

Introduction

The endosomal adaptor protein p14, also known as the late endosomal/lysosomal adaptor and mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) activator/regulator complex 2 (LAMTOR2) (Sparber et al. 2015), is specifically required to regulate endosomal traffic and cellular proliferation (Rezaei et al. 2009). If there are biallelic mutations within its 3′-untranslated region (UTR), proper processing of p14 mRNA is suppressed (Speckmann et al. 2017).

The p14/LAMTOR2 deficiency is transmitted through an autosomal recessive pattern (Rezaei et al. 2009) and causes reduced p14 protein expression (Taub et al. 2012).

This deficiency is characterized by severe neutropenia and leads to disorder at lysosomes in neutrophils, cytotoxic T cells, and melanocytes, besides reduced numbers of B cell subsets (Rezaei et al. 2009).

Clinical Presentation

Patients with p14/LAMTOR2 deficiency present early-onset recurrent respiratory infections (Taub et al. 2012; Rezaei et al. 2009), oculocutaneous hypopigmentation, short stature, and coarse facial features (Rezaei et al. 2009; Klein and Welte 2010).

The infections usually occur by the age of 1 year. The most common present features are cutaneous infections, superficial abscesses, oral ulcers, otitis media, and recurrent pneumonia. Frequent aphthous stomatitis and gingival hyperplasia lead to loss of permanent teeth in childhood.

These patients have high susceptibility to extracellular pathogens, such as *Pseudomonas aeruginosa*, *Escherichia coli*, and *Streptococcus pneumoniae*, which occurs on a secondary basis because of deficient intracellular organelle fusion in neutrophils and B and T cells. Furthermore, it was demonstrated that the endosomal adaptor

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protein p14 is an essential component of the defense against intracellular pathogens as well, such as *Salmonella* (Taub et al. 2012).

Laboratory Findings and Diagnostic Testing

Presence of severe neutropenia associated with early-onset severe and recurrent infections should raise suspicion of p14/LAMTOR2 deficiency, especially in the presence of short stature, oculocutaneous hypopigmentation, and coarse facial features.

Patients typically have persistent severe neutropenia with absolute neutrophil count of less than 500/mm^3. In relation to complete blood cell count, patients usually present an increased number of platelets, monocytes, and eosinophils, while mild anemia is frequently seen. The p14/LAMTOR2 deficiency is associated with disorders in other elements of the immune system, such as reduced numbers of B cell subgroups and deficient function of cytotoxic T cells (Rezaei et al. 2009). Memory B cells can be reduced in these patients as well as low serum IgM levels. There are some reports of patients who presented low levels of IgG during adolescence. However, neutrophil maturation in the bone marrow seems to be normal (Rezaei et al. 2009; Klein and Welte 2010).

The diagnosis of this immunodeficiency is made through genetic evaluation that identifies homozygous point mutation in the 3′-untranslated region (3′-UTR) of the gene that encodes the endosomal adaptor molecule p14 (Rezaei et al. 2009; Klein and Welte 2010). This mutation causes a reduction at p14 protein levels that, consequently, leads to neutrophils with a modified ultrastructure of azurophilic granules and diminished microbicidal activity in phagosomes (Klein and Welte 2010). Besides that, the cells with p14 deficiency present a marked delocalization of late endosomes and show a deficiency in cytokine receptor-mediated ERK (extracellular signaling-regulated kinase) phosphorylation (Klein and Welte 2010; Klein 2009).

Treatment and Prognosis

Timely referral to a clinical immunologist and/or a hematologist remains key to the successful management of patients with p14/LAMTOR2 deficiency, as delay in starting the appropriate treatment reflects in high mortality.

The main goal of therapeutic for patients with severe congenital neutropenia is to reestablish the adequate antibacterial host defense. The first option of therapy is the use of recombinant human granulocyte colony-stimulating factor (GCSF) (Klein 2009). Before the emergence of this therapy, morbidity and mortality among patients with severe neutropenia in childhood were elevated due to severe and recurrent bacterial infections. Today, the improvement of quality of life and survival into adulthood is possible due to GCSF (Rezaei et al. 2009; Klein and Welte 2010). Approximately 90% or more of the patients have a good response to GCSF and experience an increase of neutrophil number and a consequently reduced number of infections and days of hospitalization.

Patients who do not respond to the therapy with GCSF are candidates to be submitted to allogeneic hematopoietic stem cell transplantation as a curative therapeutic strategy (Klein 2009).

Gammaglobulin replacement therapy can be indicated for the group of patients with low IgG levels, especially if these patients present recurrent infections (Speckmann et al. 2017).

It is strongly recommended that all patients should be followed up at least twice a year and complete blood cell counts should be performed at least every 3 months (Welte et al. 2006).

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