

Mutations in *IKBKG* (*NEMO*) and Hypohydrotic Ectodermal Dysplasia with Immune Deficiency – an Overview

Introduction

Hypohydrotic ectodermal dysplasia with immune deficiency (HED-ID) is a rare immunodeficiency disorder with an estimated incidence of 1 in 250,000 live male births (1). HED-ID is a heterogeneous disorder, characterized by increased susceptibility to severe, recurrent, and atypical infections and abnormal development of ectoderm-derived skin structures, including teeth, hair, nails, and eccrine sweat glands (for comprehensive reviews, refer to references 2-5). Early diagnosis of HED-ID is important, since timely initiation of treatment can prevent complications and improve prognosis (1). X-linked recessive, hypomorphic mutations in *IKBKG* have been implicated in HED-ID.

Molecular Pathophysiology

The *IKBKG* gene product, NF κ B essential modulator (NEMO; also called IKK γ), is a subunit of the inhibitor of NF κ B kinase (IKK) complex, which plays an important role in the regulation of NF κ B-dependent transcriptional activation. NF κ B is found in the cytoplasm of most cells (6) and functions to regulate transcription of genes involved in immunity, inflammation, apoptosis, adhesion, and cell growth in response to signals from a variety of different receptors (reviewed in 7-10). NF κ B activity is regulated by the inhibitor of NF κ B (I κ B), which in turn is controlled by the IKK complex. The IKK complex promotes phosphorylation of I κ B, thereby targeting I κ B for degradation and releasing inhibition of NF κ B activity. The IKK complex is comprised of three subunits; IKK α and IKK β are the catalytic subunits, while NEMO (IKK γ) provides a structural scaffold for the assembly and regulation of the IKK complex (7, 11). Mutations in *IKBKG* that disrupt, but do not completely abolish, NEMO activity lead to reduced I κ B

phosphorylation and degradation and thereby result in impaired NF κ B activation. Such hypomorphic mutations are typically located towards the C-terminus of NEMO. The immunodeficiency associated with mutations in *IKBKG* is due to defective NF κ B activation in response to signaling by a variety of receptors important for both innate and adaptive immune function, including the Toll-like receptors (TLR), the interleukin-1 β (IL-1 β), IL-12, and IL-18 receptors, and the tumor necrosis factor α (TNF- α) receptor. Defects in signaling through the CD40 receptor can lead to hypogammaglobulinemia. The ectodermal dysplasia (ED) phenotype arises from impaired NF κ B activation in response to the ectodysplasin receptor (4, 12).

Clinical Presentation

HED-ID is characterized by ED, manifesting as dry skin due to lack of eccrine sweat glands, fine, sparse hair, and conical or missing teeth, as well as defects in both adaptive and innate immunity, allowing recurrent bacterial, viral, and mycobacterial infections. HED-ID patients typically have normal B- and T-cell levels, but are often hypogammaglobulinemic and demonstrate impaired specific antibody generation in response to polysaccharide antigens (2). A subset of patients exhibit elevated IgM levels or more commonly, elevated levels of IgA (1, 13). NK cells are present at normal levels, but are functionally deficient. Infections with *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella*, *Salmonella*, and *Pseudomonas* species are commonly observed, giving rise to bacterial sepsis, pneumonia, meningitis, deep skin infections, otitis, or sinusitis. Repeated respiratory tract infections can lead to lymphadenitis and bronchiectasis. Common viral infections include Herpes simplex virus, adenovirus, and Human papilloma virus. Infection with Herpes simplex virus-1 encephalitis has been reported

to be fatal, despite prompt treatment (5). Mycobacterial infections have been observed in ~51% of HED-ID patients (1, 12), and in rare cases fungal infections such as *Pneumocystis carinii* have also been reported (12, 14). *IKBKG* mutations that result in an elongated NEMO protein cause a clinically more severe phenotype associated with more diverse and severe infections and, in addition, osteopetrosis and lymphedema (12, 14-16) and in one case, hemophagocytic disease (17). A milder form of the disease, characterized by immunodeficiency without any signs of ED, has also been described (18).

Of note, mutations in *IKBKG* that result in a complete loss of NEMO activity are prenatally lethal in males. In females, such mutations are associated with an X-linked dominant ectodermal phenotype known as incontinentia pigmenti (IP). IP is characterized by ectodermal scarring, hyperpigmentation, and other ectodermal defects. Women with IP typically do not suffer from immune deficiency, likely due to the presence of a normal copy of NEMO in immune cells due to skewed X-inactivation (reviewed in 2, 4, 5)

Diagnosis

HED-ID is suspected in male infants and young children presenting with ED and recurrent, severe infections by bacterial, viral, and/or mycobacterial pathogens. Diagnosis of HED-ID currently relies on detection of im-

paired antibody response to polysaccharide antigens, reduced levels of immunoglobulins, and diminished NK-cell cytotoxicity, and is supported by a family history of ED and recurrent, persistent, or atypical infections in males or a family history of *IKBKG*-related HED-ID. In young infants, in whom the symptoms of ED may not yet be obvious, HED-ID may be confused with other causes of hypogammaglobulinemia, such as hyper IgM syndrome. HED-ID is an X-linked disorder and therefore primarily affects males, although one case of a female with HED-ID due to skewed X-inactivation has been reported (19). Asymptomatic female carriers of mutations in *IKBKG* place their sons at a 50% risk of being affected with the disease. Since published studies have established a clear relationship between hypomorphic mutations in *IKBKG* and HED-ID, a diagnosis of HED-ID can be confirmed or established through genetic testing. Genetic testing also allows detection of asymptomatic carriers, improving genetic counseling, and facilitating early diagnosis and timely treatment of affected descendants.

Treatment

The standard of treatment for HED-ID is intravenous immunoglobulin (IVIG) therapy and prophylactic antibiotics. In one case, a patient was successfully treated with hematopoietic stem cell transplantation (reviewed in 1).

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