ARTICLE

Incontinentia Pigmenti: A Summary Review of This Rare Ectodermal Dysplasia With Neurologic Manifestations, Including Treatment Protocols

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ABSTRACT

Incontinentia pigmenti is a rare neuroectodermal dysplasia caused by a defect in the *IKBKG* gene (formerly known as NEMO). There are 27.6 new cases per year worldwide; 65% to 75% are sporadic mutations, and 25% to 35% are familial. It is usually lethal in males, but females survive because of X-inactivation mosaicism. The disorder is typically identified by unique skin findings, a series of four stages that emerge throughout the first year of life. The central nervous system manifestations in the eye and in the brain cause the most disability. Defects of hair, nails, and teeth occur, and there can be other systemic involvement. Surveillance protocols for medical management have been established by the Incontinentia Pigmenti International Foundation. This article will summarize the existing knowledge of this condition and detail the protocols to help manage the care of the infant or child who presents with incontinentia pigmenti. J Pediatr Health Care. (2017) ■, ■-■.

KEY WORDS

Child neurology, incontinentia pigmenti, neuroectodermal dysplasia, rare disease, treatment protocol

The primary objective of this review article is to provide an easy reference for providers to guide appropriate management on incontinentia pigmenti (IP). A description of the disease process is coupled with management protocols.

METHODS

Literature on the topic was searched comprehensively using PubMed to identify peer-reviewed publications. Twenty-two articles published between 1999 and 2017 were reviewed. Current care protocols were obtained from the Incontinentia Pigmenti International Foundation.

ETIOLOGY

IKBKG (formerly known as nuclear factor-kappa B [NF-κB] essential modulator [NEMO]) is a gene that sits on the X chromosome at Xq28. The common IP deletion is at exons 4 through 10, occurring in 80% of known cases. *IKBKG* activates the NF-κB pathway, which is involved in hundreds of immune, inflammatory, and apoptotic pathways (Schmitz, Mattioli, Buss, & Kracht, 2004).

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Normally, NF-κB protects against cell death from tumor necrosis factor-α–induced apoptosis, and it plays a role in protecting the integrity of brain endothelial cells and the blood–brain barrier (Ruggieri & Practicò, 2015). It is maintained within cells in its inactive state and becomes activated to induce an inflammatory response to a threat such as a bacterial or viral infection, hypoxia, or stress (Scheurle & Ursini, 2015). When activated, NF-κB enters the nucleus of a cell and activates a variety of genes that participate in immune and inflammatory responses. In IP, the *IKBKG* derangement results in a truncated NF-κB that either is unable to protect against apoptosis or becomes pro-apoptotic; hence, cell death can occur in response to a variety of potential stimuli (Courtois & Smahi, 2006).

IP is an X-linked condition. In X inheritance, all females inherit one X chromosome from each parent, and one of the X chromosomes is inactivated through the process of lyonization. Inactivation of one X chromosome is never 100% complete, so all females are functionally mosaic. If there are defective genes on the active X chromosome, then epigenetic factors can turn off most of the defective genes in a process called skewed X inactivation, but up to 15% of genes escape inactivation (Carrel & Willard, 2005; Molho-Pessach & Schaffer, 2011). In females with IP, the mosaicism results in two differing cell lines, one with normally functioning NF-κB and one that functions abnormally. The mutation can occur in germ cells of either parent or can occur after conception. Because male fetuses with IP do not have a compensatory healthy X chromosome, the condition is commonly lethal, although a small number of males survive because of a genetic variant.

In females with IP, both the typical and the atypical cell lines develop alongside each other, along Blaschko lines. Blaschko lines reflect the path of migration embryonic stem cells take in their maturation from the embryologic endoderm to the skin surface. These lines are normally invisible, unless a pigmentary disease of the skin illuminates them.

PATHOGENESIS

At the time of birth (or sometimes before birth), the wild-type NF-κB cells and NF-κB mutant cells of a female infant with IP compete with each other on the skin surface, along the Blaschko lines. The abnormal cells have an increased susceptibility to apoptosis related to TNF-α cytokines. In response to an unknown factor, mutated cells produce interleukin, and an inflammatory response is mounted from the wild-type NF-κB cells nearby (Courtois & Smahi, 2006). The mutant skin cells are killed by the wild-type cells through apoptosis (Abe et al., 2011; Poziomczyk et al., 2014). This produces the primary stage of skin changes (Stage 1, the inflammatory/vesicular stage), which is characteristic of the disorder at birth (Shah, 2016). If some of the *IKBKG*-deficient cells survive the first wave of cell death, there can be a second wave of cell death, producing the secondary stage of skin changes in IP (Courtois & Smahi, 2006; Meuwissen & Mancini, 2012). The entire line of mutant NF-κB cells is never completely destroyed, and vesicular flare-ups can occur throughout life in response to febrile illnesses.

Although skin findings are the most prominent and frequent, the eyes, brain, bones, teeth, hair, and nails are also involved. The pathogenesis in the central nervous system (CNS) is not as clearly understood and may involve several different pathologies. NF-κB is present in all cell types, and in the CNS, it is present in neurons, astrocytes, microglia, and oligodendrocytes, where it plays a role in preventing apoptosis and protects the integrity of brain endothelial cells and the blood–brain barrier (Ruggieri & Practicò, 2015). The CNS phenotype is variable. It is not yet known if the CNS involvement is immune-modulated by the destruction of neurons and glial cells from a disordered NF-κB pathway, if there is microvascular pathology, or if both of these pathologies are involved. In mouse models of IP, there are a high number of apoptotic cells in the CNS (Muller, Courtois, Ursini, & Schwaninger, 2017). This supports the idea that ischemia due to vascular changes of small and medium cerebral vessels leads to infarcts, white matter loss, corpus callosum changes, and brain malformations (Meuwissen & Mancini, 2012; Minić, Trpinac, & Obradović, 2013). Inflammation may play a role in initiating small and medium cerebral vessel disease, which can be identified on magnetic resonance imaging (MRI) and magnetic resonance angiography within the first week of life (Muller et al., 2017). Disruption in the blood–brain barrier may sway the balance in favor of proconvulsive factors, explaining the incidence of seizures in IP unrelated to ischemic stroke (Muller et al., 2017). The occurrence of small vessel pathology also supports the concept that vascular occlusion, infarct, and neovascularization lead to retinal detachment (Muller et al., 2017).

CLINICAL MANIFESTATIONS

Phenotypic expression of the disorder is variable, ranging from very mild to very severe.

Skin Findings

The skin findings in IP are the sole major criteria for the disorder, found in 100% of patients, produced by the pathophysiology of *IKBKG*-deficient cells being killed by *IKBKG* wild-type cells along the Blaschko lines of the skin. The manifestations sequence through four stages.

Stage I (Figure 1) is known as the *vesicular* or *inflammatory stage,* identified by papules, vesicles, and pustules with a linear pattern along the lines of Blaschko, primarily on the extremities, although sometimes also on the trunk, head, neck, and, rarely, on the face. The lesions present at birth or within the first 2 weeks for as many as 90% of patients and disappear by age 4 months, but they can appear later on. Flare-ups of lesions are also known to happen in