



## Case report

# Incontinentia pigmenti with secondary Raynaud's phenomenon: A case report and review of the literature

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## ABSTRACT

**Purpose:** To describe a patient with incontinentia pigmenti (IP) and Raynaud's phenomenon (RP).**Observations:** A 5 year-old girl with history of IP was noted to have RP. Visual acuity was unaffected in both eyes, and fundus examination demonstrated regressed peripheral neovascularization. Photos of the patient's hands demonstrated pale discoloration associated with exposure to cold.**Conclusions and importance:** IP, known to affect small cerebral and retinal blood vessels, can also affect the small blood vessels in the extremities, resulting in secondary RP.© 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

A 5-year old girl with incontinentia pigmenti developed secondary Raynaud's phenomenon. The relationship between the two conditions is discussed.

## 2. Case report

An infant was diagnosed with incontinentia pigmenti (IP) shortly after birth at 37.5 weeks gestation. She developed a blistering rash on her upper and lower extremities and trunk which was biopsied and found to be consistent with IP. Genetic testing was performed and demonstrated deletion of the NEMO, or IKBKG gene, on the X-chromosome, confirming the diagnosis. There was no family history of this condition.

At three months of age, the child underwent laser photocoagulation to the peripheral avascular retina in the right eye to treat neovascularization and vitreous hemorrhage. She developed recurrent vitreous hemorrhage in the same eye and had repeat laser photocoagulation at 5 years of age (Fig. 1). She did well

following this, with visual acuities of 20/20 in the right eye and 20/25 in the left eye.

During a routine retina follow-up visit, when the child was 5 years old, her father disclosed that he noticed for the last several weeks, when the patient's hands became cold, they turned blue, white, and then red (Fig. 2). During these episodes, the child's hands became numb and slightly painful. The symptoms would resolve after several minutes in a warm environment and never occurred in normal temperature conditions.

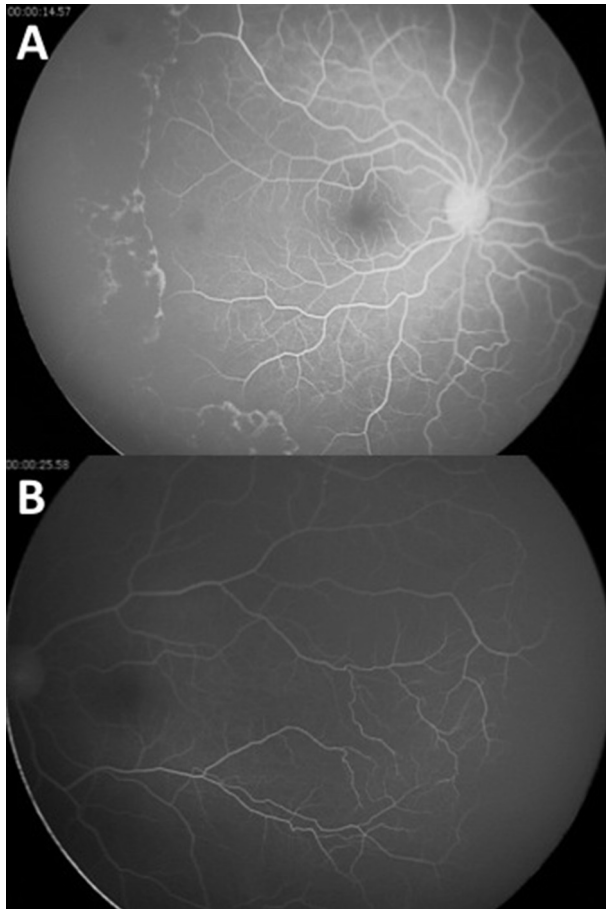
The patient was diagnosed with secondary Raynauds phenomenon related to IP. She was referred to pediatric rheumatology for evaluation and treatment. Of note, the patient had no neurologic sequelae of IP, including no developmental delay or seizures.

## 3. Discussion

IP is a rare genetic disorder with neurocutaneous manifestations. It is an x-linked dominantly inherited syndrome, making most cases female, as the condition is typically lethal to affected males in utero. IP results from a mutation in the IKBKG (inhibitor of the kappa light polypeptide gene enhance in B-cells, kinase gamma) gene, located on the X chromosome at position q28.<sup>1–8</sup> This gene is part of a complex that regulates activity of NF-kB (nuclear factor kappa-light-chain enhancer of activated B cells), a family of transcription factor proteins that regulates immune response and also prevents apoptosis.<sup>1–8</sup> Mutations present in IP typically cause loss of function or reduced function of IKBKG, which

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**Fig. 1.** Fluorescein angiography of the right eye showing laser scars in treated peripheral retina (A) and of the left eye showing peripheral retinal nonperfusion (B). No leakage was seen in later frames of both eyes.



**Fig. 2.** The patient's hands during an episode of Raynaud's phenomenon, demonstrating erythema of the hands with blanching of the fingertips.

in turn leads to cellular apoptosis and over-expression of chemotactic factors, resulting in local inflammation in the skin and blood vessels.<sup>1–8</sup>

The classic manifestations of IP are cutaneous, cerebral, ocular, and dental abnormalities. There are four phases of characteristic cutaneous abnormalities, starting with a vesicular rash that

develops soon after birth, followed by verrucous papules in the first weeks to months, progressing to hyperpigmented patches, which later become areas of hypopigmentation.<sup>1,8</sup> Characteristic cerebral abnormalities include seizures, cognitive and motor delays, and cerebral ischemia resulting from vascular occlusion.<sup>1,9</sup> Ocular manifestations of IP include peripheral retinal nonperfusion, neo-vascularization, hemorrhage, and exudative or tractional detachments.<sup>1</sup> Dental abnormalities include absence of teeth, or small or abnormally shaped teeth.<sup>1</sup> The effect of IP on small blood vessels throughout these organ systems is well documented.

Raynaud's phenomenon is a syndrome characterized by recurrent episodes of vasospasm resulting from chemical or physical stress. These episodes typically last for 20 minutes and most frequently affect the hands or feet. Classically, RP has three phases: pallor (ischemia), cyanosis (deoxygenization), and erythema of the affected extremity (reperfusion). RP can be either primary, or related to an underlying condition. Numerous causes of secondary RP have been described including connective tissue disease such as rheumatoid arthritis, vasculitis such as Wegener's, hematologic abnormalities including multiple myeloma, and related to certain medications such as clonidine.<sup>10,11</sup>

Vascular tone results from the interaction between the endothelial cells lining blood vessels, the vascular smooth muscle, and the autonomic nerves that control vascular muscle tone. Vascular tone is affected by physical activity, temperature, emotional state, and factors related to the vessels themselves. In RP, a prolonged vasoconstrictive response results in local tissue ischemia.<sup>10,11</sup>

Several theories explaining pathogenesis of Raynaud's phenomenon have particular relevance to patients with IP. In IP, reduced function of NF- $\kappa$ B leads to increased levels of cytokines, particularly IL-1 and TNF- $\alpha$ , as well as abnormally high levels of TNF-induced cellular apoptosis.<sup>1,2</sup> It is thought that these cascades result in vaso-occlusive complications of IP including retinal artery and cerebral ischemia. We hypothesize that Raynaud's phenomenon in IP results from a similar mechanism whereby higher-than-normal levels of inflammatory cytokines result in a disruption of endothelial cell homeostasis, causing local endothelial cell apoptosis as well as release of chemical mediators from surviving endothelial cells including endothelin-1, a potent vasoconstrictor.<sup>12</sup> This increased basal tone of the blood vessels, in addition to remodeling occurring secondary to damage to endothelial cells and resulting in a smaller-caliber vessel lumen could make patients with IP more susceptible to physiologic temperature-induced vasoconstriction and result in the RP phenotype.

This is the first report of Raynaud's phenomenon associated with the diagnosis of incontinentia pigmenti. Further research into the pathogenesis of both conditions may elucidate more clearly the underlying mechanisms which link the two.

#### 4. Patient consent

The patient's parent gave verbal consent for the publication of this case; however, this case contains no personal information that could identify the patient.

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None.

#### Conflict of interest

The authors report no conflict of interest.

## Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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