IKBKG Mutation With Incontinentia Pigmenti and Ring-Enhancing Encephalopathy

Incontinentia pigmenti (IP, Bloch-Sulzberger syndrome) is an X-linked dominant genodermatosis affecting skin and other organs, including the brain, with variable expressivity. Incontinentia pigmenti results from mutations in the inhibitor of κ-β-nucleotide kinase-γ gene (IKBKG), which is located on Xq28. Deletions in this gene result in loss of function, leading to a wide variety of manifestations.1 This mutation is often lethal in males, resulting in miscarriage of male fetuses. Previously proposed revised diagnostic criteria2 included as major criteria any of 4 types of IP skin lesions and several minor criteria including anomalies of the brain, eyes, oral cavity, breasts, nipples, hair, and nails in a typical context of multiple male miscarriages and characteristic skin histopathology findings.

**Report of a Case** | An infant girl, the product of consanguineous parents, presented at birth with erythematous vesicles on her hands, progressing to scaly, erythematous plaques on her head, neck, trunk, and extremities in a blaschkoid pattern. There were no neurological symptoms. Initial concern for infection led to several investigations. Results from blood culture and herpes simplex virus culture of a vesicle were negative. Cerebrospinal fluid showed elevated protein level of 0.063 g/dL (range, 0.015-0.06 g/dL; to convert to grams per liter, multiply by 0.0167), and the alanine aminotransferase level was elevated to 807 U/L (range, 10-80 units/L; to convert to microkatals per liter, multiply by 0.0167), and the glucose level of 52 mg/dL, and 0.004 nucleated cells/L, with negative herpes simplex virus polymerase chain reaction results. Aspartate aminotransferase level was elevated to 1355 U/L (range, 10-80 units/L; to convert to microkatals per liter, multiply by 0.0167), and the alanine aminotransferase level was elevated to 807 U/L (range, 10-50 U/L; to convert to microkatals per liter, multiply by 0.0167).

Fundoscopy revealed bilateral preretinal and retinal hemorrhages, extending to the maculae, as commonly seen in vaginally delivered infants. Brain magnetic resonance imaging showed multiple areas of restricted diffusion and intraparenchymal and leptomeningeal enhancement resembling hemophagocytic lymphohistiocytosis (Figure). DNA sequencing for a panel of genes associated with hemophagocytic lymphohistiocytosis was negative. Skin histopathological examination revealed dense inflammatory infiltrate with a myriad of eosinophils, prominent spongiosis with intraepidermal vesicles containing eosinophils, and several necrotic keratinocytes, consistent with the inflammatory stage of IP. The child harbored a common known pathogenic deletion in IKBKG, also known as activator of NF-κ-β or NEMO.

This study was approved by the University of Texas Southwestern Medical Center institutional review board.

**Discussion** | Skin manifestations are commonly the first symptom and occur in nearly all patients with IP. They follow Blaschko lines. Our patient had inflammatory lesions (Figure). Eye abnormalities include retinal anomalies, such as telangiectasia, hemorrhage, arteriovenous anomastomoses, neovascularization, and retinal avascularity, or anomalies involving vitreous and lens, microphthalmia, and cataracts. Minor criteria include skin appendage abnormalities including the absence of pilosebaceous glands; alopecia; sparse, wooly hair; anomalies of eyebrows and eyelashes; nail pitting; dystrophy; and subungual or perungual tumors.3 Nipple and dental anomalies may also be present. Neurological manifestations occur in the first month of life in two-thirds of cases with neurological involvement, which comprise as much as one-third of all IP cases.4 They range from a single seizure to psychomotor delay, learning disabilities, hemiplegia, epilepsy, cerebellar ataxia, microcephaly, childhood encephalomyelitis, and stroke-like episodes. Magnetic resonance imaging may reveal white matter and corpus callosum abnormalities, cortical malformations, cerebro atrophy, and cerebral or cerebellar hemorrhage.5,6 Although stroke-like lesions secondary to focal cortical and white matter necrosis in a nonvascular distribution have been reported in IP, ring enhancement is unusual. Our patient manifested ring enhancement in areas of restricted diffusion together with subtle, diffuse intraparenchymal, cerebellar, and leptomeningeal enhancement.

**Conclusions** | The rarity of IP together with its myriad clinical presentations poses a significant diagnostic challenge. The presentation of IP may mimic other blaschkoid pigmentary disorders such as hypomelanosis of Ito, focal dermal hypoplasia (Goltz syndrome), or herpes simplex virus infection. The neurological syndrome of IP is even less specific. In the absence of cerebral Citrobacter or fungal infection, the diffuse radially distributed ring-enhancement appearance of our case by magnetic resonance imaging is most suggestive of cellular loss along migrational trajectories.

Deepali Eksambe, MD
Nnenna Agim, MD
Naseem Uddin, MD
Garrett Gotway, MD, PhD
Juan M. Pascual, MD, PhD

**Author Affiliations:** Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas (Eksambe, Pascual); Department of Pediatrics, The University of Texas Southwestern Medical Center, Dallas (Eksambe, Pascual); Department of Dermatology, The University of Texas Southwestern Medical Center, Dallas (Agim); Department of Pathology, The University of Texas Southwestern Medical Center, Dallas (Uddin); Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas (Gotway); Eugene McDermott Center for Human Growth & Development/Center for Human Genetics, The University of Texas Southwestern Medical Center, Dallas (Gotway, Pascual); Department of Physiology, The University of Texas Southwestern Medical Center, Dallas (Pascual); Rare Brain Disorders Program, The University of Texas Southwestern Medical Center, Dallas (Pascual).

**Corresponding Author:** Juan M. Pascual, MD, PhD, Rare Brain Disorders Program, The University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Mail Code 8813, Dallas, TX 75390-8813 (juan.pascual@utsouthwestern.edu).

---

Figure. Manifestations of Incontinentia Pigmenti Associated With IKBKG Deletion

A, Rash on the torso. B, Rash in blaschkoid pattern in the upper extremity. C and D, Skin biopsy showing inflammatory stage lesions typical of incontinentia pigmenti (hematoxylin-eosin; C, original magnification ×100 and D, original magnification ×400). The white arrowheads indicate dyskeratotic keratinocytes; red arrowheads, spongiosis; blue arrowheads, intraepidermal and dermal inflammatory infiltrate including eosinophils and lymphocytes; black arrowheads, intraepidermal vesicles containing eosinophils; and yellow arrowhead, normal skin at the edge of the biopsy for comparison. E, The first 4 columns of images show diffusion-weighted axial magnetic resonance imaging (MRI) scans obtained across the entire encephalon demonstrating areas of restricted diffusion throughout the right cerebral hemispheres. The images in the fifth column show postcontrast axial fluid-attenuated inversion recovery MRI images illustrating ring enhancement in areas of restricted diffusion.
COMMENT & RESPONSE

Treating In-Hospital Stroke

To the Editor Saltman et al\(^1\) found delays in the evaluation and treatment of patients who had a stroke while hospitalized for another condition compared with those whose strokes occurred in the community. A “standardized approach to the recognition and management of in-hospital stroke” by developing “targeted code stroke protocols…similar to those used in the emergency department”\(^\) was suggested.\(^2\) We previously reported the usefulness of such a protocol for hospitalized patients, comparing the yield of “stroke codes” between in-hospital and emergency department (ED) settings in a single institution.\(^2\) We found that hospitalized patients for whom a stroke code was activated were less likely to have a stroke/transient ischemic attack (26.8% in-hospital vs 51.4% ED; \(P < .001\)) and less likely to be treated with intravenous tissue plasminogen activator (odds ratio, 0.27; 95% CI, 0.07-0.97; \(P = .03\)). Conditions not necessitating immediate neurologic care accounted for 63.4% of in-hospital stroke codes compared with 31.3% of those arising in the ED (\(P < .001\)). Altered mental status was the sole presenting symptom in 48% of the hospitalized patients compared with only 10% of ED patients (\(P < .001\)) and was independently associated with a stroke mimic (odds ratio, 63.52; 95% CI, 7.37-547.69; \(P < .001\)). There was no association between the diagnosis of an in-hospital stroke mimic and patient age, sex, race/ethnicity, or nursing shift.

Similar to the study by Saltman et al,\(^1\) we found that the proportion of hospitalized patients with acute ischemic stroke who were treated with intravenous tissue plasminogen activator after activation of an in-hospital code stroke was small, and it was lower than for those who presented to the ED (2.7% vs 25.9%, respectively; \(P = .004\)). We suggested that although a standardized stroke code protocol may be an initial step for improving treatment rates among hospitalized patients, it is not likely to entirely eliminate the differences as compared with patients evaluated in the ED because of the high proportions of stroke mimics and treatment contraindications in hospitalized patients. In addition to having a standardized in-hospital stroke code protocol, training all hospital personnel in accurate stroke recognition will help improve the identification of those patients appropriate for intravenous tissue plasminogen activator or endovascular therapy and optimize resource use.

Nada El Hussein, MD, MHSc
Larry B. Goldstein, MD

Author Affiliations: Wake Forest Baptist Medical Center, Winston Salem, North Carolina (El Hussein); University of Kentucky, Lexington (Goldstein).

Corresponding Author: Nada El Hussein, MD, MHSc, Wake Forest Baptist Medical Center, Medical Center Boulevard, Winston Salem, NC 27157 (nelhussein@wakehealth.edu).

Conflict of Interest Disclosures: None reported.


In Reply We thank El Hussein and Goldstein for their comments and for highlighting the challenges that exist in distinguishing strokes from conditions that mimic strokes in hospitalized patients.\(^3\) The findings from their study lend support for the training of hospital personnel in accurate stroke recognition in conjunction with the development of in-hospital code stroke protocols.

Although many patients with in-hospital stroke may be ineligible for thrombolytic therapy, use of code stroke protocols to streamline stroke identification and management may facilitate access to other aspects of stroke care, including transfer to a designated stroke unit; access to specialized physiotherapy, occupational therapy, and swallowing assessments; timely initiation of medications for secondary stroke prevention; and appropriate discharge planning with referral to inpatient or outpatient stroke rehabilitation. Moreover, the recent demonstration of the superiority of mechanical thrombectomy over systemic thrombolysis alone for patients with large-artery occlusions\(^4\)-\(^5\) widens the scope for treatment of patients with in-hospital stroke who may have contraindications to systemic thrombolysis, thereby increasing the yield of timely diagnosis in this population.

Alexandra P. Saltman, MD
Moira K. Kapral, MD, MSc, FRCP(C)

Author Affiliations: Department of Medicine, University of Toronto, Mount Sinai Hospital, Toronto, Ontario, Canada.

Corresponding Author: Alexandra P. Saltman, MD, Department of Medicine, University of Toronto, Mount Sinai Hospital, Room 427, 600 University Ave, Toronto, ON MSG 1X5, Canada (cmr@mtsniain.on.ca).

Conflict of Interest Disclosures: None reported.