Leukoencephalopathy: Unusual Sonographic Finding in a Neonate With Incontinentia Pigmenti

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Incontinentia pigmenti (IP) is a rare X-linked dominant neurocutaneous syndrome chiefly involving the ectodermal tissues, such as the skin, teeth, hair, eyes, and central nervous system (CNS). The diagnosis is usually made when the pathognomonic skin lesions are present; these typically appear in 4 stages: erythematous vesicular rash, verrucous patches, swirling hyperpigmentation, and atrophic scarring. The exact pathogenesis and timing of neurologic involvement are not well known. It often manifests in the neonatal period with seizures paralleling the eruption of the vesicular rash. White matter abnormalities have been reported in IP. However, to our best knowledge, the sonographic characterization of white matter involvement has rarely been described. We report a case of IP with hyperechogenicity of the white matter on cranial sonography. The aim of this report is to suggest that IP should be considered as one etiology of leukoencephalopathy in neonates with vesicular eruption.

Case Report

The female neonate was the second child born to healthy nonconsanguineous parents. There were no prenatal complications. The family history was noncontributory. She was born by an uncomplicated cesarean delivery at 37 weeks’ gestation. The Apgar scores were 9 at 1 minute and 10 at 5 minute. Her birth weight was 3390 g (90th percentile); her length was 51 cm (90th percentile); and her occipitofrontal circumference was 34 cm (75th percentile). After birth, she developed normally. However, skin changes were observed at delivery, with a vesicular eruption on an erythematous base being evident on her trunk and all limbs (Figure 1). The pattern of the eruption was linear in some areas and became more linear over the following days, with new vesicles erupting. Her face was spared.
Physical examination disclosed no abnormal findings except for the skin lesions. Neurologic and fundoscopic examination disclosed no abnormal findings. Hair and nail abnormalities were not observed. Neonatal herpes simplex virus infection was initially considered. Routine laboratory examinations revealed no abnormal findings except for eosinophilia (20% eosinophils). Results from a cerebrospinal fluid analysis for the white blood cell count, protein, glucose, and culture tests, and polymerase chain reaction for herpes simplex virus types 1 and 2 were normal. Chromosome analysis revealed a normal 46,XX female karyotype.

At the age of 11 days, cranial sonography was performed using an Acuson 128XP ultrasound scanner (Siemens Medical Solutions, Mountain View, CA) equipped with a 7.0-MHz transducer. Sonography (Figure 2) showed abnormal increased echogenicity over right frontal subcortical white matter. The cerebellum and brain stem appeared normal. Magnetic resonance imaging of the brain (Figure 3) showed hypointensity on a T1-weighted image and hyperintensity on a T2-weighted image at the right frontal subcortical white matter. A skin biopsy was performed. The histopathologic results showed acanthosis, an intradermal vesicle of eosinophils, and dermal infiltration of eosinophils and mononuclear cells. The diagnosis of IP was made at that time.

The skin rash waxed and waned over the following weeks but never completely disappeared. At 6 months of age, the rash had transformed into the whorled hyperpigmentation characteristic of IP. There were no seizures or retinal abnormalities. However, developmental milestones showed mild delay with poor rolling over and mild left limb weakness.

**Discussion**

Incontinentia pigmenti or Bloch-Sulzberger syndrome is an X-linked dominant neurocutaneous syndrome. There are cutaneous, orthopedic, ocular, behavioral, and developmental manifestations. The clinical findings in this case were consistent with a diagnosis of IP. The presence of leukoencephalopathy, however, is unusual and has been reported in only a few cases. The sonographic findings were consistent with leukoencephalopathy, and the MRI showed hyperintensity on T2-weighted images in the right frontal subcortical white matter. The histopathologic findings of acanthosis, intradermal vesicle of eosinophils, and dermal infiltration of eosinophils and mononuclear cells were consistent with the diagnosis of IP. The development of leukoencephalopathy in this case suggests a possible association between IP and leukoencephalopathy. Further studies are needed to elucidate the pathogenesis of leukoencephalopathy in IP.

![Figure 1. Linear vesicular eruptions on an erythematous base on the trunk and right lower limb of a neonate with IP.](image1)

**Figure 1.** Linear vesicular eruptions on an erythematous base on the trunk and right lower limb of a neonate with IP.

![Figure 2. Coronal (A) and right parasagittal (B) cranial sonograms showing abnormal increased echogenicity over the right frontal subcortical white matter (arrows).](image2)

**Figure 2.** Coronal (A) and right parasagittal (B) cranial sonograms showing abnormal increased echogenicity over the right frontal subcortical white matter (arrows).
disorder with cutaneous, dental, hair, ocular, and CNS abnormalities, thought to result from defective melanocyte or melanoblast proliferation and migration. Incontinentia pigmenti occurs almost exclusively in girls and is usually prenatal-ly lethal in boys. The term *incontinentia pigmenti* is derived from the dislocation (“incontinentia”) of the melanin pigment from the basal cell layer of the epidermis to the upper dermis. Skin manifestations of IP are well characterized and pathognomonic. They are divided into 4 stages: stage 1, characterized by crops of vesicles in a linear distribution, which are often present at birth or develop in the first week of life in most cases; stage 2, characterized by hyperkeratotic and verrucous papules; stage 3, characterized by whorls of hyperpigmentation; and stage 4, characterized by scarring hypopigmentation. The skin lesions are distributed along the Blaschko lines (clusters of epidermal cells of similar clonal origin), which delineate the paths of ectodermal cell migration during embryonic development of the skin. Analogies of the Blaschko lines are seen in the lens and iris of the eye, the teeth, and bone, but there is no commonly accepted analogy to Blaschko lines in the brain.

At least 2 forms of IP are known: an X-linked dominant disorder linked with Xq28 and a sporadic form associated with an Xp11.21 break point. Our patient probably belonged to the latter group. The incidence of CNS involvement is said to be higher in the sporadic form of the disease and may reach 30% to 50%. Seizures, spasticity, hemiparesis, developmental delays, mental retardation, and cerebellar ataxia are the most commonly reported manifestations. Central nervous system involvement in the neonatal period, which most often manifests as seizures, is a poor prognostic sign. The neuropathologic findings in IP include microcephaly, polymicrogyria, small cavities in the white matter, focal necrosis, neuronal loss, acute hemorrhagic encephalopathy, massive edema, and uleerya. Although the pathogenesis for CNS abnormalities in IP is unknown, developmental, inflammatory, destructive, and vascular mechanisms have been suggested.

Incontinentia pigmenti is known to involve the cerebral white matter. However, to our best knowledge, the sonographic features of white matter involvement have rarely been described. In our patient, a right frontal subcortical white matter lesion was identified as a hyperechoic area on cranial sonography, which was confirmed via magnetic resonance imaging. The etiology of white matter abnormalities is unknown.

Figure 3. Axial T1-weighted (repetition time, 540 milliseconds; echo time, 20 milliseconds) brain (A) and T2-weighted (repetition time, 4200 milliseconds; echo time, 99 milliseconds) coronal (B) magnetic resonance images showing hypointensity on the T1-weighted image and hyperintensity on the T2-weighted image in the right frontal subcortical white matter (arrows).
A vascular occlusive phenomenon has been suggested.2,6,8,13 Lee et al2 reported several cases of cerebral infarction with IP. They concluded that it was possible that these vascular occlusive changes may share common pathophysiologic characteristic with those seen in the retinal vasculature and that the CNS changes in patients with IP may be the result of small-vessel occlusion in the brain. Hart et al6 reported a case of IP with hemorrhagic necrosis of the brain and small attenuated arterial involvement in the middle and posterior cerebral arterial branches on a magnetic resonance angiographic study. Kasai et al13 also reported an IP case with cerebral infarction in multiple arterial regions of the brain, evaluated by single-photon emission computed tomography, which was able to show sluggish blood flow in the brain. Although both large- and small-vessel diseases have been reported, Maingay-de Groof et al8 postulated that neonatal cerebral infarction in IP is probably a disorder of medium-sized or small arteries. Incontinentia pigmeni is associated with ischemic strokes, as are other neurocutaneous syndromes, such as neurofibromatosis, tuberous sclerosis complex, and Sturge-Weber syndrome.

Other diseases causing cerebral white matter abnormalities in neonates are Canavan disease, Alexander disease, Krabbe disease, Pelizaeus-Merzbacher disease, Aicardi-Goutieres syndrome, Zellweger syndrome, neonatal adrenoleukodystrophy, and mitochondrial disorder.14 All of these were excluded in our patient because of clinical or biochemical discordances.

In conclusion, hyperechoic lesions in the white matter on cranial sonography in neonates are nonspecific. However, IP should be included in the differential diagnosis if a neonate has a vesicular eruption and hyperechoic white matter lesions on cranial sonography.

References