

## Case Reports

# Insights Into the Pathogenesis of Cerebral Lesions in Incontinentia Pigmenti

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**We report the case of a neonate with incontinentia pigmenti and seizures on day 4 of life who underwent magnetic resonance imaging and angiography scanning at 8, 13, and 21 days of age. The serial magnetic resonance images demonstrated the evolution of acute microvascular hemorrhagic infarcts in the periventricular white matter in the first week of life. The associated magnetic resonance angiogram findings consisted of decreased branching and poor filling of intracerebral vessels. This report adds important insights into the nature and timing of cerebral lesions in incontinentia pigmenti. © 2003 by Elsevier Inc. All rights reserved.**

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## Introduction

Incontinentia pigmenti is a rare X-linked dominant neurocutaneous syndrome primarily affecting ectodermal and mesodermal tissue. The pathognomonic findings include skin changes which follow Blaschko's lines [1], with a distinct pattern of development in three stages: vesiculobullous, verrucous, and, finally, swirled pigmentation [2]. In the vast majority of cases, the onset of skin changes is before 6 weeks of age [2]. Other organ systems involved

include dental (90%), skeletal (40%), central nervous system (CNS) (40-50%) and ocular (35%) [2,3].

The clinical expression of CNS involvement in incontinentia pigmenti includes epilepsy, mental retardation, hemiparesis, spasticity, microcephaly, and cerebellar ataxia [2]. The pathogenesis of the CNS lesion in incontinentia pigmenti remains unclear, although more recent brain-imaging techniques, such as magnetic resonance imaging (MRI) and magnetic resonance angiogram (MRA), have provided newer insights into the nature of the CNS pathology [4,5]. Magnetic resonance studies have demonstrated scattered cortical neuronal and white-matter necrosis [6,7], hypoplasia of the corpus callosum [4,5,8,9], periventricular white-matter cystic lesions [10,11], neuronal heterotopia [5], and cerebral atrophy [4,9,11,12]. There are only rare reports of brain imaging performed in the neonatal period [4,6,7].

The timing of the CNS involvement in incontinentia pigmenti has not been clearly defined. CNS symptoms, particularly seizures, have been documented in the first week of life [4,7,8], within the first year [8], and later in childhood [4]. A more diffuse encephalopathy has been observed in the neonatal period [7]. In view of the neonatal onset of clinical neurologic symptoms and the fact that the vast majority of skin changes appear in the first 6 weeks of life in incontinentia pigmenti, proposing that the CNS lesion may develop and evolve at this time is reasonable. This notion is supported by a case reported by Yoshikawa et al. [12] in which MRI changes were observed at 1 month and had resolved on repeated imaging at 7 months.

Reported is the case of an infant female with incontinentia pigmenti who underwent MRI/MRA scanning at 8, 13, and 21 days of age. The principal imaging findings were periventricular foci of abnormal signal, consistent with microvascular hemorrhagic infarcts, suggestive of microvascular ischemia. The MRA findings of angiopathy suggest that the etiology of the infarcts is of vascular origin.

## Case Report

This infant female was born at 40 weeks gestation in a regional center via a normal vaginal delivery and after an uneventful pregnancy. Her mother was gravida 2 para 2 with no significant medical history. There was no known family history of incontinentia pigmenti. The infant was born in good condition with a birth weight of 3400 g. However, skin changes were observed at delivery, with a vesicular eruption on an

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Figure 1. Rash on the infant's hand in the neonatal period, exhibiting the typical early-stage vesiculo-bullous rash along Blaschko's lines.

erythematous base being evident on her arms and trunk. The pattern of the eruption was linear in some areas and became more linear over the following days to week, with new vesicles erupting and older lesions crusting (Fig 1). Her face was spared.

On day 4, she developed seizure activity consisting of focal clonic jerking of her arms (left more than right), each seizure lasting several minutes. Neurologic examination revealed evidence of a mild encephalopathy, with a prominent head lag, generalized weakness, and marked jaw jerk and gag reflex. Numerous test results were normal and included full blood cell count; blood sugar level; serum electrolyte, calcium, magnesium, and C-reactive protein levels; serology; and viral and bacterial cultures. Cranial ultrasound scan result was normal. She began receiving gentamicin, penicillin, acyclovir, and phenobarbitone. The eosinophil count was initially within normal limits and then only marginally elevated on day 9 at a level of 2.1. Renal ultrasound, audiology, and ophthalmology assessment results were normal. She experienced no further seizures after she began receiving phenobarbitone, so this medication was discontinued on day 6. An electroencephalogram result on day 14 was normal. A skin biopsy undertaken on day 9 of life confirmed the diagnosis of incontinentia pigmenti.

The first MRI was performed on day 8 and demonstrated multiple scattered foci of decreased diffusion of irregular size and shape within the periventricular white matter (Fig 2A). These foci exhibited decreased signal on T<sub>2</sub>-weighted scans. Thus, the signal characteristics suggested the presence of blood products and were consistent with microvascular hemorrhagic infarcts in the periventricular white matter. The second MRI was performed on day 13 and included an MRA sequence. This study demonstrated normalization of the apparent diffusion coefficient on diffusion-weighted imaging and extensive hyperintensity on T<sub>1</sub>- and

T<sub>2</sub>-weighted scans in the periventricular zones around both lateral ventricles, extending bilaterally into the centrum semi-ovale and the subcortical white matter. The features were consistent with hemorrhagic necrosis, affecting the cerebral white matter predominantly in the periventricular regions. MRA revealed considerably decreased branching of intracerebral vessels and poor filling within the distal middle and posterior cerebral artery branches (Fig 2B).

MRI on day 21 revealed persisting changes in signal intensity on the T<sub>1</sub>-weighted scans, with no extension of the region or nature of abnormality in comparison with the previous scan. On T<sub>2</sub>-weighted images, however, there was a small increase in hyperintensity in the central portion of some lesions, indicative of extracellular methemoglobin and cystic formation in the periventricular white matter (Fig 2C).

On follow-up at one and a half months, her cutaneous changes had become verrucous, and neurologic examination revealed normal tone and power. She had experienced no further seizures. Her left eye had been observed to be intermittently convergent. Ophthalmology review under general anesthetic at 2 months of age demonstrated retinal vascular abnormalities bilaterally.

## Discussion

This case report provides important insight into the timing and pathogenesis of CNS lesions in incontinentia pigmenti by demonstrating the early neonatal occurrence of periventricular hemorrhagic infarcts and a cerebral microangiopathy.

The earliest magnetic resonance imaging documented in incontinentia pigmenti was reported by Shuper et al. [7], who described a 3-day-old infant, initially assessed with computed tomography and then, on day 13 by MRI, with diffuse right-sided hemorrhagic necrosis. MRI studies have also been undertaken in older infants and have demonstrated cystic abnormalities and chronic periventricular white-matter lesions with increased intensity on T<sub>2</sub>-weighted images [4,8,10,12]. This patient's marked periventricular white-matter injury is consistent with these earlier reports of a dominant cerebral white-matter pathology, although we now clearly document the early neonatal occurrence of this lesion.

The potential pathogenic mechanisms proposed for the CNS lesion in incontinentia pigmenti have included inflammatory, developmental, destructive, vascular, and infectious processes [1,2,7,13]. The findings of microvascular hemorrhagic infarcts in the periventricular white matter and associated MRA changes of decreased branching and

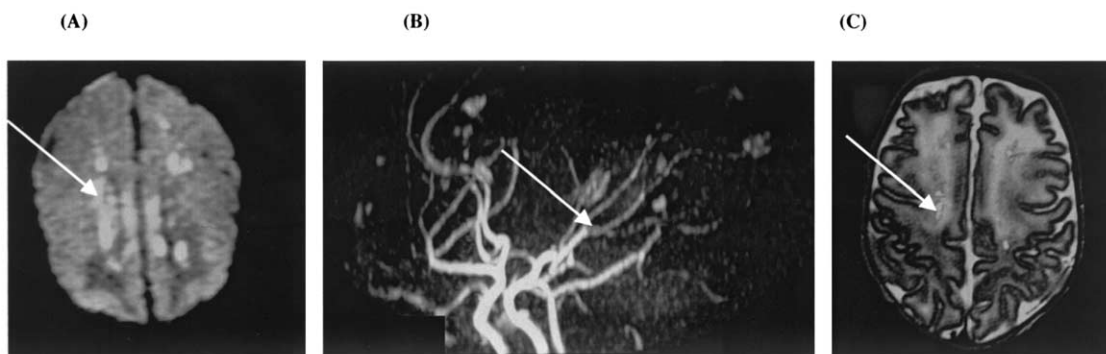


Figure 2. Image A demonstrates the results of the diffusion-weighted imaging (epi-DWI TR4000/TE100;  $b=1000$  s/mm<sup>2</sup>) at the level of the centrum semiovale on day 8 and demonstrates multiple regions of restricted diffusion in the periventricular white matter (arrow in A). B demonstrates the MRA undertaken on day 13, indicating regions of decreased branching and filling defects in the middle cerebral artery (arrow). C depicts an axial T<sub>2</sub> (TR5000/TE95)-weighted image on day 21, demonstrating cystic changes in the periventricular white matter.

filling of intracerebral vessels are indicative of a microangiopathic process. The neuropathologic findings in incontinentia pigmenti have been inconsistent, with some suggesting an inflammatory process [1] and others manifesting no evidence of inflammation [7,13]. Siemes et al. [13], in their case report of two siblings with incontinentia pigmenti, demonstrated macroscopic evidence of fresh hemorrhagic necrosis with evidence of perivenous and capillary hemorrhage and vascular congestion in the cerebral white matter. Evidence of inflammation surrounding the hemorrhage was regarded as a secondary phenomenon.

The importance of a vasculopathy as the major pathogenetic mechanism for CNS pathology in incontinentia pigmenti is supported by the common feature of retinal vascular abnormalities in these patients [14]. The retinal vascular changes which have been observed in IP include peripheral retinal vascular nonperfusion, macular infarction, macular neovascularization, and preretinal neovascularization [15-17]. The majority of other ocular changes observed, such as retinal detachment, cataract, microphthalmia, strabismus, and nystagmus, have been considered secondary to these vascular changes [3,15-17]. Macular vasculopathy and ischemia have been documented early in incontinentia pigmenti, with subsequent development of neovascularization, in the prospective cohort study of 12 infants by Goldberg [16]. It has been suggested that the ischemia and vascular occlusive phenomena observed in the retina may also occur in the CNS [1,4]. Noteworthy in this context is a documented correlation between the severity of the CNS involvement and the retinal vascular occlusive disease [4].

MRA is an important tool for assessing vasculopathy in the CNS. MRA has recently been demonstrated to have similar sensitivity for cerebral arterial disease in childhood stroke [18], although the sensitivity of MRA for small-vessel disease remains controversial. However, MRA studies have been reported only rarely in IP. Pelligrino and Shah [19] studied a 4.5-year-old female who manifested incontinentia pigmenti, presented with the acute onset of hemiparesis, and exhibited an occlusion of the left middle cerebral artery on MRA. Lee et al. [4] reported a series of seven patients with incontinentia pigmenti who were investigated with MRI, MRA, and spectroscopic imaging. One of the patients, a 56-year-old female with no neurologic signs or symptoms, manifested a right-sided internal carotid artery aneurysm. In another case, a 31-month-old infant with a history of seizures and generalized cerebral atrophy manifested decreased distal branching of the left middle cerebral artery. Apparently, there are no previously documented MRA studies in the neonatal period or infancy. This study correlated the microvascular hemorrhagic infarcts observed on MRI with MRA changes of decreased branching and poor filling of vessels, thus confirming a microangiopathic process with associated hemorrhagic necrosis.

This case demonstrates that in incontinentia pigmenti there is a microangiopathic process with secondary ischemia at a time of particular vulnerability of the neonatal brain. The dominant pathology is in the cerebral white matter, despite

involvement of a major vessel, which supplies both white matter and cerebral cortex, which is consistent with the particular vulnerability of neonatal white matter to ischemic insults [20]. The CNS pathology correlated with the initial evolution of skin changes. Thus, the findings reported here provide insight into the importance of cerebrovascular pathology in incontinentia pigmenti and into the high-risk nature of the neonatal period for occurrence of CNS lesions in incontinentia pigmenti. An understanding of the nature and the timing of the CNS lesion in incontinentia pigmenti may provide avenues for neuroprotection and intervention.

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