

# Incontinentia Pigmenti Associated with Cerebral Palsy and Cerebral Leukomalacia: A Case Report and Literature Review

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**Abstract:** Incontinentia pigmenti (IP) is a multisystem disorder with characteristic cutaneous signs. After the skin, the central nervous system is the next most affected system. We report a child with IP and left-sided hemiparesis and cerebral periventricular leukomalacia on magnetic resonance imaging (MRI). The MRI findings would support ischemia sustained perinatally.

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Incontinentia pigmenti (IP) was first described by Garrod in 1906 (1). It was further defined by Bardach in 1925 (2) and by Bloch in 1926 (3). It is a multisystem disorder that is inherited in an X-linked dominant fashion with lethality in males. The skin features are diagnostic and classically occur in four stages, although not all stages may be observed:

- Stage 1: Erythema, vesicles, and bullae typically configured in a linear pattern.
- Stage 2: Papules, verrucous lesions, and hyperkeratosis.
- Stage 3: Hyperpigmentation.
- Stage 4: Hypopigmentation and atrophy of the skin.

Other systems that may be involved include the teeth (hypodontia, microdontia, dysplasia, and delayed eruption) (3–6); the musculoskeletal system (hemivertebrae, kyphoscoliosis, extra rib, syndactyly, hemiatrophy, and short arms and legs); the eyes (strabismus, retinal dysplasia, retinal detachment, uveitis, keratitis, cataract, retrorenal dysplasia, blue sclerae, and pigment retinopathy); the hair (alopecia); and the central nervous

system (mental deficiency, microcephaly, spasticity, seizures, and magnetic resonance imaging [MRI] change). Ischemia of the peripheral retinal field has also been described (7).

## CASE REPORT

A full-term infant girl was born by uncomplicated vaginal delivery as the first child of unrelated parents. On day 4 she developed focal seizures which rapidly generalized. They resolved after 12 hours with no sequelae. A cranial ultrasound performed at the time was normal. At 6 weeks of age she presented with a 4-week history of a blistering eruption, which had started on her hands and then spread to her limbs. Examination revealed bullae arranged in a linear pattern on the hands and fingers and overlying the Achilles tendon (Fig. 1). A clinical diagnosis of IP was suspected and confirmed by skin biopsy (Fig. 2).

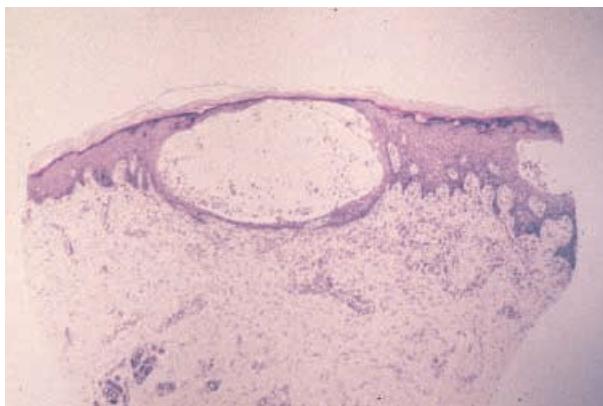
By the age of 4 months, her blisters were replaced by keratotic and verruciform lesions (Fig. 3). The growth

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**Figure 1.** Hand and fingers at 6 weeks of age show hyperkeratosis and bullae arranged in a linear pattern.



**Figure 2.** Intraepidermal bulla set in an acanthotic and dyskeratotic epidermis. (Hematoxylin-eosin; magnification 250 $\times$ .)

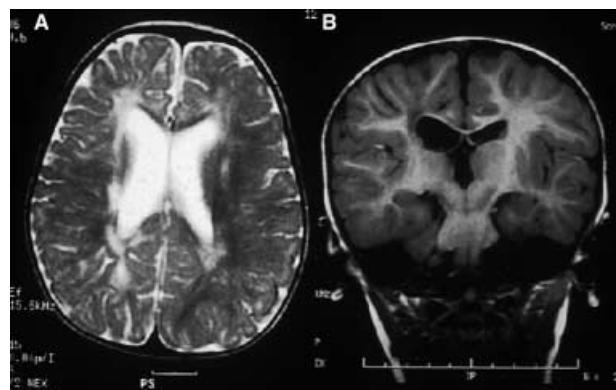


**Figure 3.** Hand at 4 months of age with a hyperkeratotic and verruciform lesion.

and development of the infant were well within normal limits. However, at 6 months of age the parents noticed that she did not appear to be using her left arm and leg.



**Figure 4.** Perineum at 1 year of age showing classical splashed and whorled macular pigmentation.



**Figure 5.** MRI scan at 14 months of age. **(A)** T2-weighted axial image shows high signal areas in the periventricular white matter due to gliosis. **(B)** Coronal image shows dilated lateral ventricles secondary to loss of volume of the adjacent white matter. Note the close proximity of the cortical gray matter to the ventricular margins. These changes are more marked on the right side.

Examination revealed increased tone and reflexes on the left together with left sensory inattention.

At the age of 1 year she had developed linear hyperpigmentation on her right shin and left calf. In addition, she had splashed and whorled macular pigmented areas, characteristic of IP, on the perineum and abdomen (Fig. 4). Her neurologic signs did not progress significantly; she continued to have a mild left hemiparesis. Delayed eruption of the teeth was noted, with only one incisor evident at the age of 1 year. No ophthalmologic abnormalities were detected. MRI scan of her brain performed at 14 months of age showed changes typical of end-stage periventricular leukomalacia (Fig. 5). The changes were more marked on the right side, in keeping with the neurologic signs. At the age 18 months she was walking and starting to talk. Her left hemiparesis has remained mild and has not progressed. She has kept up with her main developmental milestones.

Examination of her mother found no evidence of IP. Genetic analysis using blood from our patient revealed a deletion mutation at the *NEMO* gene, but this mutation was negative in the mother's blood. It confirmed our clinical impression of a new mutation.

## DISCUSSION

Incontinentia pigmenti is a familial, X-linked, neurocutaneous syndrome. Mutations in the *NEMO* gene, which encodes a critical component of the neurofibromatosis kappa-B (NF- $\kappa$ B) pathway, were found to be responsible for IP (8,9). Most cases of IP are due to a recurrent deletion within *NEMO* that removes exons 4–10 (8–10). The male hemizygous state usually results in early fetal loss, and the vast majority of cases are female (male: female ratio of 1:37) (4). Surviving male patients are described in the literature. A number of reported male cases have an XXY karyotype, however, Aradhya et al (8) recently showed that males could also have IP caused by duplication mutations of a cytosine tract in exon 10 of *NEMO*.

Neurologic involvement occurs in approximately one-third of cases. Seizures, global developmental delay, and spastic paresis are the most common manifestations of neurologic involvement (11) and may occur very early in the disease. Using MRI, Yoshikawa et al (12) detected a cavity in the brain of a 1-month-old infant girl with IP. It was nonprogressive and the pathophysiology was poorly understood. A number of studies of histopathologic and neuroradiologic observations have speculated that vascular anomalies causing ischemia or an abnormal protein triggering an encephalitic process may be responsible for the neurologic complications of IP.

Pauscal-Castroviejo et al (13) described brain changes noted on MRI in four girls with IP; there were hyperintensities on T1- and T2-weighted images that extended through the cortical and subcortical zones. The changes were bilateral in two patients and unilateral in the other two. Associated white matter anomalies were seen in both cerebral hemispheres in three of the four girls. The most severe lesions were mainly in the subcortical white matter. These were diffuse and homogeneous, involving the cortex, ependymal, and subependymal zones. There was also associated cerebral hemiatrophy and hypoplasia of the corpus callosum with cerebellar hemiatrophy in two of them.

Similar lesions were demonstrated as low densities by computed tomography (CT) scan and hyperintensities by MRI in other studies of IP (14–16). There was good correlation between the MRI changes, neuronal dysplasia, and neuronal loss on histologic observation (13,14). The authors suggested that the changes on MRI

coincided well with an infection/vaccinal process that led to encephalitis with variable expression and encephaloclastic effect on the central nervous system (CNS) (15–17).

In an MRI brain study of two sisters with IP, Aydigoz and Midia (18) found hypoplasia of the corpus callosum, enlargement of the lateral ventricles, and periventricular white matter. They also found microphthalmia and retinal detachment. They postulated that these changes could represent cerebral and retinal ischemia arising from a periventricular infiltrate in the cerebral hemisphere and retinal arteriolar system.

Lee et al (19) did a prospective case study of seven patients with IP using MRI, magnetic resonance (MR) angiography, and multislice proton MR spectroscopic imaging. Five of the patients had abnormal MRI changes in the form of increased T2 signals, ventricular enlargement, white matter infarcts, cerebral atrophy, hemorrhages and ischemia, and evidence of cerebral infarction. In three severely affected patients there were similarities to periventricular leukomalacia, a condition of premature infants in which a global hypoxic insult leads to infarction of the vascular watershed regions in the periventricular white matter. There was an association between CNS ischemic changes and retinal vascular occlusive disease. MR angiographic studies were abnormal in two patients. One had a carotid aneurysm, which could have resulted from neonatal damage of the involved vessels. In the other patient, branches of the left cerebral artery could not be visualized, possibly due to reduced blood flow in a hemisphere with reduced cortical volumes. Four of five patients undergoing spectroscopic imaging showed reduced *N*-acetyl aspartate, which has been shown to be a neuronal marker, reflecting a neuronal loss, and increased lactate levels, signifying chronic ischemia. They concluded that at least some of the CNS abnormalities were the result of vascular occlusive events and resultant ischemia similar to that seen in the retina. Other studies suggested the same kind of ischemic changes for the retina (20–22).

Kasai et al (23) reported a case of cerebral infarction in multiple arterial regions of the brain in IP, evaluated with single-photon emission computed tomography (SPECT), which was also able to detect sluggish blood flow in the brain. They recommended IP should be included among the neurocutaneous syndromes associated with ischemic strokes and advocated the use of aspirin as prophylaxis.

In summary, we report a patient with IP who had neurologic signs and changes on MRI. MRI features were highly suggestive of global ischemia during intrauterine life and are entirely consistent with the

nonprogressive neurologic deficit observed clinically. In addition, we reviewed the current literature, which would suggest a relationship between vascular insult and the neurologic findings in IP.

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