# A rare cause of neonatal seizure: incontinentia pigmenti

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**Incontinentia pigmenti (IP) is a rare genetic multisystem disorder that may affect many organs including the skin, bone, eyes and the central nervous system. Central nervous system manifestations are seen in 30% of cases with seizures and mental retardation. Seizures occurring as the presenting sign of IP are rarely reported.**

**We report a case of a female newborn with IP who had seizures on day 4 of life, which were followed in her second month by the development of the characteristic cutaneous changes for IP. With this case report, we would like to emphasize the need for inclusion of IP in the differential diagnosis of neonatal seizures.**

***Key words: incontinentia pigmenti, neonatal seizures, NF-kappa B essential modulator (NEMO) gene mutation.***

Incontinentia pigmenti (IP) is an uncommon, X-linked dominant genodermatosis with accompanying multisystem pathologies. As the disease is fatal for males in utero, almost all patients with IP are females[1,2]. The IP gene is localized on chromosome Xq28. Recently it was shown that the causative mutation is located on the NEMO (NF-kappa B essential modulator) gene. Along with the typical skin lesions, affected females have highly variable abnormalities of the musculoskeletal system, eyes, teeth and central nervous system (CNS). The skin lesions in IP classically evolve through four stages, although not all stages may be observed; namely, stages with erythema and vesicles, verrucous lesions, hyperpigmentation, and finally atrophic hypopigmentation[1,2].

Central nervous system manifestations include seizures, which often start in the first week of life, spastic tetraplegia and diplegia, mental retardation, microcephaly, and magnetic resonance imaging (MRI) changes[3-9].

We report the case of a female newborn whose initial manifestation was seizures. The case later developed other findings of IP, and NEMO gene mutation was found.

## Case Report

A four-day-old female newborn was referred to our center with seizures. Delivery had been normal at term following an uneventful pregnancy. Her mother's medical history revealed an intrauterine death of a male fetus. The parents, who were nonconsanguineous, had a two-year-old healthy boy.

The patient's weight was 3400 g (50-75 percentile), length 48 cm (25 percentile) and head circumference 34.5 cm (50-75 percentile). Her seizures consisted of deviation of eyes, facial twitching, focal clonic jerking of her arms, transient apneic spells and hiccup. The general physical examination revealed no abnormality of the skin, nails, oral mucosa and other systems, including neurological and ophthalmological examinations. Numerous test results were within normal limits and included complete blood count, electrolytes, renal and liver function tests and urine analysis, arterial blood gas and C-reactive protein levels. Urine, blood, and cerebrospinal fluid (CSF) cultures were negative for bacteria, and serology was negative for TORCH infections. Tandem mass spectrometry screening was

also normal. Karyotype was 46,XX. Cranial ultrasound showed no pathology. EEG was abnormal and showed multifocal spikes over both hemispheres. MRI also showed markedly abnormal signal in the right occipitotemporal cortex, specifically an increase in T2 signal, suggesting cortical edema. These findings suggested hypoxic–ischemic encephalopathy (Fig. 1). Neurological examination and the timing of the seizures, however, were not consistent with hypoxia. The patient was then followed for other possible causes of seizures. Seizures became controlled after she began receiving phenobarbital therapy.

In the 6th week of life, the child was observed to have developed a widespread reticular hyperpigmentation on her trunk and all extremities with special predominance in the inguinal regions (Fig. 2). A clinical diagnosis of IP was suspected. A closer follow-up in the following months revealed the development of erythematous and vesicular lesions, which transformed into hyperkeratotic papular lesions by the 4th month. By the 6th month, lesions had resolved with ill-defined linear and whorled hyperpigmented macules most prominently in the inguinal and axillary regions. Clinical diagnosis of IP was confirmed by skin biopsy findings consistent with the vesicular stage of the disease.

Examination of the patient's mother and maternal aunt showed nail and teeth manifestations of IP.

Genetic analysis using peripheral blood lymphocytes from our patient, her mother and maternal aunt revealed deletion mutation at the NEMO gene. The proband's father and brother were not mutation carriers.

The patient was followed up at bi-monthly intervals in our department. At six months of age, MRI disclosed the disappearance of the

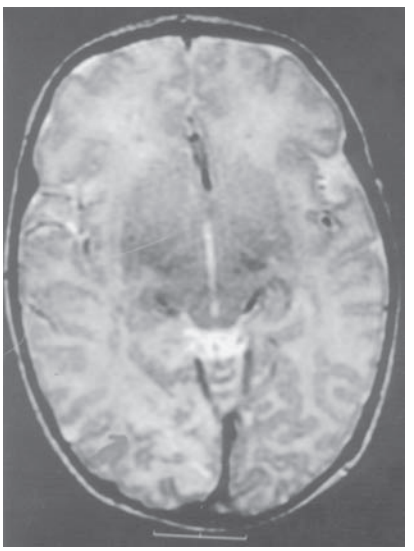

**Fig. 1.** T2-weighted axial MRI images showed increase in T2 signal, suggesting cortical edema.

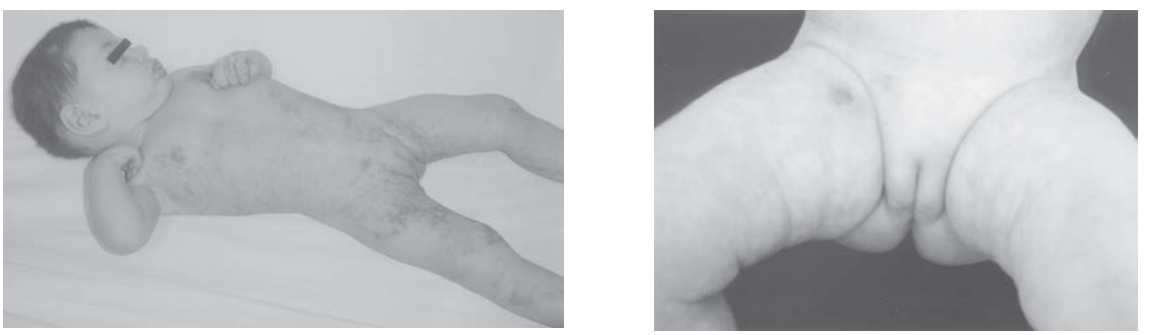

**Fig. 2.** Erythematous and vesicular lesions, some of which have transformed into hyperkeratotic papular lesions.

previously observed signal abnormalities. She developed normally and had neither seizures nor neurological or ophthalmologic signs.

## Discussion

There are many abnormalities associated with IP, and our patient first presented with CNS manifestations, which appear in approximately 40-50% of patients. Seizures are the most common CNS finding, but others include mental retardation, microcephaly, cerebellar ataxia, hemiparesis, motor retardation, cerebral infarction and destructive encephalopathy[7]. Similar to our case, Hubert et al.[3] and Porksen et al.[4] described newborn infants whose first manifestation was a neonatal seizure on the first and fifth days of life, respectively. It has been reported that seizures during the neonatal period have a poor prognosis for normal development. If ocular and CNS abnormalities do not appear by the age of one year, then prognosis for normal vision and neurologic development is good. In this patient, follow-up did not reveal any neurologic abnormalities.

Abnormal MRI findings in IP include cerebral atrophy, hypoplasia of the corpus callosum, white matter lesions, hemorrhagic necrosis and edema. Although the pathogenesis of CNS involvement in IP is unknown, inflammatory pathologies, destructive mechanisms and small vessel occlusive phenomena have been suggested[7]. Pascual-Castroviejo et al.[8] described brain changes on MRI in four girls with IP. Lee et al.[9] reported abnormal MRI changes in five of the seven patients and similarities to periventricular leukomalacia in three patients. Furthermore Shah et al.[10] reported a child with IP and cerebral periventricular leukomalacia on MRI. In our patient, the MRI evidence of ischemic lesions was initially thought to be secondary to hypoxic-ischemic encephalopathy, but careful neurologic examination failed to substantiate this hypothesis. Bacterial cultures of CSF, blood and urine were negative; TORCH serology was also negative, excluding an infectious cause. Eventually, in the second month of life with the pathognomonic skin lesions of IP, a diagnosis of CNS complication of this genodermatosis was made.

Yoshikawa et al.[7] reported a 12-month-old female with IP, in whom MRI disclosed a small transient lesion in the white matter. Although the pathogenesis is unknown, transient CNS involvement might have occurred in early infancy as did the fading skin lesions. Similarly, in our case, MRI revealed the disappearance of the previously observed signal abnormalities.

Incontinentia pigmenti, caused by NEMO-gene mutations, affects predominantly females as is typical of an X-linked dominant disorder. In most cases of IP, these mutations are due to recurrent deletions within encompassing exons 4-10[8,10-12]. Although surviving male patients are described in the literature, the male hemizygous state usually results in early fetal loss. The presence of the mutations in the mother and patient prompted us to give genetic counseling, as each female offspring has a 50% chance of being affected. Therefore, prenatal or preimplantation molecular genetic analyses have been suggested.

In summary, we present a patient with IP who initially showed neurologic signs rather than the characteristic cutaneous changes. Thus, we would like to emphasize the need for repeated full-body examinations in newborns with neurologic symptoms and remind physicians that IP needs to be included in the list of differential diagnoses of neonatal seizures, at least in the female population.

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