

# Incontinentia Pigmenti Associated with Seizures: A Case Report and Literature Review

SW HUANG, CF HU, CC WANG, SJ CHEN

## Abstract

Incontinentia pigmenti (IP) is a rare, multisystemic X-linked disorder. It mainly affects females, and rarely affected men survive. It is characterised by evolving abnormalities of the skin and other organs, including central nervous system (CNS) anomalies that may be associated with seizures, motor impairment, and intellectual insufficiency. We describe an 8-year-old girl who presented with skin manifestations of IP at 3 months and seizures from 1 year of age but without mention of IP. Subsequently, her skin lesions evolved typically and seizures became frequently. Brain magnetic resonance imaging revealed frontoparietal encephalomalacia. Genetic testing showed a c.520-523dupCAGG mutation on exon 5, which was found in some other Taiwanese patients with IP. Remarkably, the patient's overall development was normal, with no signs of intellectual insufficiency or deterioration, despite encephalomalacia. Our findings suggest that brain destruction of IP can develop even antenatally and seizure can attack after then. Nevertheless, further studies are needed for precise mechanism of CNS anomalies in IP.

## Key words

Encephalomalacia; *IKBK*G gene; Incontinentia pigmenti; Seizure

## Introduction

Incontinentia pigmenti (IP), is a multisystemic disorder inherited in an X-linked dominant manner that is lethal in most affected males which was first reported in 1906.<sup>1</sup> This

disorder is characterised by a combination of skin changes and anomalies of other systems and organs, including the central nervous system (CNS), eyes, and teeth. Its estimated prevalence is 0.2/100,000.<sup>2</sup> Mutation of the gene for inhibitor of nuclear factor  $\kappa$ B (NF- $\kappa$ B) kinase  $\gamma$ , *IKBK*G, previously named *NEMO* on chromosome Xq28 was disclosed to cause IP.<sup>3</sup> Approximately 60-88% of patients with IP were examined the mutation, a common deletion of exons 4-10.<sup>4</sup>

The diagnosis of IP is based mainly on skin characteristics, which present typically in four stages, even not all stages may be observed in every given case.<sup>5</sup> The pigmented lesions are the hallmark of IP and are distributed in macular whorls, reticulated patches, flecks, and linear streaks along Blaschko's lines.

CNS anomalies are common in patients with IP and represent the most potentially lethal aspect of the disease. The most frequent types of CNS anomalies in IP are seizures, motor impairment, and intellectual insufficiency.<sup>2</sup> The pathophysiology of these CNS anomalies may be relevant to vascular injury, inflammatory mechanisms, or disturbed apoptosis during development, but the precise mechanisms remain to be confirmed.<sup>2,6</sup> In the present report

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we describe a patient with IP with seizures, and encephalomalacia demonstrated by brain MRI. However, her performance and motor function are intact, implying such insult of CNS occurred during fetal or early prenatal stage.

## Case Report

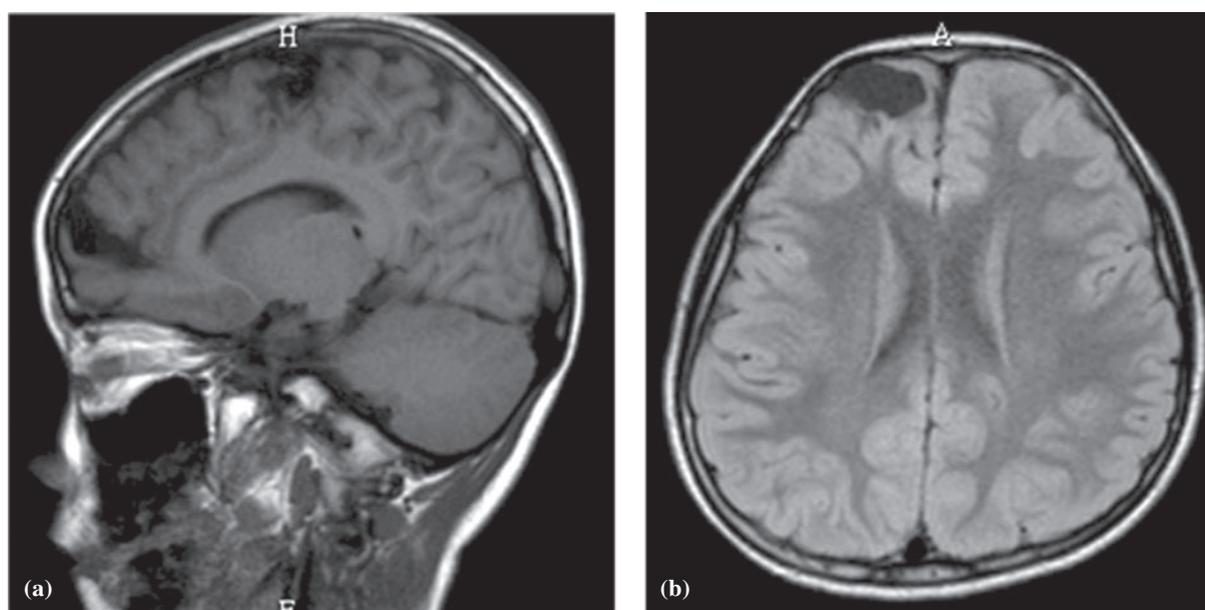
The patient was an 8-year-old girl born by spontaneous vaginal delivery with no significant asphyxia at birth. Her mother had some hyperpigmented lesions on her extremities and a history of three spontaneous abortions of male fetuses. At 3 months of age, the girl presented with a verrucous skin rash on her extremities. She experienced a generalised seizure at 1 year of age, for which she was hospitalised and underwent brain magnetic resonance imaging (MRI), which revealed two areas of encephalomalacia in the frontoparietal region. Magnetic resonance angiography revealed no obviously abnormal results. She experienced another generalised seizure at 4 years of age. At that time, hyperpigmented macules were present on her trunk, arms, and thighs along Blaschko's lines. Her parents refused permission for a skin biopsy. At 8 years of age, she presented with episodic generalised tonic-clonic seizures with jerking of the arms, which lasted for approximately 30 minutes and then stopped gradually. The patient was

hospitalised for further evaluation.

Electroencephalography showed repetitive spike-and-slow waves over the right frontoparietal area of the brain. Brain MRI confirmed encephalomalacia at the same sites identified previously, with no additional areas of destruction (Figure 1). She presented with hyperpigmented, linear streaks over her entire body (Figure 2). Skin biopsy revealed many melanocytes in the papillary dermis and focal basal cell degeneration compatible with stage 3 of IP. The typical clinical and histopathological findings were adequate to reach a clinical diagnosis of IP. In addition, molecular testing showed a c.520-523dupCAGG mutation on exon 5 of the *IKBKKG* gene. This mutation has been reported in Taiwanese patients with IP by Lee et al.<sup>7</sup> The patient was treated with anti-epileptic medication as Oxcarbazepine, with no recurrence of seizures. No intellectual insufficiency or deterioration was noted during outpatient follow-up, despite encephalomalacia. The patient did not demonstrate any other abnormalities, such as dental or ocular manifestations, associated with IP.

## Discussion

NF- $\kappa$ B is widely known for its role in the control of cell division and apoptosis. This is particularly apparent in the nervous system, where active NF- $\kappa$ B protects against



**Figure 1** Brain magnetic resonance imaging at 8 years of age showing two areas of encephalomalacia.

neuronal damage and apoptosis caused by brain injury, hypoxia, and excitotoxicity induced by seizures. Some female *NEMO* +/- mice were shown to have high numbers of apoptotic cells, and the hypothesis that cells lacking *NEMO* protein are prone to apoptosis was also confirmed in a mouse model.<sup>8</sup> Since apoptosis plays a key role during brain development, an excess of apoptotic cells may cause cerebral damage before birth.<sup>6</sup> In our patient, although three episodic seizures occurred within 8 years, brain destruction was noted by MRI after the first seizure, suggesting that brain tissue had been destroyed prior to the occurrence of any seizures.

Landy and Donnai defined the diagnostic criteria for IP in 1993.<sup>9</sup> CNS anomalies are one of the frequent presentations among patients with IP, even they were not included in this diagnostic criteria.<sup>2,6</sup> Minić et al found that 30.44% of patients with IP had CNS anomalies,<sup>2</sup> while Carney and Hadj-Rabia et al. found that 30.5% and 32.5% of patients with IP, respectively, had CNS anomalies.<sup>6</sup> Minić et al. subsequently proposed an update to the diagnostic criteria for IP to include CNS anomalies.<sup>5</sup> The most frequent CNS presentation of IP is seizures.<sup>2,6</sup> Notably, in our case, the patient's mother had similar skin manifestations but no history of seizures. This is in line with the retrospective case series reported by Phan et al, in which none of the relatives of patients with IP had a history of seizures, or intellectual or physical disability. It is possible that IP may remain undiagnosed in patients with a milder phenotype who

lack neurological manifestations.<sup>10</sup>

Encephalomalacia involves softening or loss of brain tissue that occurs after cerebral infarction, cerebral ischaemia, infection, craniocerebral trauma, or other injury. However, although the current patient was found to have encephalomalacia by brain MRI, no obvious developmental delay was detected at follow-up. Brain imaging offers important information on the morphologic aspects of CNS lesions. The white matter seems to be especially vulnerable in IP-related CNS lesions.<sup>6</sup> Periventricular leukomalacia is the most common form and is also observed in premature newborns when hypoxic insult leads to infarction of the vascular watershed regions in the periventricular white matter. Other findings in patients with IP and seizures include patchy gliotic white matter changes, haemorrhagic necrosis, and hypoplasia of the corpus callosum.<sup>6</sup> Minić et al found that brain infarction or necrosis, brain atrophy, and corpus callosum lesions were common in patients with IP, according to the results of brain imaging.<sup>2</sup>

The pathogenesis of CNS lesions in IP remains controversial. Lee et al performed a prospective case study of IP patients using MRI and found a correlation between MRI changes and cerebral infarction.<sup>6</sup> Meuwissen et al reviewed 44 cases of IP with neurological features and found that brain imaging showed variable degrees of vascular insufficiency due to ischaemia or necrosis in 36 patients.<sup>6</sup> Given that skin and CNS both have ectodermal origins, they may share a similar pathogenesis associated with apoptosis



**Figure 2** (a, b) Skin features at 8 years of age consisted of hyperpigmented, linear streaks along Blaschko's lines. (c) Skin biopsy revealed abundant dermal melanophages compatible with the pigmentary stage of IP.

of *IKBKG*-mutated cells. Apoptosis plays a key role in all affected tissues, including the skin and CNS, which precedes vascular changes in IP.<sup>2</sup> Meuwissen et al proposed that most seizures in IP patients were a manifestation of cerebrovascular damage, and that most presented during the neonatal period, but with some occurring during childhood.<sup>6</sup> The cerebral pathology of IP can develop antenatally, and the encephalomalacia in the current patient may have been a sequela of earlier cerebrovascular damage.

In conclusion, neurological anomalies are important findings in IP and seizures occur frequently among them. These neurological aspects have been included in the 2014 updated minor criteria for IP. No definite pathogenesis has yet been determined to account for CNS lesions in IP, but some reports have speculated that vascular changes associated with ischaemia or necrosis, and sequential apoptosis since the antenatal period, may contribute to these anomalies. Further studies are needed to clarify the pathophysiological mechanisms of CNS manifestations in IP.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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