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Clinical Observations

Effectiveness of Corticosteroid Therapy for Acute Neurological Symptoms in Incontinentia Pigmenti

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ABSTRACT

BACKGROUND: Incontinentia pigmenti is a rare neurocutaneous disorder that may result in neurological symptoms in addition to its characteristic skin rashes. The pathogenesis of central nervous system disorders in incontinentia pigmenti remains unclear, but it has been suggested that vascular abnormalities and inflammatory processes may play important roles. Notably, there is no established treatment for central nervous system disorders in incontinentia pigmenti. We report a neonate with acute neurological symptoms of incontinentia pigmenti who was effectively treated with corticosteroid therapy. We review the literature and discuss the pathophysiology, diagnosis, and treatment of acute central nervous system disorders in incontinentia pigmenti. **PATIENT DESCRIPTION:** A 15-day-old girl with incontinentia pigmenti experienced neurological symptoms such as decreased level of consciousness and a weak sucking reflex. Magnetic resonance imaging revealed multiple cerebral infarctions. We administered corticosteroid therapy, and the symptoms improved immediately and significantly. **CONCLUSION:** We suggest that corticosteroid therapy may be an effective treatment during the acute phase of central nervous system dysfunction due to incontinentia pigmenti. It is important to determine the existence of acute phase lesions on magnetic resonance imaging when neurological symptoms occur or worsen.

Keywords: incontinentia pigmenti, neurological symptoms, central nervous system disorder, encephalopathy, corticosteroid therapy, neonate

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Introduction

Incontinentia pigmenti is caused by mutations in the X-linked gene encoding nuclear factor-kappa B essential modulator (*NEMO*), which is required for nuclear factor-kappa B activation and therefore plays key roles in many immune, inflammatory, and apoptotic pathways. Incontinentia pigmenti most commonly affects ectodermal tissues such as the skin, teeth, eyes, and central nervous system (CNS). Approximately 30% of patients with incontinentia pigmenti experience neurological symptoms, including seizures, motor impairment, microcephaly, mental retardation, and occasionally encephalopathy-like symptoms such as coma or disturbed consciousness.[1,2] The pathogenesis of the CNS disorders in incontinentia pigmenti remains unclear.[3,4] There is no established treatment for CNS disorders in incontinentia pigmenti. Here, we describe a neonate with acute neurological symptoms of incontinentia pigmenti, who was effectively treated with corticosteroid therapy. Magnetic resonance imaging (MRI) was very useful for detecting acute phase lesions. We report our experience and considerations regarding the

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pathophysiology, diagnosis, and treatment of acute neurological symptoms in incontinentia pigmenti.

Patient Presentation

This girl was born in a local hospital at 37 weeks of gestation with a birth weight of 2165 g and Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. She was the second child of nonconsanguineous parents, and her family members, including her brother, had no remarkable medical history. Her mother had no symptoms of incontinentia pigmenti, including during infancy, but she had a history of spontaneous abortion. The patient had abnormal skin lesions at birth: a rash and blisters on her trunk and an alopecia lesion on her scalp. On day 1, her abnormal skin lesions improved, but on day 4, the skin lesions deteriorated and she showed decreased level of consciousness and a weak sucking reflex. She was transferred to another neonatal intensive care unit. Her skin lesions and level of consciousness gradually improved, but on day 13 they deteriorated again. MRI revealed multiple high-intensity lesions on diffusion-weighted images (DWI) suggesting multiple cerebral infarctions, and she was transferred to our hospital on day 15. C-reactive protein, complete blood cell counts, and coagulative and fibrinogenic function were normal, and viral and bacterial cultures were negative. Cardiac ultrasound imaging revealed no thrombi.

After transfer, she exhibited encephalopathy (no sucking reflex and little reaction to stimuli). An erythematous and vesiculobullous rash appeared on her arms, legs, face, and trunk, and spread linearly along Blaschko lines (Fig 1A). Based on her characteristic skin lesions, we made a diagnosis of incontinentia pigmenti. An amplitude-integrated electroencephalogram showed a discontinuous abnormal pattern. MRI revealed acute phase lesions with multiple spotty high-intensity areas on DWI in the right frontal lobe, bilateral temporal lobes, thalamus, and basal ganglia, which were compatible with multiple cerebral infarctions due to vasculopathy (Fig 2A). Simultaneously, chronic phase lesions with encephalomalacia were also present in both frontal lobes, the left parietal lobe, and both occipital lobes (Fig 2B,C). We considered that the acute phase lesions revealed active inflammation and started corticosteroid therapy with prednisolone (2 mg/kg/day) on day 15. On the next day, her skin lesions and consciousness improved immediately and significantly (Fig 1B), and her sucking reflex also recovered. The background pattern on amplitude-integrated electroencephalogram also improved to a continuous pattern. MRI on day 19 showed no new lesions, and the spotty high-intensity areas on DWI decreased (Fig 2D-F). After 1 week, we gradually reduced the dose of prednisolone and stopped it on day 33. MRI on day 43 showed no new lesions and no deterioration of the acute phase lesions; however, increased atrophy of the chronic phase lesions was observed (Fig 2G-I). There were no retinal abnormalities. She was discharged from our hospital on day 47. At 6 months, her head control was incomplete. At 7 months, she developed West syndrome and is currently being treated with adrenocorticotropic hormone therapy.

Discussion

This child's findings suggest two important points. First, corticosteroid therapy was effective for acute neurological symptoms of incontinentia pigmenti. Second, MRI revealed acute phase lesions and chronic phase lesions simultaneously, compatible with her clinical course.

The pathogenesis of the CNS disorders in incontinentia pigmenti remains unclear,[3,4] but it has been reported that vascular abnormalities and inflammatory processes may play important roles in CNS disorders. In individuals with incontinentia pigmenti, mutations in *NEMO* gene can lead to apoptosis, and apoptotic changes may precede vascular changes and influence cerebral microvascularization.[5] In fact, MRI and magnetic resonance angiography in incontinentia pigmenti reveal vascular abnormalities such as cerebral infarction, hemorrhage,[3,4] or decreased branching and poor filling of vessels.[4] In retinal lesions, ischemia and vascular occlusive phenomena are observed, so it is likely that they also occur in the CNS.[3–7] Some reports suggest that inflammation also plays an important role. Many authors report perivascular and intravascular eosinophilic infiltration in the CNS, skin, and retinal lesions in incontinentia pigmenti. Maingay-de Groof et al.[8] reported that mutation of *NEMO* leads to activation of eotaxin, a potent eosinophil-selective chemokine, which is strongly expressed by endothelial cells in incontinentia pigmenti and correlates with perivascular and intravascular eosinophilic infiltration. Apoptosis leads to inflammatory responses inducing the synthesis and release of various chemokines, including eotaxin, and subsequent eosinophil infiltration and microvascular occlusion.[5,8] Thus, one hypothesis is that CNS disorders in incontinentia pigmenti result from disorders of angiogenesis or small vessel angiitis due to *NEMO* gene mutation. The clinical course of our patient (multiple infarctions and effectiveness of corticosteroids) supports this hypothesis.

There are only a few reports regarding the treatment of the acute phase of CNS disorders in incontinentia pigmenti, and there is no established treatment. Considering that inflammatory processes may play an important role in CNS disorders in incontinentia pigmenti, it may be reasonable to administer corticosteroidal anti-inflammatory therapies for the acute phase of CNS disorders. In our patient, neurological symptoms (disturbed consciousness and weak sucking reflex) and skin lesions improved immediately and

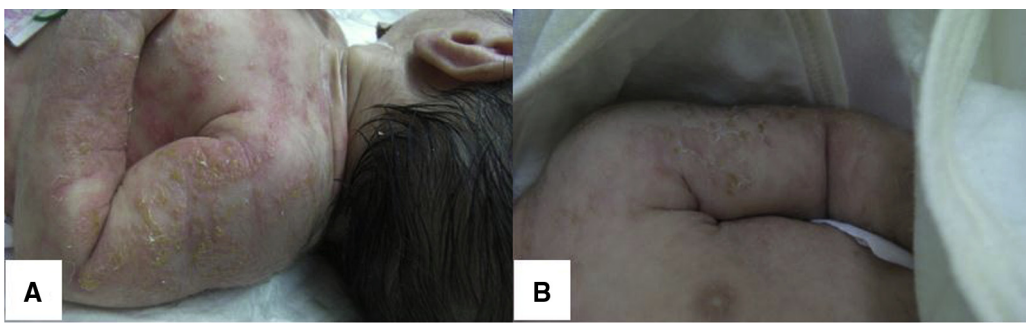

FIGURE 1.
(A) Skin lesions on day 15: an erythematous and vesiculobullous rash appeared on her arms and trunk, and spread linearly along Blaschko lines. (B) Skin lesions on day 16 (the day after initiation of corticosteroid therapy): skin lesions improved. (The color version of this figure is available in the online edition.)