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Original article

Early infantile manifestations of incontinentia pigmenti mimicking acute encephalopathy

Shinpei Abe [a,*], Akihisa Okumura [a], Shin-ichiro Hamano [b], Manabu Tanaka [b], Takashi Shiihara [c], Koichi Aizaki [d], Tomohiko Tsuru [d], Yasuhisa Toribe [e], Hiroshi Arai [f], Toshiaki Shimizu [a]

[a] *Department of Pediatrics, Juntendo University School of Medicine, Tokyo, Japan*
[b] *Division of Neurology, Saitama Children's Medical Center, Saitama, Japan*
[c] *Department of Neurology, Gunma Children's Medical Center, Gunma, Japan*
[d] *Department of Pediatrics, Matsudo City Hospital, Chiba, Japan*
[e] *Department of Pediatric Neurology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan*
[f] *Department of Pediatric Neurology, Morinomiya Hospital, Osaka, Japan*

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Abstract

Objective: We retrospectively reviewed six patients with incontinentia pigmenti (IP) who had encephalopathic manifestations during early infancy.

Methods: We enrolled six patients who met the following criteria from the mailing list of the Annual Zao Conference: (1) diagnosis of IP; (2) encephalopathic manifestations with reduced consciousness and clusters of seizures by 6 months of age; and (3) no evidence of central nervous system infection or metabolic derangement.

Results: The onset of the encephalopathic events was within the first 2 months of life in all but one patient. All had clusters of focal clonic seizures. The duration of seizures was typically 5 min. The seizures ceased within 5 days in all patients. Various degrees of reduced consciousness were observed in association with the frequent seizures. Diffusion-weighted imaging during the acute phase showed reduced water diffusion in the subcortical white matter, corpus callosum, basal ganglia, thalami, and internal capsule in two patients. Scattered subcortical white matter lesions were observed on fluid-attenuated inversion-recovery images in two patients.

Conclusions: The encephalopathic manifestations in patients with incontinentia pigmenti were characterized by seizure clusters and reduced consciousness, albeit of relatively short duration. Magnetic resonance imaging abnormalities were predominant in the subcortical areas in most patients.

Keywords: Incontinentia pigmenti; Encephalopathic manifestation; MRI; Diffusion-weighted image; Early infancy

1. Introduction

Incontinentia pigmenti (IP) is a rare neurocutaneous syndrome characterized by skin lesions and disorders of various organs, including the central nervous system (CNS), eyes, teeth, and hair. The skin lesions specific to IP are present at birth or develop soon after birth. The skin lesions are classified into four stages: the vesicular, verrucous, pigmented, and atrophic scarring stages. Mutations of the NEMO (NF-κB essential modulator) gene located at Xq28 are responsible for IP [1]. NEMO is required for the activation of NF-κB, which protects against apoptosis and controls immune and

* Corresponding author. Address: Department of Pediatrics, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Tel.: +81 3 3813 3111; fax: +81 3 5800 1580.
E-mail address: shiabe@juntendo.ac.jp (S. Abe).

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inflammatory responses and cell adhesion [2]. IP cells with NEMO mutations lack NF-κB activation completely and are exquisitely sensitive to tumor necrosis factor alpha (TNF-α)-induced apoptosis [3]. The pathology of IP is characterized by extensive X-inactivation skewing [3], which reflects an efficient mechanism of counter-selection affecting cells expressing the mutated X chromosome. This extensive skewing is not seen in the antenatal epidermis, but in the epidermis after IP dermatosis.

One third of the patients with IP have CNS disorders, which manifest as seizures, microcephaly, mental retardation, hemiparesis, and spasticity. Several reports have described the neuroradiological findings and pathogenesis of IP, whereas the CNS manifestations of patients with IP are not fully understood.

We treated a patient with IP who had a cluster of severe seizures accompanied by reduced consciousness at 1 month of age. Although acute encephalopathy of unknown origin was first suspected in this patient, we later attributed the event to the CNS involvement of IP itself. We presented this patient at the Annual Zao Conference on Pediatric Neurology, where the clinical and neuroimaging features attracted the attention of the participants. Consequently, we attempted to clarify the features of the early infantile manifestations in children with IP mimicking acute encephalopathy. We present the results of a retrospective review of six patients with IP who had encephalopathic manifestations during early infancy.

2. Patients and methods

We collected patients who met the following criteria through the mailing list of the Annual Zao Conference on Pediatric Neurology: (1) diagnosis of IP based on the characteristic skin lesions; (2) encephalopathic manifestations with reduced consciousness, and seizure clusters or status epilepticus before 6 months of age; and (3) no evidence of CNS infection or metabolic derangement. The mailing list of the Annual Zao Conference includes more than 400 pediatric neurologists from all over Japan. This study was approved by the institutional review board of Juntendo University School of Medicine.

The patients were collected after we presented our patient (Patient 1) at the Annual Zao Conference in February 2007. Six patients who met the entry criteria were recruited, including our patient. We sent a structured questionnaire to each patient's attending pediatric neurologist. Magnetic resonance imaging (MRI) data were also collected. We reviewed the MRI and clinical features of the patients. At present, the mutation of the NEMO gene has not been examined in any of the patients.

3. Results

3.1. Patient report

The clinical course of Patient 1 was as follows. The patient was born after 38 weeks of gestation with a birth weight of 3354 g. Her mother had been diagnosed with IP, although the patient's older sister was not affected. Her perinatal history was unremarkable, although she was diagnosed with IP based on the histopathological findings of the characteristic skin lesions, which had appeared immediately after birth. She had a cluster of generalized convulsions lasting for a few minutes at 44 days of age. On admission, she was semi-comatose and had verrucous skin lesions. Her body temperature was 36.3 °C. The physical and neurological examination did not reveal any other abnormalities. Mild increases in white blood cells and eosinophils were observed (white blood cell count 15,800/μl with 12% eosinophils); no other abnormalities were found in the hematological, blood chemistry, or cerebrospinal fluid examinations. MRI the day after admission revealed patchy reduced diffusion in the subcortical and deep white matter, predominantly in the right frontal area, right thalamus, and basal ganglia (Fig. 1). On the same day, the electroencephalogram (EEG) showed right frontal dominant slowing of the background activity. Initially, she was diagnosed with acute encephalopathy of unknown origin and treated with glycerol, midazolam, dexamethasone, and acyclovir. Her convulsions were controlled after the dose of midazolam was increased to 0.3 mg/kg/h. She regained consciousness 10 days after the onset.

At 32 months of age, she presented with moderate mental retardation and mild left hemiplegia. Focal epilepsy developed at 9 months of age. Her seizures were characterized by clonic convulsions of the right upper and lower extremities with preserved consciousness. Phenobarbital was ineffective, and her seizures were controlled after gabapentin was added at 23 months of age. MRI at 10 months of age showed cystic encephalomalacia in the right frontal area predominantly (Fig. 1).

3.2. Patient characteristics (Table 1)

The patients were all female. Their pregnancy and delivery were unremarkable. Three patients had family histories of IP. All patients had vesicular eruptions appearing immediately after birth and were diagnosed with IP clinically or pathologically. Four patients had disorders in organs other than the skin and CNS: three had ocular disorders, one had a dental disorder, and one had superior vena cava syndrome. The average follow-up period was 47 months (range 7–123 months).