Childs Nerv Syst (2008) 24:525–528
DOI 10.1007/s00381-007-0550-z

CASE REPORT

Serial changes in white matter lesions in a neonate with incontinentia pigmenti

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Received: 1 November 2007 / Published online: 21 December 2007

Abstract
Case report We report an infant who presented with clinical manifestations of incontinentia pigmenti (IP). Despite experiencing seizures in the early neonatal period, the patient had normal growth and development until recently. However, follow-up magnetic resonance imaging revealed sequential changes in white matter lesions.
Discussion The pathogenesis of neurological involvement in IP has not been clearly elucidated and appears to be associated with various mechanisms, including developmental, destructive, and vascular processes. We have attempted to explain the pathogenesis of IP through these changes.

Keywords Incontinentia pigmenti · Magnetic resonance imaging · Pathogenesis

Introduction

Incontinentia pigmenti (IP) is a neurocutaneous disorder characterized by skin manifestations and associated malformations of the retina, teeth, and central nervous system (CNS) [1]. The neurological symptoms of IP include seizures, microcephaly, and developmental delay; the prognosis for normal cognitive development is poor, particularly if seizures occur early in life [1, 2]. The exact pathogenesis and timing of neurological involvement are not well known. However, findings consistent with the diagnosis of cerebral infarction and a correlation between retinal and cerebral vascular involvement support the hypothesis that vascular disease plays a major role in the pathogenesis of cerebral lesions and thus neurological involvement in patients with IP [3].

The magnetic resonance imaging (MRI) findings associated with IP include periventricular leukomalacia, hypoplasia of the corpus callosum, gray matter heterotopia, cerebellar lesions, encephalomalacia, multiple cerebral infarctions, and vessel abnormalities [4–7]. Despite a number of reports on the various MRI findings in IP, there is limited information on the imaging findings of cerebral lesions in infants [2, 4]. In this paper, we present the sequential changes in white matter lesions revealed by MRI in a case of IP. In addition, we have attempted to explain the pathogenesis of IP through these changes that were detected by brain imaging.

Case report

A female term infant was admitted at birth due to skin vesicles mainly on the lower limbs. The physical and routine laboratory examinations were normal. Three days after birth, these skin lesions increased in size and number, and a skin biopsy was performed. Six days after birth, the skin lesions spread to the trunk and became crusted pustules or hyperkeratotic lesions over time (Fig. 1a and b) . Pathology revealed exocytosis of eosinophils, spongiosis in the epidermis, and intraepidermal vesicle formation. The infant was diagnosed with IP because of these findings of characteristic skin lesions.

On the ninth day of life, the patient developed frequent clonic seizures associated with cyanosis and bradycardia.

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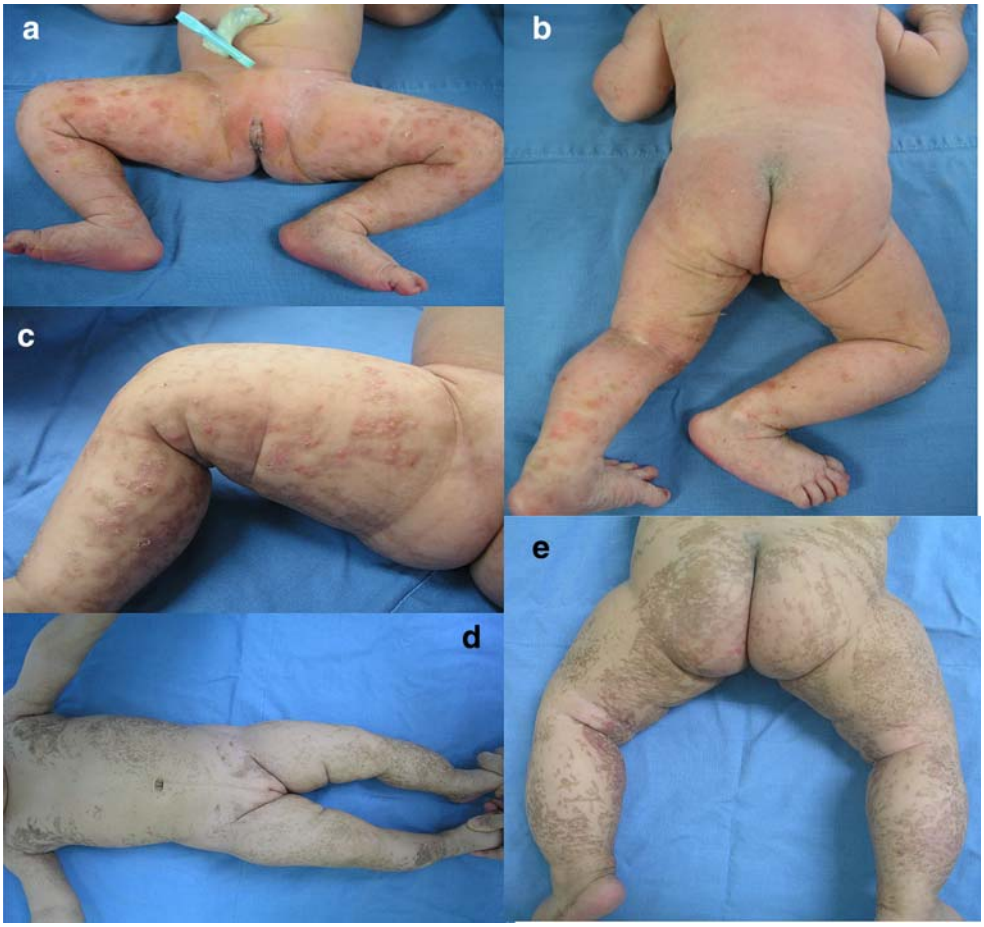

Fig. 1 Skin lesions **a** and **b** at birth, **c** at 3 months of age, and **d** and **e** at 6 months of age

The follow-up laboratory results were normal. Intravenous lorazepam and phenobarbital were administrated. In the MRI examination of the brain, multiple dot-like lesions in the corona radiata of both cerebral hemispheres appeared hypointense on T2-weighted images. Some of the lesions appeared hyperintense on T1-weighted images (Fig. 2a and b). No further spreading of the skin lesions was observed. Ophthalmologic examination demonstrated left retinal vascular changes, characterized by ectatic tortuous veins, arteriovenous anastomoses, and peripheral retinal ischemia. Laser photocoagulation was performed on the 11th day of life, and the lesions regressed.

At the age of 1 month, the dry and hyperkeratotic lesions forming involuted verrucous plaques, which were mainly present on the lower limbs. At the age of 3 months, hyperpigmented lesions were distributed in a macular whirl on the limbs and trunk, the vesicles recurred, and verrucous lesions developed occasionally (Fig. 1c). The patient could

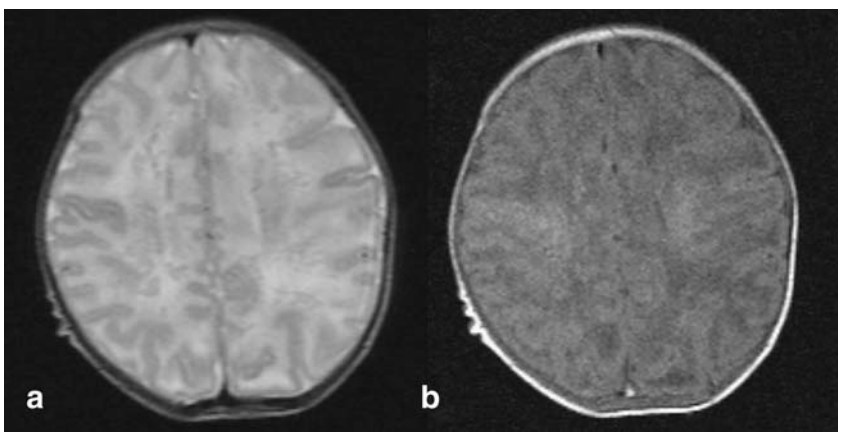

Fig. 2 On day 9 of life, the axial T2-weighted MR image (TR/TE, 4,000/99) showed multiple dot-like lesions with low signal intensity in the corona radiata of both cerebral hemispheres (**a**). The axial T1-weighted MR image (TR/TE, 540/12) revealed multiple dot-like high signal intensity in the same regions (**b**)

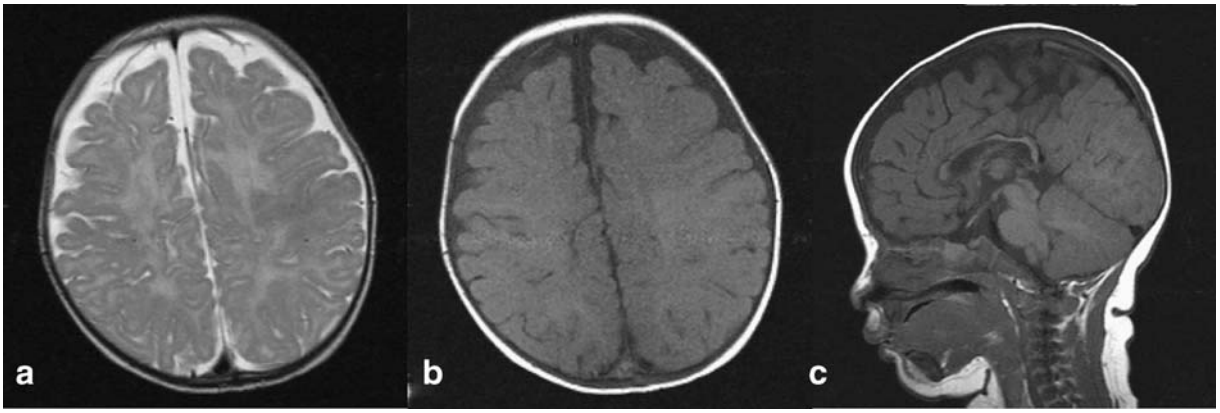

Fig. 3 At 6 months of life, axial T2- and T1-weighted MR images demonstrated resolution of previously noted, multiple, dot-like lesions in the corona radiata of both cerebral hemispheres (**a** and **b**). The midline sagittal T1-weighted image showed mild thinning in the body portion of the corpus callosum corresponding to the patient's age (**c**)

lift her head and chest in the prone position and had no head lag when pulled to the sitting position. Administration of phenobarbital was discontinued.

At the age of 6 months, the pigmented lesions persisted (Fig. 1d and e). The infant had normal growth and development at this time. Follow-up brain MRI showed resolution of the previously noted lesions with mild diffuse thinning of the body portion of the corpus callosum corresponding to her age (Fig. 3a, b, and c).

The patient is now 17 months old; the developmental milestones are within normal limits and the head circumference is normal. However, the initial periventricular white matter lesions that had appeared to resolve have recurred. In addition, there was a marked hypoplasia of the corpus callosum (Fig. 4).

Discussion

The clinical manifestations of IP are variable and range from skin lesions to severe neurological involvement. The neurological symptoms and signs of IP include seizure, mental retardation, delayed psychomotor development, microcephaly, cerebellar ataxia, hemiparesis, and coma [8]. The MRI findings in IP include cerebral atrophy [1], hypoplasia of the corpus callosum [1], white matter lesions [4, 9], and hemorrhagic necrosis [9]. In a case of acute hemorrhagic encephalopathy with IP, it was speculated that an expressed mutant protein could cause either developmental brain malformations or a destructive process in the CNS [10]. It was described as periventricular hemorrhagic infarcts and cerebral microangiopathy [11]. A girl and her mother with IP had similar ischemic stroke events resulting from an occlusion of the left middle cerebral artery, which was detected by MRI [12]. The importance of vasculopathy as the major mechanism underlying CNS pathology in IP was reported; this is supported by the common features of retinal vascular abnormalities and the documented correlation between the severity of CNS involvement and retinal vascular occlusive disease [2]. In contrast, it was reported that an infant with neonatal seizures and a vesicular rash had

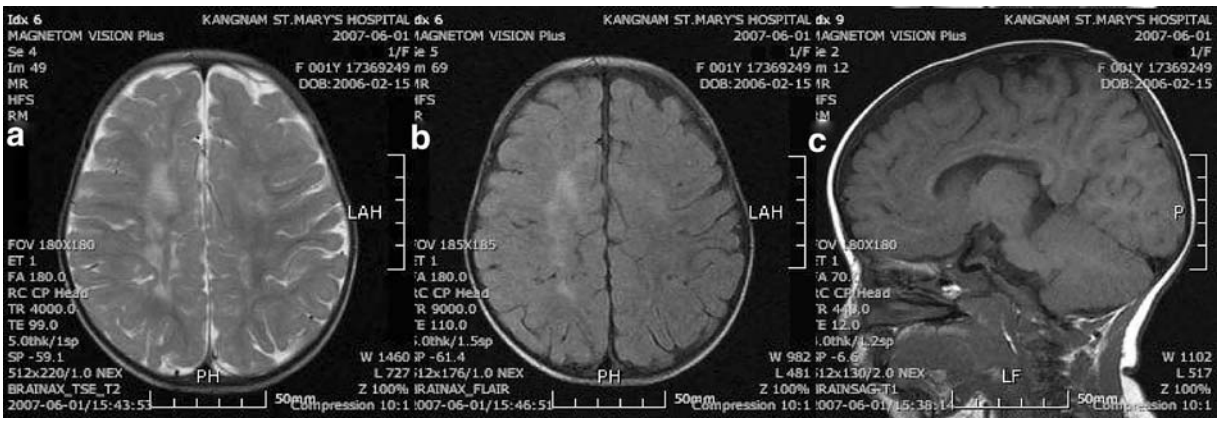

Fig. 4 At 15 months of life, axial T2-weighted (TR/TE, 9,000/110) and flare MR images (TR/TE, 4,000/99) showed high-signal areas in the periventricular white matter of the cerebral hemispheres, suggesting periventricular leukomalacia (**a** and **b**). These changes are more marked on the right side. The midline sagittal T1-weighted image (TR/TE, 440/12) revealed marked hypoplasia of the corpus callosum (**c**)

no overt vascular abnormalities but a diffuse inflammatory process [13]. Another report described a few cases with unilateral micropolygyria and multiple focal neuronal loss, porencephaly, or severe cortical atrophy that could have resulted from ischemic injuries during fetal life [14]. Therefore, the pathogenesis underlying CNS involvement in IP appears to be associated with various mechanisms, including developmental, destructive, vascular, and infectious processes.

It is known that the neurological lesions in patients with IP, once identified, change little over time. However, in least one patient, a white matter lesion has unusually resolved over time [15]. In this case, after the disappearance of the initial lesions in the corona radiata, hypoplasia of the corpus callosum and periventricular white matter lesions appeared again after all. These sequential changes suggest that CNS involvement in IP is similar to ischemic lesions occurring at a time of particular vulnerability of the premature brain.

Some authors have reported that the MRI findings in IP may predict the clinical course of the disease [1]. Brain lesions were most prominent in patients with neonatal cutaneous lesions and either seizures or ocular abnormalities. These patients showed a gradual decrease of the head circumference percentile during the first year of life and neurologic sequelae; patients with mild cutaneous lesions and without neurological symptoms had no MRI abnormalities. At first, because of improvement of the initial white matter lesions, we believed that the neuroradiological findings in the patient were favorable despite the early symptoms, including severe cutaneous lesions, neonatal seizures, and ocular abnormalities. However, the periventricular white matter lesions recurred and hypoplasia of the corpus callosum appeared markedly despite the achievement of normal developmental milestones and normal head circumference.

In summary, although the pathogenesis and progression of neurological involvement in IP have not been clearly elucidated, we suspect that ischemic insults that originate in the intrauterine environment are important in the development of IP. Furthermore, we demonstrated that follow-up neuroimaging should be performed once severe neonatal symptoms, including neurological and ocular impairment are detected, even if progression through the developmental milestones is normal, head circumference is unremarkable, and the symptoms associated with IP improve.

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