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Neonatal Seizures in Two Sisters with Incontinentia Pigmenti

Abstract

Familial incontinentia pigmenti (IP) (OMIM #308300) is a rare genetic disorder which segregates in an X-linked dominant way. The female-to-male ratio ranges from 20 to 37:1. In affected females IP causes highly variable abnormalities of the skin, hair, nails, teeth, eyes, and central nervous system (CNS). Cardiovascular anomalies, cerebral infarction, and immune dysfunction are rare complications of IP. The pathogenesis of cerebral changes in IP remains elusive. We report the case of two IP-affected sisters who presented in each case with neonatal seizures on the fifth day of life. Via cranial magnetic resonance tomographic imaging (MRI) different types of lesions in both hemispheres were demonstrable in both patients. To date the pathogenetic mechanisms for the cerebral lesions are not fully understood. However, multiple microscopic infarcts could serve as a possible explanation. The clinical course and the neurological development of the older child are favorable and so far the younger sibling appears to be developing normally, which is uncommon for patients with early onset of neurological symptoms. Symptomatic seizures in IP are an important differential diagnosis in benign non-familial and familial neonatal seizures.

Key words

Neonatal seizures · incontinentia pigmenti · magnetic resonance imaging (MRI)

Introduction

Familial incontinentia pigmenti (IP) (OMIM #308300) is a rare genodermatosis that segregates as an X-linked dominant disorder [9,11]. The female-to-male ratio ranges from 20 to 37:1. In most of the cases mutations leading to IP are male-lethal, which is responsible for the high rate of abortions and miscarriages in females with IP. In affected females IP causes highly variable abnormalities of the skin, hair, nails, teeth, eyes, and central nervous system (CNS). Seldom complications are cerebral infarction and cardiovascular anomalies [6,7]. The incidence of leukemias and solid tumors of the kidney might be increased [3]. The prominent skin signs occur in four characteristic cutaneous stages: perinatal inflammatory vesicles, verrucous patches, a distinctive pattern of hyperpigmentation following the lines of Blaschko in the third stage finally leading to hypopigmented macules [11,16]. CNS involvement occurs in one third to one half of the cases, presenting as mental retardation, cerebral palsy, or seizures [8,10]. In newborns the prominent neurological feature is the onset of seizures on the second or third day often confined to one side of the body. We describe the clinical course of a family in which both daughters presented with neonatal seizures at the age of 5 days. Postnatal cranial MRI demonstrated several lesions in the grey matter in both children. Subsequently the diagnosis of IP was confirmed in the mother and seems to be probable in the grandmother as well.

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Patients and Methods

Hospital admission and out-patient charts were reviewed. Routine EEG was recorded using the 10–20 international system during the symptomatic and asymptomatic episodes. Cranial magnetic resonance imaging (MRI) with axial and coronal T₁- and T₂-weighted MR images (spin echo, 0.5 T Gyroscan, Philips) was performed on both girls at the age of three weeks in the first daughter (patient 1) and of two weeks in her younger sister (patient 2), respectively.

Results

Case reports

Case 1

We report an almost 4-year-old girl (IV-9 in the pedigree, see Fig. 1) who developed neonatal seizures at the age of 5 days. The girl is the first child of non-consanguineous Caucasian parents. The infant was born after an unremarkable pregnancy. On her first day of life the skin showed a papular rash. At the age of five days she developed initially focal seizures with right-side accentuation and later generalized seizures and a status epilepticus. Electroencephalography (EEG) showed a normal basic activity with intermittent signs of tiredness but no clear epileptic dysregulation. The diagnostic steps yielded no infection or other underlying cause as a metabolic disease or an imbalance of electrolytes, the cerebral ultrasound on the fifth day of life showed a periventricular hyperdensity and in the sequelae some small cysts up to 3.5 mm in diameter located right parietal along the frontal horn of the lateral ventricle. The infant was treated with phenytoin. The seizures ceased on the 8th day of life and did not recur. The antiepileptic treatment was continued for two months and then stopped without complications. A native MRI of the CNS at the age of three weeks demonstrated small liquor-intense supratentorial regions of infarction with involvement of the cortex and the subcortical grey matter on both sides (Fig. 2). In addition some solitary focal lesions of a few millimeters diameter with on T₁-weighting light and on T₂-weighting dark enhancement presented on both sides of the periventricular grey matter.

In spite of these structural cerebral changes, the further neurological development of the child was favorable and the milestones of development were reached without delay. A normal EEG was recorded at the age of nine weeks. The skin lesions developed through the typical stages of IP and now present as hyperpigmented, slightly curved streaks on both sides of the trunk. A dental manifestation of the IP appeared during the following years with characteristic cone-shaped front teeth.

Case 2

The girl is the sister of patient 1 and the family's second child (IV-10 in the pedigree, Fig. 1). Pregnancy and delivery revealed no abnormalities. Starting on day one she exhibited a papular rash, distributed along the lines of Blaschko. The papules developed into vesicles. At the age of five days she developed neonatal seizures, first appearing as oral automatisms, then with a right-sided accentuated focal pattern of cloni of the extremities but without generalization. EEG showed a normal basic activity with some steep waves on the right hemisphere but no further signs of epilepsy. The laboratory findings were normal with no signs of infection or metabolic disease, a cerebral ultrasound showed no pathology. Apart from a mild hyperirritability no abnormalities were seen on clinical examination. Her skin showed a maculopapulous exanthema and some vesicle eruptions with an asymmetric linear pattern at the extremities. The seizures were self-limiting and ceased on her 6th day of life without anticonvulsive treatment. An MRI was performed at the age of two weeks and showed a few hypointense (T₂-weighted) and multiple hyperintense (T₁-weighted) round lesions in the periventricular white matter in both hemispheres with enhancement after administration of contrast medium (Figs. 3, 4, and 5). Another, possibly, perivascular enhancement was seen on both sides located parietal along Virchow Robinson's space. Three, about 0.5 cm diameter, fat isointense formations suspect of lipomas were located on the left side infratentorial lying ventral of the hypoplastic sinus. No watershed infarction-like lesions were seen.

At the age of six weeks a normal EEG control was recorded. The skin still showed the papulovesicular exanthema with only a slight regression. No ocular manifestation has been found so far, the ultrasound of the hip only displayed a mild dysplasia. Chro-

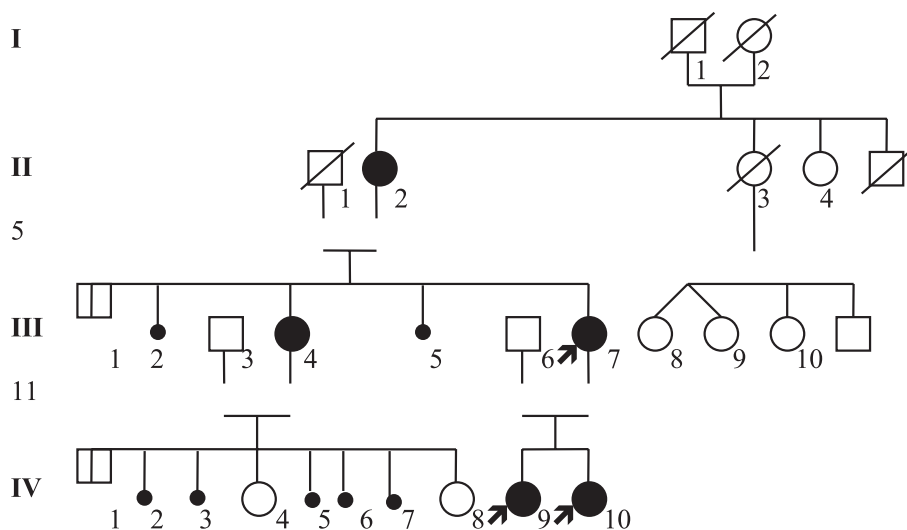


Fig. 1 Pedigree of the family (circles: females, squares: male persons, fulfilled/black circles: affected females, little circles: abortions, crossed out symbols: dead persons, arrows: pointing the patients and their mother).

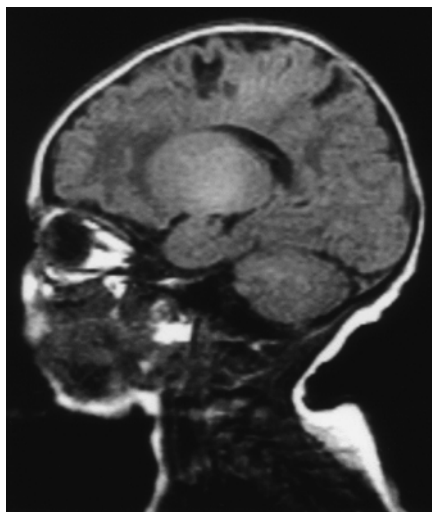


Fig. 2 Cranial MRI of patient 1 at the age of three weeks: The parasagittal right (T₁) image shows hypointense regions like watershed infarctions.

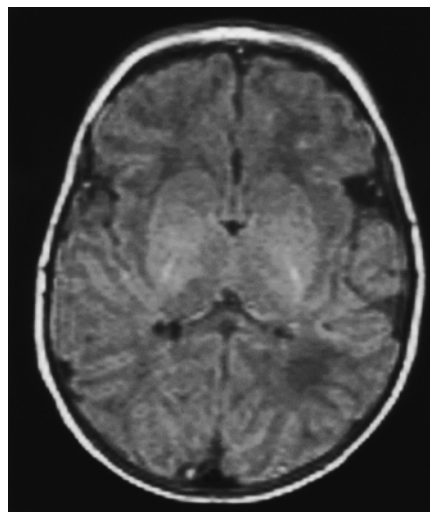


Fig. 3 Cranial MRI of patient 2 at the age of two weeks: Axial (T₁) image shows multiple hyperintense foci in the periventricular white matter.

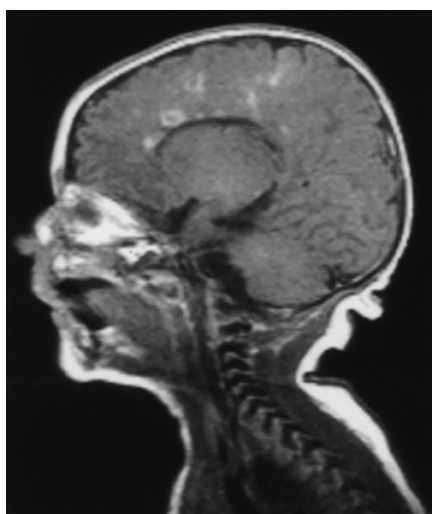


Fig. 4 Same patient as Fig. 3. Parasagittal right image (T₁ after Gd-injection) shows multiple areas with ring-, point, and linear-like enhancement parietal in the white matter.

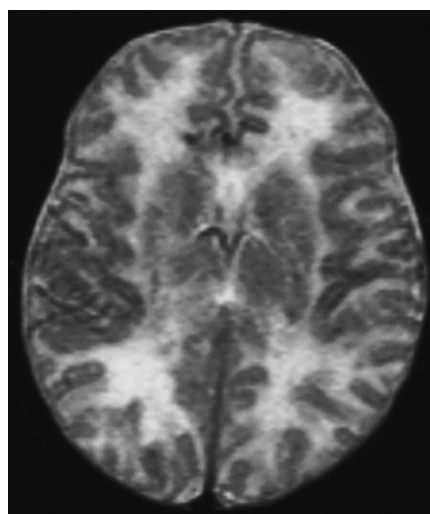


Fig. 5 Same patient as Fig. 3. Axial (T₂) image shows few hypointense foci in the periventricular white matter.

mosomal analysis revealed a normal female karyotype 46,XX. The further development of the patient appears to be age adequate.

Family history (pedigree see Fig. 1)

Genetic counseling was carried out in the family. The mother (III-7) reported on analogous symptoms as a child. At the age of two years she developed characteristic marble cake-like hyperpigmentations on her chest and her calves. She is missing eight premolars; other teeth show the typical peg shape. The mother's sister (III-4) and the common mother (the grandmother of the girls, II-2) were reported to have small and bad teeth, too. Additionally, the grandmother was reported to have had alopecia after her pregnancies. There is a history of miscarriages of the grandmother and mother's sister. DNA analysis was rejected by the mother because the result has no consequences for therapy or prenatal diagnosis.

Discussion

We report on two siblings with IP. The initial symptoms were characteristic skin lesions followed by neonatal seizures at day five in both patients. Familial IP is an X-linked dominant disorder

caused by mutations in the *NEMO* gene. By sequence alignment, Jin and Jeang [14] mapped the human *NEMO* gene to chromosome Xq28. The International Incontinentia Pigmenti Consortium [14] demonstrated that mutations in *NEMO* cause incontinentia pigmenti [15,16,]. *NEMO* is essential for NF-kappa-B activation, which normally protects against TNF-alpha-induced apoptosis. IP cells are therefore highly sensitive to proapoptotic signals. Most of the clinical symptoms can be related to known functions of the NF-kappa-B pathway such as, for example, the relevance of a normal activity for the development of fibroblasts and osteoclasts [6,14]. Initially, IP was considered to constitute a lethal factor in males. Recent reports have shown that some males may survive, showing symptoms of IP or presenting with a phenotype of hypohidrotic ectodermal dysplasia and features of immunodeficiency [1,6,17].

Several mechanisms for the induction of the cerebral changes in IP (developmental, inflammatory, occlusive or destructive) are discussed [8]. In our index patients the MRI findings resemble each other as well as the pattern of clinical symptoms during the first days of life. The pathogenesis of the patients' cerebral changes is difficult to determine. They might be the result of infarctions that took place soon after birth and led to the seizures. The MRI shows small infarction-like foci in the watershed zones,

sustaining this assumption. The hemostatic parameters were within the normal range and no diagnostic results were indicative for a thrombophilia. But microinfarction seems to be an explanation of the cerebral changes only to some extent. Two reports of additional single photon emission computer tomography (SPECT) revealed a reduced blood flow in the area of the lesions suspicious of a post-infarctional state [5]. We found multiple small nummular lesions in the second patient, which cannot simply be caused by a hypoxic event. The latter findings resemble the MRI lesions found in a four-week-old girl with IP and a lesion with low intensity in T₁- and high intensity in T₂-weighted imaging [16]. MRI control imaging at seven months demonstrated a nearly complete regression of the abnormal findings. Her development followed until the age of one year was normal. The so far favorable neurological outcome after early onset with neonatal seizures differs from most reported cases of IP in the literature. This leaves some doubt that the seizures are connected with the IP. As the onset of the seizures was at the fifth day, one differential diagnosis is non-familial-neonatal seizures. EEG findings were unspecific and only temporary. A series of MR findings of eight patients with incontinentia pigmenti showed only cerebral abnormalities in patients with neurological sequelae [8]. The few post-mortem analyses of the brain in IP give a broad picture from necrotic foci in the white matter and cortex to a destructive process with scarring and white matter cavity as well as inflammatory processes with diffuse cell infiltration [10]. The enhancement of the lesions after injection of the contrast medium in patient 2 is indicative for an inflammatory process. More presymptomatic MR images would be essential to distinguish between a developmental destructive process or lesions as a result of infarctions. In the majority of patients, the cerebral changes appear to be stable, though progressive or even regressive processes are described [5,6,10]. To evaluate the dynamics of the changes at least one follow-up investigation even with a stable clinical picture should be performed. Genetic counseling is obligatory and a chromosome analysis should be done to exclude gonosomal aberrations or mosaics. A screening for IP-related medical conditions and follow-up investigations are necessary to exclude associated disease and should consider the neurological, dermal, ocular, dental, and orthopedic symptoms. As associated malignant disease, immunodeficiency and vascular anomalies have been described, they should be ruled out as well.

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