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ORIGINAL PAPER

Therapy resistant neonatal seizures, linear vesicular rash, and unusually early neuroradiological changes: incontinentia pigmenti

A case report, literature review and insight into pathogenesis

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Abstract
Case presentation A substance abusing G2P1 mother spontaneously delivered at term an appropriate for gestational age girl. Neonatal seizures appeared at 21 hours and empiric anticonvulsive and antimicrobial treatment was started. At 25 hours, first vesicles appeared. While routine evaluations remained normal, a head CT revealed multifocal ischemic injuries, and a later MRI showed multifocal petechiae and diffusion abnormalities in the corticospinal tracts. The clinical diagnosis of incontinentia pigmenti (stage 1) was secured by histopathology. Follow-up at 13 months showed global developmental delay.
Discussion We discuss the unusually early bilateral, fronto-occipital corticomedullar ischemias (CT day 3). On the MR imaging (day 7) extensive symmetric cerebral corticomedullar destruction and diffusion sequences with corticospinal tracts abnormalities are seen, which then evolve (day 26) to extensive symmetric cerebral destruction. We review the literature, genetics, suspected pathophysiology and possible neonatal manifestation.
Conclusion Incontinentia pigmenti is rare and, therefore, diagnosis is frequently delayed. Nevertheless, in the setting of therapy refractory seizures, excluded infections, and linear vesicular rash, a high index of suspicion is needed. This is the first report of simultaneous corticomedullar involvement as early as the third day of life.

Keywords Neonatal · Seizure · Incontinentia pigmenti (IP) · NEMO · NF-κB · IκB

Introduction

The neonatal diagnosis of incontinentia pigmenti (IP), despite specific clinical features, is often delayed and made by exclusion once the infectious work-up is negative. As in

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the setting of vesicular exanthemas and therapy resistant seizures, neonates are empirically treated for suspected neonatal herpes encephalitis and/or bacterial meningitis. The clinical diagnosis is secured by pathognomonic histological changes in the affected skin.

We would like to draw attention to this frequently (initially) missed diagnosis and describe a girl with clinical and histological features of IP and unusual simultaneous corticomedullar involvement as early as 3 days of life, as previous neuroradiological magnetic resonance imaging (MRI) reports showed either white [20] or grey matter involvement [48].

We review the current literature and discuss the known pathophysiology.

Case presentation

A gravida 2, para 1 mother using crack, methyl-amphetamine, cocaine, nicotine, and ethanol during pregnancy spontaneously delivered at term an adequate for gestational age girl after 2 hours of ruptured membranes. Family history included a grandmother with a brain aneurysm and a grandfather with apoplexy. TORCH and Group B streptococcus screening were negative. The immediate postnatal period was uneventful. At 21 hours of age, right arm jerking and eye deviation were noted. Intermittently, the infant was pink, having a normal muscular tone with a normal fontanel but weak suck. Phenobarbital, ampicillin, gentamicin and acyclovir were started. The initial hematological and chemical work-up was normal, CSF was xanthochromic but sterile (incl. immune-fluorescence testing for HSV). The blood culture grew coagulase negative staphylococcus, which was regarded as a contaminant. A head ultrasound showed a right sided grade I intraventricular hemorrhage with a small germinolytic cyst.

Four hours after the seizure onset, linear vesicles along the lines of Blaschko appeared. Despite therapeutic levels of phenobarbital, apneas, profound desaturations, right sided twitching, tongue protrusion, and eye deviation persisted. The EEG showed an unspecific moderate background suppression, multifocal spikes, and sharp waves arousing from the left hemisphere.

On day 3 of life, a head CT showed bilateral, multifocal ischemic injuries in the occipital and frontal areas (Fig. 1a).

On day 4, a diffuse maculo-papular rash over the trunk and the upper extremities was thought to be a reaction to phenobarbital. As seizures persisted, phenytoin was added. On day 7, an MRI showed multifocal petechiae (Fig. 1b) and abnormal diffusion of the corticospinal tracts (Fig. 1c).

Furthermore, echocardiography, coagulation, congenital infection, and the inborn errors of metabolism screening remained normal. A dermatologist suggested the diagnosis of incontinentia pigmenti (IP), vesico-bullous stage (stage I, Fig. 1e), which was confirmed by skin biopsy (Fig. 1f).

A later MRI (day 26) showed extensive symmetric cerebral destruction involving both gray and white matter (Fig. 1d), corresponding to the areas of restricted diffusion documented on day of life 7 (Fig. 1e). The MR-angiography showed decreased intravascular flow in the middle cerebral arteries but no structural changes. At that point, phenobarbital was a

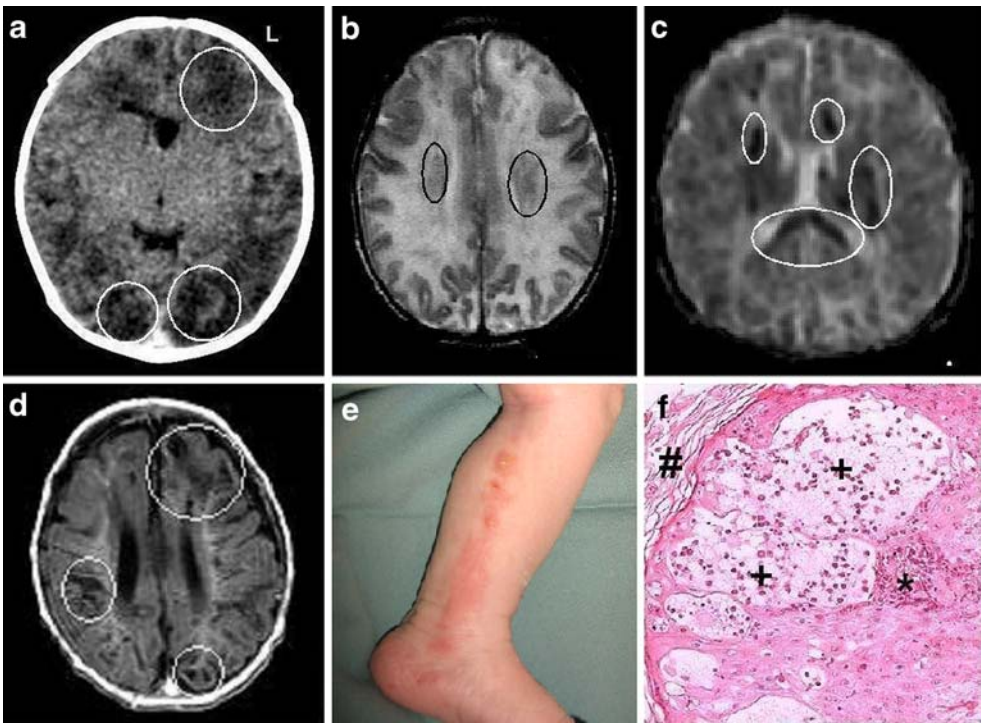

Fig. 1 **a** Head CT (without contrast, day 3): frontal and occipital patchy low density changes in the cortex and white matter (*white circles*). **b** Head MRI (T2, day 7): general white matter hyperintensity with foci of low signal intensity (*black circles*). **c** Head MRI (day 7): diffusion sequences with cortico-spinal tracts abnormalities (*white circles*). **d** Head MRI (T1, day 26): extensive symmetric cerebral destruction of gray and white matter (*white circles*). **e** Inside left leg (day 2): linear vesicular exanthema along the lines of Blaschko. **f** Skin biopsy (H&E, 200x): IP, vesico-bullous stage with pathognomonic intra-epidermal eosinophils (*) and vesicles (+), covered by the stratum corneum (#)

sufficient anticonvulsant therapy. Fundoscopy showed 360° of peripheral avascularity in both eyes. Bilateral laser coagulation to prevent neovascularization and retinal detachment was performed and repeated at 3 months.

At 13 months of age, she presented with a severe global developmental delay with intermittent seizures. The skin was atrophic along the lines of Blaschko, and she developed recurrent episodes of inflammatory vesicular and verrucous skin lesions, usually associated with febrile illnesses. No more imaging or EEG studies were performed.

Discussion

We describe a newborn girl with clinical and histological features of IP and with, as yet unreported, early simultaneous corticomedullar involvement. The first report by Garrod in 1906 described the histological melanin deposits in the corium, based on the concept that the corium was 'incontinent' for melanin [12]. Later reports followed in 1925 [3] and 1926 [4]. The reported incidence is around 1:40,000 (M:F ratio 1:37) [6]. IP is X-linked dominant and usually lethal in males [46]. The reported living males were in the setting of Klinefelter Syndrome or gonadal mosaicism [28, 37, 38]. The International Incontinentia Pigmenti Consortium reported that IP is caused by a genomic rearrangement of the gene for the nuclear factor kappa B (NF-κB) essential modulator (*NEMO*) [42]. The gene is located 200 kb proximal to the factor VIII locus and is required for the activation of the transcription factor NF-κB which is central to many immune, inflammatory, and apoptotic pathways [2, 14, 24]. In resting cells, NF-κB is kept inactive by inhibitory proteins of the IκB family. NF-κB activation is induced by the IκB Kinase (IKK) complex and NEMO [23, 25, 51]. After activation by inflammatory stimuli such as tumor necrosis factor (TNF), interleukin-1 (IL-1), or bacterial lipopolisaccharide (LPS), NF-κB is released and accumulated in the nucleus and activates its target genes [19]. NEMO is essential for NF-κB activation by proinflammatory signals [13]. Therefore, IP is due to genomic rearrangements which make NF-κB activation defective [42].

In the mouse model, it is postulated that autonomous proliferation of NEMO deficient keratinocytes, combined with apoptosis of some NEMO-deficient cells, triggers the expression of proinflammatory mediators by the neighboring wild-type keratinocytes resulting in the development of the cutaneous lesions [32]. Nevertheless, several mechanisms triggering the disease remain unanswered. Nenci at al. suggest that the cutaneous lesions are triggered by the presence of NEMO-deficient cells but that the mosaic presence of NEMO-deficient and wild-type keratinocytes is not needed for disease induction [32]. On the other hand, as apoptosis is a prominent feature in NEMO deficient keratinocytes, their replacement by wild-type cells is thought to explain the cutaneous healing [39]. The pathophysiology of the cerebral lesions is not fully understood [34].

Four clinical stages are defined:

- Stage 1, vesico-bullous (first 2 weeks of life): vesicles and erythema along Blaschko's lines
- Stage 2, verrucous (after several weeks, lasting for weeks): hyperkeratosis, verrucosis on erythematous base. Usually lower limbs. Evolving from stage 1 or unaffected skin
- Stage 3, hyperpigmentation (3–6 months, lasting months to years): asymmetrical, hyperpigmented streaks/whorls along Blaschko's lines
- Stage 4, hypopigmentation (late infancy and adolescence): skin atrophy typically on the flexor side of lower limbs

The most commonly described presenting symptoms in the neonatal period are vesicular rash, exanthema, therapy refractory seizures, paresis [22, 40, 45], and head circumference increase [41]. More unusual features include persistent pulmonary hypertension (PPHN) [16], alopezia [16, 47], or in the later neonatal period, low concentrations of IgG subclasses [33].

The differential diagnosis of the vesico-bullous stage includes neonatal infections (herpes simplex, herpes zoster, candidiasis, or syphilis) and various congenital cutaneous conditions (impetigo bullosa, epidermolysis bullosa simplex, transient neonatal pustular melanosis, drug induced rash, hyperkeratosis epidermolytica, and dermatitis herpetiforme) [6, 8, 10, 18, 29].

Our neuroradiological findings are unusual, as previous reports from the neonatal period have mentioned:

- Cortical atrophy and ventricular enlargement (CT on day 2) [49]
- Polymicrogyria in the perisylvan area and cortical dysplasia (MRI on day 5) [16]
- Cortical necrosis with subcortical hemorrhage (MRI on day 3) [48]
- Restricted diffusion in the periventricular area (MRI on day 8) and filling defects in the middle cerebral artery (MR-angiography on day 13) [21]
- Diffuse hemispheric hemorrhagic necrosis (MRI on day 15) [41]

MRI findings in older children include periventricular leukomalacia [31, 40], cerebellar abnormalities [35], corpus callosum hypoplasia [31], encephalomalacia [9], multiple cerebral infarctions [26], vascular abnormalities [21, 30], unilateral middle cerebral artery occlusion [36], and transient white matter injury [50].

However, presence of changes in the neuroradiological imaging does not necessarily mean neurodevelopmental impairment [5]. The pathophysiology of the cerebral and retinal problems have not yet been observed in NEMO +/− mice yet. Therefore, the pathophysiology is not yet understood, and an inflammatory origin is speculated [1].

Our patient was prenatally exposed to cocaine but our radiological findings are not explained by this factor. King et al. reported that neurosonographic structural changes were not more frequent than in healthy controls and were of similar nature [27]. In their cohort, the blood flow in the anterior cerebral artery of cocaine exposed babies increased from day 1 to day 2 and was not explained by a difference in blood pressure. Our observation was a decreased flow in the middle cerebral artery, as had also been seen by others [21]. Other authors reported an association between antenatal cocaine exposure and schizencephaly, interhemispheric cysts [15], pachygyria [17], periventricular leukomalacia [20], cerebral infarction [7], and intraventricular hemorrhage [43].

Our case was diagnosed clinically by the dermatologist and confirmed by histopathology. Therefore, in the presence of a vesicular exanthema following the lines of Blaschko, persisting seizures, and excluded infection, a high index of suspicion is needed. Noteworthy are two previous reports showing coexistence of IP and neonatal HSV infection [11, 44]. Diagnosis is be confirmed by pathognomonic histology.

The prognostic value of imaging is controversial, as one report describes cerebral features of IP in a neurologically normal child [5], whereas in a retrospective cohort, neuroradiological changes are only seen in symptomatic patients [33]. Fundoscopy is mandatory as ocular involvement is frequent; intervention may be necessary and related to neurological involvement. Furthermore, after discharge, periodic ophthalmological and neurological follow-up visits are recommended as well as punctual stomatological controls.

Conclusion

We present a classical case of IP with unusual neuroradiological findings: early diffusion changes and the evolution of initial cortical and white matter hemorrhage into diffuse necrosis and atrophy. This natural progression most likely explains the global developmental delay observed at 13 months.

The reports in the MRI era describe few neonates with white matter or cortical involvement, with one case of transient white matter injury.

Although neurological symptoms are frequent in IP, the mechanisms of cerebral involvement are not yet fully understood and further research is needed.

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