Therapy resistant neonatal seizures with vesicular rash: incontinentia pigmenti
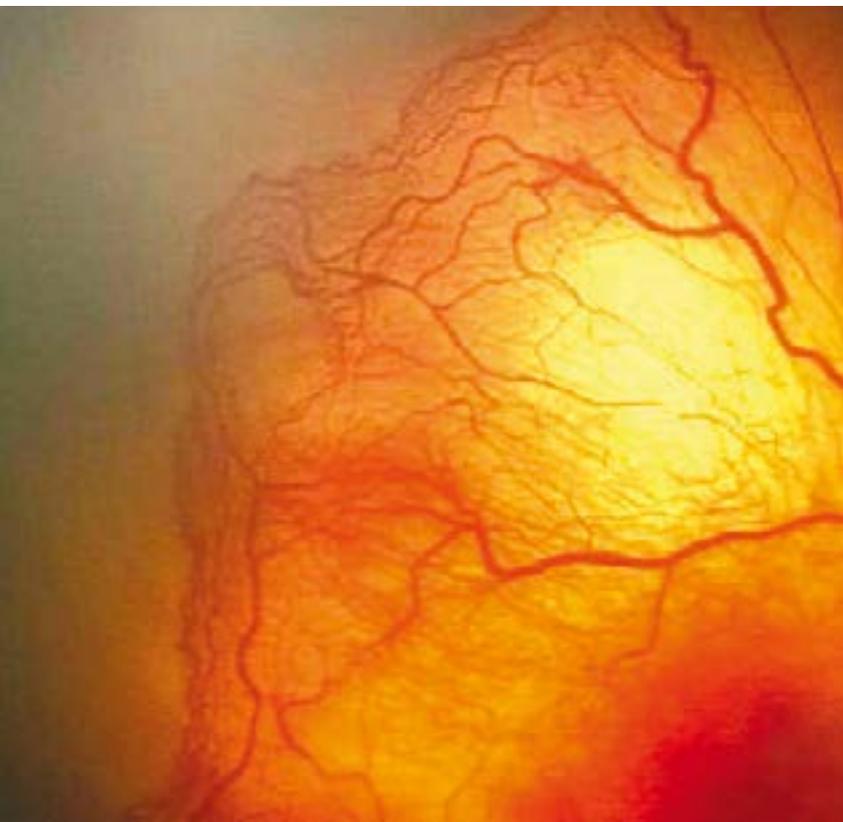
Kaczala G, Messer AM, Poskitt KJ, Prendville JS, Gardiner J, Senger C, Departments of Neonatology (KG, MAM), Radiology (PKJ), Dermatology (PJS), Ophthalmology (GJ), and Pathology (SC), British Columbia Children's Hospital, Vancouver, BC, Canada

We describe an adequate for gestational age girl born at term by spontaneous vaginal delivery after 2 hours of ruptured membranes. The G2/P1 mother had consumed crack, methylamphetamine, cocaine, nicotine and ethanol during pregnancy. The family history includes a grandmother with a brain aneurysm and a grandfather with apoplexy. Maternal serologies were negative for VDRL, HIV, HBV, HCV and protective for rubella. Group B streptococcus screening was negative at 38 weeks. The immediate perinatal period was uneventful until right arm jerking and eye deviation to the left was noted at 21 hours of age. In the interval the infant was crying, non cyanotic, having a normal muscular tone with a normal anterior fontanel and a weak suck. Initial treatment was started with phenobarbital, ampicillin, gentamicin and acyclovir.

Hematological and chemical work-up was normal. The CSF was xanthochromic; cultures (incl. immunofluorescence for HSV type 1 and 2) were sterile and acyclovir was stopped. The blood culture grew coagulasenegative staphylococcus. A repeat blood culture on day 3 remained negative. The antibiotics were discontinued after 5 days.

A head ultrasound showed a grade I periventricular/intraventricular hemorrhage on the right and a small germinolysis cyst in the anterior right lateral horn.

The first vesicular lesion on the left arm (Fig. 1), left leg, left wrist and the left cubital fossa appeared 4 hours after the initial seizures (at 25 hours of life).

Despite phenobarbital concentrations in the therapeutic range, apneas, desaturations with cyanotic episodes, right sided twitching, tongue protrusion and eye deviation for seconds were repeatedly reported and 2 more doses were administered.

The EEG on day of life 3 showed a severely abnormal pattern with moderate suppression, moderately discontinued, frequent multi-focal spikes and positive sharp waves arousing more frequently from the left than the right side.

A head CT showed no structural abnormality but multifocal patchy low density changes in the cortex and white matter, mostly in the occipital and frontal parts (Fig. 2) which were thought to represent multifocal ischemic injuries.

On day of life 4, an episode of a generalized maculopapular rash without vesicles over the trunk and the proximal extremities was noted and initially interpreted as a hypersensitivity reaction to phenobarbital. When seizures persisted phenytoin was added.

Fig. 1

Patient at the age of 25 hours: vesicular rash appearing on the left arm (identical changes were seen on the left leg).

A first head MRI on day 7 showed extensively abnormal cerebral signals: T1 hyperintensity in the cortex of both posteromedial lobes and in the lentiform nuclei (Fig. 3); general T2 hyperintensity of the white matter with numerous foci of low signal intensity indicating the presence of multi-focal petechial hemorrhages including the cortex (Fig. 4); diffusion sequences with mildly increased signal in the ventral aspects of the cerebral peduncles and pons through to the medulla suggesting abnormality of the corti-cospinal tracts (Fig. 5).
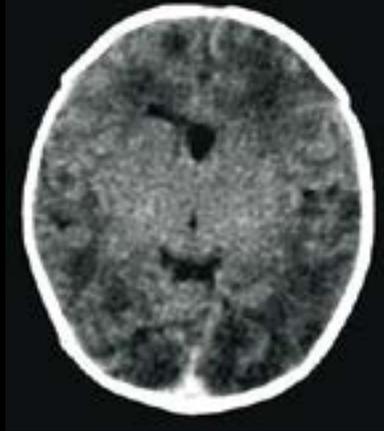
Fig. 2

Head CT: multifocal patchy low density changes in the cortex and white matter.

Head MRI (T1, day 7): T1 hyperintensity in the cortex and lentiform nuclei.
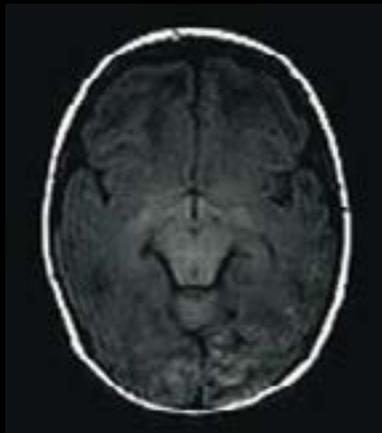
Fig. 3

Fig. 4

Head MRI (T2, day 7): general T2 hyperintensity of the white matter with foci of low signal intensity.

Head MRI (diffusion sequences, day 7): abnormalities of the corticospinal tracts.
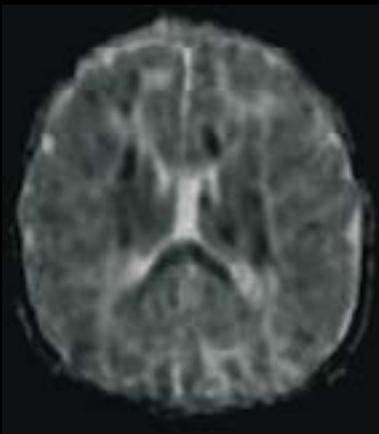
Fig. 5

A coagulation work-up including homocysteine, PT, INR, fibrinogen, aPTT, factor V Leiden, antithrombin III, protein C and S was normal. The prothrombin gene G20210A had a normal genotype. Infection investigations (CMV, Toxoplasma gondii and Treponema pallidum) and the screening for inborn errors of metabolism remained normal. An echocardiography excluded a cardiac source of emboli.

Finally, a dermatological consultation established the diagnosis of incontinentia pigmenti, vesico-bullous stage (stage I), which was confirmed in a skin biopsy (Fig. 6). An ophthalmologic examination to assess ocular involvement on day 15 of life showed 360 degrees of avascularity in the periphery of the right eye and avascularity in the temporal periphery of the left eye, consistent with the underlying diagnosis (Fig. 7). On day 22 of life, bilateral retinal laser therapy was performed because of the risk of neovascularization and retinal detachment. This procedure was repeated at 3 months.

MRI on day of life 26 showed extensive symmetric cerebral destruction involving both gray and white matter, corresponding to the areas of restricted diffusion documented on day of life 7 (Fig. 8, 9). An MR angiography showed decreased intravascular flow in the main cerebral arteries without any structural changes explaining the distally occurring necrosis (Fig. 10).

Garrod published the first report of incontinentia pigmenti (IP) in 1906 and described the histology with deposits of melanin pigment in the corium, basing the designation on the idea that the basal layer of the epidermis is ‚incontinent' for melanin (1). Further reports followed in 1925 (2) and 1926 (3).

Although the incidence was repeatedly reported to be around 1:40'000 with a male:female ratio of 1:37, the National Institute of Health's (NIH) Office for Rare Diseases (ORD) has classified the disease as rare, suggesting an incidence of less than 1:200'000 (4). IP is an X-linked dominant trait that is usually lethal in males. Few reported cases of living males are reported in the setting of Klinefelter syndrome or gonadal mosaicism (5, 6).

The IP consortium linked the gene locus for IP to the factor VIII gene in Xq28 (7). The gene for NEMO (NF-kappaB essential modulator)/ IKKgamma (IkappaB kinase-gamma) has been mapped to a position 200 kilobases proximal to the factor VIII locus. NEMO is a 23-kb gene composed of 10 exons with 3 alternative noncoding first exons, 1a, 1b, and 1c (8). It is required for the activation of the transcription factor NF-kappaB and is central to many immune, inflammatory and apoptotic pathways.
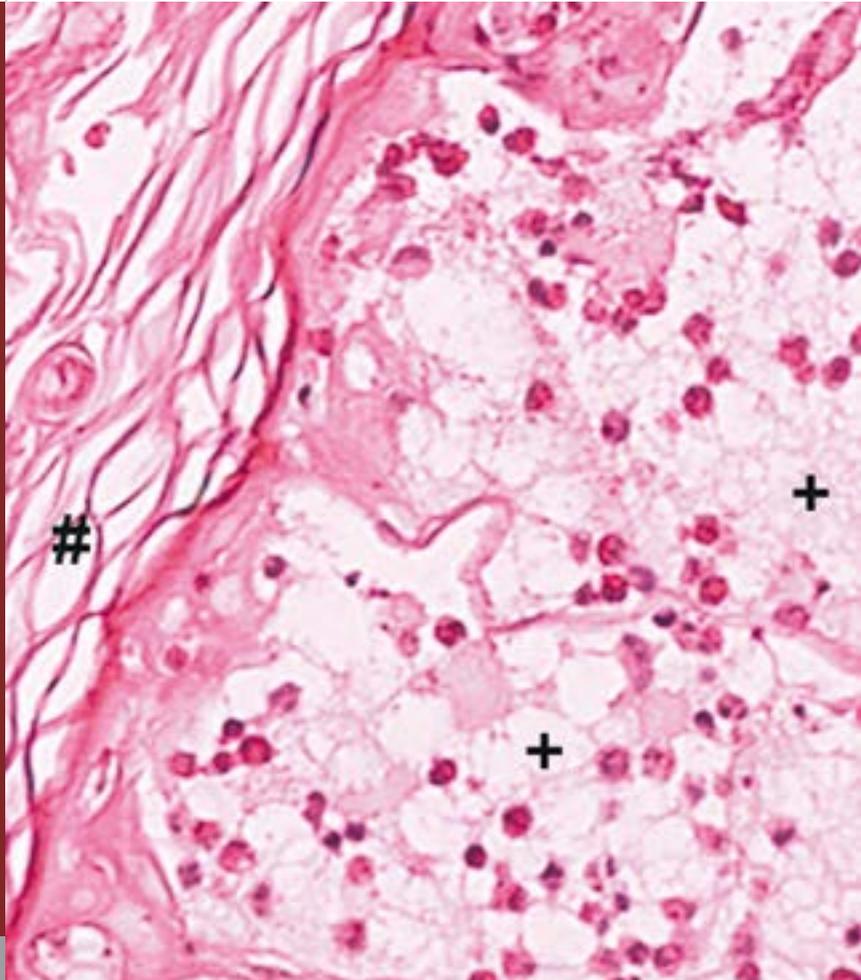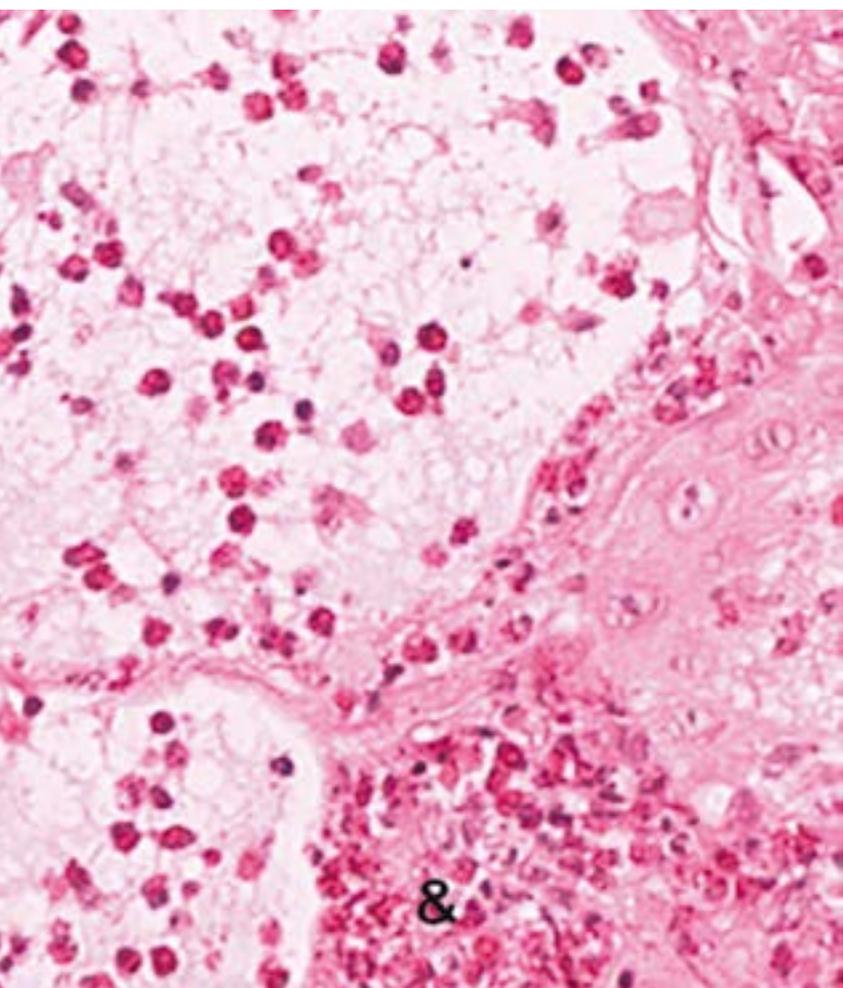
Skin biopsy: incontinentia pigmenti, vesico-bullous stage with pathognomonic intraepidermal eosino-phils (&) and vesicles (+), covered by the stratum corneum (#).

Shahi et al. showed that most cases of IP are due to mutations of this locus and that a new genomic rearrangement accounts for 80% of new mutations, as a consequence, NF-kappaB activation is defective in IP cells (7).

The 4 clinical stages described for IP (9) are:

1. Vesico-bullous stage: erythema, vesicles and bullae in a linear pattern following the lines of Blaschko (representing the lines of embryonic cell migration) (10), typically occurring in the first 2 weeks of life (Fig. 1).

2. Verrucous stage: hyperkeratosis, verrucae on erythematous base usually affecting the distal extremities, occurring after several weeks, lasting for weeks; these lesions may evolve from stage 1 lesions or from previously unaffected skin.

3. Hyperpigmentation: usually appearing between the age of 3 to 6 months and lasting from months to years, usually in the form of asymmetrically distributed hyperpigmented streaks or whorls along the lines of Blaschko.

4. Hypopigmentation and atrophy of the skin: becoming evident any time between the late infant age and adolescence and lasting a lifetime; these changes are typically located on the flexor side of the lower extremities.

Fig. 7

Fundoscopy: portion of the peripheral 360 degrees avascularity (right eye).

Head MRI (T1, day 26): extensive symmetric cerebral destruction of gray and white matter.
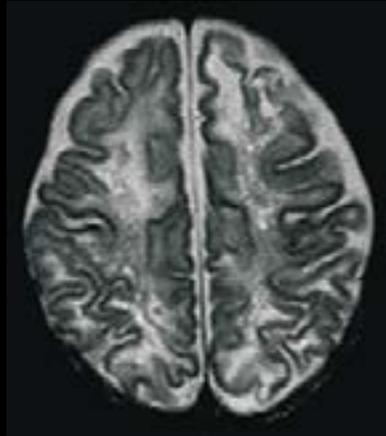
Fig. 8

Fig. 9

*Head MRT (T2, day 26): extensive symmetric
cerebral destruction of grey ans white matter.*

*MRA (day 26): decreased flow in the main cerebral
arteries without vascular structural changes.*

Fig. 10

Wieacker et al. hypothesized that the described evolution of lesions are representing death of the cells having the mutant-bearing X chromosome active and being replaced by cells having the normal X chromosome active (11).

Several case reports mention the involvement of other systems, including teeth (hypodontia, microdontia, dysplasia or delayed eruption) (3, 4, 12); the musculoskeletal system (hemivertebrae, kyphoscolyosis, extra rib, syndactyly, hemiatrophy or short arms or legs); the eyes (strabism, retinal dysplasia or detachment, uveitis, keratitis, cataract, retrolental fibroplasias, blue sclerae, pseudoglioma, retinal hypovascularization or pigment retinopathy); skin and hair (hypoplasia of eyebrows or lashes, onychomycosis-like dystrophy, subungual fibromas, alopecia); and the central nervous system (mental deficiency, macrocephaly, spasticity, ataxia, seizures, destructive encephalopathy, cerebral infarction).

The differential diagnosis of the vesico-bullous stage of IP includes (4, 9, 13, 14, 15): infections (neonatal HSV, HZV, congenital candidiasis, congenital syphilis) and other skin disorders (bullous impetigo, epidermolysis bullosa simplex, transient neonatal pustular melanosis, Letterer-Siwe disease, blistering drug-induced rash, epidermolytic hyperkeratosis, allergic contact dermatitis and neonatal dermatitis herpetiformis).

In a series of 5 non-newborn girls with IP, Pascual-Castroviejo et al. described the clinical and neuroimaging findings (16). The lesions involved cortex, subcortical and deep white matter, ependymal and subependymal zones. Affected areas did not correspond to vascular territories. The corpus callosum showed generalized or localized atrophy in the five patients with cerebral hemispheric lesions. Parenchymal changes were more evident in T1 than T2 weighted images. Interestingly, parenchymal abnormalities were most severe in patients with neonatal severe cutaneous lesions, especially if these were located on the scalp. Cerebral lesions were present from birth or the first months of life and changed little thereafter and are thought to be responsible for the progressive microcephaly within the first year of life in IP. They speculated that the acute appearance and distribution of the cerebral lesions during the neonatal period, associated with stage 1 scalp lesions, suggested an acute inflammatory etiology of non-progressive course. Ocular lesions were directly related to the cerebral abnormalities.

Hennel et al. described white matter injury restricted to the white matter on day of life 8 (17), whereas Wolf et al. reported an neonatal case with diffuse necrosis restricted to the cortex (18). Interestingly, Yoshikawa et al. reported on a IP patient with a small white matter lesion which could not be reproduced at 7 months of age, suggesting similarities to the fading course of the cutaneous changes (19).

In our case, the diagnosis was made by the pediatric dermatologist and verified by histopathology. After reviewing several case reports, this seems to be the rule rather than an exception. Therefore, when confronted with a patient with an exanthema following the lines of Blaschko, neonatal seizures refractory to standard treatment and after ruling out an infection, IP should be considered and the diagnosis must be confirmed by unequivocal histopathology. In order to assess the extent of the initial cerebral and ocular involvement, CNS imaging and ophthalmologic examination should be performed. MRA does not seem to have a high enough resolution to detect the microangiopathic changes.

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Swiss Society of Neonatology
www.neonet.ch
webmaster@neonet.ch