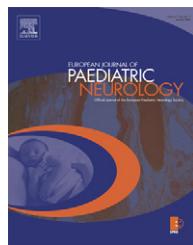




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Original article

Extensive cerebral infarction in the newborn due to incontinentia pigmenti

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ABSTRACT

Introduction: Incontinentia pigmenti (IP) is a rare X-linked dominant neuroectodermal multisystem disorder characterized by skin lesions following Blaschko lines. In almost all patients the skin is involved and in 30–50% the central nervous system (CNS) is. Vascular occlusive phenomena probably play a role in CNS involvement. Whether these vascular changes are based on macro- or microvascular disease in the neonatal presentation is not fully understood.

Patients and methods: We describe two patients with IP with neonatal seizures related to cerebral infarction. In comparison, we reviewed reports of ischaemic cerebrovascular injury in neonatal IP.

Results: No descriptions of documented large artery occlusion in neonatal IP was found in the literature. One of our patients showed striatal arteriopathy, never described before in IP. Extensive injury in one of our cases was heterogeneous, mixing healthy with diseased areas within large arterial fields.

Conclusions: We postulate that neonatal cerebral infarction in IP is a macrovascular disorder of medium sized or small arteries. The pattern of arterial involvement might follow hypothetical brain Blaschko lines. The extent of cerebral involvement probably results from genetic mosaicism in which Lyonisation leads to endothelial apoptosis, similar to the process in the skin.

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Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; CNS, central nervous system; EEG, electroencephalography; IP, incontinentia pigmenti; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NEMO, nuclear factor Kappa-B essential modulator; SPECT, single photon emission computed tomography; US, ultrasound (imaging)

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1. Introduction

Incontinentia pigmenti (IP) is an X-linked dominant condition primarily affecting ectodermal tissue, mostly in females, rarely in boys. The term is derived from the dislocation (incontinence) of melanin pigment from the basal-cell layer of the epidermis to the upper dermis. IP is a multisystem disorder also known as Bloch–Sulzberger syndrome, characterized by skin lesions following Blaschko lines¹ with a distinct pattern of development in four stages: vesiculopapulous, verrucous and hyperpigmentation stage; finally (not in all cases) there is a fourth stage of linear anhidrotic hypopigmented lesions. Other tissues involved are teeth, hair, nails, eyes and in 30–50% the central nervous system (CNS). The clinical expression of CNS involvement includes epilepsy, mental retardation, hemiparesis, spasticity, microcephaly and cerebellar ataxia.² The pathogenesis of CNS involvement is partly understood, vascular occlusive phenomena probably play a role. Whether these changes are based on macro- or microvascular disease in the neonatal presentation is not fully clear. The focus of this report is to get insight in the vascular pattern of the cerebral lesions of IP because this might be relevant for treatment in the future.

2. Patients and methods

We report two patients with vesiculopustulous eruptions in the first days of life caused by IP and with subsequent neonatal seizures related to cerebral infarction. Cranial magnetic resonance imaging (MRI) was obtained using axial and coronal T1- and T2-weighted sequences.

3. Results

3.1. Case report

3.1.1. Case 1

A 3340 g term female was born in a local hospital via normal vaginal delivery after an uneventful pregnancy. Her mother was a healthy G2P1 with a healthy 6-year-old son. The girl was well at birth, with Apgar scores of 9 and 10 at 1 and 5 min, respectively. Papulovesiculous eruptions on an erythematous base on arms and legs were observed on the first day. The remaining clinical exam was normal, including a normal neurologic status. The infant was well for the first 5 days, but skin eruptions increased over trunk, face and scalp and a particular linear pattern was seen on the arms. On day 5 she developed seizures, at first jerking of the left arm, followed by clonic seizures of both arms and legs, each lasting several minutes. Seizure treatment required loading plus maintenance of phenobarbitone and midazolam. This resulted in respiratory insufficiency for which she was intubated and referred to our center. No abnormalities were found in the full blood cell count, serum electrolytes, glucose, PT, APTT, C-reactive protein and blood cultures. In the bloodsmear the eosinophil count was $0.6 \times 10^9 \text{ L}^{-1}$ (normal range 0.05–0.25). Lumbar puncture was not done. Skin biopsy demonstrated

dermal eosinophilic infiltrates with spongiosis and some apoptotic (dyskeratotic) cells characteristic of IP. EEG indicated multiple multifocal epileptiform discharges, with a preference for the left temporal region. MRI (Fig. 1) demonstrated a swollen left cerebral hemisphere consistent with non-haemorrhagic infarction, and sparing of striatum and thalamus. Parts of the cortical areas of middle cerebral artery (MCA) and anterior cerebral artery (ACA) were skipped by the process. Additionally, there were multiple infratentorial non-haemorrhagic lesions in the left cerebellar hemisphere. The pattern of cerebellar and cerebral injury was inconsistent with large artery occlusion and the large arteries of the circle of Willis were patent on magnetic resonance angiography (MRA) (including M1 on both sides; A1 on the left was not visualized, Fig. 1). These extensive brain changes were in contrast with limited skin findings. Eye examination revealed minor haemorrhagic spots in the left macula. Genetic analysis revealed a deletion exon 4–10 in the nuclear factor Kappa-B essential modulator (NEMO) gene associated with IP. This mutation was absent in the mother's blood, suggesting a de novo event or germ line mutation.

3.1.2. Case 2

A second patient presented also in a local hospital. Her mother was a healthy G1P0 with primary infertility. She was born after an uneventful IVF-induced pregnancy. Because of premature rupture of the membranes and a beta-haemolytic streptococcus in cultures of ear and perineum she was treated with amoxicillin. She developed erythematous skin eruptions on the dorsal side of both arms and on the flexor side of both legs towards the gluteal region. Treatment was switched to erythromycin. The erythematous skin eruptions became papulovesiculous, a skin biopsy revealed eosinophilic spongiosis, the diagnosis of IP was suspected. She developed focal seizures arrested with phenobarbitone loading and maintenance. An EEG showed no abnormalities. Neonatal brain ultrasound (imaging) (US) revealed striatal arteriopathy (Fig. 2). MRI at the age of 6 weeks showed atrophy of the cerebellar vermis. A repeat MRI at the age of 4 years confirmed cerebellar atrophy (Fig. 3). A neonatal eye exam revealed ischaemic lesions in the periphery of both eyes suggestive of IP. Karyotyping of peripheral blood lymphocytes revealed a mosaic 45,X/46,XX abnormality (mosaic Turner syndrome). Sequencing of all the exons and adjacent intron-exon boundaries of the NEMO gene, in DNA isolated from peripheral lymphocytes, showed no mutations. This does not exclude small exon deletions/duplications or intronic mutations. The girl developed left hemiparesis, a vision in both eyes of 10%, abnormalities of dentition and hair, with additional hyperpigmentation of the skin lesions confirming the clinical diagnosis IP. Hyperpigmented streaks in axilla and proximal parts of the legs still persist. She has a healthy brother and there is no history of skin changes in the family.

4. Discussion

We summarized published reports of ischaemic cerebrovascular accidents in newborn patients with IP, including only

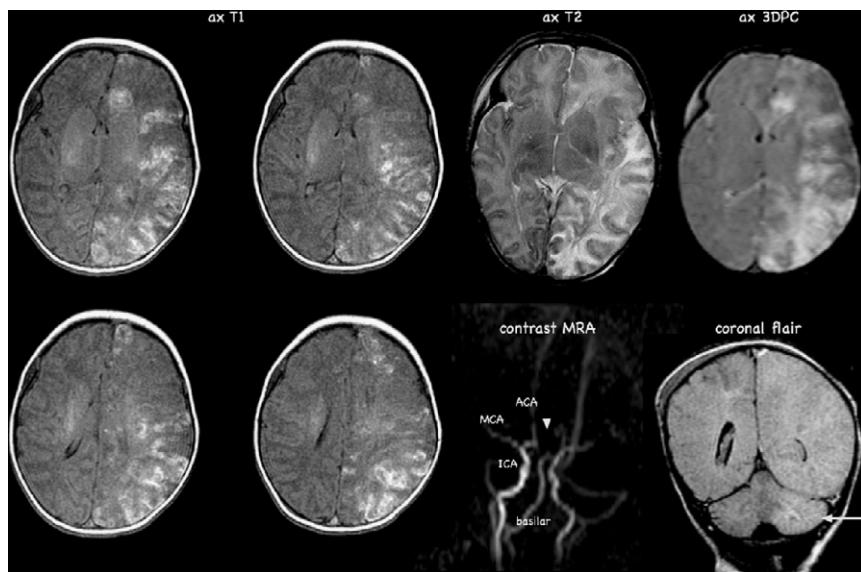


Fig. 1 – Patient 1: scheme of MR aspects on day 6; extensive signal intensity changes on T1- and T2- weighted sequences; involvement of cerebellum (arrow) depicted on a coronal FLAIR image; an image from the 3D T1 weighted gradient sequences with intravenous Gadolinium shows incomplete but extensive rupture of the blood brain barrier in several arterial fields; the circle of Willis is intact (except for non-filling of the A1 part on the left, arrow) on the 3D phase contrast (PC) sequence performed 3 days later. Definite abnormalities within the large arteries may not have been observed due to insufficient resolution of MRA images.

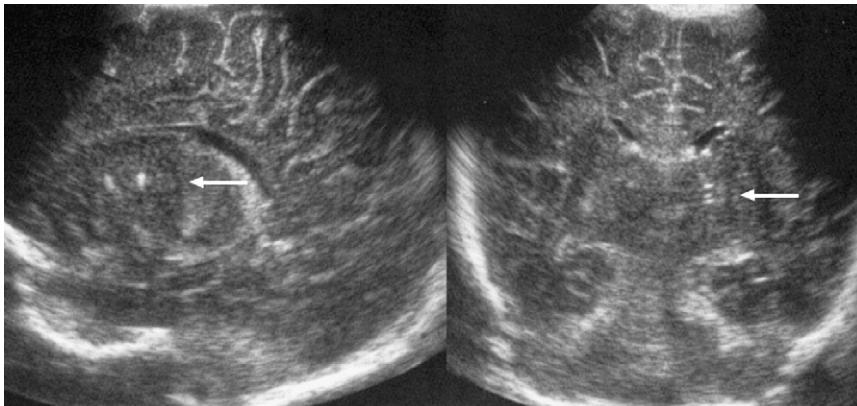


Fig. 2 – Patient 2: neonatal brain US scans in coronal and parasagittal (right) views: the arrows point to hyperechoic streaks along striatal arteries, similar to the aspect of arteritis in congenital infections like CMV.

cases ($N = 17$) with neonatal seizures and/or neonatal brain imaging (Table 1). We scrutinized these studies with the question whether damage was likely caused by a macro- or microvascular process. A microvascular pattern can be defined as within pre-capillary arterioles, capillaries and post-capillary venules (blood vessels $<100\text{ }\mu\text{m}$).³ The challenge was to find instances of large artery stroke in the newborn presentation of IP.

Large arteries were defined as starting from the circle of Willis (diameter around $0.5\text{--}1\text{ mm}$).⁴ Branches from these large arteries were referred to as middle sized. For example, striatal perforators, and their branches were referred to as small arteries. Lenticulostriate “arteries” in adults range in diameter from 80 to $1400\text{ }\mu\text{m}$.⁵

Twelve of the 17 infants presented with seizures on days 3–5 of life. The lesions reported were bilateral in 13 and

unilateral in 4. Most bilateral lesions were asymmetrical. The arterial regions involved seemed to be mainly of MCA and ACA, less often posterior cerebral artery (PCA), but interpretation was difficult because none of the infants had typical large artery strokes and imaging availability was incomplete. Cavitation was observed in several instances, suggesting the lesion can lead to frank infarction. Cavitation however cannot point out the originally affected vessel size. Only Hennel et al.⁶ reported acute MRA changes in large arteries. Our MRA findings in patient 2 are not of sufficient resolution to convincingly illustrate the site of occlusion, but they exclude complete obstruction of the large arteries near the circle of Willis.

This review brings additional insights into the vascular lesions of IP in the neonatal period, as put forward in a report by Wolf et al.⁷ There are no descriptions of documented large

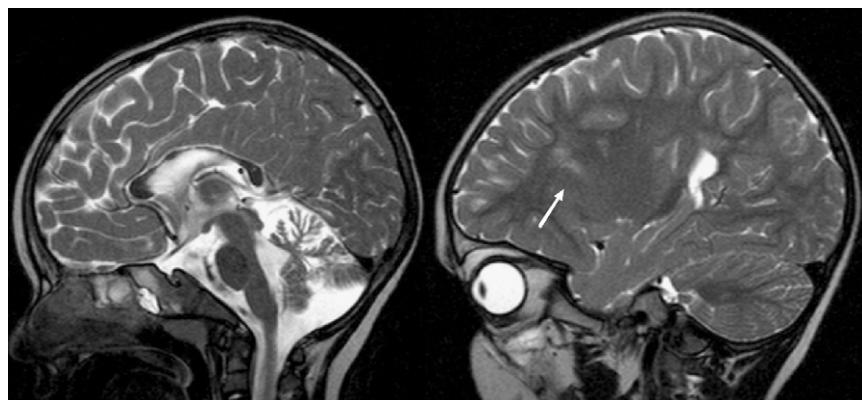


Fig. 3 – Patient 2: sagittal T2-weighted MRI at 4 years: extensive atrophy of cerebellar vermis in the left panel; stripes of hypersignal from gliosis (arrows) in white matter of the centrum semi-ovale in a parasagittal section between insula and thalamus (right panel). Very thin corpus callosum probably due to atrophy.

Table 1 – Literature review of neonatal brain injury with IP

Study Symmetrical	MRA		Presentation	MRI at	Arterial area	Laterality
Shuper et al. ¹¹	Day 3	15 days	ACA, MCA	Bilateral	–	–
Mangano and Barbagallo ¹⁸	Day 4	21 months	MCA left, ACA	Bilateral	–	–
Chatkupt et al. ²⁷	Day 3	13 days	MCA, ACA right, PCA right	Bilateral	–	–
Pascual- Castroviejo et al. ¹⁹	Day 4	Infancy	PCA, MCA, ACA	Unilateral	–	–
Lee et al. ¹⁶	Day 3	Infancy	MCA right	Unilateral	–	Unremarkable
	Day 1	Infancy	PCA, MCA left	Bilateral	–	Left MCA not visualized
Aydingoz and Midia ²⁸	Day 5 5 months	5 years 2 years	MCA MCA	Unilateral Bilateral	– +	–
Yoshikawa et al. ¹³	Day 2 (skin only)	28 days	–	Unilateral	–	–
Fiorillo et al. ²⁹	Day 4	11 days	ACA, MCA	Bilateral	+	–
Hennel et al. ⁶	Day 4	8 days	ACA, MCA	Bilateral	+	Decreased branching, poor filling ACA/PCA
Porksen et al. ³⁰	Day 5	3 weeks	MCA	Bilateral	–	–
	Day 5	14 days	MCA	Bilateral	+	–
Shah et al. ³¹	Day 4	14 months	MCA, ACA, PCA	Bilateral	–	–
Wolf et al. ⁷	Day 2	3 days	MCA, ACA and PCA: all left	Bilateral	–	–
Maingay-De Groof, this report	Day 5	13 days	MCA left, PCA left, ACA right	Bilateral	–	Fig. 1
	Day 12	6 weeks	MCA	Bilateral	+	–

artery occlusion in neonatal IP, although large artery occlusion has been documented in childhood.⁸ Striatal arteriopathy, detectable on US as an indicator of arteritis in middle sized MCA-derived perforator arteries, was never reported so far but sonographic descriptions were not available in any of the reports tabulated. We found vermis atrophy in one of our patients, incidentally mentioned before, the vascular nature of which is questionable.

The pathogenesis of the CNS changes in patients with IP is incompletely understood. Previous investigators have proposed developmental, inflammatory, destructive, infectious and vascular mechanisms on the basis of imaging or histology. O'Doherty and Norman reported a patient with polymicrogyria, unduly thickened cortical gray matter lacking normal lamination and unilateral pyramid tract hypoplasia. They mentioned unexplained areas of focal necrosis within

central white matter, loss of neurons within gyri and patchy loss of Purkinje cells and granule cells in the cerebellum.⁹ Hauw et al.¹⁰ reported ulygryria together with a diffuse inflammatory process with perivascular infiltration of lymphocytes, histiocytes, eosinophils, mononuclear cells and macrophages. Shuper et al.¹¹ described an acute destructive encephalopathy with neuroradiographic findings of haemorrhagic necrosis and brain edema. Encephalitis with haemorrhagic necrosis of white matter and venous inflammation was seen by Siemes et al.¹² and they postulated an inflammatory mechanism following vaccination. Yoshikawa et al.¹³ described in the brain of a 1-month-old infant with IP a solitary white matter lesion, partially disappeared at 7 months of age. Ocular manifestations included arteriolar occlusion and subsequent neovascularization, and infarction.^{14,15} Lee et al.¹⁶ postulated that vascular occlusive phenomena seen in the retina may appear in the CNS as well.

Ischaemic cerebrovascular accidents in the neonatal period are recognized as a complication of IP. The question is raised whether these vascular changes are based on macro- or microvascular processes. Hennel et al. indicate that the findings of microvascular haemorrhagic infarcts in the periventricular white matter and associated MRA changes of decreased branching and filling of intracerebral arteries are indicative of a micro-angiopathic arterial process.⁶ Given that we documented involvement of lenticulostriate arteries in our second case, it is likely that IP affects middle and small sized arteries in the newborn brain, perhaps in addition to the postulated microarterial involvement. There are no data available of size of these perforators in the perinatal period, but they likely vary from the arteriolar to the arterial range. Kasai et al. reported cerebral infarction in multiple arterial regions in the brain in IP: with single photon emission computed tomography (SPECT) sluggish blood flow was detected in the brain but there were no macrovascular occlusions on MRA.¹⁷ MRA was unremarkable in two infants studied by Lee et al.¹⁶ Pellegrino and Shah did report MCA occlusion in a 4-year-old girl with IP with acute onset of hemiparesis suggesting IP should be included in the differential diagnosis of ischaemic stroke in females.⁸ This suggests that large artery occlusion might be possible at any age, but is certainly uncommon in the newborn period. Brain changes in IP are often bilateral and in the anterior circulation, but occlusion of large arteries is exceptional. There is even the suggestion that venous lesions may be mixed together with lesions of small- or middle-sized arteries and that ischaemia as well as brain inflammation co-occur.¹¹ We found no reports of systemic venous thrombi that might have led to embolic stroke in IP. Repeated injury from vasculopathy leads to secondary atrophy and callosal thinning.^{18,19}

IP is an X-linked dominant neurocutaneous disorder with a high female:male sex ratio of 20–37:1 with male lethality. The genetic defect for IP has been mapped to the locus Xq28, a region known to encode nuclear factor kappa-B essential modulator (NEMO).²⁰ NEMO is involved in regulating the nuclear factor kappa-B activation, which in turn regulates the expression of genes involved in immune and stress response, inflammatory reaction, cell adhesion and protection against apoptosis.²¹ The skin lesions seen in IP are the result of cell-autonomous loss of NEMO activity that makes the involved

skin cells vulnerable to apoptosis when exposed to cytokines.²² The skin lesions follow the Blaschko lines (clusters of epidermal cells of similar clonal origin), a pattern of skin lesions only seen in X-linked skin disorders as a result of genetic mosaicism.²³ Analogies of the Blaschko lines are seen in the lens and iris of the eye, the teeth and bone, but there is no commonly accepted analogy to Blaschko lines in the brain. One patient with IP had partial myelination defects that might be interpreted as a consequence of Lyonization.²⁴ It is suggested the mutation in the NEMO gene leads to activation of eotaxin, a potent eosinophil-selective chemokine, which is strongly expressed by endothelial cells in IP and is correlated with perivascular and intravascular eosinophilic infiltration. The apoptosis results in an upregulation of cytokines like eotaxin, inducing vaso-occlusion as a result of eosinophilic degranulation.^{25,26} This could support the hypothesis that in IP cerebral lesions result from unfavorable Lyonisation in cells of the brain that leads to endothelial apoptosis, similar to the process in the skin. Hypothetically the pattern of arterial involvement could follow an analogy of the Blaschko lines in the brain.

In conclusion, neonatal cerebral infarction in IP is probably a disorder of medium sized or small arteries. On MRI, the infarcted areas do not have a classical macrovascular distribution and from scarce MRA experience occlusion of arteries at the circle of Willis have not been reported yet. High-resolution angiographic studies of acute neonatal lesions in IP may in the future show the actual site of occlusion distal in the arterial tree.

REFERENCES

1. Cohen BA. Incontinentia pigmenti. *Neurol Clin* 1987;5: 361–77.
2. Carney RG. Incontinentia pigmenti. A world statistical analysis. *Arch Dermatol* 1976;112:535–42.
3. del Zoppo GJ. Microvascular changes during cerebral ischemia and reperfusion. *Cerebrovasc Brain Metab Rev* 1994;6:47–96.
4. Bevan RD, Vijayakumaran E, Gentry A, Wellman T, Bevan JA. Intrinsic tone of cerebral artery segments of human infants between 23 weeks of gestation and term. *Pediatr Res* 1998;43:20–7.
5. Marinkovic S, Gibo H, Milisavljevic M, Cetkovic M. Anatomic and clinical correlations of the lenticulostriate arteries. *Clin Anat* 2001;14:190–5.
6. Hennel SJ, Ekert PG, Volpe JJ, Inder TE. Insights into the pathogenesis of cerebral lesions in incontinentia pigmenti. *Pediatr Neurol* 2003;29:148–50.
7. Wolf NI, Kramer N, Harting I, Seitz A, Ebinger F, Poschl J, et al. Diffuse cortical necrosis in a neonate with incontinentia pigmenti and an encephalitis-like presentation. *Am J Neuroradiol* 2005;26:1580–2.
8. Pellegrino RJ, Shah AJ. Vascular occlusion associated with incontinentia pigmenti. *Pediatr Neurol* 1994;10:73–4.
9. O'Doherty NJ, Norman RM. Incontinentia pigmenti (Bloch-Sulzberger syndrome) with cerebral malformation. *Dev Med Child Neurol* 1968;10:168–74.
10. Hauw JJ, Perie G, Bonnette J, Escourrolle R. Neuropathological study of incontinentia pigmenti. Anatomical case report (author's transl). *Acta Neuropathol (Berl)* 1977;38:159–62.
11. Shuper A, Bryan RN, Singer HS. Destructive encephalopathy in incontinentia pigmenti: a primary disorder? *Pediatr Neurol* 1990;6:137–40.

12. Siemes H, Schneider H, Dening D, Hanefeld F. Encephalitis in two members of a family with incontinentia pigmenti (Bloch-Sulzberger syndrome). The possible role of inflammation in the pathogenesis of CNS involvement. *Eur J Pediatr* 1978;129:103–15.
13. Yoshikawa H, Uehara Y, Abe T, Oda Y. Disappearance of a white matter lesion in incontinentia pigmenti. *Pediatr Neurol* 2000;23:364–7.
14. Goldberg MF. The blinding mechanisms of incontinentia pigmenti. *Ophthalmic Genet* 1994;15:69–76.
15. Goldberg MF, Custis PH. Retinal and other manifestations of incontinentia pigmenti (Bloch-Sulzberger syndrome). *Ophthalmology* 1993;100:1645–54.
16. Lee AG, Goldberg MF, Gillard JH, Barker PB, Bryan RN. Intracranial assessment of incontinentia pigmenti using magnetic resonance imaging, angiography, and spectroscopic imaging. *Arch Pediatr Adolesc Med* 1995;149:573–80.
17. Kasai T, Kato Z, Matsui E, Sakai A, Nishida T, Kondo N, et al. Cerebral infarction in incontinentia pigmenti: the first report of a case evaluated by single photon emission computed tomography. *Acta Paediatr* 1997;86:665–7.
18. Mangano S, Barbagallo A. Incontinentia pigmenti: clinical and neuroradiologic features. *Brain Dev* 1993;15:362–6.
19. Pascual-Castroviejo I, Roche MC, Martinez Fernandez V, Perez-Romero M, Escudero RM, Garcia-Penas JJ, et al. Incontinentia pigmenti: MR demonstration of brain changes. *Am J Neuroradiol* 1994;15:1521–7.
20. Jin DY, Jeang KT. Isolation of full-length cDNA and chromosomal localization of human NF-κappaB modulator NEMO to Xq28. *J Biomed Sci* 1999;6:115–20.
21. Smahi A, Courtois G, Rabia SH, Doffinger R, Bodemer C, Munnich A, et al. The NF-κappaB signalling pathway in human diseases: from incontinentia pigmenti to ectodermal dysplasias and immune-deficiency syndromes. *Hum Mol Genet* 2002;11:2371–5.
22. Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A, et al. Genomic rearrangement in NEMO impairs NF-κappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. *Nature* 2000;405:466–72.
23. Happel R. Lyonization and the lines of Blaschko. *Hum Genet* 1985;70:200–6.
24. Rott HD. Extracutaneous analogies of Blaschko lines. *Am J Med Genet* 1999;85:338–41.
25. Goldberg MF. The skin is not the predominant problem in incontinentia pigmenti. *Arch Dermatol* 2004;140:748–50.
26. Jean-Baptiste S, O'Toole EA, Chen M, Guitart J, Paller A, Chan LS. Expression of eotaxin, an eosinophil-selective chemokine, parallels eosinophil accumulation in the vesiculobullous stage of incontinentia pigmenti. *Clin Exp Immunol* 2002;127:470–8.
27. Chatkupt S, Gozo AO, Wolansky LJ, Sun S. Characteristic MR findings in a neonate with incontinentia pigmenti. *Am J Roentgenol* 1993;160:372–4.
28. Aydingoz U, Midia M. Central nervous system involvement in incontinentia pigmenti: cranial MRI of two siblings. *Neuroradiology* 1998;40:364–6.
29. Fiorillo L, Sinclair DB, O'Byrne ML, Krol AL. Bilateral cerebrovascular accidents in incontinentia pigmenti. *Pediatr Neurol* 2003;29:66–8.
30. Porksen G, Pfeiffer C, Hahn G, Poppe M, Friebel D, Kreuz F, et al. Neonatal seizures in two sisters with incontinentia pigmenti. *Neuropediatrics* 2004;35:139–42.
31. Shah SN, Gibbs S, Upton CJ, Pickworth FE, Garioch JJ. Incontinentia pigmenti associated with cerebral palsy and cerebral leukomalacia: a case report and literature review. *Pediatr Dermatol* 2003;20:491–4.