

SCIENTIFIC CORRESPONDENCE

Novel corneal features in two males with incontinentia pigmenti

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Incontinentia pigmenti (IP) is a rare X linked genetic disorder, which predominantly affects females. The mutations are usually lethal in males. Two male cases are presented; a genetic mosaic for the common IP deletion and another in whom the genetic abnormality has not yet been characterised. Emphasis is placed on the ocular features present in this disorder and in particular a novel corneal feature and its possible aetiology.

Incontinentia pigmenti (IP) is a rare, multisystem, X linked dominant disorder, which is usually lethal in males (less than 3% of cases are male¹). Recently, deletions in the gene for NEMO (NF- κ B essential modulator), have been shown to cause 80% of cases of IP.² NF- κ B is a transcription factor involved in immune and inflammatory responses and in protecting cells from tumour necrosis factor induced apoptosis. Disruption of the *NEMO* gene leads to diminished NF- κ B activity and susceptibility of cells to apoptosis. In males carrying a *NEMO* mutation this is linked to embryonic lethality and in females it results in skewed X inactivation.^{3,4}

The clinical features of IP are associated with ectodermal tissue abnormalities including skin, hair, nails, teeth, eyes, and central nervous system. The major diagnostic features of the condition are dermatological, occurring in four classic stages⁵ with variable timing: (1) neonatal erythema and vesicles; (2) verrucous lesions with hyperkeratosis; (3) classic streaky hyperpigmentation following Blaschko's lines, leaving; (4) pallor, atrophy, hairlessness, and scarring, by the second decade. Skin biopsies show a macrophage led, type II cytotoxic inflammation (with macrophage phagocytosis of dyskeratotic keratinocytes and melanocytes) associated with an eosinophilia and an abnormal vascular response.⁶ This represents death of cells carrying the active mutated gene along lines of embryonic cellular migration (Blaschko's lines). Remaining fibroblasts show extreme skewed X inactivation.^{3,4}

The diagnosis is made on clinical grounds, the major dermatological features aided by histological confirmation; other features are variably present and there is often a family history of multiple male miscarriages.⁵ When the full phenotype associated with *NEMO* mutations and rearrangements becomes apparent it is possible that the current diagnostic criteria will be revised. Allelic conditions may also be identified which will increase the understanding of the function of NF- κ B.

Apart from the effects upon the eyes and central nervous system the course of incontinentia pigmenti is relatively benign. Ocular abnormalities (Table 1) occur in 35%¹ or more⁷ and 19% of patients are at risk of severe visual loss in one or both eyes.¹ The commonest reported are strabismus (present in 18.2%) and a retrolental mass or pseudoglioma (15.4%).¹ Peripheral retinal fibrovascular changes may be progressive and ablation of the ischaemic retina may arrest the fibrovascular process which otherwise may lead to tractional

Table 1 Ocular features described in incontinentia pigmenti

Part of the eye affected	Description
Lids	Ptosis ²¹
Nasolacrimal duct	Congenital obstruction ²⁸
Control of eye movements	Strabismus ^{1, 7, 17, 19, 21, 23}
Abnormalities of globe size	Nystagmus ^{22, 23}
	Microphthalmos ²³
	Buphthalmos ²²
Conjunctiva	Hyperpigmentation ²⁹
Sclera	Blue ^{19, 20}
Corneal abnormalities	See text
Iris	Atrophy with pigmentary irregularities ²³
Lens	Hypoplasia and synaechiae ⁷
	Congenital cataract (usually associated with retinal detachment) ^{1, 7, 22, 23}
Vitreous	Persistent fetal vasculature ³⁰
Fovea	Haemorrhage
	Foveal hypoplasia ³¹
Peripheral retina	Macular aneurysms ^{8, 9}
	Fibrovascular proliferation and traction retinal detachment ^{15, 17, 22, 25, 31}
	Vascular anomalies—eg, microaneurysms, arteriovenous shunts, neovascularisation associated with an avascular zone ^{8, 9, 17, 23, 32}
Optic disc	Neovascularisation ³³
RPE	Atrophy ^{1, 7, 17, 32}
	Pigmentary changes ^{13, 15, 23, 29, 34}

retinal detachment.^{8–12} Unrecognised, this may present as a retrolental mass. Histological examination of the posterior segment of such eyes shows nodular accumulations of macrophages containing melanin with overlying proliferation of the retinal pigment epithelium (RPE)^{13, 14} and foreign body giant cells.¹⁵

Descriptions of affected males are limited by their rarity. Until 1998, 43 males with suspected IP were reported; only 28 met diagnostic criteria.¹⁶ Of the 28, nine (32%) had ocular or visual abnormalities.¹⁶ Sex chromosome aneuploidy (XXY, Klinefelter's syndrome) was present in 17%.^{16, 17} Although affected males with normal karyotypes have previously been reported, only very recently has somatic mosaicism for the common deletion been demonstrated.¹⁸

We present two male children: a mosaic for the common IP mutation who re-presented with a spontaneous vitreous haemorrhage and in whom novel bilateral corneal changes were noted and; a second affected male with a similar but unilateral corneal change.

CASE REPORTS

Case 1

A 9 year old boy with a typical clinical history of IP but no family history of the disorder presented with a dense left vitreous haemorrhage and reduced visual acuity following minor

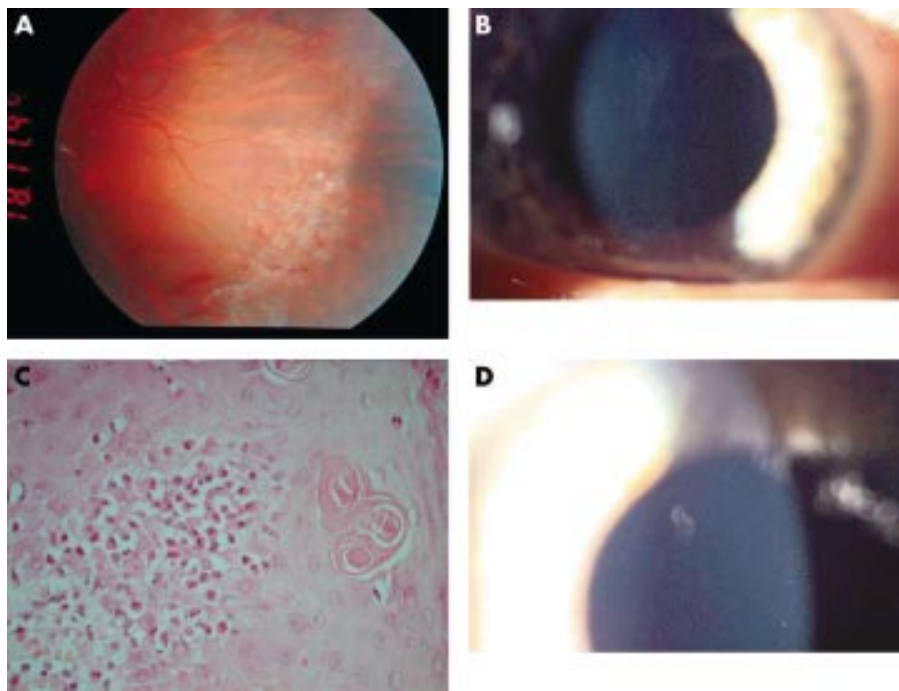


Figure 1 (A) Case 1: fundus photograph showing retinal changes on the left eye. There is preretinal gliosis associated with an area of peripheral vascular changes. (B) Case 1: anterior segment photograph showing the distribution of anterior stromal corneal changes. These changes are distributed in the shape of an hourglass, and the changes were symmetrical in both eyes. (C) Case 2: histological findings of neonatal skin biopsy. This section stained with haematoxylin and eosin shows eosinophils (characterised by a bilobed nucleus and granular, pink cytoplasm). This phase strongly supports the diagnosis. Magnification $\times 180$. (D) Case 2: an anterior segment photograph showing the distribution of corneal changes.

trauma. B-scan ultrasound revealed no evidence of retinal pathology and no clear separation of the posterior hyaloid face.

The diagnosis of IP was made in the early postnatal period following the investigation of typical skin lesions and a skin biopsy (showing massive epithelial cell proliferation, dyskeratotic cells, and infiltration of eosinophils). Other features included sparse hair and eyebrows, some atrophic scalp skin, and hypodontia with several malformed crowns. Neurological and visual development are normal. Recently, polymerase chain reaction (PCR) and Southern blot analysis of DNA of blood and neonatal fibroblasts revealed him to be a postzygotic somatic mosaic for the IP mutation.¹⁸

As the vitreous haemorrhage resolved, unaided visual acuity returned to 6/5. Abnormal telangiectatic vessels and some preretinal fibrosis were found in the left eye (Fig 1A). In the right retina there was closure of the temporal vasculature with an associated peau d'orange appearance and a patch of retinal pigment epithelial atrophy and heavy choroidal pigmentation.

The spontaneous vitreous haemorrhage was probably a result of bleeding from the temporal retinal vascular abnormalities. There was no evidence of active fibrovascular proliferation and in the absence of clear separation of the posterior hyaloid face it was decided to continue with regular observation.

Pupillary reaction, colour vision, visual fields, and ocular movements were normal. Bilateral symmetrical vertically oriented corneal subepithelial/anterior stromal opacities in an hourglass configuration were present (Fig 1B). This resembled small white bubbles, of differing sizes, in the anterior stroma. The epithelium, tear film, and corneal sensation were normal. At 7 months of age, bilateral media opacities were noted, raising the possibility that corneal changes were already present.

Case 2

This was the youngest of four sons, of healthy non-consanguineous parents. His father, however, has a distant female cousin who has IP with the classic deletion not subsequently found in her mother.² A diagnosis of IP was made in infancy. At 3 days post partum asymptomatic blisters on an erythematous base appeared on his right leg, right arm, and abdomen. By 1 month of age some had become hyperpigmented and there were also hyperkeratotic lesions on his right

calf. A skin biopsy was taken from one of the blistered areas (Fig 1C). He had an external torsional deformity of his right tibia at the age of 3 years, which gradually reduced. At age 9 he developed some non-specific pains in his right distal tibia (after a fall), with no obvious cause and no abnormality on x ray. These have resolved. His dentition shows some mildly hypoplastic teeth. Chromosome analysis, from both blood and skin, showed a normal male karyotype but genetic analysis has yet to reveal a mutation. He remains fit and well and is visually asymptomatic.

When last reviewed, at 10 years of age unaided visual acuity was 6/5 in both eyes, and pupillary reactions, ocular movements, colour vision, and visual fields were clinically normal. A small area of subepithelial and anterior stromal scarring was present in his left cornea (Fig 1D). Again the anterior stromal change consisted of small white scar-like bubbles of different sizes. Corneal epithelium, sensation, and tear film were normal. The right fundus showed some inferior depigmentation and the left some early paving stone changes inferiorly.

DISCUSSION

We describe two male cases of IP with similar corneal features of markedly different distribution. We believe that the corneal changes represent a process analogous to that occurring in the skin. In case 1, a mosaic for the classic IP deletion, the corneal changes are bilateral and symmetrical. In case 2, fulfilling clinical diagnostic criteria, the corneal change is monocular and localised. This is in keeping with the other clinical features of IP, which are typically variably present and patchily distributed.

Previous reports of corneal changes in IP are varied and include band shaped keratopathy in a phthisical eye with a retinal "glioma"¹⁹; bilateral superficial round lesions like bullous keratopathy, involving the epithelium and the adjacent stroma²⁰; a small, flattened cornea with corneal flecks at sites of iridocorneal attachments with an irregularly broadened and opacified limbus²¹; megalocornea secondary to congenital glaucoma resulting from an iris cyst²²; "bilateral superficial minimal non-staining corneal irregularity"¹⁵; corneal oedema associated with cataract²³; and epithelial disturbance (staining with fluorescein) with "mid-stromal mild

haziness."²⁴ Histological studies of eyes enucleated in the presence of a retrolental mass report no corneal abnormalities.^{13–15, 25} Subepithelial and anterior stromal changes found in five females in a series of 30,⁷ may be similar, but no comment was made on their significance.

Neither case had another cause identified to explain these changes. The pattern of changes may represent a primary abnormality of the epithelium, stromal keratocytes, or migratory cells—for example, Langerhans cells. The development of both the definitive corneal stroma and epithelium is dependent upon a number of complex inductions and cellular migrations. Cellular migrations directed towards the centre of the cornea could produce hourglass patterns or patchy changes.

The mouse model for this condition suggests that NEMO (IKBK γ) deficient cells trigger an inflammatory response that eventually leads to their death²⁶ and increased apoptosis of keratinocytes with inflammation occurs.²⁷ The corneal changes are compatible with previous inflammation.

This report describes a novel corneal feature in this rare and interesting disorder. We find it in male cases, which are very uncommon in IP. We have not observed these changes in female cases although they probably do occur.⁷ We suggest that these corneal changes are analogous to the classic dermatological features present in IP, arising from the genetic abnormality causing apoptosis and inflammation.

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