Incontinentia pigmenti (Bloch-Sulzberger syndrome) and retinal changes*

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SUMMARY Incontinentia pigmenti is associated with various anomalies in 80% of cases. Among the most important are the ocular abnormalities and more particularly a retrolental mass with detachment of a dysplastic retina. At the basis of this manifestation are retinal vascular changes, characterised at first by ectatic tortuous veins and arteriovenous anastomoses as well as by aneurysmal-like dilatations.

Incontinentia pigmenti, of which more than 300 cases are known at the present time, was first described by Bloch¹ and Sulzberger.² In 63% of the patients it is congenital or appears during the first week after birth, rarely during the first year of life, and unusually after one year of age. It is not a pure genodermatosis, but in reality an oculo-dento-cerebro-cutaneous syndrome or an ecto- and mesodermal dysplastic syndrome (Figs. 1 and 2).

The cutaneous manifestations display 3 successive stages:

First stage. This stage, which is seen in 50% of cases, is characterised by erythematous, vesicular, and bullous patches. They are irregularly disseminated and associated with blood eosinophilia, which disappears after a few weeks.

Second stage. This stage, which is seen in 1/3 of cases, is characterised by pustular, papular, lichenoid, and hyperkeratotic lesions. These verrucose elements are disseminated or linearly arranged. The granitic surface of the warts may be covered in places by thick crusts due to the bullae. The warty elements appear

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Fig. 2 Ocular changes in Bloch-Sulzberger syndrome. (After Nishimura et al.³³)

Fig. 1 *Incontinentia pigmenti*. Retinal arteries and veins appear normal up to the equator. At the temporal equator they arborise and form irregular kinked arteriovenous shunts with aneurysmal dilations. Sclerotic ghost vessels, clumps, and masses of dense white preretinal tissue are seen. From this zone to the ora the retina is avascular (lack of perfusion). A sinusoid cavity filled with blood developed. (After Watzke et al.³⁵).

Fig. 3 *Incontinentia pigmenti*. Chocolate-brown, patchy pigmentations affecting the trunk and showing jagged limits, irradiating in spider legs.

Fig. 7 *Incontinentia pigmenti*. Irregular epidermis. Slightly thickened stratum corneum. Superficial layer of the dermis displays numerous chromatophores filled with pigment granules. In the middle and deep layers capillaries surrounded by a cuff of lymphocytes and histiocytes.

some weeks or even months later. They are more numerous at the extremities and disappear either completely or leaving achromic or atrophic patches.

Third stage. This stage is characterised by a typical, chocolate brown, patchy or splashy, streaky or whorled pigmentation, which develops asymmetrically and affects the trunk and the extremities (Fig. 3), the face nearly always remaining free. The pigmentation is arranged in patches, plaques, or striae. The pigmented patches, which may be a few mm in diameter, show distinct but jagged limits, irradiating in spider legs. The plaques, which may reach 2–5 cm in diameter, have jagged margins. The striae, which may be wavy, form parallel or swirling stripes, suggesting the appearance of 'marble cake'. They

may anastomose and form networks or display verticillate or irregular arabesques.

The pigmentation gradually fades and often disappears completely at adult age (20 years).

A cicatricial alopecia or alopecia of the Brocq pseudoalopecia type and ungual dystrophies are observed in 38% of cases.³

The histopathology of the cutaneous lesions is interesting. In the first stage small vesicles, laden with numerous eosinophils, are seen. They are surrounded by dyskeratotic cells with acidophil hyaline cytoplasm. The dermis is infiltrated by eosinophils and mononuclears. These changes often resemble Duhring's herpetiform dermatitis. In the second stage, the verrucose stage, a monocellular dys- and

hyperkeratosis is observed. There is a papillomatosis of the dermis as well as a mononuclear infiltration with some melanophages. In the third stage numerous macrophages, laden with melanin, are found in the superficial dermis. They apparently originate from the basal layer of the epidermis, which presents with a liquefactive and vacuolar degeneration and is very poor in pigments. There is, moreover, an extensive dropping off of melanin granules into the dermis, where they are either free or absorbed by chromatophores (or melanophores), increased in number.

Associated anomalies

Associated anomalies of incontinentia pigmenti are seen in 80% of cases according to Carney.³

Anomalies of the central nervous system are observed in more than 30% of cases³: microcephaly, hydrocephaly, seizures, epilepsy, motor disturbances, spastic and paralytic disorders, Little's disease, mental deficiency, EEG abnormalities.

Psychomotor or developmental retardation is not frequent.

Dental abnormalities are seen in 1/3 of the patients and according to Carney³ even in 65% of cases. They include partial absence of teeth, pegged and malformed teeth, retarded dentition, etc.

Bony abnormalities are seen in more than 20% of cases. Skull deformities, kyphoscoliosis, hip dislocation, and congenital calcifying chondrodystrophy have been observed.

Congenital cardiopathies are rare.

Other abnormalities are seen in nearly 14% of cases³: dwarfism, cleft palate, cleft lip, ear anomalies, clubfoot, spina bifida, etc.

Ocular abnormalities are frequent. Carney³ reviewed 464 references in the world literature. In nearly 20% of cases there were serious ocular abnormalities and in 15% milder anomalies (35%). Other authors came to the same percentage (26% for Graham Scott *et al.*,⁴ 32% for Findlay⁵). The ocular abnormalities are mostly unilateral. They may be bilateral, and then one eye is usually more severely affected than the fellow eye. One may observe nystagmus,⁶ strabismus,⁶ microphthalmos, ptosis, blue sclera, pigmentation of the conjunctiva,⁷ corneal scars or clouding,^{8,9} irregular iris pigmentation, seclusion of the pupil,¹⁰ absence of the anterior chamber,⁹ congenital cataract,⁸ atrophy of the ciliary body¹⁰ phtisis bulbi,¹¹ optic atrophy,^{6,8,12,13} vitreous changes or haemorrhages, persistence of the hyaloid artery, and myopia.

Inflammatory affections, such as uveitis, papillitis, chorioretinitis,^{14,15} and metastatic ophthalmia, have been observed, and consequently some authors^{14,16,17} accept an inflammatory aetiology of the disease.

The most typical ocular abnormality in incontinentia pigmenti is a retrolental mass with detachment of a dysplastic retina. It is seen in 11.5% of cases according to Carney and Carney Jr.¹⁸ This mass has been described under different names, but it is always the same lesion. It has been called either persistence and hyperplasia of the primary vitreous,^{5,10,19,20} or pseudoglioma^{1,4,12,21,22} or retrolental fibroplasia.^{5,6,18,23,24}

Very often at the time of diagnosis we are in presence of the final stage, which does not allow a pathogenic and exact view of the lesions.¹⁰

Uemura *et al.*²⁵ made a histopathological examination. They found a fibrovascular tissue, a massive gliosis of the retina, a cholesterol granuloma, and an enlarged choroid with pigment proliferation. Mensheha-Manhart *et al.*²⁶ observed a nodular proliferation of the pigment epithelium. The nodules contained macrophages laden with melanin and lipofuscin. These pigment epithelium changes may affect the neurosensory retina and lead to retinal dysplasia or retinal detachment.

Retinal abnormalities

Many retinal abnormalities have been described in incontinentia pigmenti.

Fischbein *et al.*²⁷ observed myriad small patches of depigmentation and pigment variegation scattered diffusely throughout the fundi. Towards the periphery they became more confluent.

A pseudoretinoblastoma-like retinal dysplasia has been observed.²⁸ Jensen²⁹ described also a large, whitish, membrane-like formation, protruding into the vitreous and displaying vascularised processes to the retina, which was centrally depigmented and had elongated islands of dense pigmentation in the periphery.

Retinitis proliferans, avascular peripheral retina, glial strands of the retina, anomalies of the retinal pigment epithelium,¹⁰ microaneurysms,³⁰ and telangiectasia have been observed. Also seen are inferotemporal congenital ablatio falciformis with retinal vessels drawn into and bordered by pigment clumps,^{5,31} haemorrhagic and pigmentary retinitis,¹² abnormal retinal pigmentations,^{6-8,23,24,27,29,32,33} retinal dysplasia with rosettes and areas of pigment proliferation,^{6,10,19,24} and detachment of a dysplastic retina.^{5,6,10,20,23,31,34}

All the mentioned retinal abnormalities are probably the consequence of retinal vascular changes, which are at the basis of the pseudoglioma or retrolental mass. These vascular changes are characterised by slackened and ectatic veins, formation of rete mirabile, and pathological venous anastomoses, as well as oedema of the posterior pole.^{5,7,14,21,22}

The two most important papers on the retinal vascular changes are those of Watzke *et al.*³⁵ and Nishimura *et al.*³³

Watzke *et al.*³⁵ examined 19 cases of incontinentia pigmenti: 5 of these patients showed a unilateral and 2 a bilateral zone of abnormal arteriovenous connections and preretinal fibrotic tissue at the temporal equator with no perfusion peripheral to it. As the retinal vessels approached the temporal equator, both venules and arterioles became tortuous, kinked, and irregular in calibre. They arborised the equator and connected in the form of arteriovenous anastomoses. Aneurysm-like dilatations and branching frond-like clusters of new vessels occurred. The extreme periphery was avascular. Some vessels were sclerotic and consisted of white lines. Abnormal kinked, tortuous vessels could also be seen in the macular region. Late fluorescein leakage from intraretinal shunts and microvascular anomalies was observed. In one case the lesions were progressive.

Nishimura *et al.*³³ stated that, although hypoplasia of the retinal vessels has been thought to be the primary change in incontinentia pigmenti,^{21 22 35} the development of the retinal vessels in their case was first normal. They concluded that the avascular areas in the peripheral fundi were formed secondarily to obstruction of the vascular bed and that the cause of this obstruction was circulatory insufficiency. Photocoagulation was applied in one eye and the progress of vascular proliferation could be prevented.

On the first ophthalmoscopic examination at 13 days of age circulatory disturbances of the retina were found in both eyes. Oedema was seen in the posterior retina in association with slight narrowing and exaggeration of reflexes of the arterioles. At 34 days of age, however, the retinal venules became dilated and tortuous, and vascular anastomosis was seen at several places along the equator of the retina. The peripheral retina of all 4 quadrants appeared to be avascular due to obstruction of the vessels. Subsequently, on the temporal side of the left eye, there was rapid expansion towards the posterior aspect of the avascular region due to obstruction of the blood vessels in the peripheral retina. New anastomoses of the venules were observed. Fluorescein angiography at 43 days of age indicated absence of fluorescence in the avascular areas, marked retardation of circulation time in the retina, and increased permeability of the blood vessel walls. Shunt vessels of the anastomosis were engorged and leaky. Furthermore, at 62 days of age neovascularisation associated with formation of rete mirabile was observed in a superior temporal portion of the posterior retina.

It is obvious that in order to detect the real primary vessel changes, the patients have to be examined very

early, which is usually not the case. On the other hand pseudoglioma is probably the end stage of the retinal vascular changes.

In conclusion, and according to Carney,³ strabismus is seen in 18.2% of cases, blindness in 7.5%, cataract in 4%, optic atrophy in 4%, retinal pigmentation in 4%, pseudoglioma in 3.5%, retinal detachment in 2.9%, microphthalmos in 2.9%, and retinal telangiectasia and ectasia in 2.2% of cases.

Except for some extracutaneous associations, such as the retinal abnormalities, the course of incontinentia pigmenti is benign.

Distinguishing factors

Franceschetti and Jadassohn³⁶ demonstrated that incontinentia pigmenti or Bloch-Sulzberger syndrome has to be separated from the reticular infantile pigmentary dermatosis of Naegeli.³⁷ This disease appears at about 2 years of age and is characterised by: (1) Brownish, slate-grey, cutaneous pigmentation, which is morphologically reticular and widely distributed, involving particularly the neck and the trunk. This pigmentation is never preceded by an inflammatory process.

(2) Hypo- or anhidrosis due to functional deficiency of the sudoriferous glands. The pilocarpine transpiration test is weakly positive or negative. The patients complain of discomfort caused by heat and owing to vasomotor disturbances. (3) Palmoplantar keratosis. (4) No dental malformations, although the enamel may show yellow spots, no alopecia, and no ocular malformations.

Both sexes are identically affected. The inheritance is obviously autosomal dominant.

Incontinentia pigmenti of Bloch-Sulzberger must also be distinguished from incontinentia pigmenti achromians, which was first described by Ito³⁸ and which is a rare neurocutaneous syndrome. In 35% of cases the depigmented skin patches existed at birth, in 50% they developed during the first year of life, and in 15% at a later period. Fewer than 50 cases have been reported. It is characterised as follows.

There are hypopigmented patches of the skin. In 50% of cases there are anomalies of the central nervous system (mental retardation, convulsive seizures, EEG abnormalities). In 37% of cases there are other abnormalities: skull deformities, ear anomalies, spina bifida occulta, cleft palate, congenital dislocation of the hip, scoliosis, syndactyly, leg discrepancy. In 31.5% of cases there are ocular anomalies: amblyopia, strabismus, nystagmus, corectopia, opaque cornea, megalocornea, microphthalmia, malformations of the iris and the chamber angle,³⁹ retinal pigmentary abnormality, tessellated

Fig. 4 As in fig. 3.

Fig. 5 Same pigment abnormalities as in Figs. 3 and 4 but at the level of the legs.

Fig. 6 As in Fig. 5.

fundus, choroidal atrophy or central choroidal sclerosis,³⁹ optic atrophy.

Histologically the hypopigmented skin shows neither inflammatory changes nor dropping off of melanin granules into the dermis. However, the melanin granules in the basal layer of the epidermis are either decreased or absent,⁴⁰ and there are no DOPA-positive cells.

The disease is more frequent in females, the female to male ratio being 3.3:1. Familial cases have been reported, and they suggest an autosomal dominant inheritance.

Inheritance

In considering inheritance of Bloch-Sulzberger syndrome what is obvious is the predominance of the female sex. The female to male ratio has been reported as 70:3,³⁶ 86:5,⁴ 231:13,⁴¹ and 653:16.³

Only one pair of affected monozygotic twins is known. They were concordant.⁴² Many familial cases have been reported.^{15 19 43-45} According to Morgan⁴⁶ the familial occurrence exists in 15-40% of cases and according to Carney³ even in 55.4%, 2 or more members of the family being affected.

Some authors consider the inheritance to be autosomal dominant with female sex limitation, others that there is prenatal lethality for the males. Kuster and Olbing⁵⁰ reported a mentally retarded woman with incomplete dentition and a history of

skin lesions at birth. She had one son and 11 daughters. Six of the girls showed incomplete dentition and incontinentia pigmenti.

Autosomal X chromosome translocation is another possibility, although no chromosomal abnormalities have been found.⁵¹ Cytoplasmic inheritance with lethality in the male could account for some pedigree patterns. Moreover, a viral aetiology has been suggested by Haber,¹⁶ and cytoplasmic inclusions have been identified.

At present it is generally accepted that there is an X-linked dominance with prenatal lethality in the male.^{18 47-49} The phenotype in the affected females might be consistent with random X chromosome inactivation as in the Lyon hypothesis.

Case reports

We had the opportunity of examining 3 cases of incontinentia pigmenti.

Case I was a girl, 4 years of age, who had no ocular abnormalities.

Case II was a girl, 15 months of age, who was born normally. The mother had congenital incontinentia pigmenti, which disappeared at age 13 and was associated with a jaw anomaly. The child also presented with an incontinentia pigmenti on the internal aspect of the thighs and lower legs.

Ophthalmological examination revealed a nystagmus and a total bilateral retinal detachment

Fig. 8 As in Fig. 7.

Fig. 9 As in Fig. 7.

more pronounced on the right. The electroretinogram was completely extinguished, which suggests a retinal dysplasia.

Case III was also a girl, 7 years of age. She displayed a typical incontinentia pigmenti of the trunk and the legs (Figs. 3–6). The teeth are in a very bad condition. On the ophthalmological point of view, a nystagmus and an infero-internal strabismus of the right eye with hyperaction of the inferior oblique were noted. At the right eye there was an optic atrophy with distinct margins; at the left eye the

disc was normal, but there was a temporal cone. Both fundi were albinoid and studded with pigmentary dust. The retinal vessels were very thin. There was a myopia of -10 D at the right and -14 D at the left. The right iris was variegated. No other ocular anomalies were noted. The electroretinogram was subnormal on both sides (R.E.: photopic *b* wave $40 \mu\text{V}$, scotopic *a* wave $80 \mu\text{V}$ and scotopic *b* wave $100 \mu\text{V}$. L.E.: photopic *a* wave $25 \mu\text{V}$, photopic *b* wave $40 \mu\text{V}$, scotopic *a* wave $100 \mu\text{V}$ and scotopic *b* wave $120 \mu\text{V}$). The right eye had only light perception.

The histopathological examination of a skin patch with incontinentia pigmenti shows an irregular epidermis (Fig. 7–9). The stratum corneum is slightly thickened, but orthokeratotic. The stratum granulosum consists of one or 2 cellular layers. The stratum mucosum is normal. The basal layer is also normal, and there are no melanin granules. On the contrary, the superficial layer of the dermis displays numerous chromatophores, filled with pigment granules. In the middle and deep layers the capillaries are surrounded by a cuff of lymphocytes and histiocytes.

Conclusion

Incontinentia pigmenti or Bloch-Sulzberger syndrome is a very distinct disease ophthalmologically as well as genetically. Affected males are exceptional, and X-linked dominant inheritance may be accepted. The retrolental mass, which is seen in many cases, is the end stage of a process which starts with circulatory insufficiency and vascular anomalies. The process nevertheless does not always and necessarily evolve to the end stage, as is shown by our case II. It may stop at any stage, as in our case III, in which the retinal lesions and the vascular anomalies are minimal.

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