

Incontinentia Pigmenti

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Abstract

Incontinentia pigmenti (IP) is an X-linked dominant single-gene disorder of skin pigmentation with neurologic, ophthalmologic, and dental involvement. IP is characterized by abnormalities of the tissues and organs derived from the ectoderm and mesoderm. The locus for IP is genetically linked to the factor VIII gene on chromosome band Xq28. Mutations in NEMO/IKK- γ , which encodes a critical component of the nuclear factor- κ B (NF- κ B) signaling pathway, are responsible for IP. IP is a rare disease (about 700 cases reported) with a worldwide distribution, more common among white patients.

Characteristic skin lesions are usually present at birth in approximately 90% of patients, or they develop in early infancy. The skin changes evolve in 4 stages in a fixed chronological order. Skin, hair, nails, dental abnormalities, seizures, developmental delay, mental retardation, ataxia, spastic abnormalities, microcephaly, cerebral atrophy, hypoplasia of the corpus callosum, periventricular cerebral edema may occur in more than 50% of reported cases. Ocular defects, atrophic patchy alopecia, dwarfism, clubfoot, spina bifida, hemiatrophy, and congenital hip dislocation, are reported.

Treatment of cutaneous lesions is usually not required. Standard wound care should be provided in case of inflammation. Regular dental care is necessary. Pediatric ophthalmologist or retinal specialist consultations are essential. Seizures should be treated with anticonvulsants. Abnormal fibrovascular proliferation can be treated with photocoagulation.

Keywords

Bloch-Sulzberger syndrome, skin pigmentation disorders, *factor VIII* gene, *NEMO/IKK- γ* mutations, (NF- κ B) signaling pathway

Definition

Incontinentia pigmenti (IP), sometimes termed Bloch-Sulzberger syndrome, is a rare X-linked, dominantly hereditary disorder of the developing organs and tissues of ectodermal and mesodermal origin (1). The name derives from the incontinence of melanin in the superficial

dermis during the third, pigmentary stage of the disease (2).

Epidemiology

Although its prevalence is unknown, more than 700 cases have been reported in the world literature up-to-date. Most cases have been

described in white persons, although other races are affected as well. The occurrence of IP in male patients is unusual, with a worldwide total of 28 cases found in a recent literature review (3).

Etiology

It seems that there is a genetic background in the pathogenesis of this syndrome. About 50% of the IP cases have a positive family history (2). There must be an X-linked dominant trait that is usually lethal in males. More than 95% of the reported cases are females, the few males affected being probably result of spontaneous mutations (4). These mutations are suspected to produce a failure of immune tolerance in ectodermal tissues, resulting in an autoimmune-like reaction in heterozygote girls and a fetal graft versus host like disease in homozygous boys (5).

Five infant boys with the disease also had evidence of [Klinefelter's syndrome](#) (47, XXY) that may have played a role in their survival because the second X chromosome protected them from intrauterine death. Also, hypomorphic alleles may play a role on the survival of males with IP, with less deleterious mutations and presentations along a proposed continuum from IP to [anhidrotic ectodermal dysplasia](#) with immunodeficiency (3). The rare occurrence of IP in males can be explained by one of the following three mechanisms: half chromatid hypothesis, unstable permutations or higher rate of *de novo* germ line mutations (6). In general, cases attributed to IP in male patients should be carefully investigated and chromosomal analysis should be performed, to run out an alternate diagnosis (3).

It is now recognized that during early embryogenesis of mammalian female organism, X chromosome inactivation or lyonization results in a mosaic population of cells: some cells have an active paternal X chromosome whereas others have an active maternal X chromosome. It has been hypothesized that the segmental and streaked manifestations of IP may be consequential to tissue mosaicism from random X inactivation, with the normal X chromosome active in uninvolved skin and the IP X chromosome active in involved skin (1). In female patients, the clinical findings may be subtle, reflecting extreme lyonization.

It is now known that IP is caused by the *NEMO* gene, which encodes a regulatory component of the I kappa B kinase, required to activate the nuclear factor-kappa B (NF-kB) pathway (1). The locus of IP has been found close to the factor VIII gene on chromosome Xq28. The gene for NF-kB essential modulator has been mapped to

a position 200 kilobases proximal to the factor VIII locus. NF-kB essential modulator mutations impair NF-kB activation and cause IP (7). When activated, NF-kB controls the expression of multiple genes including cytokines and chemokines and protects cells against apoptosis (3). A severely truncated NEMO protein will leave the cells susceptible to proapoptotic signals. This explains why in IP the functionally aberrant cell clone is eliminated by apoptosis and why the skin lesions containing apoptotic cells at birth eventually heal after elimination of NEMO-defective cells. It is obvious that such a deleterious mutation of a vital gene can only survive in a mosaic state. Hemizygous male embryos die *in utero* because of severe apoptosis. Apparently, the inflammatory and vesicular stage, occurring during the neonatal period, reflects apoptosis that eliminates the functionally aberrant cell clone. It is important to realize, however, that this elimination is not complete because inflammatory stages characterized by vesiculation and eosinophilia may recur even in adult patients (8).

Clinical features

The clinical presentations of IP vary considerably even among family members. They range from subtle cutaneous and dental involvement, recognized after the diagnosis, in a relative to severe and incapacitating neurological and ophthalmological manifestations. Those differences in expressivity have been attributed to lyonization in females, resulting in functional mosaicism.

Severity of the disease process in the small number of live-born male patients is generally not greater than that in the affected females. Many male patients have disease expression limited to cutaneous involvement of one or two limbs (3). The skin changes evolve in stages in a fixed chronological order.

The first stage is present in 90% of the patients at birth or within the first two weeks of life (2). It is possible that earlier inflammatory stages can occur *in utero* and not progress after birth. Clear, tense bullae on inflammatory bases in linear groups develop on the limb in recurrent crops; less often, they are generalized (4). They tend to follow the lines of Blaschko (3, 9). Recurrence of stage 1 lesions can be seldom observed. The frequency of such late recurrences, sometimes several years after the neonatal period, remains unknown. Thus, a diagnosis of IP could be considered in the case of a child, presenting recurrent inflammatory lesions of

unknown origin along the Blaschko lines (10). The bullae are accompanied or followed by smooth, red nodules or plaques, often irregularly linear, on the limbs and trunk. The plaques may be extensive and may precede the bullae. They may be bluish purple in color and may ulcerate (4). The face is usually spared, although scalp lesions are quite common (3). Lesions on the extremities frequently progress to stage 2 of the disease, with a possibility of scarring during the fourth (atrophic) stage: those on the torso typically heal without atrophy. Recurrences may be accompanied by pruritus. However, such recurrences are usually short-lived and less severe than the original eruption.

The second stage, which is marked by linear verrucous lesions similar to the first stage pattern, follows usually between the second and sixth weeks of life. It persists for a few months and in 80% of cases fades by the age of six months (2). Linear warty lesions may appear on the back of the hands and feet, particularly on the fingers and toes. Warty lesions around the nails with underlying lytic bone lesions have occurred in adolescence (4). They are highly evocative on the scalp. Late onset of focal verrucous lesions has been reported (10).

The third stage, unrelated to the sites of the previous stages, consists of brownish linear and whorled streaks that follow the lines of Blaschko, with a wide range of involvement mainly on the trunk (2). The pigmentation ranges in color from blue-gray or slate to brown. The bizarre "splashed" or "Chinese figure" distribution is diagnostic. Multiple linear and macular teleangiectasias have occasionally been present (4).

A fraction of patients (about 14%) exhibits a **fourth stage** which appears as a residual hypopigmentation in the areas of the previous hypopigmentation, without atrophy; 28% of the patients show only small, hairless, atrophic patches (2) that may be anhidrotic (4). The most common distribution is on the extremities in 77% of cases with predilection for posterior calves and very infrequent involvement of the torso. Side lighting may be used for better visualization of atrophic patches whereas Wood's lamp examination may assist in the diagnosis of hypopigmented streaks (3). Such lesions might be the only remaining sign of childhood disease and may then be of importance, in counseling parents who already have an affected child (4). The hair is usually normal but in about 25% of the cases,

patches of cicatricial alopecia resembling pseudopelade, are present from birth, or develop in infancy at or near the vertex (4). It often follows inflammation and vesiculation in the area (3). Two cases of whorled scarring alopecia associated with IP that follow the lines of Blaschko, have been reported. They reflect functional X-chromosome mosaicism (7).

The nails are usually normal but may be small and dystrophic (7). Nail pitting, onychogryposis and subungual hyperkeratosis have been observed (10). Subungual and periungual keratotic tumors may appear at a later stage, typically between puberty and the third decade, although one case has been reported in a 10-year old. Fingers are affected more often than toes. The tumors may regress spontaneously but usually continue to grow, causing nail dystrophy and, most importantly, destruction of the underlying bone of the terminal phalanx. The lytic lesions may occur secondary to pressure from the overlying tumors or represent primary bone manifestation of IP (3).

Palmoplantar hyperhidrosis can also be present (2). Supernumerary nipples have been reported (10). In over half of the reported cases, organs other than the skin or its appendages have been involved (4).

Skull defects such as microcephaly, cleft palate, cleft lip and ear abnormalities are encountered (11).

Skeletal malformations include: syndactyly, hemiatrophy, shortening of arms and legs, dwarfism and spina bifida (9).

Dental abnormalities are the most common non-cutaneous manifestation of IP, occurring in more than 80% of all patients, with nearly 65% presenting major anomalies. These findings have substantive diagnostic importance because they persist for life, in contrast to the skin abnormalities. Both the deciduous and permanent dentition may be affected (3). Delayed dentition (18%), partial anodontia (43%) and cone or peg-shaped teeth (30%) are the most usual (4).

Ocular defects are found in about 40% of the cases, many patients being blind. Asymmetric involvement is the most common, although bilateral ocular lesions may occur as well (3). The defects include strabismus, cataract, conjunctival pigmentosa uveitis, optic atrophy, retinal vascular abnormalities, blue sclerae, exudative chorioretinitis and a condition resembling retrolental fibroplasia. Microphthalmia also occurs (2, 4, 7, 12).

Retinal lesions may affect the peripheral retina or the macula and generally appear to be a result of vaso-occlusive events and ischemia with subsequent compensatory vasoproliferation. They become evident between the neonatal period and 1 year of age, emphasizing the need for frequent ophthalmologic evaluation during this time. The prognosis for normal vision in a child without demonstrable findings within the first year of life is generally considered good. However, once established, the retinal changes may evolve slowly during many years or progress quickly to retinal detachment and blindness during the course of weeks (3).

Central nervous system (CNS) disorders occurs in about 25% of cases. They include seizures, mental retardation, spasticity, cerebral atrophy, hemiparesis and encephalopathy (4).

There has been one report of seizures presenting as the initial disorder (6). They occur early in life and are associated with ocular defects (2, 4, 8, 12). Eosinophilia up to 50% in the peripheral blood is usual when acute inflammatory skin changes are present. The highest levels are documented at 3 to 5 weeks of life. There is evidence of both neutrophil and lymphocyte dysfunction; altered immunological reactivity is observed in some patients (4).

Course and prognosis

The prognosis is generally good and depends on extracutaneous manifestations. There is a poor prognosis and developmental delay in patients with seizures during the first weeks of life. Absence of seizures and normal developmental milestones appear to predict a good prognosis (4). Intensity of skin manifestations and eosinophil count are not related to more severe visceral involvement and have no prognostic value (10).

Pathology

The bullae are situated beneath the horny layer or within a spongiotic epidermis. The dermis shows non-specific inflammatory changes with a cellular infiltrate, including numerous eosinophils. The infiltrate extends into the epidermis and the contents of the bullae may consist predominantly of eosinophils. The lichenoid papules show hyperkeratosis, acanthosis and oedema of the basal layer, many cells of which are degenerated. Macrophages laden with melanin are present in the upper dermis. The presence of eosinophils in epidermal and dermal infiltrates can be explained by the presence in the early vesicular stage of basophils which

release eosinophil chemotactic factor of anaphylaxis and by the release of eotaxin by activated keratinocytes (4). After degranulation, eosinophilic proteases may cause degradation of tonofilaments and desmosomes, resulting in spongiosis and eventual blister formation.

Recurrences frequently occur after the onset of a febrile illness, during which circulating inflammatory cytokines tend to increase and may therefore trigger a second episode (3). Eosinophil chemotactic activity has been demonstrated in patients with IP in the blister fluid and in eluates of crusted scales overlying the lesions (3, 13). In the warty lesions the hyperkeratosis is further increased and within the irregularly acanthotic epidermis hyaline bodies represent individual cell keratinization (4). Focal dyskeratosis occurs very early, persists until the onset of stage 4 lesions and is clearly determined to be related to keratinocyte apoptosis (10). The pigmented patches show diminution or absence of pigment in the basal cells and large quantities of melanin in melanophages in the upper dermis. The epidermis may be normal or slightly acanthotic (4).

Stage 4 presents as atrophic epidermis with a loss of rete ridges and dermal sweat coils. The only remnants of the pilosebaceous apparatus are orphaned erector pili muscles. Basal melanocytes are structurally normal but are significantly reduced in quantity. Colloid bodies similar to Civatte bodies of lichen planus and lupus erythematosus have also been identified in the upper dermis, by means of electron microscopy (3). In all three stages, melanophages are present (4).

Differential diagnosis

The combination of bullae with linear, nodular or warty lesions in a female infant is pathognomonic (4). Peripheral eosinophilia and radiographic changes of distal phalanges are suggestive signs in early stages (5). Other diseases to take into consideration are shown in Table 1

Table 1. Differential diagnosis of Incontinentia Pigmenti

Stage of IP	Differential diagnosis
First	Infectious: Bullous impetigo, herpes simplex, varicella, Langerhans cell histiocytosis. Immune-mediated: Dermatitis herpetiformis, epidermolysis bullosa acquisita, bullous systemic lupus erythematosus, linear IgA bullous dermatosis, bullous pemphigoid, pemphigus vulgaris, heritable epidermolysis bullosa, bullous mastocytosis. Child abuse.
Second	Verrucae vulgaris, linear epidermal nevi.
Third	Linear and whorled nevoid hypomelanosis, dermatopathia pigmentosa reticularis, Naegeli-Francoschett-Jadessoohn syndrome, X-linked dominant chondrodysplasia punctata. pigment mosaicism.
Various	Goltz syndrome.

Antenatal diagnosis

As IP is a X-linked dominant disease, a family counseling should be offered (4). A single mutation of NEMO gene, resulting in the deletion of exons 4 through 10, is found to account for more than 80% of all IP cases. The high frequency of this specific deletion facilitates mutational detection for the majority of families and offers a possibility of prenatal diagnosis (3).

Treatment

The inflammatory lesions, particularly if denuded, should be treated with standard wound care to avoid secondary infections (5). Spontaneous improvement and resolution of skin lesions is the general rule. The use of lasers in the treatment of hyperpigmentation should be discouraged because it has been reported to trigger an extensive vesiculobullous eruption. Concerning the teeth, referral for radiologic evaluation and dental intervention by the age of 2 years is appropriate.

Regular visits to a pediatric ophthalmologist or a retinal specialist familiar with retinopathy of prematurity, are essential during the first year of life. A complete neurologic examination is warranted for all infants with newly diagnosed IP. Neonatal seizures are an important prognostic indicator and may predict developmental delay. Seizures occasionally develop in later childhood or adolescence, but are generally easy to control

with appropriate anticonvulsant therapy and usually do not result in other impairment of the CNS or mental retardation if late in onset. Therefore, parents should be reassured of good prognosis if neurological deficits do not develop during infancy (3).

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