Chapter 8
Incontinentia Pigmenti

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Contents

Abbreviations

CBCT	Cone beam computed tomography
CNS	Central nervous system
DWI	Diffusion-weighted imaging
EEG	Electroencephalography
IKBKG	Inhibitor of κB kinase gamma
IP	Incontinentia pigmenti
IV	Intravenous
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NEMO	Nuclear factor-κB essential modulator
NF-κB	Nuclear factor-κB

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OCT	Optical coherence tomography
OT	Occupational therapy
PCR	Polymerase chain reaction
PT	Physiotherapy
RPE	Retinal pigment epithelium
SLT	Speech and language therapy
STIPs	Subungual tumors of IP
SWI	Susceptibility-weighted imaging
TNF	Tumor necrosis factor
VGEF	Vascular endothelial growth factor
XR	X-ray

Introduction

Incontinentia pigmenti (IP, OMIM # 308300), or Bloch-Sulzberger syndrome, is an X-linked dominant genodermatosis with multisystem involvement and highly variable phenotypic expressivity. It is caused by loss-of-function mutations in the *IKBKG* gene (*inhibitor of κB kinase gamma*) located on chromosome Xq28. In 80% of known cases, the molecular changes consist of a deletion at exons 4–10 [1, 2]. *IKBKG* gene encodes the NEMO (nuclear factor-κB essential modulator) regulatory protein, which in turn activates the NF-κB signaling pathway involved in a variety of cellular processes including inflammatory reactions, immune function, stress response, and suppression of apoptosis [3]. While NF-κB is present in all cell types, this transcription factor plays an essential role in the development and homeostasis of ectodermal tissues [4–8]. As a result, *IKBKG* mutations which disrupt the NEMO/NF-kB interaction can result in severe disorders of the skin and other ectodermal tissues.

The estimated birth prevalence of IP is ~0.7–1.2 in 100,000, with new de novo mutations accounting for approximately 65% of affected individuals [9–11]. The disorder is seen primarily in females as the moderating effects of X-chromosome mosaicism (*lyonization*) allow for survival. Male fetuses with pathogenic *IKBKG* null mutations miscarry in utero due to absence of the gene product. However, IP may occasionally occur in males with somatic mosaicism or XXY karyotype (Klinefelter syndrome) [12]. Affected males with both somatic and germline mosaicism may transmit the *IKBKG* pathogenic variant to their daughters [13].

Less deleterious (hypomorphic) *IKBKG* mutations that impair but do not abolish function can also give rise to surviving males with genetically related (allelic) disorders to IP. Clinical features vary in severity based on the residual function of the mutated protein. Male patients may present with ectodermal dysplasia and immunodeficiency (OMIM #300291) or X-linked recessive immunodeficiency (OMIM #300636) [14–17]. Female carriers of these mutations may be asymptomatic or have mild clinical signs of IP [18].

Clinical Characteristics

IP is typically identified by characteristic skin findings, accompanied by a spectrum of neuroectodermal manifestations affecting the eyes, nails, hair, teeth, and central nervous system (CNS). These clinical features are highly variable with no clear genotype-phenotype correlation. Cutaneous and extracutaneous manifestations have been found to occur with similar frequency in both male and female patients [19–21]. However, individuals clinically diagnosed with IP but lacking an identifiable mutation are more likely to be male and have a milder clinical phenotype (lower incidences of dental and hair anomalies) [21].

The heterogeneous presentation of IP is suspected to be a result of variable *IKBKG* gene expression between cell lines due to functional (skewed lyonization) or somatic X chromosome mosaicism, as well as the pleiotropic role of the encoded NEMO protein [2, 3, 6, 22, 23]. During gestation, cell lines expressing the mutated X chromosome (NEMO-deficient) migrate along pathways of embryonic development. Postnatally, the severity of clinical findings that begin to emerge reflects the extent of affected cell lines and the degree of expression of the mutated X chromosome.

Skin

The cutaneous manifestations of IP occur in all affected patients, although they may be subtle and not always recognized. They are the most common first presentation of the disease, with a median age of onset of 29.9 days after birth [24], although it is not uncommon for patients to be born with vesicular lesions. These skin findings are clinically diagnostic, classically evolving through four successive and overlapping stages, not all of which occurring in each affected individual.

Stage 1 (Vesicular or Inflammatory Stage) This stage is characterized by crops of superficial papules, vesicles, and/or pustules on a linear erythematous base, following the lines of Blaschko (Fig. 8.1). In the majority of cases, these lesions are diffusely distributed over both the trunk and limbs bilaterally, while the lower limbs are the most common site of involvement overall [25–28]. Lesions on the scalp/vertex, but sparing the face, are also commonly reported. An important exception to this typical pattern is the male IP phenotype which is more likely to present with focal or unilateral stage 1 skin findings [20]. This is reported to occur in 15% of affected male patients, but does not correspond to a milder overall disease as the majority eventually progress to develop bilateral skin lesions and multisystem abnormalities [20].

Stage 1 skin lesions are observed in an estimated ~80–92% of cases [20, 21, 25, 26, 28–31], presenting at birth or within the first month of life in 90% of all affected patients and before the first year in 99% [32]. Less commonly, they may occur in

utero or after 1 year of age, leading to diagnostic confusion [25, 26, 28]. The lesions tend to heal over weeks and can be replaced with new crops within the linear erythema before typically clearing by 4–6 months of age in most children. Reoccurrence of milder, self-limited vesicular eruptions can occur later in life in association with acute febrile illnesses [33–35].

Stage 2 (Verrucous Stage) The lesions in this stage are hyperkeratotic, warty papules and plaques arranged linearly along the lines of Blaschko (Fig. 8.1), but not necessarily in the same location as the stage 1 lesion. They are most commonly seen on the distal extremities, especially the digits and ankles. Scalp and neck involvement can occasionally be seen, but the trunk and face are seldomly affected [25, 26, 28, 36].

The frequency of occurrence varies within the published literature, with most studies reporting rates between ~70–85% [20, 25, 26, 29, 30] and ~15–30% [21, 27, 28, 36, 37]. It has been suggested that this large discrepancy is due to underrecognition/reporting, as stage 2 lesions are typically short lived, more localized, and diminished in appearance compared to the stage 1 vesicular eruption. Their appearance within the first 2 months often overlaps with stage 1 lesions, with ~40–50% presenting within the first month and 95–100% within the first year of life [26, 32]. Early onset as the first sign of IP has also been reported [26, 27, 37], both with and without coinciding vesicular lesions suggestive of intrauterine stage 1 lesions. While their duration varies and can last for years, an estimated 80% clear by 6 months when present [33].

Stage 3 (Hyperpigmented Stage) Stage 3 is defined by the development of linear or whorled streaks of brown-gray macular hyperpigmentation along *Blaschko's lines* (Fig. 8.1). While the extent of involvement is variable, these lesions are most commonly distributed on the trunk and limbs, frequently affecting the nipples as well as the axillae and groin [25, 26, 28].

This stage is traditionally the hallmark of IP, giving the condition its name, with characteristic lesions occurring in an estimated ~70–100% affected patients [20, 21, 25, 26, 28–31]. However, the published literature recognizes that the reported prevalence of this stage is highly influenced by the variable extent of involvement, age of assessment, and duration of follow-up. Most cases present around 6 months of age as stage 2 lesions are resolving, with 83–89% presenting before 1 year [26, 32]. Occasionally it precedes all other stages and presents at birth [20, 26, 27, 34], while approximately one third will occur within the first month [26, 32]. These lesions usually persist throughout childhood and gradually fade during early adolescence, with ~25% of cases faded by 10 years of age and almost complete disappearance by 16 years [26, 33, 38]. However, areas of residual localized hyperpigmentation may persist into adulthood for some patients, particularly on the legs, axillae, and groin [9, 31, 35, 39].

Stage 4 (Atrophic or Hypopigmented Stage) This stage is characterized by linear atrophic, hairless, and hypopigmented lesions following *Blaschko's lines* (Fig. 8.1).

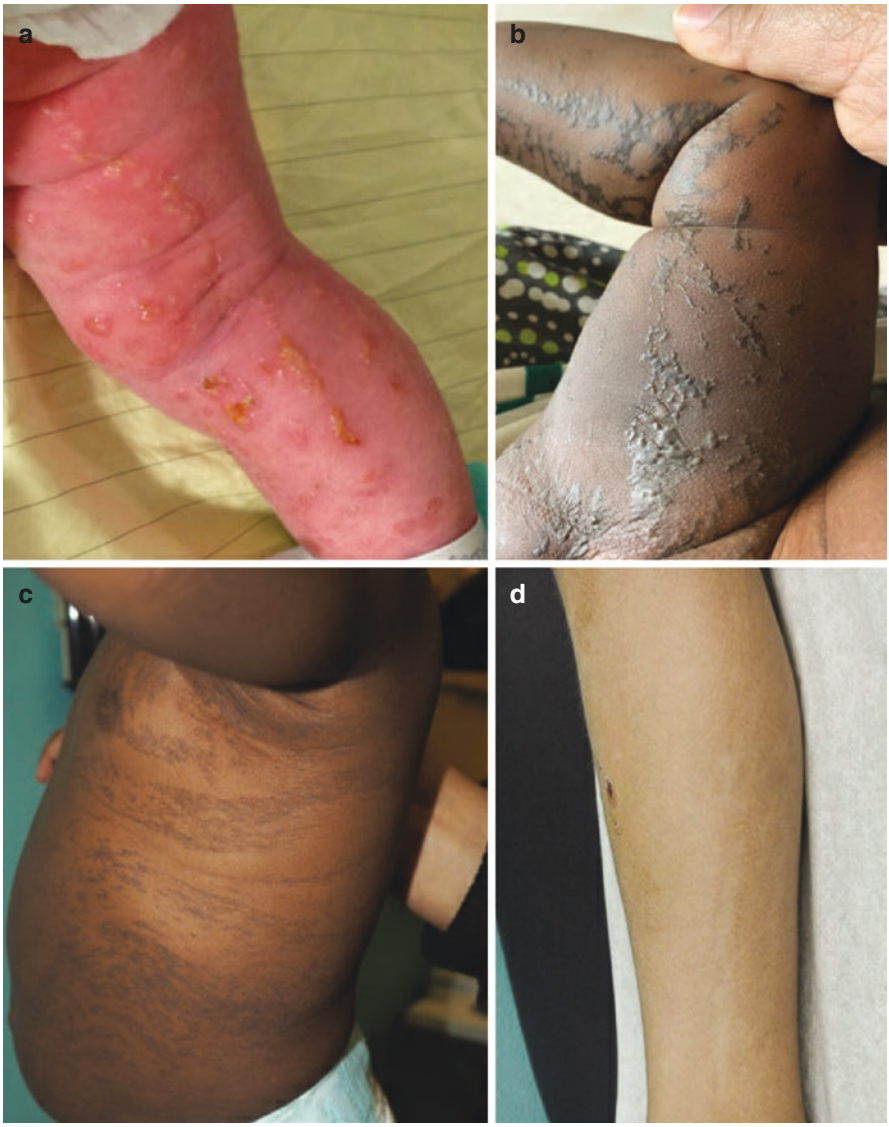

Fig. 8.1 Cutaneous lesions of incontinentia pigmenti along Blaschko lines. (**a**) Stage 1 vesicular lesions. (**b**) Stage 2 verrucous lesions. (**c**) Stage 3 linear hyperpigmentation. (**d**) Stage 4 linear hypopigmentation and atrophy

While the lower limbs are almost always involved, lesions are most frequently observed on both the upper and lower extremities [25, 26, 28, 35, 36, 39]. Stage 4 lesions characteristically demonstrate histologically an absence of pilosebaceous units and eccrine glands on biopsy, corresponding clinically to absence of hair or sweating within the affected areas. While lesions have been shown to have decreased

melanocytes/melanin in the epidermal basal layer [35], there remains inconsistency within the published literature regarding whether or not they are truly hypopigmented [9, 33]. It has been proposed that the difference in pigmentation is a minor factor and that the observed contrast with normal skin is instead due to loss of hair follicles and eccrine glands and reduced vascularity secondary to underlying ectatic vessels [9, 33, 35, 36, 40].

Stage 4 lesions are seldomly seen within the pediatric IP phenotype, with occurrence ranging from 0 to 42% [20, 21, 25–28, 30, 37]. In contrast, reported rates in the adult population are much higher at 80–100% [29, 31]. A proposed explanation for this variation is that stage 4 lesions are often subtle and may be unnoticed or overshadowed during childhood/adolescence when they overlap with the cutaneous manifestations from earlier stages of IP [28, 35]. Traditionally believed to develop during adolescence as stage 3 lesions were fading, a more precise assessment of age of onset has yet to be determined. When present, these lesions are permanent and are a subtle, but essential clinical diagnostic finding, alongside extracutaneous anomalies, in identifying undiagnosed adult IP patients [31, 35].

The pathophysiologic mechanisms underlying the IP skin phenotype are thought to be due to the mosaic pattern of NEMO-deficient and wild-type skin cells and a complex signaling cascade between the two which leads to the destruction of the deficient cells. Affected females exhibit skewed X chromosome inactivation (lyonization) which varies between cell lines, preferentially selecting to silence the mutated NEMO locus. For unknown reasons, this process appears to be less complete in the skin, resulting in a greater number of keratinocytes expressing the mutated gene (NEMO-deficient) [6].

The elimination of these cells appears to start around the time of birth when they begin to release pro-inflammatory interleukins in response to an unidentified trigger. In reply, the neighboring wild-type cells produce the cytokine tumor necrosis factor (TNF), which then induces apoptosis in susceptible NEMO-deficient cells. It also propagates inflammatory and hyperproliferative signaling among wild-type cells creating a positive feedback loop, amplifying the cellular reaction [6]. In addition, the combination of interleukin and TNF signaling at this time appears to result in a large increase in eotaxin expression from keratinocytes and endothelial cells [23]. This chemokine initiates eosinophilic recruitment leading to characteristic stage 1 dermal-epidermal infiltration, as well as peripheral blood eosinophilia (as high as 65%) which occurs in ~50–88% of patients [25–28]. Pathologically, this translates into local eosinophil degranulation resulting in spongiosis and epidermal vesicle/blister formation.

The entire inflammatory reaction is transient and continues until the initiating triggers, NEMO-deficient cells, are eradicated, at which time the stage 1 lesions disappear. However, if some survive, they can trigger reoccurrence of the inflammatory vesicular reaction later in life during periods of elevated circulating inflammatory cytokines, such as in febrile illness [6].

The keratinocyte hyperproliferation seen in stage 2 of IP has not yet been fully explained. The proliferation of wild-type cells has been proposed as the most likely

explanation, at least partly in response to the hyperproliferative signaling that was propagated during the preceding inflammatory stage [23].

The initial inflammatory process causes disruptions of the basal layer of the epidermis leading to the release (incontinence) of melanin into the papillary dermis. Macrophages then phagocytize the melanin or epidermal melanocytes (becoming melanophages) and settle in the dermis, thus causing dermal melanosis. Histopathological examination of stage 3 lesions mirrors these expected findings (see Chap. 4) [35, 39].

It has been proposed that stage 4 skin changes are the result of post-inflammatory dermal scarring which leads to reduced vascularity and loss of dermal appendages [23]. An alternative suggestion is that these findings may represent mosaic congenital skin dysplasia due to abnormal ectodermal tissue development and organization in IP. This implies that stage 4 changes are present since birth, only becoming visible after puberty when increased hair growth, hair density, and tanning on adjacent skin highlights the affected areas [31].

Central Nervous System

Of all the clinical features of IP, it is the neurologic involvement which is associated with the greatest degree of morbidity [41]. These anomalies are typically limited to the CNS and present with significant phenotypic variability. This can range from a single seizure to neonatal/childhood encephalopathy, disseminated encephalomyelitis, or ischemic stroke with devastating motor and cognitive impairment [42]. Mortality can occur, often as a result of insurmountable damage to the antenatal nervous system or status epilepticus. It has been observed that CNS abnormalities are most severe in IP patients with extensive cutaneous involvement, especially if lesions are located on the head and neck [43, 44].

CNS anomalies occur in an estimated ~30–31.5% of IP patients [22, 32, 42, 45]. However, it has been suggested that the true incidence may be lower in acknowledgment of undiagnosed individuals who have a milder phenotype and no neurological manifestations [29]. Among IP patients with CNS anomalies, almost 60% will develop their first neurological symptom within 1 week of life, 70% within 1 month, and almost 90% within 1 year [46].

Seizures are the most common neurological manifestation of IP, accounting for 42% of all CNS anomalies and affecting ~20–42% of all IP patients [32, 42]. Severity ranges from a single event in a lifetime to chronic epilepsy and seizure (see Chap. 50) disorders such as infantile spasms [47]. They also vary in type, although focal clonic episodes are most frequently reported [42]. Onset fluctuates from 12 h postpartum to 10 years; however the majority present within the first 2 weeks of life and almost all by 1 year [42].

Cognitive impairments, including intellectual and learning disabilities, characterize ~20% of neurological manifestations and occur in 29% of all patients [32, 43]. However, published literature further investigating the neurocognitive profile of

IP patients is limited. A pair of studies involving small cohorts of female IP patients were completed by *Pizzamiglio et al.* in 2014 and 2017. The first suggested that learning disabilities, particularly in arithmetic and reading, were common in IP and represented a CNS manifestation of the disease [47]. The second demonstrated mild to severe intellectual disability in approximately one third of the cohort with no correlation to CNS anomalies. In addition, they found that of school-aged patients without intellectual disability, half had learning disabilities in arithmetic, thus emphasizing the importance of early assessment, before school age, to identify and address any such deficits [48].

Psychomotor delays encompass ~26% of all CNS anomalies and affect 16.5% of patients [32, 42]. These include cerebral palsy, hemiplegia, hemiparesis, spasticity, and cerebellar ataxia. Similar to other CNS changes in IP, the risk and severity of motor impairment corresponds to the degree of CNS vasculopathy.

Microcephaly has been reported to represent 4% of CNS anomalies and affects 11% of IP patients [32, 42]. Additional CNS structural abnormalities that have been described include corpus callosum hypoplasia/agenesis, cerebellar atrophy, and cortical malformations such as polymicrogyria or neuronal heterotopia [9, 42, 45]. Despite these numerous findings, it is suspected that primary developmental defects in IP are rare and that most of these abnormalities are indicative of insults in the antenatal period due to microvasculature changes. This is supported by the results of brain imaging in affected patients which most commonly show evidence of vascular compromise including cerebral/cerebellar ischemia, necrosis, and hemorrhage [46, 49, 50].

Overall, two main patterns of neuroimaging have been described in IP patients with CNS manifestations. The first includes periventricular white matter changes (most often leukomalacia) with or without ventricular dilatation, corpus callosum hypoplasia, and mild cortical atrophy. The second involves severe cortical anomalies suggestive of acute/chronic ischemia, including areas of restricted diffusion without vascular territory, microbleeds, and severe atrophy with secondary structural abnormalities [39]. CNS manifestations are generally considered a poor prognostic sign in IP; however, neuroimaging findings may not necessarily correspond to the severity of the observed phenotypic (see Chap. 3). White matter changes in particular have been reported in neurologically intact IP patients [51], and involvement has been shown to both progress and resolve over time [49, 51, 52]. This emphasizes the importance of early neurological evaluation and follow-up of identified anomalies.

The pathogenesis of CNS anomalies in IP is still not entirely understood. *IKBKG* is present in all cell types including neurons, astrocytes, microglia, and oligodendrocytes. Considering the shared ectodermal origin with the skin, it has been postulated that apoptosis of susceptible NEMO-deficient neurons or glial cells could lead to IP CNS lesions (see Chap. 4). However, it has been shown that NEMO deficiency does not compromise the survival of these cells but rather that impaired NF-kB signaling may protect against neuronal cell death [53, 54]. Instead, NEMO deficiency does result in apoptosis of cerebral endothelial cells and impairment of the blood-brain barrier [55]. This suggests a primary vascular etiology to CNS

anomalies, compromised small vessels, and reduced blood flow in the neovasculature resulting in various degrees of ischemia and inflammation. This etiology is consistent with the clinical course, as antenatal insults to the developing CNS present acutely in neonates/infants before resolving with variable neurological sequelae [42].

Disruption in the blood-brain barrier may also have a pro-convulsive influence, increasing IP patients' susceptibility to seizures, even in the absence of ischemia [55]. However, it has been argued that this hypothesis of primary vascular dysfunction does not account for cerebral white matter and cortex changes that are not associated with vascular territories [44]. Similar to the process which occurs in the skin, a possible explanation for this observation may be radial migration of endothelial progenitor cells along Blaschko line analogs in the CNS, as well as mosaicism in the degree of NEMO deficiency/X chromosome lyonization [55–57].

Ocular

Ophthalmologic manifestations, when present, can lead to significant functional impairment [58, 59]. Screening for these features is therefore critical in patients with suspected IP as early recognition and intervention can substantially influence patient outcomes (see Chap. 47). The prevalence of ophthalmic findings among IP patients is frequently cited as ~30–38%. This range is based on a pair of comprehensive ocular-focused meta-analyses, as well as a large cohort study of 308 IP patients published in 2014 [22, 32, 59]. Since that time, similar rates have been mirrored among smaller cohort studies [21], while others vary between 11 and 77% [28, 60, 61].

Ocular manifestations of IP are generally divided into retinal and non-retinal findings, which occur in approximately the same ratio (53% vs. 47%) respectively [22]. Overall, an estimated ~55–70% of these anomalies are potentially vision threatening, with the majority (72–75%) related to retina involvement [22, 59].

Retinal abnormalities in IP primarily present in neonates and during early infancy. They are characterized by vasculopathy of the developing vessels which can lead to both peripheral and macular changes. Peripheral avascularity is considered the classic retinal finding [62, 63].

However, persistent fetal vasculature and varying degrees of vascular occlusion can also result in a spectrum of other anomalies. These range from changes in the pigment epithelium secondary to ischemia to neovascularization and partial/total retinal detachment with end-stage complications [62]. Peng et al. have recently proposed a five-stage classification system for these IP-associated retinopathy findings [60]. Retinal detachment is the most common cause of vision loss in IP with an estimated occurrence in 22–27% of eyes among investigated IP populations [60, 61]. Identified risk factors include peripheral neovascularization or ischemic optic neuropathy on initial examination [61]. A bimodal age pattern has been observed similar to that seen in retinopathy of prematurity [61]. Tractional detachment occurs

in pediatric patients due to contraction of fibrovascular tissue, with onset as early as 1 week and most by 2.5 years. In older individuals, rhegmatogenous detachment results from the development of holes in atrophic, avascular retina [60, 61]. This lifelong risk for progression emphasizes the importance of early identification and long-term monitoring of retinal abnormalities.

Nonretinal ocular manifestations often develop later than retinal issues but typically present before 2 years of age [62]. The most common of these findings are strabismus and nystagmus, which represent ~13–18% of all ocular IP anomalies and often occur in association with refractory errors [22, 59]. Along with optic neuropathy (~1–3%), these nonretinal findings are suspected to commonly result from underlying retinal pathology. Lens anomalies (~2–5%) include congenital cataracts, which are classified as an IP feature and affect an estimated ~5–6% of patients [21, 60]. Other nonretinal findings include microphthalmos (~2–3%) and corneal anomalies (~3%). This includes corneal epithelial keratopathy, which presents as asymptomatic whorl-like patterns of superficial or subepithelial opacities that are hypothesized to represent extracutaneous Blaschko lines [55, 60, 62, 64].

Advances in medical imaging have provided tremendous insight into the possible pathogenesis of the associated retinal anomalies in IP. Recent studies utilizing optical coherence tomography (OCT) imaging and multimodal extensions have supported the theory that the neural tissue changes in the retina (often thinning) are the result of primary vascular defects [65–67]. In particular, serial imaging on a limited number of patients has demonstrated the presence of vascular abnormalities preceding the pathological structural findings which subsequently evolved over time [66]. Addressing other proposed mechanisms for the neuronal changes, these studies failed to find evidence of abnormalities in the retinal pigment epithelium (RPE) or primary defects in neural architecture from abnormal NF-kB signaling [68]. Overall, these findings correspond with an ischemic mechanism for IP ocular lesions and are consistent with the small vessel vasculopathy which also contributes to the development of CNS anomalies.

Dental and Oral

After skin lesions, dental and oral anomalies are considered the most common clinical characteristics of IP. These are seldomly life-threatening but can have significant impact on the quality of life of IP patients. The prevalence fluctuates within the published IP literature due to the wide array of findings, differences in patient cohorts, and variability in which odontological manifestations were measured/reported. An occurrence rate of ~43–55% has previously been suggested in the IP literature [32, 46]. However, with increased awareness of the potential findings, within the last 10 years the occurrence rates among additional smaller IP cohorts have fluctuated from 50 to 77% [28, 60, 69] and have been recorded as high as 86–92% in adult IP populations [31, 35].

When present, congenital tooth agenesis is one of the most frequently reported dental anomalies, with ~60–90% of IP cases experiencing the absence of at least one tooth (hypodontia) and ~44–70% missing six or more (oligodontia) [61, 70, 71]. Overall, tooth agenesis affects the maxillary more frequently than the mandibular arch, as well as permanent (~90%) more than primary/deciduous teeth (~60%) [70]. The maxillary lateral incisors are the most common missing primary teeth, while agenesis of the second molars (maxillary > mandibular) are the most frequently affected permanent dentition [70].

Aberrations in crown formation are also common. These occur in an estimated ~70–100% of IP patients, most commonly affecting the central and lateral incisors in both primary and permanent dentition [60, 69–73]. These morphological abnormalities manifest as teeth with abnormal shape (conical, pegged, tulip, or notched), accessory cusps (molars), or microdontia.

Less common odontological anomalies associated with IP include malocclusion, delayed dentition, and arched palate. In a small cohort study, varying degrees of malocclusion were observed in a total of 71% of IP patients, although the frequency within the larger affected population has not yet been described [70]. It has been proposed that this finding may be a direct result of oligodontia in IP patients considering the established link between tooth agenesis and impaired alveolar development within the dental arches [74]. Primary teeth typically start to erupt after ~6 months of age; however delayed dentition has been reported to affect ~18% of IP patients [55]. This observation suggests that identification of dental anomalies as an early (<1-year) diagnostic tool may have limited use. On the other hand, oral anomalies that have been associated with IP (high-arched palate, cleft lip/palate) may be immediately detected after birth. While these anomalies account for only ~5% of odontological anomalies in the IP population, they occur ~10× more frequently than in the general population and thus may be diagnostic especially if associated with other features of IP [46]. In addition, both dental and oral anomalies are permanent findings (if uncorrected) and therefore have unique diagnostic value, especially in individuals with mild IP phenotypes or undiagnosed older patients in whom cutaneous manifestations have improved/faded [46, 69, 71].

Hair

Hair anomalies have been one of the minor clinical diagnostic criteria for IP since they were first proposed by *Landy and Donnai* in 1993 [36]. Along with the absence of pilosebaceous units noted in stage 4 skin lesions, approximately 26–32% of pediatric [20, 21, 26] and 60–65% of adult [31, 35] IP patients have other hair anomalies. Alopecia is the most common reported finding in both populations. It occurs particularly at the vertex of the scalp and is often preceded by vesicular or verrucous lesions at the site of involvement. Abnormalities in hair texture and density have also been well described, evolving with age and affecting the scalp, eyebrows, and

eyelashes. This presents with varying frequency as thin, sparse hair in childhood and progresses to woolly hair in adulthood (~40–50%), which is described as dull, wiry, and uncombable [31, 35].

Nails

A variety of nail anomalies have been described in association with IP, though none are pathognomonic. These are reported to develop in ~10–15% of affected individuals, usually after puberty during late adolescence or early adulthood [22, 32, 75]. The changes are typically seen on fingers more than toes, although all nails may be affected. The most common finding is nail dystrophy, with the spectrum of involvement ranging from mild pitting/ridging, koilonychia, or a yellow hue to severe nail disruption resembling onychomycosis. While nail anomalies are mostly transient and completely resolve, recurrent and persistent changes have also been reported [31, 36, 76].

Painful subungual hyperkeratotic lesions have also been observed in female patients, referred to as subungual tumors of IP (STIPs) [77]. Onset of these lesions is usually slightly later then nail dystrophy, typically in the mid-20s and most frequently on the fingers. Their histology mirrors the verrucous stage of IP showing hyperkeratosis, acanthosis, papillomatosis, and focal dermal dyskeratosis [78, 79]. As such, it has been suggested that they should be considered a late recurrence of the verrucous stage [35, 80]. Recognition is important as they may erode the underlying distal phalanx via pressure necrosis. However, identification and diagnosis are often delayed as lesions are frequently misdiagnosed as squamous cell carcinomas or keratoacanthomas [78]. Defining characteristics of STIPs include their recurrence in young women with multiple lesions over the course of several years and accompanying signs of IP. They rarely resolve on their own and patients usually seek treatment because of excruciating pain and disability [77, 78].

Other

Anomalies of the breast and nipples have been reported to occur in greater frequency in patients with IP than compared to the general population. Supernumerary nipples are the most common finding, but other abnormalities involving the nipple (*hypoplasia/inversion*) or breast (hypoplasia/aplasia, asymmetry, hypogalactia) can also occur [22]. Reported occurrence rates among general IP cohorts range from 2 to 10% of patients [21, 26, 33], while increased frequencies from ~12 to 30% have been observed among adult patients [31, 35]. It has been suggested that this

discrepancy is due to a focus on neonates and pre-pubertal children in the published literature.

There have been a small number of case reports describing female IP patients with immunodeficiency who presented with recurrent infections [80, 81]. In addition, a large cohort of IP patients found that ~11% had suffered from recurrent infections, suggesting that this may be a feature of the condition in a minority of patients. Recently, *Ohnishi et al.* provided evidence that such cases of immunodeficiency in female IP patients result from hypomorphic *IKBKG* mutations and a delay in skewed lyonization within immune cells [82].

Both pulmonary hypertension and cardiovascular abnormalities have been described as rare complications of IP. A variety of skeletal anomalies have also been reported in IP including limb asymmetry, talipes, contractures, dislocations, and scoliosis. However, it has been noted that these almost always occur secondary to severe neurological deficits [33, 81].

Diagnosis

Clinical Diagnosis

The clinical diagnostic criteria for IP were first proposed by Landy and Donnai in 1993. They were refined by *Minic et al.* in 2013 to account for new genetic findings and reflect a growing recognition of the wide variety of associated extracutaneous clinical features of IP. Recently, updates to these criteria have been proposed by a multidisciplinary consensus group from Europe [39]. These suggestions modernize the criteria descriptions, adjust the major/minor categories, and overall decrease the number of criteria required in order to reach the diagnostic threshold. These changes emphasize early diagnosis so that appropriate monitoring and treatment can be initiated, particularly for extracutaneous manifestations with potentially serious long-term sequelae.

The updated criteria are outlined in Table 8.1. The major criteria remain any of the four IP skin stages, with the addition of dental anomalies (Table 8.1) and identification of the common recurrent *IKBKG* gene rearrangement (deletion of exons 4–10). Eosinophilia in association with stage 1 lesions has been nominated as a minor criterion, while CNS anomalies and a history of male miscarriages have been removed from this category. It is suggested that once IP is diagnosed, it may offer more meaningful interpretation of possible unexplained neurological, ophthalmological manifestations and/or obstetric complications (such as miscarriage). In addition, the descriptions of the clinical and histological criteria (summarized in Tables 8.1 and 8.2) have been updated to provide greater detail which reflects the most recent understandings from published literature.

Table 8.1 Updated diagnostic criteria for incontinentia pigmenti, according to *Landy and Donnai* and updated by multidisciplinary consensus recommendations [39]

Major criteria	Minor criteria
• Typical neonatal rash with erythema and vesicles (stage 1) • Verrucous papules or plaques along Blaschko's lines (stage 2) • Typical hyperpigmentation along Blaschko's lines fading in adolescence (stage 3) • Linear, atrophic, hairless lesions on limbs (stage 4) or scarring alopecia of the vertex (stages 3 or 4) • Teeth: dental agenesis (hypodontia or oligodontia), shape anomalies (peg-shaped incisors, conical teeth, molar cusp pattern alteration), and delayed eruption • Common recurrent rearrangement (deletion of exons 4–10 of *IKBKG* gene)	• Eosinophilia (stage 1) • Hair: alopecia or woolly hair (dull and dry) • Nails: punctuate depressions, onychogryphosis • Mammary gland involvement (hypoplasia, asymmetry, hypogalactia) and/or nipple involvement (inverted nipples, supernumerary, difficulty in feeding) • Characteristic skin histology • Retina: peripheral neovascularization
Conditions for establishing IP diagnosis	
If no evidence of IP in a first-degree female: • Presence of at least one major criterion is sufficient for the diagnosis of IP If a first-degree female relative is affected: • One minor criterion is sufficient for IP diagnosis	

The complete absence of minor criteria should induce some doubt about the diagnosis

Molecular Diagnosis

In most cases, the diagnosis of IP is first made clinically in neonates. A molecular analysis of DNA extracted from peripheral blood is then required to confirm the diagnosis. This facilitates identification of a pathogenic *IKBKG* mutation and allows appropriate genetic counseling. A targeted analysis (with long-range PCR) of the common deletion of exons 4–10 of *IKBKG* should be completed first as this accounts for 80% of known cases [1, 2].

In the case of a negative result (or *concurrent with targeted analysis*), *IKBKG* should be sequenced in search of a point mutation, a deletion, or a duplication of different sizes [9]. The causative mutation cannot be identified using modern genetic testing methodology in approximately 5% of cases [33]. Analyses of *IKBKG*/NEMO mutations are complicated by the presence of a nonfunctional *IKBKGP1* pseudogene (deletion of first 2 exons), which is highly homologous to *IKBKG*/NEMO [39].

In affected individuals in whom an *IKBKG* pathogenic variant is not identified by the above methods, a skin biopsy of affected skin should be considered to look for a somatic mutation [33]. This is particularly important for the detection of post-zygotic mosaic variants in affected males in whom blood leucocytes carrying the mutation undergo selective apoptosis over time [19]. Karyotyping should also be

Table 8.2 The four stages of cutaneous lesions of IP, their evolution, and histopathological findings, as described within multidisciplinary consensus recommendations [39]

Stage	Lesion morphology	Stage onset	Skin histopathological findings
Stage 1: vesiculobullous	Vesiculo-pustules and erythema	Within the first few weeks to 18 months	Eosinophilic spongiosis and intraepidermal vesicles containing eosinophils. Many dyskeratotic (apoptotic) keratinocytes in the epidermis, numerous eosinophils, and some lymphocytes in the dermis
Stage 2: verrucous	Verrucous lesions	Within the first few months; usually lasts for a few months	Papillomatosis, hyperkeratosis, and acanthosis of the epidermis. Many apoptotic cells in the epidermis, sometimes disposed in clusters. Minimal perivascular lymphocytes, no more eosinophils. Major melanin incontinence
Stage 3: hyperpigmented	Hyperpigmentation	Within the first months, gradually decreasing until complete/ incomplete disappearance May persist resulting in localized residual lesions (often axillary or inguinal folds)	Marked melanin incontinence with numerous melanophages in the dermis. No more epidermal hyperplasia. Scattered apoptotic cells in the epidermis. Slight lymphocytic inflammation in the upper dermis
Stage 4: atrophic/ hypopigmented	Hypopigmentation	Most likely present from childhood even if persistently overlooked throughout life	Slight atrophy and some scattered apoptotic cells in the epidermis, hypopigmentation of the epidermis, a reduced number of melanocytes, thickened and homogenized dermis with a complete absence of hair follicles and sweat glands. There is no melanin incontinence and no inflammatory cells, and the elastic network is normal

considered for male patients due to the possibility of IP in the setting of XXY aneuploidy (Klinefelter syndrome).

When a mutation has been identified, prenatal screening can be performed for at-risk women by analysis of DNA extracted by either amniocentesis or chorionic villus sampling. In the case of in vitro fertilization, a pre-implantation diagnosis is also possible [39].

Therapy and Prognosis

The management and follow-up of patients with IP should involve a coordinated multidisciplinary team (MDT), although involved services will vary based on each patients' clinical presentation and needs. Comprehensive care can often involve a dermatologist, ophthalmologist, pediatric neurologist, developmental pediatrician, dentist/orthodontist, genetic counselor, rehabilitation services, and more. Unfortunately, there are currently no known therapeutic interventions that address the NEMO/NF-kB pathway or prevent the various manifestations of IP. Thus, the goal of management is symptom control, which involves early identification and treatment of anomalies within the affected systems in order to minimize/prevent secondary complications [9]. The same multidisciplinary consensus group from Europe who recently provided updates to the IP clinical diagnostic criteria has also created recommendations for the surveillance and management of patients [39]. In addition, *Donnai* and *Jones* recently published a review of IP which includes recommendation for the evaluation and treatment of common findings [33]. The information from these two sources was reviewed and integrated with the existing guidelines [9] in order to provide as comprehensive an overview as possible for the current management strategies in IP (Table 8.3).

Table 8.3 Assessment, surveillance, and management recommendations for IP patients [9, 33, 39]

Assessment/surveillance	Management
Dermatology	
• Careful monitoring in first few months of life • Every 3 months until 1 year, then annually until 5 years. As needed afterward • Photo-documentation is very useful • Assessment of the hair and nails should be completed at each visit • If diagnosis is uncertain, skin biopsy and serology for peripheral eosinophilia can be considered • Adjust visit schedule as needed according to patient (i.e., infection, prolonged/profuse inflammatory lesions, or disabling verrucous lesions) • Consider annual visit in a tertiary center, with MDT assessment as needed, until adulthood	• Referral to a pediatric dermatologist is recommended for all patients • Emphasis on hygiene to prevent secondary infection, especially in neonates • No specific treatments to hasten healing of vesicular or verrucous lesions – Wound care and treatment of secondary infection as needed – Topical emollients, steroids, or calcineurin inhibitors for symptom management – Topical retinoids have been used for verrucous lesions which are symptomatic of impact function (limb/digit mobility) – Reassure families that lesions will improve with time • No interventions are generally required for hyper-/hypopigmented lesions – Laser treatment of hyperpigmented lesions should be avoided (risk of triggering recurrence of inflammatory eruptions) – Photoprotection recommended (risk of cutaneous inflammation and pigmentation) • Unless there is infection/pain, surgical treatment of nail dystrophy is not indicated

Table 8.3 (continued)

Assessment/surveillance	Management
Ophthalmology	
At diagnosis: • Urgent ophthalmology assessment of the peripheral retina (with pupillary dilatation) • If peripheral vasculopathy is present, further assessment under general anesthesia ± laser treatment (ideally with retinal photography and fluorescein angiography)	• Urgent referral to ophthalmology at time of diagnosis • Prophylactic ablation (laser photocoagulation or cryotherapy) ± adjunct therapy (anti-VGEF) to prevent retinal detachment in patients with documented progression of retinal vasculopathy (neovascularization, vitreous traction or hemorrhage) • Warn adults of the symptoms of retinal tear or detachment (bimodal occurrence)
Follow-up: • In the case of normal results of the initial examination: – Repeat evaluation at months 1, 2, 3, 6, 12, 18, and 24 of life, then annually for life • In the case of early laser treatment: – Clinical examinations on days 15, 30, 45, 60, and 90 post-treatment – Follow-up then if results are normal on the initial examination	
Neurology	
At diagnosis: Full neurological examination at diagnosis→ 2 situations: 1. If no neurological manifestation is observed at birth: – Neurocognitive examination at 9 and 24 months – Brain MRI at 2 ½ years old 2. If neurological manifestation is observed at birth: – EEG: during neonatal period, at 4 and 24 months – Brain MRI: during neonatal period (DWI and SWI) and at 30 months	• Referral to pediatric neurologist to help guide management • In the neonatal period, treatments have two objectives: 1. Anti-epileptic treatments for seizures – Treatments vary according to seizure semiology and the age of the patient – Phenobarbital often gives poor seizure control in infantile IP 2. Anti-inflammatory treatment to limit neurological consequences – Steroids have been proposed as a first line of treatment, including IV methylprednisolone followed by a weaning course of oral steroids – TNF blockers have been used in a punctual manner – Gene therapy has been proposed for mitigation of severe cerebrovascular pathology • Rehabilitation with PT, SLT, and OT should be initiated as early as possible for management of neurological sequelae • Intervention for intellectual impairment and developmental delay is the same as in the general population

(continued)

Table 8.3 (continued)

Assessment/surveillance	Management
Follow-up: • Regular neurological and epileptological follow-up, as needed: – At least every 6 months in the first 3 years • Systematic neurocognitive assessment: – At 5 years of age upon the initiation of elementary school • Renewal of cognitive assessment if evidence of developmental delay or at regular intervals if adverse neurological signs in early life – Neuropsychological assessment – Psychomotor, orthoptics, and/or speech assessment – Detailed evaluation of neurocognitive abilities (developmental pediatrician)	
Odontology	
During childhood and adolescence: • Regular biannual dental checks starting at 1 year • At 3–4 years: evaluate for prosthetic treatment if multiple agenesis or dental problems interfering with feeding and/or speech • At 6 years: first panoramic XR evaluating agenesis in a permanent set of teeth and early assessment of dentofacial orthopedics • At 7 years: evaluation for restorative treatment of the permanent conoid incisors for speech and/or aesthetic problems • At 9–12 years: monitor growth/eruption of permanent teeth with second panoramic XR when necessary • At 12 years: consider pre-prosthetic and pre-implant orthodontic treatment for malpositioned teeth and subsequent prosthetic procedures • End of growth: definitive implant-prosthetic rehabilitation	• Educate affected individuals and/or parents about oral hygiene to maintain and preserve teeth • Orthodontic treatment with braces, surgical removal, crowns, and prostheses may be necessary in affected individuals. Indications for these interventions are based on specialist assessment • Prosthetic, implant-prosthetic, and orthodontic rehabilitation in adulthood as needed • Dental CBCT imaging is required prior to dental implants ± need for bone and/or mucogingival grafts

Table 8.3 (continued)

Assessment/surveillance	Management
In adulthood: • MDT assessment involving implantologists, periodontologists, and specialists in dentofacial orthopedics and in prosthesis	
Breast	
• Assess thorax at each visit for the presence of supernumerary nipples and other breast abnormalities	• Most individuals with supernumerary nipples have no major problem • The development of a supernumerary breast at puberty may necessitate surgical removal • In women with breast aplasia or hypoplasia, surgical reconstruction may be indicated and is standard
Counseling and patient support	
At diagnosis (or anytime thereafter): • Genetic counseling and patient education • Evaluation of relatives at risk • Psychological counseling **In adulthood** • Transition coordination • Family planning • Pregnancy support	• Genetic counseling should be offered to all patients/families in order to provide information on the nature, inheritance, and implications of IP so that they can make informed medical and personal decisions • Therapeutic patient education programs help to support patients and families • At-risk relatives of an affected individual should be examined for suggestive features and offered genetic consultation (± genetic testing) • Counseling can help patients/families cope with the psychosocial impacts of IP and should be offered to all, regardless of the IP severity • Facilitated transition from pediatric to adult care helps fulfill the medical, psychosocial, and educational needs of young adult IP patients • Appropriate to revisit genetic counseling for affected patients before pregnancy to discuss potential risks to offspring, prenatal screening, and reproductive options • Fertility is not impaired for affected female patients. The risk of spontaneous abortion is higher, particularly for male fetuses. If prior retinal anomalies exist, there may be risk of progression and/or detachment during labor/delivery
To other	
• Other therapeutic managements should be guided by appropriate specialists, if/when other IP manifestations are observed (e.g., cardiovascular complications)	

MDT multidisciplinary team, *VGEF* vascular endothelial growth factor, *MRI* magnetic resonance imaging, *DWI* diffusion-weighted imaging, *SWI* susceptibility-weighted imaging, *EEG* electroencephalography, *IV* intravenous, *TNF* tumor necrosis factor, *PT* physiotherapy, *OT* occupational therapy, *SLT* speech and language therapy, *XR* X-ray, *CBCT* cone beam computed tomography

Early neonatal neurological and ophthalmological manifestations have the greatest impact on IP patients' long-term prognosis and morbidity. As with phenotype, the IP sequelae vary in form and severity between patients based on the extent to which associated systems are involved. Abnormalities of the skin, hair, or teeth can be permanent and may be a cause of distress for some patients. Patients without CNS or ophthalmologic involvement usually have normal physical and cognitive development, as well as an ordinary life expectancy.Conflict of InterestThere are no conflicts of interests relevant to this article to disclose from all identified authors.

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Patient Consent Family consent has been obtained in writing.

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