DOI: 10.1111/jdv.16403 JEADV

POSITION STATEMENT

Multidisciplinary consensus recommendations from a European network for the diagnosis and practical management of patients with incontinentia pigmenti

C. Bodemer,[1,*] A. Diociaiuti,[2] S. Hadj-Rabia,[1] M.P. Robert,[3] I. Desguerre,[4] M.-C. Manière,[5] M. de la Dure-Molla,[6] P. De Liso,[7] M. Federici,[8] A. Galeotti,[9] F. Fusco,[10] S. Fraitag,[11] C. Demily,[12] C. Taieb,[13] M. Valeria Ursini,[10] M. El Hachem,[2] J. Steffann[14]

[1]Department of Dermatology, Reference Centre for Genodermatoses (MAGEC) Necker Enfants Malades Hospital, Imagine Institute, FIMARAD, ERN-Skin, Paris Centre University, Paris, France
[2]Department of Dermatology, ERN-Skin, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[3]Department of Ophthalmology, Imagine Institute, Necker Enfants Malades Hospital, Paris Centre University France, Paris, France
[4]Department of Pediatric Neurology, Imagine Institute, Necker Enfants Malades Hospital, Paris Centre University France, Paris, France
[5]Department of Pediatric Odontology, Expert Centre (MAFACE), Strasbourg Hospital, Université de Chirurgie Dentaire, Strasbourg, France
[6]Expert Centre for Rare Face and Oral Cavity Malformations, Rothschild Cavity, Paris, France
[7]Neurology Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[8]Ophthalmology Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[9]Dentistry Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[10]Institute of Genetics and Biophysics 'Adriano Buzzati-Traverso', IGB-CNR, Naples, Italy
[11]Department of Pathology, Necker Enfants Malades Hospital, Paris, France
[12]Reference Centre Génopsy, CRMR Maladies Rares à Expression Psychiatrique, Centre Hospitalier Le Vinatier, Bron, France
[13]National Network for Rare Diseases FIMARA, Necker Enfants Malades Hospital, Paris, France
[14]Department of Genetics, Imagine Institute, Necker Enfants Malades Hospital, Paris Centre Université, Paris, France
*Correspondance: C. Bodemer. E-mail: christine.bodemer@aphp.fr

Abstract

Background Incontinentia pigmenti (IP) is a rare multisystemic X-linked dominant genetic disorder characterized by highly diagnostic skin lesions. The disease can be misdiagnosed in infants, and complications affecting the eyes and/or the brain can be severe. Our objective was to highlight the urgency of an appropriate diagnosis and management strategy, as soon as the first symptoms appear, and the need for a well-codified monitoring strategy for each child.

Methods An in-depth literature review using a large number of databases was conducted. The selection criteria for articles were literature review articles on the disease, case series and retrospective studies based on the disease, clinical studies (randomized or not) on treatment, articles discussing patient care and management (treatment, diagnosis, care pathways), and recommendations. The research period was from 2000 until 2018. A group of multidisciplinary experts in IP management was involved, issued from different healthcare providers of the European Network for Rare Skin Diseases (ERN-Skin). The final recommendations have been submitted to two patient representative associations and to a general practitioner and a neonatal specialist prior to their finalization.

Results and conclusion The diagnosis of IP must be promptly performed to detect potential extracutaneous manifestations, thus allowing the timely implementation of specific therapeutic and monitoring strategies. Eye involvement can be a therapeutic urgency, and central nervous system (CNS) involvement requires a very rigorous long-term follow-up. Assessments and patient support should take into account the possible co-occurrence of various symptoms (including motor, visual and cognitive symptoms).

Received: 24 November 2019; revised: 28 February 2020; Accepted: 10 March 2020

Conflicts of interest

The authors have no conflict of interest to disclose.

Funding sources

The study was funded by FIMARAD: French national network for rare skin diseases.

Introduction

Incontinentia pigmenti (IP; MIM 308300) is a rare (estimated incidence of 0.7 cases per 100 000 births), X-linked-dominant multisystemic ectodermal dysplasia caused by inherited mutations (10–25% of patients) or sporadic *de novo* mutations (>75%) of the inhibitor of nuclear factor kappa B kinase subunit gamma (*IKBKG/NEMO*) gene.[1,2]

The *IKBKG* gene encodes the nuclear factor kappa B essential modulator (NEMO/IKKG) protein, a subunit of the IkB kinase complex that is involved in the activation of nuclear factor kappa B (NF-κB). The typical phenotype is due to functional mosaicism, resulting from the physiological mechanism of random inactivation of one of the X chromosomes. It is usually lethal in male foetuses and manifests in female neonates by a predominantly acral, vesiculopustular rash, characterized by a rapidly linear pattern along Blaschko's lines. Retinal and central nervous system (CNS) impairments are rarer than skin involvement but might be severe with lifelong sequelae. These impairments have to be detected as soon as possible to introduce at once specific therapies.

The rarity and complexity of the multisystemic involvement of IP challenge its appropriate management. To date, there are no multidisciplinary recommendations on global IP management. The objective of this article was to highlight the urgency of an early and appropriate diagnosis and to provide a global well-codified monitoring strategy for the disease diagnosis and the specific management of IP patients, adapted to their symptoms and needs. The recommendation will be conceived to provide practical support for the management of patients both in a hospital setting and in community care, in reference centres and in the medical community, for physicians (dermatologists, neonatologists, paediatricians, neurologists, ophthalmologists, radiologists, geneticists, dentists, general practitioners, pathologists, physiotherapists, psychologists, etc.). French expert healthcare providers (HCPs) for IP, coordinated by the French national network for rare skin diseases (FIMARAD) and Italian expert HCPS, involved in the certified European Network for Rare Skin Disorders (ERN-Skin; *skin.ern-net.eu*), have worked together by sharing their expertise and integrating a critical review of the literature data and a consensual agreement of experts for the practical management of this rare disease.

Material and methods

The recommendation has been developed according to a rigorous method, including the following:

1 An in-depth analysis of *literature data* conducted by specialists in each speciality involved in IP management and issued from the French and Italian *expert multidisciplinary teams* including two healthcare providers (HCPs) from the certified European Network for Rare Skin Disorders (ERN-Skin);
2 A summary of these data, including recommendations from the specialists of the two HCPs;
3 *Multiple reviews of an initial document that* has circulated among the experts of the two HCPs; and
4 A proofreading of the recommendations by French and Italian IP patient representatives, a general practitioner and a neonatal specialist prior to its finalization.

Literature data

The authors conducted an in-depth literature review using the following databases: MEDLINE, BDSP, Irdes, Refdoc, EMBASE, the National Library for Public Health, Google Scholar, Current Contents, SciSearch, EconLit, EURONHEED (European Network of Health Economics Evaluation Databases), University of York databases (DARE, NHS EED, HTA) and the Cochrane Library. The following Internet websites were accessed: Société savante (dermatology); Patient Association; Orphanet; Therapeutic; HAS; NIH; PHE/EMA; and PHAC. The research period was from 2000 until 2018. *The key words* for the research were incontinentia pigmenti; Bloch-Sulzberger syndrome; Bloch-Siemens syndrome; Blaschko's lines; diagnosis; diagnostic; screening; detection; guidelines; practice management; treatment; examination; test; process; health care; pathways; system flow. *The selection criteria for articles were as follows*: literature review articles on the disease; case series and retrospective studies based on the disease; clinical studies (randomized or not) on treatment; and articles presenting patient care and management (treatment, diagnosis, care pathways). The study selection processes were carried out in two phases: (i) a screening of titles and abstracts was performed by one person to see whether they met the inclusion criteria, and this preselection was validated by a second person; (ii) final decisions about the included articles were made by examining the full articles. Duplicate studies were eliminated. Of the 336 studies reviewed, 64 were retained.

Group of experts

French and Italian experts from the two ERN-SKIN HCPs involving several specialized teams concerned with the management of IP patients (dermatology, ophthalmology, neurology, odontology, pathology, genetics). The final version of the recommendations has been submitted to two patient associations (IPF, Incontinentia-Pigmenti.fr; and I.P.ASS.I. Onlus, Incontinentia Pigmenti Associazione Italiana).

Consensus committee

A consensus committee including an expert representative of each medical field involved in IP management was organized. All these experts are authors of the manuscript. Several meetings (face-to-face meetings and/or conference call meetings) were established until the professionals agreed on the consensus recommendations.

Results

A review of the literature revealed a low number of randomized controlled trials, including small heterogeneous groups of patients, without standardization of outcome measures. The level of evidence in the majority of cases was of level 4 (retrospective studies, case series), grade C (low level of scientific evidence). More than 15 consensus committee meetings were organized. The final manuscript, approved by all the French and Italian experts of 2 ERN-Skin HCPs, permitted us to propose the following consensual recommendations integrating a professional agreement of experts for this rare disease.

Diagnosis

In most cases, the diagnosis of IP is clinical in neonates and infants but can be confirmed by molecular analyses.

Clinical diagnosis of IP

The clinical criteria for IP diagnosis proposed in 1993 by Landy and Donnai have been updated including recent clinical and histological characteristics.[3,4] This update is summarized in Table 1. In the absence of a family history, the presence of at least one major criterion is sufficient for the diagnosis of IP. If a first-degree female parent is affected, one minor criterion is sufficient for IP diagnosis. The complete absence of minor criteria should induce some doubt about the diagnosis.

Table 1 Updated diagnostic criteria for IP[3,4] from the criteria of Landy and Donnai, (*J Med Genet* 1993, 30: 53–59)

Major criteria
• Typical neonatal rash (see description) 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 rearrangement of exons 4 to 10 of *IKBKG* gene)
Minor criteria
• Eosinophilia (Stage 1) • Hair: alopecia or woolly hair (dull and dry) • Nails: punctuate depressions, onychogryphosis (or ram's horn nails) • Mammary gland involvement (hypoplasia, asymmetry, hypogalactia) and/or nipple involvement (inverted nipples, supernumerary, difficulty in feeding) • Characteristic skin histology • Retina: peripheral neovascularization

Diagnosis

Clinical diagnosis: The importance of the neonatal period

The cutaneous lesions The cutaneous lesions (Fig. 1) are major criteria. Four stages are well characterized; they are reported in Table 2 with their main differential diagnoses. The initial inflammatory vesiculopustular stage (*Stage 1*) is classically followed by manifestations of papular-verrucous plaques (*Stage 2*) and hyperpigmented macular lesions along Blaschko's lines (*Stage 3*). The lesions can be profuse or limited in number. Such lesions are highly diagnostic when they occur in a female neonate, have a predominant acral topography with a linear distribution on Blaschko's lines, and fade away spontaneously in early childhood (*Stages 1 and 2*), or gradually until adolescence (Stage 3).[2–5] Eosinophilia is reported during Stage 1 but is common during the first months of life. Therefore, eosinophilia might be considered as a minor criterion in association with the lesions of Stage 1. It is essential to emphasize that IP can be exceptionally observed in male neonates, and the diagnostic criteria remain entirely valid.[6] *Stage 4* lesions are usually linear, hypopigmented and hairless, and are observed predominantly on the limbs and persisting throughout life. They might be very discreet and require a skin biopsy to lead to the diagnosis.[7] In most patients, the successive or combined Stages 1 and 2 outbreaks occurring during the first months of life regress spontaneously. However, later outbreaks, linear and tracing Blaschko's lines, have sometimes been observed several years after the neonatal period, often triggered by a viral infection.[8,9] Thus, it is necessary to consider an analysis of the cutaneous histology, based on clinical similarities to IP, even if there is no prior IP diagnosis. In cases of late and painful subungual verrucous lesions, histological analysis is particularly important to rule out benign or malignant nail tumours.[10] Areas of alopecia could correspond to a scar of inflammatory (Stage 1) and verrucous lesions (Stage 2). These areas are usually located on the vertex and may be small and not very visible. Hair, eyelashes and eyebrows are usually thin and sparse. Scalp hair may also present with a 'woolly' texture (without characteristic abnormalities of the hair shaft). Mild to severe nail abnormalities may also be observed, such as striations or thickening, but these are non-pathognomonic signs for IP.[2–6,11]

Skin histology[7,12] can be very helpful for the diagnosis, typically showing the following characteristics.

Stage 1 (vesiculobullous stage): eosinophilic spongiosis and intraepidermal vesicles containing eosinophils. Many dyskeratotic (apoptotic) keratinocytes in the epidermis, numerous eosinophils and some lymphocytes in the dermis are seen. *Stage 2* (verrucous lesions): papillomatosis, hyperkeratosis and acanthosis of the epidermis. Many apoptotic cells in the epidermis,

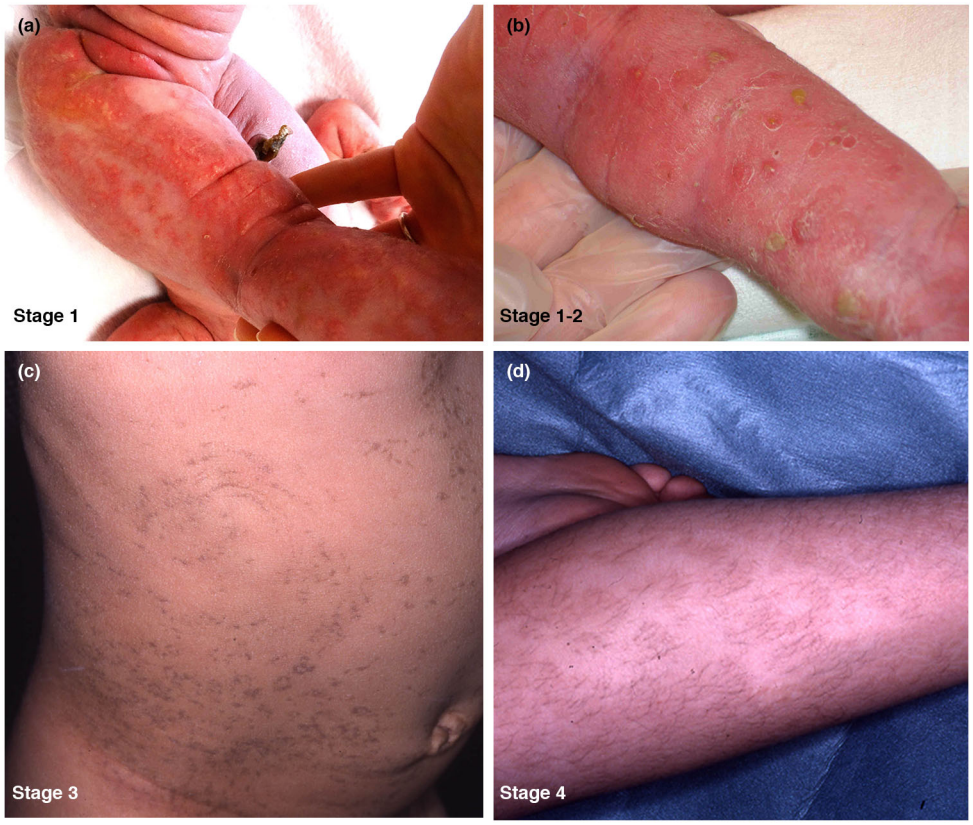

Figure 1 The 4 stages of the cutaneous manifestations in IP patients. All the lesions follow Blaschko's lines: (a) Stage 1: inflammatory vesiculopustular. (b) Stage 2: papular-verrucous plaque. (c) Stage 3: hyperpigmented macular lesions. (d) Stage 4: hypopigmented and hairless linear lesions.

Table 2 The four stages of cutaneous lesions of IP, their evolution and differential diagnoses

Stage	Clinical manifestation (Importance Of Blaschko's linear disposition)	Stage onset	Differential diagnosis
Stage 1: Vesiculobullous stage	Erythema (redness) and vesiculopustules or blisters with acral and linear disposition	Within the first few weeks of life up to 18 months	Usually bacterial and viral infections (HSV, VZV) and dermatoses with blistering in early infancy (e.g. epidermolysis bullosa), Goltz syndrome. Importance of linear disposition
Stage 2: Verrucous stage	Verrucous lesions	Within the first few months of life; usually lasts for a few months	Verrucae vulgaris (simple warts), chondrodysplasia, epidermal naevus
Stage 3: Hyperpigmented stage	Hyperpigmentation	Within the first months of life, gradually decreasing until complete or incomplete disappearance. May persist in adults, leading to persistent localized and residual lesions (usually in axillary or inguinal folds)	Pigmentary mosaicism. Importance of spontaneous regression of lesions in the case of IP
Stage 4: Atrophic/ hypopigmented stage	Hypopigmentation	Most likely present from childhood even if persistently undervalued throughout life	Vitiligo, hypomelanosis of Ito. Importance of the skin biopsy

sometimes disposed in clusters. Minimal perivascular lymphocytes, no more eosinophils. Major melanin incontinence. *Stage 3* (linear hyperpigmentation): 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* (hypopigmented and hairless linear lesions): 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, no inflammatory cells, and the elastic network is normal. Stage 4 appears not to be related to previous stages of IP.[12] The association of eosinophilic spongiosis (Stage 1), hyperkeratosis (Stage 2), melanin incontinence (Stage 3) and keratinocyte apoptosis (at all stages) should be considered highly suggestive of IP. At Stage 4, histological analysis can be particularly useful; such lesions may be the only skin diagnostic sign of undiagnosed IP in an adult.[12] A characteristic aspect is the absence of appendage(s) associated with keratinocyte apoptosis, which should be thoroughly screened for. Other types of pigmented mosaicism with lesions along Blaschko's lines do exist. The main characteristics of these differential diagnoses of the different stages are reported in Table 2.

Ocular abnormalities Between 35 and 70% of patients with IP show ocular involvement, including early active retinal vasculopathy (the most common abnormality, which may lead to retinal detachment and blindness), optic nerve damage or asymptomatic corneal abnormalities (cornea verticillata). Strabismus or nystagmus may result from these manifestations. Early screening and care can prevent the complications of retinal vasculopathy.[2–5,13–15] Ocular manifestations may vary from one patient to another. They comprise (i) *cornea verticillata*, indicative of IP in infants, but sometimes difficult to diagnose; (ii) multifocal hypo- and/or hyperpigmented lesions of the pigmented retinal epithelium; (iii) macular vascular lesions, resulting in a flat macula, the presence of which may be clinically detected by abnormal foveal reflection and by retinal thinning, observable via optical coherence tomography (OCT); (iv) the consequences of the peripheral vasculopathy, which are best described by fluorescein angiography and may progress in the following order in the absence of treatment: zones of non-perfusion in the peripheral retina, arteriovenous anastomoses, retinal haemorrhages, neovascularization, dragged vessels especially to the temporal periphery evident on retinal examination, and tractional retinal detachment; and, more rarely, (v) the atrophy or hypoplasia of the optic nerves.

Neurological involvement Incontinentia pigmenti may go along with CNS impairment.[2–5,16–21] The CNS phenotype is variable, and even if the pathogenesis is not clearly understood, there is evidence that both inflammation and microvascular insult can result in infarcts and brain atrophy. CNS disorders may include seizures (42%), microcephaly, motor impairment (hemiparesis, paraparesis or tetraparesis; 26%), intellectual disability and learning difficulties (until 20%). Some neurological disorders are lethal, such as excessive damage to the antenatal CNS or status epilepticus. Usually, 88% of CNS problems manifest by the end of the first year of life, although seizures and recurrent strokes can occur later during childhood in 10% of patients.

Early neonatal neurological and ophthalmological manifestations affect long-term patient prognosis and the occurrence of disabilities. Most patients without neonatal CNS abnormalities usually have normal physical and cognitive development. During the neonatal period, a neurological clinical evaluation is recommended, following an accurate dermatological examination. Dermatological lesions may be minimal and go undetected, while the pathology may manifest as partial seizures, as early as 24 h from birth, and most generally in the first days of life. An electroencephalogram (EEG) and a brain MRI should be performed to confirm the diagnosis. Two main patterns of brain MRI are reported: (i) mild anomalies of the periventricular white matter with T2-weighted hypersignal occasionally associated with mild cortical atrophy and the atrophy of the corpus and (ii) severe cortical anomalies suggestive of a vascular disease, including multiple areas of acute diffusion restriction without vascular territory, contrast uptake, microbleeds, severe atrophy and images consistent with ischaemic sequelae (focal cortical atrophy, ulegyria). After neurological evaluation, an anti-epileptic and/or corticosteroid treatment should be prescribed when needed.

Cognitive impairments, when present Cognitive impairment, when present, can range from severe intellectual deficiency to learning disorders without intellectual disability (particularly dyslexia and dyscalculia). It is not yet known whether certain cognitive functions are more likely to be affected than others. In addition, cognitive impairments were observed without any motor disorders.[22–26]

Other clinical manifestations Mammary gland complications are relatively common and constitute a minor diagnostic criterion (Table 1). Bone anomalies[27] as well as lethal forms of pulmonary hypertension have been described[28,29] often in isolated cases.

Clinical diagnosis of IP: in adolescents and adults: persistent or permanent clinical criteria are very helpful, outside of the neonatal period and in adolescence and adulthood, when the diagnosis of IP is unknown[3] (Table 1).

Residual hyperpigmented lesions (Stage 3), often located on the folds, *or permanent alopecic linear hypopigmentation* (Stage 4), often located on the legs, may be the only observed IP manifestation in adult women. Heat intolerance is frequently mentioned by the patients, while hypohidrosis might be reported.[30] A skin biopsy can be very helpful to screen for minor lesions typical of Stage 4, which could be otherwise overlooked. IP diagnosis will allow for a more meaningful interpretation of possible unexplained neurological, ophthalmological manifestations and/or obstetric complications (such as miscarriage).[12]

The phenotypic array of odontological anomalies is broad and complex.[31–33] Dental anomalies are constant in IP, and careful tooth investigation is mandatory. Particular dental abnormalities are considered as major diagnostic criterion for IP[34] (Table 1). Recent data from a systematic review included *palate anomalies* in the oral findings of IP patients[32] and in an IP diagnostic criteria update. The main anomalies are the following: multiple dental agenesis in temporary and permanent dentition (prevalence of approximately 60% and 90%, respectively), coronary morphological abnormalities (in approximately 70% of cases), delayed dentition and various types of dento-maxillary dysmorphia (class II in 40% of cases, class III in 30% of cases and/or transverse maxillo-mandibular hypodevelopment) and arched palate or an orofacial cleft.[32,33] In permanent dentition, agenesis of the lateral incisors and second maxillary premolars are the most frequent alterations, followed by agenesis of mandibular premolars.[32] Incisors frequently present shape abnormalities. Molars may grow with fewer cusps. Clinical variability is marked in IP, and Stage 4 patients with few or no lesions may present marked dental changes.[34] An early clinical and radiological examination of the oral cavity, performed by specialists in paediatric odontology, dentofacial orthopaedics, prosthesis, and imaging, is indicated. A first oral examination is recommended by the age of 2 years.

Molecular diagnosis and genetic counselling

Genetic characteristics are detailed in the 'Clinical Utility Gene Card'. IP is caused by mutations in the *IKBKG/NEMO* gene located on Xq28.[1] The detection rate of a mutation in the coding sequence of the gene is approximately 80%. A recurrent deletion of exons 4 to 10 of the *IKBKG/NEMO* gene is the most common mutation resulting in IP, but many other mutations of this gene have been reported.[35–40] We suggest the common recurrent rearrangement (deletion rearrangement of exons 4 to 10 of *IKBKG* gene as a major diagnostic criterion). No obvious genotype–phenotype correlations have been found. The identification of a mutation facilitates the confirmation of a clinical diagnosis and allows appropriate genetic counselling. An analysis of the common deletion of exons 4 to 10 of *IKBKG* must be carried out in the first instance (with long-range PCR).[39] In the case of a negative result, *IKBKG* should be sequenced in search of a point mutation, a deletion or a duplication of different sizes.[41] Analyses of *IKBKG/NEMO* mutations are complicated by the presence of a non-functional *IKBKGP1* pseudogene (arising due to the deletion of the first 2 exons), which is highly homologous to *IKBKG/NEMO*.

Incontinentia pigmenti is reported in males[6,42,43–45] with Klinefelter syndrome (karyotype 47, XXY). However, the most common mechanism of IP in boys remains a postzygotic mosaic deletion of the *IKBKG/NEMO* gene.[42] For all IP patients, a thorough examination of their mother must be carried out, looking for a skin rash, skin lesions, dental manifestations, ocular signs or a history of miscarriage. When a mutation has been identified, a prenatal diagnosis can be performed, either by amniotic fluid sampling or by choriocentesis. IP diagnosis has important limitations due to the very large phenotypic disease variability.[46] In the case of *in vitro* fertilization, a pre-implantation diagnosis is also possible and may involve the transfer of *in vitro* fertilized embryos that do not carry the maternal mutation.[47] All those approaches are discussed during a genetic counselling consultation.

Management and care pathways

Management and follow-up should be performed by a multidisciplinary expert team through a coordinated approach. The coordinator is usually the dermatologist. The care pathways and therapeutic management are illustrated in Table 3.

Cutaneous involvement and follow-up

The therapeutic strategy is symptom-related. To treat severe inflammatory/verrucous lesions, topical steroids, topical tacrolimus (avoided in newborn), and oral and IV steroids have been tested with some success in a few reports.[48–51] It is essential to keep in mind that such lesions spontaneously regress. Persistent lesions of Stage 4 are not sequelae of previous inflammatory/verrucous lesions. The benefit/risk ratio and the need of treatment must be rigorously discussed and justified. In newborns, a local antiseptic might be proposed to prevent an eventual infection. Attempts at laser treatment of hyperpigmented lesions have resulted in recurrent inflammatory attacks and should be avoided.[52] Photoprotection is recommended due to the development of cutaneous inflammation and pigmentation. Late verrucous lesions under the nail need to be diagnosed (skin biopsy) and treated when they are painful. Standard treatment consists of surgical excision with curettage of the bone. Iterative surgery may be necessary.[49] A case of complete regression following oral etretinate (retinoid) treatment for 6 months has been reported.[53] Topical retinoic acid (0.05%) has been used with success in a case with the regression of the pain and the verrucous tumour within 1 and 6 months.[54] Dermatological follow-up should be every trimester during the first year, be monthly the first 6 months of life, then every year until the age of 5, and thereafter adapted according to disease progression. This schedule should be tailored to each patient. In cases of prolonged and profuse inflammatory lesions and/or disabling verrucous wounds, more visits may be scheduled, particularly during the first year of life.

Ophthalmological involvement and follow-up

Clinical examination of the peripheral retina must be prioritized as soon as an IP clinical diagnosis is carried out. It includes a complete pupillary dilatation, according to the protocol used for retinopathy monitoring in premature children, allowing for indirect ophthalmoscopy by a physician trained in the examination of the retina of newborn infants. In the case of peripheral

Table 3 Summary card for the therapeutic management of IP patients

Dermatology	**Careful monitoring in the first months of life:** • Every trimester the first year • Every year until the age of 5 • Then according to disease progression • 1 annual visit in a reference centre, with a multidisciplinary assessment if needed, until adulthood Increased frequency of visits in cases of prolonged and profuse inflammatory lesions and disabling verrucous lesions
Ophthalmology	**At IP diagnosis:** Clinical examination of the peripheral retina (complete pupillary dilatation) If peripheral vasculopathy is present, examination under general anaesthesia (when possible, with retinal photography and fluorescein angiography)/argon laser treatment **Follow-up:** In the case of early laser treatment: clinical examinations at D15, D30, D45, M2 and M3 post-treatment. Follow-up is then continued as recommended as in the case of normal results of the initial examination In the case of normal results of the initial examination: clinical examinations at M1, M2, M3, M6, M12, M18 and M24 of life Then every year for life
Neurology	**At IP diagnosis:** Systematic neurological examination → 2 situations: • If no neurological manifestation is observed at birth: a Neurocognitive examination: at 9 months and at 24 months b Brain MRI: at 2 ½ years old • If neurological manifestation is observed at birth: a EEG: during neonatal period, at 4 months and at 24 months b Cerebral MRI: during neonatal period and at 30 months **Follow-up:** • Regular neurological and epileptological follow-up, as needed: a At least every 6 months in the first 3 years • Systematic neurocognitive assessment: a At 5 years of age upon the initiation of elementary school • Renewal of cognitive assessment → frequency according to the patient's situation: a Neuropsychological assessment b If needed, psychomotor, speech, orthoptics and/or occupational therapy assessments c Detailed evaluations of memory, executive abilities, attention, visual and spatial abilities, praxis, language (oral and written), logic/mathematical skills and social cognition • Rehabilitation with physiotherapy, psychomotor therapy and speech therapy: throughout life, or whenever necessary • Psychological management
Odontology	**During childhood and adolescence: At 2–3 years: early oral examination** • At 3–4 years: the initiation of prosthetic treatment in the case of multiple agenesis. Coronoplasty of temporary incisors in case of associated coronary morphological abnormalities • At 6 years: panoramic radiography, the evaluation of agenesis in the permanent set of teeth and early assessment of dentofacial orthopaedics • At 7 years: possible coronoplasty of permanent conoid incisors • At 9-12 years: monitoring of the growth and eruption of permanent teeth and a second panoramic radiography at 9 years • At 12 years: preprosthetic and pre-implant orthodontic treatment until the end of dental growth and growth follow-up • End of growth: definitive implant-prosthetic rehabilitation **In adulthood:** • Multidisciplinary assessment involving implantologists, periodontologists, and specialists in dentofacial orthopaedics and in prosthesis, and • prosthetic, implant-prosthetic and orthodontic rehabilitation. **In the case of dental implants:** • A CBCT sectional imaging examination is required and may be accompanied by the need for bone and/or mucogingival grafts
Other	Other therapeutic management defined by specialists, if and when less frequent lesions are observed (e.g. cardiovascular complications)

EEG, electroencephalography.

vasculopathy, the child must be referred urgently to a specialized centre for examination under general anaesthesia with fundus photography and fluorescein angiography, if possible, followed by the treatment of non-perfusion zones by external argon laser photocoagulation.[15,55–60] Strict ophthalmological monitoring with prophylactic treatment of retinal vasculopathy could efficiently prevent the early blinding complications of the disease. In the case of early laser treatment, the postlaser monitoring programme consists of clinical examinations at least at months 1, 2 and 3 post-treatment or initially twice a month according to the clinical picture and then according to the proposed follow-up programme for initial normal examinations. A new laser session is proposed in the situation of new lesions. When the initial examination is normal, the proposed clinical monitoring programme consists of clinical examinations at months 1, 2, 3, 6, 12, 18 and 24, and then every year. It is not possible to exclude the possibility of late ocular complications in IP adults (experts' advice).

Neurological involvement and follow-up

A microvascularization mechanism seems to be involved, as evidenced by neonatal MRIs, associated with cytotoxic oedema of the white matter and focal cortical lesions.[61] After the neonatal period, typical sequelae with white matter lesions are described, as well as ulegyria and cerebral calcifications in more severe cases. *In the neonatal period*, treatments have two objectives: (i) anti-epileptic treatments for symptomatic treatment of epilepticus status or repeated seizures and (ii) anti-inflammatory treatment. The use of anti-inflammatory drugs limits neurological consequences. Steroids have been proposed as a first line of treatment, including IV methylprednisolone followed by oral steroids over a few weeks.[16,62–64] TNF blockers appear interesting but have been used in a punctual manner.[29] Gene therapy has been proposed and discussed for the mitigation of severe cerebrovascular pathology.[65] Different anti-epilepsy treatments are proposed according to the seizure semiology and the age of the patient. The management of neurological sequelae is essential and must be performed as early as possible, with physiotherapy (in the case of motor impairment), speech therapy (in the case of cognitive impairment) and/or occupational therapy. This multidisciplinary long-term follow-up is essential to enable the detection and management of neurocognitive and orthopaedic complications. A regular programme for the evaluation of cognitive development must be implemented during the initial months and even the initial years of life. A systematic neurological examination is necessary at the time of diagnosis. *During the neonatal period*: (i) if no neurological injury is observed, a neurocognitive evaluation at M9 and M24 of life and brain MRI between age 2 and 3.5 years is recommended; (ii) when neurological injury is observed, a neonatal EEG and then at months 4 and 24, along with a brain MRI during the neonatal period and at month 30, are recommended. *In the evolution of the disease and throughout life*, regular neurological and epileptological follow-up are necessary, at least every 6 months for the first 3 years of life, as well as a systematic neurocognitive assessment at 5 years upon the initiation of elementary school. The frequency of cognitive assessments must be defined for each patient according to his/her needs.

Dental management and follow-up

At 2–3 years: early oral examination for the detection of any dental agenesis and coronary morphological abnormalities in the temporary set of teeth. *At 3–4 years*: evaluation for prosthetic or restorative treatments of temporary teeth if dental problems interfere with feeding and/or speech. The coronoplasty of temporary incisors, in cases of associated coronary morphological abnormalities, is discussed. *At 6 years*: panoramic radiography for the detection of agenesis of the permanent teeth and early assessments by dentofacial specialists. *At 7 years*: evaluation for restorative treatment of the permanent lateral conoid incisors for speech and/or aesthetic problems. *At 9–12 years*: monitoring of the eruption of permanent teeth[66] with panoramic radiography, when necessary. *At 12 years*, preprosthetic and pre-implant orthodontic treatment may be considered for the repositioning of malpositioned teeth and subsequent prosthetic procedures. *At the end of growth*: definitive implant-prosthetic rehabilitation (veneers or ceramic crowns if indicated and/or supra-implant fixed prostheses).[33] A multidisciplinary assessment, potentially involving implantologists, periodontologists and specialists in dentofacial orthopaedics and prosthesis, is needed to evaluate the appropriate treatment in adults, including prosthetic, implant-prosthetic and/or orthodontic rehabilitation. Cone beam computed tomography (CBCT) sectional imaging is required prior to the implantation procedure and may be accompanied by the need for bone and/or mucogingival grafts. Auto-transplantation is not recommended.

Other less classic organ involvement can be observed in rare cases (e.g. cardiovascular manifestations and pulmonary hypertension). In these cases, the specialists should be experts in IP and collaborate with the specific multidisciplinary team for IP. The objective is to guarantee the best global management of the patient. Breast anomalies (hypoplasia, asymmetrical mammary glands), nipple anomalies and reduced milk production might explain breastfeeding difficulties.[12]

Assessments and patient support

Adapted assistance, in addition to examinations, treatment and medical care, is necessary throughout childhood for IP patients. In particular, aesthetic damage and speech problems may impact children's social relationships and school activities. Psychological counselling can be essential for the child and his/her parents and must always be proposed, regardless of the severity of IP. In the case of delayed psychomotor development, additional therapeutic procedures should be promptly implemented dependent

upon patient needs and adapted throughout the different periods of life (childhood, adolescence, adulthood). Transition is an intentional, progressive and coordinated process to move the young patient from a paediatric care unit to a department for adults. This process allows adolescents and young adults with IP to be prepared to take charge of their life and health as adults. Genetic counselling might be proposed at this stage. The transition process addresses the medical, psychosocial and educational needs of these youths while considering the social, cultural, economic and environmental aspects in which these adolescents and young adults evolve. Therapeutic patient education programmes are very helpful to support patients and their families. The national patient representative in each country is essential to help and support the patients and their families in their daily life and to ensure an efficient connection with the multidisciplinary team in the reference centres.

Discussion and conclusion

IP is a multisystemic disease with rare but potentially severe organ involvement, in particular in the CNS and eyes. It is imperative to diagnose IP at early stages, as soon as vesiculobullous, crusty and predominantly acral lesions with a Blaschkoid distribution (or with a tendency towards linear pattern) are observed in female neonates. IP can also be exceptionally observed in boys, with the same clinical manifestations and complications. Following diagnosis, an ophthalmological examination must be promptly performed to avoid severe complications such as blindness. The diagnosis of these cutaneous lesions will also help to better interpret eventual neurological abnormalities. IP treatment is mainly symptomatic. A long-term follow-up of the children is necessary. It is impossible, today, to eliminate the possibility of late clinical manifestations, such as new flares of skin lesions, cognitive involvement and ocular manifestations occurring even in the adult period.

Adapted assistance, in addition to examinations, treatment and medical care, is necessary throughout childhood. Psychological support can be essential for the child and his/her parents and should always be proposed, regardless of the form of IP. More severe IP forms that may cause psychomotor delay or an offset compared to the standard reference require rapid implementation of additional therapeutic management procedures, depending on the difficulties. Follow-up must continue into adolescence and adulthood and be implemented upon patient needs.

Acknowledgements

The authors acknowledge the national French and Italian IP associations. The authors want particularly to acknowledge the patients and their families, the multidisciplinary teams of the reference centres and all the medical and paramedical specialists caring for patients, and accompanying them with dedication in their life journey. The patients in this manuscript have given written informed consent to the publication of their case details.

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