NATIONAL PROTOCOL FOR THE DIAGNOSIS AND CARE OF RARE DISEASES

INCONTINENTIA PIGMENTI

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1 INTRODUCTION

Incontinentia Pigmenti (IP), a rare X-linked dominant genetic disorder, was characterized from spontaneous and progressive skin lesions that are now known to represent a major clinical diagnostic criterion. IP is nonetheless a multi-systemic disease, presenting a variety of symptoms, including dental anomalies, alopecia, nail dystrophy and more rarely, visceral complications; complications can be particularly serious when affecting the eyes or the brain.

It is essential that the diagnosis of IP is carried out without delay, so that the detection of these complications is achieved at the earliest, thus allowing for the timely implementation of specific therapeutic and monitoring strategies.

The development of a National Diagnostic and Care Protocol (Protocole National de Diagnostic et de soins, PNDS) is much warranted for this rare disease, for which the complexity and burden on patients and their families are not well known.

This PNDS has been developed according to the most rigorous methods, including:

- An in-depth analysis of literature data

- A summary of these data, including recommendations from multidisciplinary specialist groups with expertise in different aspects of IP pathophysiology

- Multiple reviews of an initial document, including corrections and suggestions from the association of patients with IP

- Given that cutaneous lesions and severe ophthalmological and neurological complications may often develop during the neonatal period, the protocol was proofread by a general practictioner and a neonatal specialist prior to its finalization.

The analysis of data in the existing literature are summarized in tables and presented in the appendix.

Patient monitoring and care strategies are presented and discussed in different sub-chapters, each dedicated to a particular affected organ system.

The objective of this protocol is to higlight the urgency of an appropriate diagnosis and management strategy for children suffering from IP as soon as the first symptoms appear, and the necessity for a well codified monitoring strategy for each child, adapted to their needs.

A systematic summary of the PNDS is provided in chapter 7: this PNDS integrates literature data (usually from small patient groups) with the practical experiences of the group of experts.

1.1 Literature review strategy

The literature review strategy is detailed in a separate document.

Data from the literature are summarized in the appendix as follows:

- Table 4 : Clinical studies concerning IP diagnosis
- Table 5 : Clinical studies concerning patient care
- Table 6: Patient care pathways

1.2 Incontinentia Pigmenti

1.2.1 Definitions

Incontinentia pigmenti (IP) is a rare, multi-systemic ectodermal dysplasia, with an X-linked dominant transmission. It is usually lethal in male foetuses, and is manifested in female newborn infants by a predominantly acral, vesiculopustular rash, and characterized by a rapidly linear positioning along Blaschko's lines. This initial phase is classically followed by manifestations of verrucous plaques and hyperpigmented macular lesions along Blaschko's lines. These cutaneous lesions will spontaneously and progressively regress. However, pathological signs may remain in adults, such as residual hyperpigmented lesions (frequently localized in axillary or inguinal folds), linear hypopigmented lesions (frequently found on lower limbs), persistent vertex alopecia, nail dystrophy and dental abnormalities. Retinal and central nervous system (CNS) impairments are rarer and affect a minority of patients, but they have an early onset and can be severe, often resulting in life long sequelae.

The occurrence of IP in male infants is extremely rare.

1.2.2 Epidemiology

The prevalence of IP at birth is about 1/143 000, with a female to male ratio of 20: 1.

1.2.3 Etiology

IP is caused by inherited mutations (10-25%) or sporadic, *de novo* mutations (> 50%) of the Inhibitor of Nuclear Factor Kappa B Kinase Subunit Gamma (IKBKG) gene [1]. The IKBKG gene encodes the Nuclear factor-kappa-B essential modulator (NEMO) protein, which is a subunit of the IkB kinase complex, that is involved in the activation of nuclear factor-kappa B (NF-kB). NF-kB is a transcription

factor that controls the activity of many target genes coding for chemokines, cytokines, adhesion molecules and anti-apoptosis molecules. A recurrent deletion of exons 4-10 is found in 80% of IP cases[2].

1.2.4 Clinical manifestations

IP is a genodermatosis affecting the skin, teeth, eyes and central nervous system. The typical phenotype is due to functional mosaicism, a phenomenon occurring in dominant X-linked conditions, in which the physiological mechanism of random inactivation of one of the X chromosomes is maintained. Two cell populations can thus co-exist: one population in which the mutated X chromosome is inactivated, and a second population in which the the healthy X chromosome is inactivated. The affected areas correspond to cells expressing the X chromosome carrying the genetic mutation. Linear vesiculo-bullous eruptions or blisters (along Blaschko's lines) can be observed in patients at birth, or in the first days or weeks of life, that may evolve over time through successive phases, that sometimes overlap: the vesiculo-bullous and inflammatory phase, the verrucous phase, the hyperpigmentation phase, and the hypo-pigmented/atrophic phase (see 2.2.1, stages of IP progression)[3]. These cutaneous manifestations are highly characteristic in their semiotics, topography, and the fact that they occur mainly in female infants[4–6]. Extracutaneous manifestations occur in 50% of cases, their intensity and time of onset being relatively variable compared to cutaneous lesions[7]. The diagnosis is clinical in most cases, but it can be confirmed by biomolecular analysis. The clinical characteristics, diagnostic tools, potential organ complications and their management are discussed, for each organ system in the next chapter.

2 Screening and Clinical Diagnosis of Incontinentia Pigmenti and its complications

2.1 Diagnostic criteria

It is imperative to diagnose IP at the early stages, as soon as vesiculo-bullous, crusty, and predominantly acral lesions with a linear disposition (or with a tendency towards linear disposition) are observed in small girls (IP can also be observed in boys, but exceptionally). The diagnosis is urgent so that an ophthalmological examination can be performed without delay. The diagnosis of these cutaneous lesions will additionally allow for a more meaningful interpretation of eventual neurological abnormalities.

The diagnosis is mainly based on clinical criteria and genetic analysis.

Clinical criteria for the diagnosis of IP were proposed in 1993 by Landy and Donnai, and they have been updated to include more recent clinical and histological charateristics. This update is summarized in Table 1 below.

Table 1: Up to date diagnostic criteria of IP (Landy et Donnai 1993 and Hadj-Rabia et al 2003) [3,6]

MAJOR CRITERIA
- **Typical neonatal rash (see description) with erythema and vesicles (Stage 1)**
- **Eosinophilia**
- **Typical hyperpigmentation along Blaschko's lines fading in adolescence (+++) (Stage 3)**
- **Linear, atrophic, hairless lesions on limbs (Stage 4)**
- **Indicative skin histology**
MINOR CRITERIA
- **Teeth: oligodontia or anodontia, microdontia, conical teeth**
- **Hair: Alopecia or woolly hair (dull and dry)**
- **Nails: Punctuate depressions, onychogryphosis (or ram's horn nails)**
- **Retina: peripheral neovascularization**
- **Mammary gland affliction (hypoplasia, asymmetry, hypogalactia) and/or nipple affliction (umbilication, supernumerary, difficulty in feeding)**

In the absence of a family history of IP, the presence at least one major criterion is sufficient for a diagnosis of IP; the presence of minor criteria only reinforces it. If a first-degree female parent suffers from IP, the presence of a minor criterion is sufficient for a diagnosis of IP.

The complete absence of minor criteria should impart a degree of uncertainty to the diagnosis.

2.2 Cutaneous lesions[8–10]

2.2.1 Stages of IP progression

IP typically manifests in four successive stages (Table 2). The duration of each stage varies from one individual to another and the different types of lesions may co-exist. Cutaneous rashes classically occur along Blaschko's lines, which is non-pathognomonic but fairly indicative of lesions with a linear arrangement or swirling (on the trunk). The diagnosis of IP is generally more straightforward upon observation of predominantly acral vesiculo-bullous eruptions (or blisters) of a linear disposition,

especially in a female newborn. These lesions will fade away spontaneously in early childhood (stage 1 and 2), or gradually until adolescence (stage 3). The possible persistence of linear hyperpigmented residual lesions, often located in folds, is an important clinical feature for IP diagnosis in adults. Stage 4 lesions are usually linear, hypopigmented and hairless, persisting throughout life. They can be very discreet in certain cases, and may require a skin biopsy to permit better characterization.

It is important to emphasize that in most cases, the successive Stage 1 and 2 outbrakes that occur during the first months of life regress spontaneously. However, the later outbreaks, which may be linear and tracing Blaschko's lines, or verrucous and subungual, have sometimes been observed years after the neonatal period. They are often triggered by a viral infection. It is thus necessary to consider an analysis of the cutaneous histology, on the basis of clinical similarities to IP, even if prior IP diagnosis is unknown. In cases of late and painful subungual verrucous lesions, histological analysis is particularly important to rule out benign or malignant nail tumors[11].

The 4 stages of IP progression are summarized in the table below.

STAGE	CLINICAL MANIFESTATION	STAGE ONSET	DIFFERENTIAL DIAGNOSIS
STAGE 1: VESICULO-BULLOUS STAGE	Erythema (redness) and vesiculo-pustules or bullae with acral and linear disposition	Within the first few weeks of life upto 18 months	Dermatoses with blistering in early infancy. Usually, bacterial and viral infections (HSV, VZV) and epidermolysis bullosa. Importance of linear disposition.
STAGE 2: VERRUCOUS STAGE	Verrucous lesions	Within the first few months of life; usually lasts for a few months	Verrucae vulgares (simple warts), chondrodysplasia, epidermal Nevus
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 and alopecia	Probably present from childhood even if persistently undervalued throughout life	Vitiligo with localized alopecia

Table 2: The four stages of IP progression at the cutaneous level (Minic et al, 2014) [8]

2.2.2 Skin histology

Cutaneous histology typically shows eosinophilic spongiosis at stage 1, acanthosis and hyperkeratosis of the epidermis with dyskeratotic keratinocytes at stage 2, and dermal melanin deposits (melanin incontinence) at stage 3. The association of eosinophilic spongiosis (stage 1), hyperkeratosis (stage 2), melanin incontinence (stage 3), together with keratinocyte apoptosis (at all stages) should be considered highly suggestive of IP. At stage 4, histological analysis can be particularly useful as such lesions may be the only diagnostic sign in the adult of an undiagnosed IP. A characteristic aspect is the absence of an appendage associated with keratinocyte apoptosis, which should be thoroughly screened for.

2.2.3 Differential diagnosis

Stage I vesiculo-bullous lesions should be differentiated from other bullous dermatoses, such as epidermolysis bullosa, dermatitis herpetiformis, bullous impetigo, herpes simplex and congenital varicella, which generally do not present with a linear topography. Epidermal epidermolytic hamartomas with a linear arrangement along Blaschko's lines can be confused with IP.

Other types of pigmented mosaicism with lesions along Blaschko's lines do exist. However, these lesions are usually not preceded by an inflammatory phase, and they do not regress spontaneously over time, as in the case of IP.

Finally, other X-linked dermatoses have a linear presentation in afflicted girls (skin hypoplasia, chondrodysplasia punctata of the Conradi-Hünermann-Happle type, for instance). However, the appearance of those lesions is different from that of the vesicular lesions occurring in IP.

2.3 Anomalies of skin appendages (hair and nails)

Areas affected by alopecia can be located on the scalp, extremities or trunk. Alopecia on certain areas of the scalp may correspond to a scar formed as a result of a Stage I inflammatory rash, or may develop spontaneously. These alopecic zones 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 "wooly" texture (without characteristic abnormality 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].

2.4 Ophthalmic anomalies [12,13]

2.4.1 Ocular lesions

Ocular abnormalities are rarely a telltale sign for IP diagnosis. More than a third of patients show ophthalmologic damage, including early active retinal vasculopathy (the most common abnormality, which is quite serious as it may lead to blindness), optic nerve damage, or asymptomatic corneal abnormalities (cornea verticillata). Occular damage may result in retinal detachment[12] and severe visual impairment. Early screening and care can prevent these dramatic consequences.

2.4.2 Diagnostic elements for ophthalmic examination

Ophthalmic manifestations may occur variably from one patient to another; the following may occur:

- Cornea verticillata, very indicative of IP in an infant

- Multifocal hypo- and/or hyperpigmented lesions of the pigmented retinal epithelium, also very suggestive in this context

- Vascular abnormalities of the peripheral retina, which may progress in the following order in the absence of treatment: zones of non-perfusion in the peripheral vessels, arteriovenous anastomoses, neovascularization and retinal detachment

- Macular-vascular abnormalities, the presence of which may be clinically detected by abnormal foveal reflection and by retinal thinning, observable via optical coherence tomography requiring fluorescein angiography

- More rarely, atrophy or hypoplasia of the optic nerves.

2.5 Odontological anomalies

The phenotypic array of odontological anomalies associated with IP is broad and complex. The main anomalies of dentomaxillary development are the following: multiple dental agenesis in temporary and permanent dentition (prevalence of about 60% and 90%, respectively)[14], coronary morphological abnormalities (in about 70% of cases), delayed dentition and various types of dentomaxillary dysmorphosis (class II in 40% of cases, class III in 30% of cases and/or transverse maxillo-mandibulaire hypodevelopment) and arched palate or an orofacial cleft[15,16]. In permanent dentition, agenesis of the lateral incisors and second maxillary premolars are the most frequent alteration, followed by agensis of mandibular premolars[17]. Incisors frequently present abnormalities of shape (notches, absence of a proximal angle, microdontia). Molars may grow with fewer cusps. Dental

abnormalities are considered a major diagnostic criterion for IP, following a recent update of diagnostic criteria[6].

In this context, an early clinical and radiological examination of the oral cavity, performed by specialists in pediatric odontology, dento-facial orthopedics, prosthesis and imaging is indicated. A first oral exam is recommended from the age of 2 years.

2.6 CNS impairments [18,19]

CNS disorders described in the literature include convulsions in the neonatal period with the risk of partial epilepsy secondary to a lesion, and secondary cognitive impairment associated with a motor deficit (hemiparesis, paraparesis or tetraparesis) in 15 to 30% of patients[2,20]. Some neurological disorders are lethal, such as excessive damage to the antenatal CNS or status epilepticus.

Early neonatal neurological and ophthalmologic manifestations condition long-term patient prognosis and the occurrence of a disability. Most patients with no neonatal CNS abnormalities usually undergo normal physical and cognitive development.

During the neonatal period, it is recommended to perform a neurological clinical evaluation, following a dermatological examination[20,21]. Dermatological lesions may be minimal and go undetected, while the pathology may manifest as partial seizures, as early as 24 hours from birth, and most generally in the first days of life. An EEG and a brain MRI should be performed to confirm the diagnosis and antiepileptic and/or corticosteroid treatment should be prescribed if needed.

Neurological follow-up is conditioned by possible motor, cognitive and epileptic sequelae. A neurological, cognitive and MRI assessment is systematically desirable at 2-3 years of age, even in children without apparent clinical neurological anomalies.

2.7 Cognitive impairments

If present, cognitive impairments can be of varying severity, ranging from severe intellectual deficiency to learning disorders without intellectual disability (particularly dyslexia and dyscalculia). Although the literature suggests rather homogeneous profiles, the available data are not broad enough to assess whether certain cognitive functions are more likely to be affected than others. Furthermore, it is important to note that these cognitive impairments were observed without any motor disorders [18,22].

Psychiatric symptoms have been reported only once in the literature, in the case of an IP patient with bipolar disorder[23]. It is therefore not possible to establish whether there the apparent weak link between psychiatric manifestations and IP is actual, or due to a scarcity of literature data on the

subject. Nevertheless, the chromosomal region affected in IP (Xq28), appears to be associated with psychiatric disorders[24–26]. The onset of psychiatric symptoms at all ages should be considered as a possibility. These may manifest in response to motor or visual impairments, or any other clinical signs affecting the physique including the face and limbs, leading to alterations body-image perception.

2.8 Other complications of IP

Mammary gland complications are relatively common; therefore, they can be considered as a minor diagnostic criterion, as reported in Table 1. Other anomalies have been described, often in isolated clinical cases. These have included bone-related indications such syndactyly, hemi-supernumerary vertebrae, and scoliosis, as well as vascular indications such as lethal forms of pulmonary hypertension.

2.9 Unexpected cases in males [27]

Survival of the male fetus is not possible when the Incontinentia Pigmenti gene located on the only X chromosome is mutated. Nevertheless, several cases of boys with IP have been described:

- Presence of a supernumerary X chromosome: one of the two X chromosomes will undergo inactivation, as in females

- Classical post-zygotic IP mutations (also called somatic mosaicism). In this case, the IKBKG mutation is present in a limited number of cells, thus allowing survival, and IP in the male demonstrates similar clinical characteristics to females.

- Specific mutations of the IKBKG gene: very rare inherited forms have been described, associating clinical signs of hypo- or anhydrotic ectodermal dysplasia in the boy and very moderate signs of IP in the mother. Therefore, it is not IP but rather ectodermal dysplasia that is observed in the male, which is associated with immune deficiency and bone complications. The clinical consequence of these particular mutations is thus not the same as in classical forms of IP.

2.10 Incontinentia Pigmenti in adult women

The diagnosis is simple when typical manifestations occur during the neonatal period. Minor criteria related to developmental abnormalities, e.g. residual hyperpigmented lesions or permanent alopecic linear hypopigmentation (stage 4), may be the only observed manifestations of IP in adult women. When the diagnosis is not known in adults, it is important to thoroughly analyse every dermatological feature, resorting to a skin biopsy where necessary to screen for minor lesions typical of stage 4

symptoms, which could have otherwise been overlooked. Diagnosis of IP will allow for a more meaningful interpretation of possible unexplained neurological, ophthalmological and obstetric (such as miscarriage) complications.

3 Molecular diagnosis and genetic counselling

3.1 Molecular diagnosis

Genetic characteristics are detailed in the "Clinical Utility Gene Card"[28]. Incontinentia Pigmenti is caused by mutations in the IKBKG gene located on the X chromosome in the Xq28 region[28]. *De novo* mutations may occur in about two-thirds of cases, most often on the paternal allele. 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 gene is the most common mutation resulting in IP, but many other mutations of this gene have been reported[28–30]. No obvious genotype-phenotype correlations have been found.

The discovery of a mutation facilitates the confirmation of a clinical diagnosis and informs appropriate genetic counseling. An analysis of the common deletion of exons 4 to 10 on the IKBKG gene must be carried-out in the first instance (with long-range PCR)[31]. In case of a negative result, the the IKBKG gene should be sequenced in search of a point mutation, a deletion or a duplication of smaller size[32]. Analyses of IKBKG mutations may be complicated because of the presence of a non-functional IKBKGP1 pseudogene (arising due to the deletion of the first 2 exons), which is highly homologous to the IKBKG gene. The presence of this pseudogene is problematic for all types of sequencing techniques, from classical Sanger sequencing to the newer high-throughput sequencing methods.

3.2 Genetic counselling

- Incontinentia Pigmenti is the consequence of an X-linked dominant mode of transmission
- In some cases of affected boys, Klinefelter syndrome (karyotype 47, XXY) or a somatic mosaic mutation of the IKBKG gene must be considered.
- A thorough examination of the mother must be carried out, looking for a neonatal skin rash, skin lesions (such as alopecia of the scalp, hypochromic and atrophic macules tracing Blaschko's lines), dental signs which may be minimal (e.g., conical teeth, talon cusp), 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. This diagnosis has important limitations given the very large phenotypic variability in IP. In case of *in vitro* fertilization, a pre-implantation diagnosis is also possible[33] and may involve the transfer of *in vitro* fertilized embryos that do not carry the maternal mutation.

4 Management of Incontinentia pigmenti patients and care pathways

The treatment is mainly symptomatic. [5]

Patient management and follow up should be multidisciplinary. They need to be organized by a coordinator, working in collaboration an expert network. The coordinator is most often a dermatologist owing to the frequency of presentations limited to dermatological symptoms, and the early onset and highly diagnostic nature of cutaneous manifestations.

Recommendations for the management and follow up of IP patients have been compiled from literature data and expert advice, and are presented in the following sub-sections for each affected organ system.

4.1 Dermatological management and follow-up

4.1.1 Therapeutic strategy for cutaneous damage

The therapeutic strategy for cutaneous manifestations is symptom-related and limited. Several strategies have been diversely reported: local corticotherapy [34], topical tacrolimus [35], systemic corticotherapy [36], ruby laser[37], and curettage or surgical excision of verrucous lesions under the nail[38]. Topical and systemic antibiotics are not recommended[2].

It is important to highlight that cutaneous lesions regress spontaneously and progressively, and that one should be cautious not to bring about unwanted iatrogenic risks. In newborn infants, a local antiseptic is usually used to treat vesiculo-bullous lesions and to prevent an eventual infection, even though the lesions are initially sterile.

Topical corticosteroids may be employed to control an inflammatory phase when it is severe and disabling. Attempts at laser treatment of hyperpigmented lesions have resulted in recurrent inflammatory attacks and should be avoided.

Photoprotection is recommended due to the development of cutaneous inflammation and pigmentation.

Late verrucous lesions under the nail need to be diagnosed and treated when they are painful. Standard treatment consists of surgical excision with curettage of the bone. Iterative surgery may be necessary. A case of complete regression following oral etretinate (retinoid) treatment for 6 months has been reported [39]. CO_2 laser treatment can be considered on periungual tumors.

4.1.2 Dermatological follow up

Follow ups need to be attentive in the first months of life: once a month for 6 months, then twice a year until the age of 5, and thereafter adapted according to disease progression.[2] This follow up is to be adapted to each patient. In case of prolonged and profuse involvement of inflammatory lesions and disabling verrucous wounds, the frequency of visits may be higher, particularly during the first year of appearance.

4.2 Ophthalmic management and follow up [13,40–45]

4.2.1 Therapeutic strategy for ophthalmic complications

Ophthalmic complications may need to be examined and managed urgently. Clinical examination of the peripheral retina must be prioritized as soon as a clinical diagnosis of IP is carried out. It includes a complete pupillary dilatation, according to the protocol used for retinopathy monitoring in premature children (indirect ophthalmoscopy by a physician trained in the examination of the retinae of newborn infants).

In case of peripheral vasculopathy, the child must be referred urgently to a specialized center for examination under general anesthesia with retinophotography and fluorescein angiography, if possible, followed by the treatment of non-infusion zones externally by Argon laser photocoagulation.

4.2.2 Opthalmologic follow-up

D = Day and M = Month

In case of early laser treatment, the post-laser monitoring program consists of clinical examinations at D15, D30, D45, M2 and M3 post-treatment, then respects the proposed follow-up program for initial normal examinations (below). A new laser session is to be proposed in case of new lesions

- If the initial examination is normal, the proposed clinical monitoring program consists of clinical examinations at M1, M2, M3, M6, M12, M18, M24, and then for every year of the patients' life.

4.3 Neurological management

4.3.1 Neurological therapeutic strategy

The mechanism of neurological involvement is vascular (micro-vascularization), as evidenced by neonatal MRIs, and accompanied by cytotoxic edema of the white matter and focal cortical lesions.[46] Ahead of the neonatal period , classic sequelae of white matter lesions are described, as well as ulegyria and cerebral calcifications in more serious cases.

- Treatments have two objectives in the neonatal period:

1. Anti-epilepsy treatments for symptomatic treatment of epilepticus status or repeated seizures (Intra-venous (IV) Dilantin or oral antiepileptics).

2. Anti-inflammatory treatment: the convulsive condition is related to a mechanism of inflammatory vasculitis. The use of anti-inflammatory drugs can therefore be justified to try to limit the neurological consequences of such an inflammatory attack. Steroids have been proposed as a first line of treatment: IV solumedrol, followed by oral corticotherapy over a few weeks [21,47,48]. TNF blockers have been used in a punctual manner [49] and seem interesting, but have not yet been studied in the context of IP.

Gene therapy has been proposed and discussed for the mitigation of severe cerebrovascular pathology [50].

Later, different anti-epilepsy treatments will be proposed according to the activity of the lesional epilepsy, and according to the age and the semiotics of the crises.

Management of neurological sequelae is essential and must be performed as early as possible, with physiotherapy (in case of motor impairment), speech therapy (in case of cognitive impairment) and/or occupational therapy. This multidisciplinary follow-up is essential to enable the detection and management of neurocognitive and orthopedic complications. A regular program for the evaluation of cognitive development must be implemented during the initial months, and even the initial years of life. Introduction into the education system must take into account the child's needs (ANSI, adaptation of facilities for motor disabilities), followed by a structure of adapted care (SSESD or CAMSP) after completion of an application and the preparation of an MDPH file (to the Local Disability Services Office).

4.3.2 Neurological follow up

- A systematic neurological exam is necessary at the time of diagnosis. Two situations are possible:

The 1rst situation

- No neurological manifestation at birth: neurocognitive examination at M9 and M24 of life, brain MRI between year 2 and year 3.5 of life.
- Neurological manifestation(s) observed at birth: Neonatal EEG, EEG at M4 and M24 to be performed systematically; cerebral MRI during the neonatal period and at M30.

The 2nd situation

- Regular neurological and epileptological follow-up, as needed, at least every 6 months for the first 3 years of life.
- Systematic neurocognitive assessment at 5 years upon initiation of elementary school.
- The frequency of cognitive assessment repetitions (neuropsychological assessment, and if needed psychomotor, speech related, orthoptic and/or occupational therapy assessments) is to be defined for each patient based on their needs, to which one must pay continuous attention. The assessment of cognitive abilities should not be restricted to the global intelligence quotient (IQ). It must also include a detailed assessment of memory, attention, executive abilities, visual and spatial abilities, praxis, language (oral and written), logic and mathematical skills, and social cognition. The interpretation of the patient's results must account for the presence of co-morbidities (motor or visual disturbances) and any iatrogenic risk (such as from antiepileptic treatments) and must always be conveyed to the patient and his/her family.
- Early rehabilitation with physiotherapy, psychomotor therapy, and speech therapy, either privately or within an adapted care center is to be subsequently organized by the neuro-pediatrician, as needed. It will have to continue throughout life whenever necessary, with implementation of appropriate care that is person-centered (cognitive remediation, rehabilitation) and/or integrated in their habitual environment (school facilities, business facilities, specialized orientation).

4.4 Odontological management

4.4.1 During childhood and adolescence: temporary and mixed set of teeth

- 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: Initiation of prosthetic treatment with pediatric prosthesis in cases of multiple agenesis. Coronoplasty of temporary incisors in cases of associated coronary morphological abnormalities

- At 6 years: panoramic radiography, for the detection of agenesis in the permanent set of teeth, and for the early assessment of dentofacial orthopedics
- At 7 years: Possible coronoplasty of the permanent conoid incisors
- At 9-12 years: Monitoring of the growth and eruption of permanent teeth [51] and a second panoramic raiography at 9 years
- At 12 years: Pre-prosthetic and pre-implant orthodontic treatment until the end of dental growth, and growth follow up.
- End of growth [17] : definitive implant-prosthetic rehabilitation (veneers or ceramic crowns if indicated and/or supra-implant fixed prostheses).

4.4.2 In adulthood: implant-supported prosthetic rehabilitation

A multi-disciplinary assessment, potentially involving implantologists, periodontologists, and specialists in dentofacial orthopedics and prosthesis, is needed to evaluate the appropriate treatment: prosthetic, implant-prosthetic and/or orthodontic rehabilitation.

Cone beam computed tomography (CBCT) sectional imaging would be required prior to the implantation procedure and may be accompanied by the need for bone and/or muco-gingival grafts. Auto transplantation is not recommended.

4.5 Other IP complications

Other less classic lesions can be observed in rare cases (for example, cardiovascular manifestations). These will necessitate contact with a reference center specializing in IP management, where the multidisciplinary structure of the center will allow for the intervention of a specialist of the organ concerned, in collaboration with a team specialized in IP therapeutic management.

5 Patient assistance

This will depend on each patient's situation and is to be evaluated rigorously throughout the progression of the disease.

5.1 A multidisciplinary team

Adapted assistance, in addition to examinations, treatment and medical care, are necessary throughout childhood for IP patients, especially because associated complications may give rise to aesthetic abnormalities and speech problems, which may impact the child's social relationships and school activities. Psychological counselling can be essential for the child and his/her parents, and must always be proposed, whatever the form of IP. More severe IP forms that may cause delays in psychomotor development or an offset compared to the standard reference, require rapid implementation of additional therapeutic management procedures, depending on the difficulties. Assistance must continue into adolescence and adulthood. It must be implemented as early as possible upon the identification of difficulties. It can be indicated at any age, from infancy to adulthood.

Depending on the case, the following support are recommended. Although early neonatal neurological and ophthalmological manifestations, and their sequelae, concern a minority of IP patients, they may nonetheless result in the development of a major disability. The required facilities justify the additional mobilization of specialized professionals in private, public or medico-social settings (including physiotherapist, occupational therapist, speech therapist, psychomotor therapist, neuropsychologist and orthoptist).

- **Psychomotor therapy:**

Babies who move poorly can be provided with psychomotricity support starting during their first months of infancy. Psychomotor therapy may include exercises aimed to stimulate and improve their mobility. Psychomotor therapies may also be provided to older children who have difficulties with fine motor skills as a result of hemiparesis.

- **Speech therapy:**

Availability of speech therapy, either via adapted methods in a specialized care center (CAMPS) or in private with a specialist, may contribute very early on (as early as 2 or 3 years of life) to speech and language development.

- **Occupational therapy:**

Occupational therapy is often proposed later on, notably in children of school-going age, if there are difficulties in, for example, holding a pencil and writing. Alternative educational solutions may be offered and computer-based learning support can also be provided to facilitate learning.

- **Orthoptic support**:

A range of visual disorders can be compensated by adapted rehabilitation strategies involving visual motor skills.

- **Physiotherapy**:

Physiotherapy is essential for the mobilization of joints and improved movement and body control. It is often a complement to psychomotor therapy, each with different approaches.

- **Psychological care:**

Depending on the patient's cognitive difficulties and age (a particular problem for adolescent girls living with a rare disease), psychological care may be useful, or even necessary, as the period of adolescence presents additional challenges for those with handicaps. Psychological management of the aesthetic complications arising from agenesis must also to be taken into consideration.

- **Tutoring and educational support:**

Special-needs assistants and specialized computer equipment must be made available. The support of a special-needs assistant is often needed to ensure the continued participation of the child in the mainstream school system, and to compensate for any reading or writing difficulties.

To define the patients' needs according to his/her disabilities, it is necessary to seek advice from a department specialized in neurodevelopment. Neurological departments in hospitals may have recourse to reference centers specialized in rare diseases with a psychiatric outcome, which may help to improve monitoring of overall disease progression.

(Appendix 3. The Transition)

5.2 Adaptation of the patient's environment

Varying adaptations of a patient's habitual environment may help to limit the negative impacts of sensory, motor and cognitive disorders, and they are often complementary to rehabilitation and remedial care. These arrangements can be recommended in different contexts: at home, for leisure, at school or at work (for example, availability of a care assistant, a special-needs school assistant,

computer, wheelchair, or braces for the limbs). Some arrangements are granted after solicitation of the MDPH.

Special schools or professional and medico-social orientations require the constitution of an MDPH file. Depending on the patient's situation, they allow access to a range of support services, such as:

- Specialized schooling methods and centers (e.g. ULIS and IME)
- Professional training schemes (e.g. IMPro or the UEROS scheme)
- Accommodation
- Day care centers
- Employment assistance (via a disabled worker recognition status, RQTH, or centers specializing in the professional insertion of disabled persons, ESAT).

5.3 Coordinated therapeutic management

Coordination of the management of the functional and neurocognitive handicap of patients with a severe form of IP is as essential, as for all the complications leading to this type of handicap. The purpose of patient support must be defined beforehand with the patient (and his/her family), and its relevance must be regularly reassessed.

Assessments and patient support should take into account the possibility of the co-occurrence of varying symptoms (including motor, visual and cognitive symptoms), as well as the environment and lifestyle of the patient. Patient support must be coordinated to ensure the overall relevance of the management plan. The referring doctor of the patient, or the neurologist, as well as medico-social structures (e.g. CAMPS ad SESSAD) can ensure this coordination. The use of specialized hospital or medico-social teams may be necessary to allow a multidisciplinary approach in the case of complex situations (such as a network of reference centers specializing in genodermatoses, in rare diseases with psychiatric complications, in intellectual disabilities of rare cause, reference centers for learning disorders, rare handicap relay teams, and networks specialized in socio-professional rehabilitation, etc.).

Table 3: Professions involved in the support of IP patients with disabilities

PROFESSION	TYPE OF APPROACH	SPECIALTY
ORTHOPTIST	Rehabilitation of **visual function**	Visual-spatial perception, oculomotricity, visual-spatial attention, visual field
PSYCHMOTOR THERAPIST	**Body-centered** management addressing both psycological and cognitive symptoms	Body diagrams, laterality, spatio-temporal organization, gestural disorders, drawing disorders
SPEECH THERAPIST	**Language** Rehabilitation and **Communication**	Bucco-facial praxis, swallowing, phonation, verbal language, written language (reading and writing) and mathematics, augmentative and alternative communication
OCCUPATIONAL THERAPIST	**Independence and autonomy in the everyday environment**	Home modifications, orthosis, alternative communication, specialized equipment, movement disorders
NEUROPSYCHOLOGIST	**Remediation of cognitive functions in association with mood and interpersonal aspects**	Memory, executive functions, attention, social cognition, language, praxis, recognition
PSYCHOLOGIST	**Mood and interpersonal aspects, contents of one's thoughts**	Representations and experience of the illness and disability, its impact on family and social life

5.4 Practical advice - Additional support

Any special costs incurred for the child (such as for the purchase of an armchair or other equipment, special facilities, psychomotor therapy, occupational therapy, orthodontics and prosthetics) that are not covered by the social security (Assurance Maladie), or whose expenses exceed the benefits to which the family is entitiled to, can be subject to a request for financial support via the following avenues:

- The social security service of extra-legal benefits (one's local social security branch (CPAM) must be contacted for further information).
- Private insurance: the majority of private health insurance policies have funds to meet the specific needs of adherents with disabilities.
- The MDPH (Local Disability Services Office) on which the child depends. It is necessary for the child's family to contact their MDPH to review their particular allowances.
- The Incontinentia Pigmenti France Association (IPF) (via the website www.incontinentia-pigmenti.fr/ or by e-mail at incontinentiapigmenti@hotmail.fr)

6 Summary card for the therapeutic management of IP patients

DERMATOLOGY	➢ **<u>Careful monitoring in the first months of life:</u>** • Once a month for 6 months • Twice a year until the age of 5 • Then according to disease progression • 1 annual visit in a reference center, with a multidisciplinary assessment if needed, until adulthood ➢ *Increased frequency of visits in cases of prolonged and profuse inflammatory lesions and disabling verrucous lesions*
OPHTALMOLOGY	➢ **<u>Upon IP diagnosis:</u>** • Clinical examination of the peripheral retina (complete pupillary dilatation) • If peripheral vasculopathy, examination under general anesthesia (if possible, with retinophotography and fluorescein angiography) / Argon laser treatment ➢ **<u>Follow up:</u>** • In case of early laser treatment: Clinical examinations at D15, D30, D45, M2 and M3 post-treatment. Follow-up is then continued as recommended in the case of normal results of the initial examination. • In 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	➢ **<u>Upon IP diagnosis :</u>** • Systematic neurological examination → 2 situations: 1. If no neurological manifestation is observed at birth: - Neurocognitive examination: at 9 months and at 24 months - Brain MRI: at 2 ½ years old 2. If neurological manifestation is observed at birth: - EEG: During neonatal period, at 4 months and at 24 months - Cerebral MRI: During neonatal period and at 30 months ➢ **<u>Follow up</u>**: • 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 initiation of elementary school • Renewal of cognitive assessment → frequency according to the patient's situation: - Neuropsychological assessment - If needed, psychomotor, speech, orthoptics and/or occupational therapy assessments - 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	➢ **<u>During childhood and adolescence:</u>** - At 2-3 years: early oral examination - At 3-4 years: Initiation of prosthetic treatment in case of multiple agenesis. Coronoplasty of temporary incisors in case of associated coronary morphological abnormalities - At 6 years: panoramic radography, evaluation of agenesis in the permanent set of teeth and early assessment of dentofacial orthopedics - 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: Pre-prosthetic and pre-implant orthodontic treatment until the end of dental growth, and growth follow up. - End of growth: definitive implant-prosthetic rehabilitation ➢ **In adulthood:** - Multi-disciplinary assessment involving implantologists, periodontologists, specialists in dentofacial orthopedics and in prosthesis - Prosthetic, implant-prosthetic and orthodontic rehabilitation. - **In case of dental implants:** A CBCT sectional imaging examination is required and may be accompanied by the need for bone and/or muco-gingival grafts.
OTHER	➢ Other therapeutical management defined by specialists, if and when less frequent lesions are observed (e.g. cardiovascular complications)

EEG: electroencephalography

7 Appendices

Appendix 1. Literature review and selection of articles

Literature review

Sources consulted	Databases : MEDLINE, BDSP, Irdes, Refdoc, Embase, National Library for Public Health, Google scholar searches, Current contents, Sci search, EconLit, EURONHEED (European Network of Health Economics Evaluation Databases), University of York databases (DARE, NHS EED, HTA), Cochrane Library Internet websites: Société savante (dermatology) ;Patient association; Orphanet ; Therapeutic ; HAS ; NIH ; PHE/EMA ; PHAC
Research period	Starting from 2000
Retained languages	EN, FR
Key words used	Incontinentia pigmenti ; Bloch-Sulzberger syndrome ; Bloch-Siemens syndrome ; Diagnosis ; Diagnostic ; Screening ; Detection ; Guidelines ; Practice Management ; Treatment ; Exam ; Test ; Process ; Healthcare ; Pathways ; System Flow
Number of studies reviewed	336
Number of studies retained	68

Selection criteria for articles

-Literature review articles on the pathology

- Cases series and retrospective studies based on the pathology

- Clinical studies (randomized or not) on treatment
- Articles presenting patient care and management (treatment, diagnosis, care pathways), and recommendations.

Appendix 2 : Summary table of relevant literature reviewing

Table 4 Clinical studies concerning the diagnosis of IP

Author, year, reference, country	Goal	Methodology, level of evidence	Population	Intervention	Endpoint	Results and interpretation
Santa-Maria, 2017, Brazil [14]	Assessment of dental malformations	Cases series GRADE C Level 4	14	Clinical Questionnaire, Dental Exam, Radiography	Dental modifications (frequency, type and location).	Loss of 6 or more teeth in IP patients
Maahs 2014 Brazil [15]	Assessment of cephalometric analyses	Observational, cross-sectional study GRADE C Level 4	9/16	Frontal and lateral radiography	Modification of cephalometric parameters	Smallest LMMD distance measurement for IP patients
Okita 2013 Japan [52]	To describe the clinical forms of IP in Japan	Cases series GRADE C Level 4	10	Multiplex PCR, clinical and histological examinations	Landy's criterion, histopathology in newborns	Histopathological features present in 100% of patients with biopsy
O'Doherty 2011 Ireland [13]	To describe the ocular clinical forms of IP	Cases series GRADE C Level 4	11/19	Ophthalmological assessment, fluorescein angiography	Landy's criterion, Assessment of visual acuity, orthoptic evaluation, anterior segment examination, dilated retinal examination and retinoscopy	Fluorescein angiography is more sensitive than indirect ophthalmoscopy
Hadj-Rabia 2011 France [49]	To describe the clinical forms of IP	Prospective cohort GRADE B Level 2	25	Presentation of an IP clinical case	Expanded Landy's criterion	NA
Fryssira, 2010 Greece [53]	To describe the clinical forms of IP in Greece	Retrospective (1997-2007) GRADE C Level 4	12 women	Histology (biopsy), ocular, dental and neurological examinations	Landy's criterion	NA
Escudero, 2009 Spain [40]	Presentation of a clinical case	Case report GRADE C Level 4	1 case	Use of RETCam (angiography) with IV injection of sodium fluorescein (5 ml / kg)	NA	Angiography is more sensitive than ophthalmoscopy

Author, year, reference, country	Goal	Methodology, level of evidence	Population	Intervention	Endpoint	Results and interpretation
Fraitag 2009 France [54]	To describe and validate the histological forms of adult IP	Cases series GRADE C Level 4	26 Femmes, Stage 4	Skin biopsy (staining: hematoxylin-eosin, Orceine and Masson-Fontana)	Epidermis: epidermal thickness, apoptotic cells, pigmentation and number of melanocytes Dermis: capillary dilatation, pigment incontinence, round eosinophilic bodies, inflammatory cells, fibrosis, elastic fibers and skin indices	Histological assessment is a useful tool to examine moderate clinical forms of IP in adulthood.
Chang 2008 Taiwan [55]	To describe the first cases of IP in Taiwan	Retrospective, Cases series GRADE C Level 4	4	Clinical exams, eosinophil counting, skin biopsy	Landy's criterion	NA
Selvadurai 2008 [56]	To describe corneal abnormalities in IP	Case report GRADE C Level 4	1	Clinical examination, confocal microscopy and anatomo-pathology of the corneal epithelium	NA	Cornea verticillata of IP corresponds to epithelial disease with nuclear degeneration
Bell 2008 USA [57]	Presentation of a clinical case	Case report GRADE C Level 4	1	Trypsin digest	NA	NA
Pascual 2006 Spain [19]	To describe the neurological forms of IP	Prospective familial cohort (1965-2004) GRADE B Level 2	5/12	Neurological follow up	Physical examination, EEG recording, MRI	NA
Phan 2005 Australia [58]	To escribe the clinical forms of IP	Retrospective GRADE C Level 4	53	Clinical examinations	Landy's criterion	NA
Shields 2006 [59]	To describe pigmented epithelium maifestations in IP	Case report			Shields 2006	Describe the occurrence of pigmented epithelium in IP
Kim 2006 Taiwan [60]	To describe the clinical forms and	Retrospective (1995-2005) GRADE C	24	Clinical and biological exams, imaging, questionnaires	Landy's criterion	NA

Author, year, reference, country	Goal	Methodology, level of evidence	Population	Intervention	Endpoint	Results and interpretation
	complications of IP	Level 4				
Hadj-Rabia 2003 France [6]	To describe the different forms of IP	Retrospective (1986-1999) GRADE C Level 4	13/40	Landy's criterion and neuro-imaging	Landy's criterion Cranial ultrasonography, CT scan, MRI	NA
Goldberg 1998 [61]	To describe macular vascular lesions of IP	Retrospective GRADE C Level 4	12 patients	/	/	Multifocal hypo- and / or hyperpigmentations of the retinal pigment epithelium (39% of eyes), retinal vascular non-perfusions (31% of eyes), retinal detachment (8% of eyes).
Goldberg 1993 [62]	To describe the ocular complications of IP	Retrospective GRADE C Level 4	9 eyes of 13 patients	/	/	Stable capillary occlusions (2), progressive capillary occlusions (2), progressive occlusions with reopening / remodeling (3), occlusion of the central artery of the retina (1), tractional detachment of the retina (2).

Table 5 : Clinical studies concerning therapeutic management

Author, year, reference, country	Goal	Methodology, level of evidence	Population	Intervention	Endpoint	Results and interpretation
SKIN TREATMENT						
Kaya 2009 Turkey [34]	Description of the management of cutaneous manifestations of IP in a newborn	Case report GRADE C Level 4	1 newborn	Topical corticosteroid (di fluocortolone valerate 0.1%) and antiseptic (chlorquinaldol 1%) twice a day	Bullo-vesicular stage (disappearance of vesicles)	Disappearance of vesicles after 5 days of treatment
Jessup 2009 USA [35]	Description of cutaneous treatment of a newborn with IP	Case report GRADE C Level 4	1 child	Topical with tacrolimus at 0.1%	Bullo-vesicular stage (disappearance of vesicles)	Regression of the vesicles
Donati, 2009 Italy [11]	Description of the management of a patient with STIP	Case report GRADE C Level 4	1 STIP	Retinoic acid (0.05%) 2 times / day, 6 months (STIP)	Disappearance of the tumor and pain	Decrease of pain at 1 month of treatment, disappearance of clinical manifestations at 6 months
OPHTHALMOLOGICAL TREATMENT						
Batioglu 2010 Turkey [41]	Description of the management of an IP patient with ocular damage	Case report GRADE C Level 4	1 newborn	Laser photocoagulation	Cycloplegic refraction, ophthalmic examination of the retina	No signs of tractional detachment of the retina 1 year after laser treatment
Ranchod, 2010 USA [42]	Description of the management of an IP patient with ocular damage	Case report GRADE C Level 4	1 child (2 years old)	Laser photocoagulation (red diode, 764 impacts)	Ophthalmological examination of the retina	Check-up at 5 months showed complete regression of retinal neovascularization
O'Doherty 2011 Ireland [13]	To describe the ocular clinical forms of IP in Ireland	Cases series GRADE C Level 4	2/11	Laser photocoagulation	Visual acuity assessment, orthoptic assessment, anterior segment examination, dilated retinal examination	Retinopathy progression was halted after treatment, but a detachment occurred a few months later
Escudero	Presentation of a	Case report	1 child (4	Laser photocoagulation	NA	NA

Author, year, reference, country	Goal	Methodology, level of evidence	Population	Intervention	Endpoint	Results and interpretation
2009 Spain [40]	clinical case	GRADE C Level 4	months)	(Diode, 1200 impacts)		
Balaratnasingam 2009 Australia [43]	Presentation of clinical IP cases with retinal lesions	Case report GRADE C Level 4	3	Cryotherapy, laser photocoagulation	Retinal detachment is considered to be a failure of therapeutic management	Positive evolution for 1 case with cryotherapy, 1 failure for photocoagulation and 1 failure without treatment
DeVetten 2007 Canada [44]	Presentation of a clinical case of IP	Case report GRADE C Level 4	1	Laser photocoagulation (diode)	Ophthalmological examination of the retina, visual acuity	After laser treatment, regression of neovascularization was observed within 2 weeks and at 6 months. Acuity at 20/84
Nguyen 2001 USA [45]	Presentation of a clinical case of IP	Case report GRADE C Level 4	1 newborn	Laser photocoagulation (diode)	Ophthalmological examination of the retina	Regression of pathology 2 weeks after treatment, success at 4 months
DENTAL TREATMENT						
Worsaae 2007 Denmark [63]	Cases series	Case report GRADE C Level 4	1/112 cases of oligodontia	Surgical Procedures (Fixed Prosthetic Restoration on Implant)	Surgery complication	Success at the end of treatment (on average 28 months of follow-up)
Domínguez-Reyes A, et al. 2002 Spain [51]	Presentation of a clinical case of IP Discussion on dental treatment	Case report GRADE C Level 4	1 child (3 year-old girl)	/	Odontological complications	Description of the odontological lesions: delays of eruption and dental development + agenesis + conical teeth Proposed dental treatment: prosthesis, in case of loss of vertical dimension due to several tooth losses. If dental migration occurs, complex treatment with rehabilitation Lack of teeth: of great social consequence and must be considered as part of overall patient management. To recommend the practice of preventive, hygiene and dietary measures, to educate the family and the patient. The process of dental eruption and development must be closely monitored, to maintain vertical dimension and obtain the best occlusion.

Author, year, reference, country	Goal	Methodology, level of evidence	Population	Intervention	Endpoint	Results and interpretation
Chen AY, Chen K 2017 Taiwan [17]	Presentation of an IP clinical case and to implement a possible dental treatment protocol to rehabilitate dental function and aesthetics and to maintain the dental health of the IP patient	Case report GRADE C Level 4	1 child (5½ year-old girl)	/	Odontological complications, age	Clinical case, description of odontological damage: 4 temporary teeth missing and several permanent teeth missing. Suggested dental treatment: 1) regular preventive dental treatment every 6 months, 2) preservation of temporary molars that can replace missing premolars, 3) temporary prosthesis possible for mixed or permanent set of teeth, complete rehabilitation of the mouth with orthodontic treatment and implant treatment at adulthood. Discussion: if teeth are missing, the proposed treatment is based on patient age, occlusion, masticatory function, need for remodeling and alignment of teeth and possible aesthetic considerations. -> During growth: Monitoring and management of dental care would be more focused on the aesthetic correction of dental malformations and health. -> After growth: definitive planning of final treatment
Doruk C 2003 Turkey [64]	Presentation of an IP clinical case and dental treatment	Case report GRADE C Level 4	1 girl,16 years old	1) Maxillary expansion, 2) orthodontic treatments then 3) prostheses	Odontological complications	Description of the clinical case, odontological findings: missing teeth, no molar, bad tooth position, transverse maxillary deficit; conical teeth Treatment: maxillary expansion although no molar expansion (all teeth covered because no anchor teeth) and same device used in contention; was followed by fixed orthodontic devices for prosthetic purposes (preparation before prostheses for good tooth position). Orthodontic treatment: better basis for prosthetic procedures.

Author, year, reference, country	Goal	Methodology, level of evidence	Population	Intervention	Endpoint	Results and interpretation
NEUROLOGICAL TREATMENT						
Wolf 2015 Germany [47]	Clinical and neuroradiological description	Case report GRADE C Level 4	1 newborn	High dose corticosteroids (dexamethasone)	Clinical observations: rash and convulsions	Decreased convulsive activity
Tomotaki 2016 Japan [48]	Presentation of an IP clinical case	Case report GRADE C Level 4	1 newborn	Corticotherapy (prednisolone 2mg/Kg/d)	MRI exam, EEG	Cured encephalopathy
Wolf 2005 Germany [21]	Presentation of an IP clinical case	Case report GRADE C Level 4	1	phenobarbital (10 mg/kg), lorazepam (0.1 mg/kg), fosphenytoine (20 mg/kg) dexamethasone then Hydrocortisone	EEG	Cessation of convulsions, socialization

Table 6 : Care pathways

Author, year, country	Recommendations
ORAL AND DENTAL CARE PATHWAY	
Thomas 2016 France [65]	Oral therapeutic management of Incontientia Pigmenti is multidisciplinary and in some cases may bring together dental surgeons (specialized in oral medicine and oral surgery), pediatric odontologists, orthodontists and maxillofacial surgeons
HAS 2010 France [66]	« Implantoprosthetic treatment of adults with multiple dental agenesis related to a rare disease": Technical guide on the management of oligodontia and cleft palate
Santa-Maria, 2017 Brazil [14]	Dental evaluation as soon as possible, with greater attention from the age of 3 years (X-ray examinations and the implementation of multidisciplinary strategies)
OPHTHALMOLOGICAL CARE PATHWAY	
O'Doherty 2011 Ireland [13]	Assessment under general anesthesia as soon as possible. If normal retina, clinical follow-up twice a year. If abnormal retina at birth: fluorescein angiography, then clinical retinal examination every 2 weeks for 3 months, then monthly for 6 months, and then every 3 months for one year.
Bell 2007 USA [57]	Monitoring should be performed throughout life if there is damage to the retina.
Wong, 2004, UK [67]	Annual ophthalmic monitoring throughout childhood.
Holmström 2000 Sweden [68]	Ophthalmic monitoring as soon as possible: monthly up to 3-4 months of life, then every 3 months up to age 1, then twice a year until age 3, then yearly. Possiblity to stop at 3 years if no further complications manifest.
GLOBAL CARE PATHWAY	
Hadj 2003, France [6]	Multidisciplinary follow-up during the first year of life. Neurological follow-up, if neurological or ophthalmological examinations show abnormalities.
Kim 2006 Korea [60]	Close cooperation between dermatologists, pediatricians, neurologists, genetic counselors and dentists is crucial for a better understanding of IP and the prediction of the occurrence of potential abnormalities throughout life.
Morice-Picard 2013 France [2]	Dermatological and neurological examinations: Once a month for 1 year, twice a year until the age of 5 and thereafter according to disease progression. Ophthalmological examinations: Once a month up to 4 months old, every 3 months from 4 months to 1 year of age, twice a year until the age of 3, annually after 3 years old. Targeted complementary examinations: brain MRI if anomaly suspected, X-ray examination in case of skeletal anomalies.

Appendix 3. The Transition

The transition is an intentional, progressive and coordinated process to move the young patient from a pediatric care unit to a department for adults. Broadly speaking, this process allows adolescents and young adults to be prepared to **take charge of their life and health** as adults.

To do this, the transition process must address **the medical, psychosocial and educational** needs of these youths while taking into account the **social, cultural, economic and environmental** aspects in which these adolescents and young adults evolve.

The website "Transition Rare Diseases": https://transitionmaladiesrares.com/ aims to be a tool for information and knowledge sharing on everything related to the transition and transfer of patients with rare and/or chronic diseases.

Families will have access to many relevant topics, such as tools developed by professionals to facilitate the transition, transition programs developed abroad, and research projects underway in reference and specialized centers.

Appendix 4. List of participants

This work was coordinated by Dr. Charles Taieb, FIMARAD under the direction of Prof. Christine Bodemer.

Persons who participated in the development of this PNDS are as follows:

Writers

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French Association of patients

Management of declared interests

All the participants in the development of this PNDS on Incontinentia pigmenti completed a declaration of interest available on the website of the reference center.

The declaration of interest has been analyzed and taken into account, in order to avoid conflicts of interest, in accordance with HAS guidelines "Guide to declarations of interest and management of conflicts of interest" (HAS, 2010).

Appendix 5: Consultation modalities of the multidisciplinary working group

Meetings, visioconference or e-meeting

Number, meeting dates

Date	Meeting type	Participants	Objectives
10/10/2016	Virtual meeting	All	Presentation of the PNDS project by Pr Bodemer
16/10/2016			HAS Letter of Intent
10/11/2016	Meeting	All	Approval of the plan
10/01/2017	Meeting	CT CB	Literature review
21/03/2017	Meeting	CT Patient Asso	To take into account patient opinions
06/04/2017	Meeting	All	First version of literature review
13/05/2017	Meeting	CT CB	Literature review
23/06/2017	Meeting	All	Consolidated version
26/07/2017	Meeting	CT CB	Progress report
17/08/2017	Mail exchange	All	Consolidated version 2
13/11/2017	Meeting reviewing	CT MB	Consolidation
22/11/2017	Meeting	CT CB	State of progress
12/02/2018	Meeting	Ct Cb	Consolidated version 2
15/03/2018	Email Communication	All	Consolidated version 2
24/04/2018	Meeting	Ct Mb	Consolidated version 2
27/04/2018	Meeting Asso Pat	Ct Jm	Consolidated version 2
22/05/2018	Meeting	Ct Cb	Consolidated version 2
06/06/2018	Communication	Ct Fc	Consolidation
28/06/2018	Telephone MEETING	All	Consolidated version 2
15/07/2018	Communication	Ct Mb Cb	Consolidation
18/07/2018	Communication	Ct Cb	Consolidated version 3
20/07/2018	Communication	All	Consolidation
23/07/2018	Meeting	Ct Cb	Finalization of the 1st Part
26/07/2018	Meeting	Ct Cb	Finalization of the 2nd Part
30/07/2018	Communication	Ct Jm	Progress report
11/08/2018	Review by email	All	Progress report
13/08/2018	Review	CT JS	Finalization GENETICS
28/08/2018	Review	CT CB	Progress report
03/09/2018	Review	JM CT	Finalization PATIENTS
11/09/2018	Review	All	Consolidation
23/10/2018	Review	All	Final proofreading
16/11/2018	Review	All	INTRODUCTION
05/12/2019	Review	MG	Final proofreading
05/02/2019	Review	Neo Nat	Final proofreading
11/02/2019	Review	CB	Proofreading
24/02/2019	Consolidation	CB CT	Consolidation

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Appendix 7: For the attention of healthcare professionals

The authors would like to bring the following points to the attention of healthcare professionals:

- It is imperative when the patient is a young girl, to discuss the diagnosis of incontinentia pigmenti (IP) as soon as possible, upon observation of vesicular-pustular lesions that are crusty, predominantly acrale and of linear disposition (or of a similar tendancy).
- IP may occur in boys in rare cases, although it is usually lethal in the male fetus.
- That the diagnosis of IP is an urgent matter, necessitating an ophthalmological examination without delay. These cutaneous lesions will also allow an anticipation of possible neurological abnormalities.
- That IP diagnosis is based mainly on clinical criteria and genetic screening.
- In the absence of a family history, the presence of only one of the following major criteria is sufficient to confirm an IP diagnosis,
    - Typical neonatal rash with erythema and vesicles
    - Hypereosinophilia
    - Typical hyperpigmentation tracing Blaschko's lines and fading during adolescence
    - Linear alopecic and atrophic lesions, often on limbs
    - Indicative cutaneous histology