Incontinentia pigmenti*

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Abstract: Incontinentia pigmenti is a rare genodermatosis in which the skin involvement occurs in all patients. Additionally, other ectodermal tissues may be affected, such as the central nervous system, eyes, hair, nails and teeth. The disease has a X-linked dominant inheritance pattern and is usually lethal to male fetuses. The dermatological findings occur in four successive phases, following the lines of Blaschko: First phase - vesicles on an erythematous base; second phase - verrucous hyperkeratotic lesions; third phase - hyperchromic spots and fourth phase - hypochromic atrophic lesions.
Keywords: Genetic diseases, X-Linked; Incontinentia pigmenti; Pigmentation disorders

INCONTINENTIA PIGMENTI

Incontinentia pigmenti (IP) or Bloch-Sulzberger syndrome (MIM 308310) is a rare, X-linked dominant inherited genodermatosis, usually lethal in males even in the prenatal period.[1] IP is caused by mutations in the *NEMO* gene (*IKK-gamma*), located in Xq28 locus. The NEMO protein is one subunit of a complex multi-protein kinase which is crucial for the activation of the transcription factor NF-kappa B, essential in the regulation of inflammatory immune and apoptotic pathways.[1-3]

Most cases of IP are caused by mutations in NEMO, and new genomic rearrangements are responsible for 80% of the new mutations.[1] In 80% of the cases there is a deletion of exons 4 to 10 on the NEMO gene.[1,3,4,5] In addition, point mutations, such as nonsense mutations and those with change in direction can be found in exons 2 to 10. Also described are insertions and deletions, some of them leading to a shift in the reading frame.[6,7] As a result, activation of NF-kappa-B is defective in IP cells. The presence of one mutation in NEMO causes an alteration in

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cytokine production, markedly during the first year of life, which may explain the inflammatory manifestations in skin morphology.[8]

The IP penetrance is 100%, but its expression is highly variable even within families.[9] Cells expressing the mutated X-chromosome are selectively eliminated around the time of birth.[1,9] The majority of affected women present a nonrandom (skewed) X-chromosome inactivation in peripheral blood leukocytes and fibroblasts. In 98% of these women a skewed model of X-chromosome inactivation can be observed, whereas in the normal population only 10% present skewed inactivation.[9]

Among men, IP is classically considered lethal. However, in some men a karyotype 47, XXY and the skewed inactivation of X-chromosome provide protection against the morbid effects of the mutation.[4,10] Furthermore, the presence of mosaicism or less deleterious mutations in NEMO may allow some men to survive.[4,10]

CUTANEOUS MANIFESTATIONS

Cutaneous findings are indicative of the disease and usually appear following a chronological sequence, characterized by a progression through four distinct stages, although some of them may temporarily overlap or not even develop in some patients.[6]

Stage 1, known as inflammatory or vesicular stage, is characterized by the development of papules, vesicles and pustules on an erythematous base, distributed linearly along the lines of Blaschko (Figure 1). These vesicles may vary in size from 1 mm to 1 cm or more and pustules may also occur. This phase can be confused with herpes simplex or impetigo.[11] Lesions are mainly seen on the extremities, but may also occur on the trunk, head and neck. The vesicular stage occurs in 90-95% of patients. In most patients (> 90%) lesions are present at birth or develop during the first two weeks of life and then disappear by 4 months of age.[12] In some cases, they may appear after the first year of life or still during the intrauterine period.[13] Self-limited episodes of recurrent vesicular lesions are observed even in older children, in association with an acute febrile illness.[12,14]

Stage 2, also known as verrucous stage, is characterized by plaques and warty papules linearly arranged over an erythematous base, also following the lines of Blaschko (Figure 2). In general, the lesions develop on the extremities and trunk, but can also be seen on the head and neck. Its location may or may not correspond to the previous distribution of inflammation during stage 1. The occurrence of warty lesions is reported in 70% of cases. In most patients, they develop within two to six weeks and usually disappear by six months of age.[6] Occasionally, warty lesions persist into adulthood or appear later during the disease process, in the form of linear verrucous striae with a predilection for palms and soles.

Stage 3 or hyperpigmented stage is defined by the development of linear or whorled lesions, with a brownish pigmentation, which may be accompanied by atrophy (Figure 3). This stage occurs in 90-98% of patients with IP. The most common distribution of these lesions involves the trunk and extremities, but they may also be present in the skin folds on the head and neck areas. Nipples, axillae and groin can also be frequently affected by hyperpigmentation. The location of these lesions does not always correlate with areas of prior cutaneous involvement during earlier stages. This suggests that hyperpigmentation could be independent of the inflammatory process. These lesions usually develop during the first months of life and slowly disappear during adolescence. However, areas of hyperpigmentation may persist in some patients until about forty years of age, especially in the axillae and groin.[15]

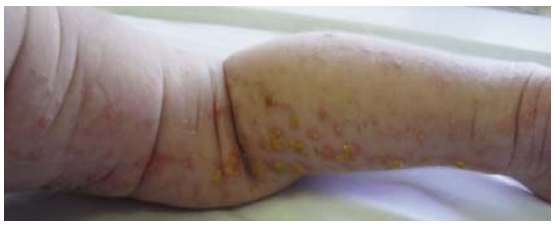

Figure 1: Stage 1: vesicopustules, following the lines of Blaschko

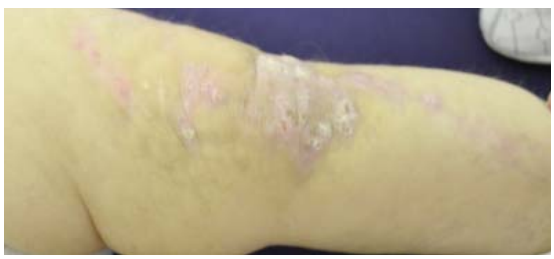

Figure 2: Stage 2: Linear verrucous plaque, following the lines of Blaschko

Figure 3: Stage 3: Hyperchromic and atrophic spots, following the lines of Blaschko

Stage 4, known as atrophic or hypopigmented, is characterized by areas of hypopigmentation, atrophy and absence of hair, most frequently observed on the lower extremities (Figure 4). These lesions usually develop during adolescence, persist into adulthood and may be permanent. They are observed in 30% to 75% of patients with IP. However, due to the subtlety of atrophic lesions, it appears that this phase may have been underreported in the past and therefore may occur in most patients with IP.[16-18]

Histopathological findings change according to the phase in which the lesions are. In the first phase, intraepidermal spongiosis with eosinophilic, neutrophilic and rarely basophilic inflammatory infiltration may be observed. Large dyskeratotic cells are usually present. The verrucous stage presents acanthosis, hyperkeratosis and papillomatosis. Eosinophils can be seen eventually. Stage 3 shows prominent pigmentary incontinence. The atrophic phase is characterized by absence of pigment in the epidermis and lack of eccrine glands.[17,18]

The hair may also be affected in IP, with changes reported in 28% to 38% of patients. Scarring alopecia, usually on the vertex, is the most common manifestation of hair involvement (Figure 5). The absence or hypoplasia of eyebrows and eyelashes may also occur. In addition, the hair can be sparse in infancy and later have a dull appearance and brittleness.[18]

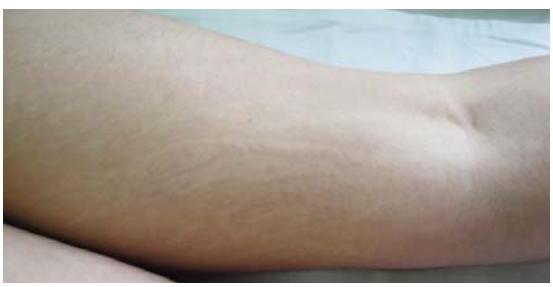

Figure 4: Atrophic and hypochromic lesions, following the lines of Blaschko

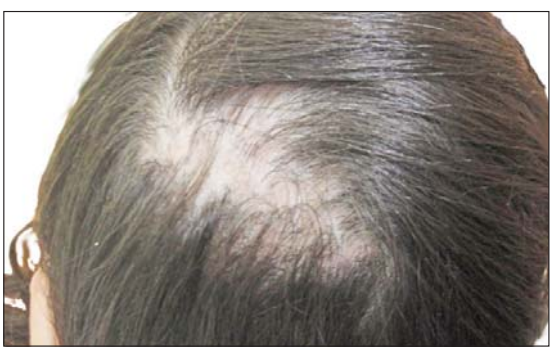

Figure 5: Area of scarring alopecia on the vertex of the scalp

Ungual alterations can affect all nails of the hands and feet or just a particular nail, and its estimated prevalence is 40%. Koilonychia and yellowish pigmentation of the nails may occur. Nail dystrophy can vary from fragile and brittle nails, with longitudinal or transverse slits up to hyperkeratosis and onycholysis. Rarely, in mild cases, nail changes may be the only manifestation of IP. Periungual and subungual keratotic tumors, associated with pain, bone deformities and lytic lesions involving the underlying phalanges may also be seen, usually in older children and adults.[19] The fingernails are more commonly affected.[18]

Landy and Donnai proposed the diagnostic criteria for IP in 1993.[20] These criteria were divided into 2 groups: one group with negative family history and another with positive family history in a first-degree relative.

In the absence of familial history, the presence of at least one major criterion * is required while the presence of minor criteria ** supports the diagnosis of IP. On account of their high incidence, the complete absence of minor criteria leads to uncertainty in diagnosis (Chart 1).

In the case of positive family history, the presence of any criterion *** strongly supports the diagnosis of IP (Chart 2).

Treatment

IP vesicopustular lesions often cause concern and because they appear in the neonatal period, other dermatoses with greater morbidity should be excluded, such as impetigo, neonatal congenital bullous dermatoses and autoimmune blistering. Cutaneous manifestations of IP do not require specific treatment, since spontaneous resolution of the lesions usually occurs. The use of topical and systemic antibiotics for vesicular lesions is not recommended.[15] The study by Kaya et al, 2009, relates rapid improvement in IP inflammatory lesions with the use of a combination of topical steroids: diflucortolone valerate/chlorquinaldol. Additional research is needed to clarify the therapeutic potential of topical corticosteroids in IP inflammatory lesions.[21]

OPHTHALMOLOGIC FINDINGS

Although ocular manifestations in Incontinentia pigmenti Syndrome are not the most common, they are often highly debilitating. Unlike dermatological symptoms, which are attenuated over the years, ocular involvement persists through the patients' lifetime, affecting their quality of life.[22]

Eye involvement occurs at a frequency of 35 to 77% on the studied populations.[22-24] In most cases, the condition is unilateral, when bilateral, one eye is less affected than the other.[25,26] Ocular abnormalities are usually associated with neurological involvement.[6,20,27]

Chart 1: Diagnostic Criteria for IP in the absence of familial history (Landy e Donnai, 1993)

*** Major criteria:**

- Typical neonatal vesicular rash (erythema, vesicles, eosinophilia)
- Typical hyperpigmentation (especially on the trunk, following the lines of Blaschko, disappearing in adolescence)
- Linear atrophic alopecic lesions

****Minor Criteria:**

- Dental abnormalities
- Alopecia
- Wooly hair, nail abnormalities
- Retinal disorders

Chart 2: Diagnostic criteria for IP in the presence of familial history (Landy e Donnai, 1993)

*****Criteria:**

- Suggestive history or evidence of typical rash
- Cutaneous manifestations of IP: hyperpigmentation, scaring lesions, atrophic lesions, and linear atrophic lesions with absence of hair, alopecia on the vertex
- Dental abnormalities
- Wooly hair
- Retinal disorders
- Multiple abortions of male fetuses

The prevalence of unilateral or bilateral blindness has been reported between 7%[22] and 23%.[23] The most characteristic and most serious injuries are the retinal ones, affecting the vascularization developing during the first months of life and the retinal pigment epithelium (RPE).[28]

Changes observed in the retina are usually secondary to retinal ischemia, and its subsequent events: proliferation of new blood vessels (with or without bleeding), exudation, pre-retinal gliosis and tractional retinal detachment.[18] The process can be self-limited, stopping at any stage, and leaving retinal sequelae, for example - avascular areas, vascular tortuosity, exudates, vitreous hemorrhage, pre-retinal fibrosis, changes in RPE pigmentation, retrolental mass and retinal detachment.[29,30]

The most typical ophthalmologic IP alteration is the presence of a retrolental mass along with retinal detachment or dysplastic retina. This change was found in 11.5% of cases, being called by several names, such as: pseudoglioma or retrolental fibroplasia.[25,31,32] A variety of funduscopic alterations including foveal hypoplasia, macular transverse abnormal vessels, coloboma and optic nerve atrophy may also occur (Figure 6).

Among the non-retinal findings, the most common are cataracts and strabismus (Figure 7). Retinal pathology has been implicated as the most likely cause of strabismus.[23] Other changes such as ptosis, microphthalmia, blue sclera, conjunctival pigmentation, corneal alterations, iris hypoplasia, uveitis, ocular globe atrophy, nystagmus and myopia have also been reported.[22,25,29]

The natural history and ophthalmic pathogenesis of this syndrome are poorly understood. It is believed that changes in retinal vasculature and in RPE are involved in the cascade of pathological events affecting the retina.[33] The ischemic process and subsequent angiogenic response are slightly similar to those of prematurity retinopathy.[34]

Due to the severity of lesions, a screening program is imperative for children with diagnosis of IP, allowing the early detection and therapeutic intervention. If untreated, these lesions may progress to retinal detachment and subsequent blindness.

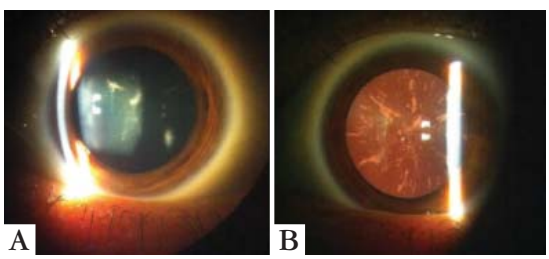

Figure 6: Anterior segment biomicroscopy showing diffuse cortical lens opacities (cataracts) in a 32 years-old patient. View by direct illumination **(a)** and retro-illumination **(b)**

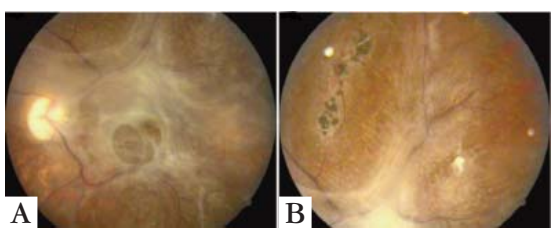

Figure 7: Fundoscopy showing (a) extensive formation of fibrous tissue at the posterior pole with flat retinal detachment and alterations in the vascular path. Vascular attenuation is seen with arterial narrowing. Pallor of the papilla, and (b) alterations of the retinal pigment epithelium. There is a diffuse mottled aspect, caused by clusters of rarefied pigments. Above the papilla, there is an area of retinal pigment hypertrophy

Treatment

Several studies have reported the benefits of laser photocoagulation or cryotherapy in ischemic regions of the retina in order to stop the progression of vasculopathy.[35,36] On the other hand, at the stage of retinal detachment, surgery is rarely successful.

The schedule of tests recommended in the literature for these patients is as follows: a pediatric ophthalmologist or a retina specialist should examine patients with a diagnosis of IP at birth and then at least monthly for the first three to four months. After this period, exams are recommended at quarterly intervals up to one year and every six months up to age three.[23] In the presence of ocular alterations the frequency of consults should be increased.

Visual prognosis is usually good for a child with no ophthalmologic findings in the first year of life.[29,37]

However, when retinal disorders are present, they can slowly or rapidly progress to retinal detachment and blindness.[30,38]

Non-retinal manifestations, such as strabismus, for example, may occur later on, typically before the age of two.[23]

NEUROLOGIC FINDINGS

Although not present in Donnai and Landy's clinical criteria, central nervous system disorders in patients with IP can have a major impact on quality of life. In general, the prevalence of CNS symptoms is approximately 30%.[22] It has been hypothesized that there is a correlation between the severity of ophthalmologic findings and the neurological phenotype.[39]

Neurological manifestations associated with IP are varied, ranging from a single episode of seizure to psychomotor retardation, intellectual impairment, hemiplegia, epilepsy, cerebellar ataxia, microcephaly, neonatal encephalopathy, encephalitis and neonatal and childhood stroke.

In 1976, Carney analyzed 653 patients clinically diagnosed with IP. In 142 of the 465 cases with sufficient information on neurological status, central nervous system (CNS) involvement was present in 30.5%.[22] Donnai and Landy (1993) questioned this figure, suggesting the occurrence of diagnostic errors, with the inclusion of cases of hypomelanosis of Ito. From their experience in an analysis of over 100 patients, they found an overall incidence of physical or intellectual disability lower than 10%, with a higher incidence of intellectual disability in sporadic cases (15%) compared with familial cases (3%).[20] Hadj-Rabia et al. conducted a clinical study in 40 patients with IP according to Donnai and Landy criteria. In 13 of 40 patients (32.5%), there was CNS involvement. Seizures were present in 10 of 13 patients with neurological deficits, and two patients died due to cerebrovascular accidents. Delayed psychomotor retardation was found in seven of 13 patients, three had intellectual disabilities and two presented spastic hemiplegia.[18]

The initial clinical neurological manifestation is reported by many authors as "pseudo encephalitis" with acute neurological symptoms, sometimes associated with a state of coma and apnea, simulating encephalitis. Cerebral necrosis and multiple infarctions were reported.[40-42]

Ischemic cerebrovascular accidents (CVA) seem to be the basis of neurological manifestation in the neonatal period. In five of seven cases with documented ischemic stroke, the onset of the disease occurred in the first week of life.[43-46] One patient developed recurrent ischemia, at five days, 10 days and three months of age.[43] The other two cases of ischemic CVA occurred at respectively two months and four years of age.[47,48] The infarcts affected the subcortical and deep white matter in 4 cases.[43-45] In three patients, the ischemic stroke affected the large cerebral arteries (middle cerebral artery, anterior cerebral artery) and, in one, it also affected the left cerebellar hemisphere.[46-48] Despite the sporadic description of large artery occlusion, microvascular occlusion appears to be an important pathogenic mechanism. A critical analysis of the available data suggests that the disease affects mainly small and medium caliber arteries in the newborn brain.

The most prevalent neurological symptoms are seizures, present in 13% to 25% of patients with IP. An analysis of 18 separate studies about IP with CNS involvement showed that 37 of 44 patients had seizures; on 35 of these patients there was information about the age of onset.[40,41,43-54] The onset of seizures ranged from 12 hours postpartum to 10 years of age. However, in the majority of cases (23 patients), seizures occurred within the first week of life. The most frequent seizures were of the focal clonic type (present in 22 of 29 cases detailing the type of crisis). Complex partial or generalized seizures have also been reported. Epileptic seizures may be single or recurrent. In three children with early-onset seizures (second and third day of life), the diagnosis of hypsarrhythmia in the EEG or the clinical diagnosis of West syndrome was made. In only 11 out of 25 cases, recurrence of seizures has been reported. The remaining 14 cases had only one episode of convulsions. EEG recording was documented in 25 of 37 patients with epilepsy. EEG patterns, however, are not specific and may reflect various types of brain damage. The results of brain imaging were documented in 37 patients with seizures, and in 36 cases the images showed abnormalities compatible with various degrees of vascular insufficiency caused by ischemia or necrosis. In one patient, the brain was reported as normal on MRI.[45] It may be concluded that, in most cases, seizures are

expressions of brain damage, usually present in childhood, in most affected patients. In a recent systematic review, the most frequent CNS disorders besides seizures, are motor deficits, mental retardation and microcephaly.[55]

In patients with seizures, radiological findings are compatible with vascular insufficiency and include the following anomalies: periventricular leukomalacia, specific gliotic changes, cavitation, damage in the basal ganglia and diffuse hemorrhagic necrosis.[40,41,42,45,53,55-62]

The brain imaging of patients with neurologic injuries were reviewed:

- White matter and corpus callosum abnormalities and cerebral atrophy:

The white substance appears to be especially vulnerable in IP patients. White matter anomalies were identified in 27 of 43 patients for whom MRI data were recorded.[40-45,49,53-56,58-60,62-64] The most common alteration is periventricular leukomalacia, but changes in subcortical white matter are also frequently found. In one patient, a small lesion was detected in the semi-oval center, without any corresponding clinical abnormality.[64] In some patients, changes in the white matter lead to cyst or cavity formation.[40,57,58,64] We also observed an increase in the incidence of Virchow Robin spaces, delayed myelination, ventricular dilatation, cerebral atrophy and hypoplasia of the corpus callosum.[40,42,45,51,53,54,58,59,60,63,65,66]

- Cerebral hemorrhage: hemorrhagic components were seen in 8 patients, probably secondary to ischemic events. Encephalomalacia with bilateral hemorrhagic necrosis and generalized tissue destruction was observed in five patients.[42,49,54,56,67] Subtle hemorrhagic infarction of the periventricular white matter microvasculature is also described.[41]

- Cerebellar abnormalities: only one of the reported patients presented atrophy of cerebellar hemispheres.[46]

- Cortical malformation: in one of the patients, polymicrogyria in the perisylvian region was observed along with cortical dysplasia seen in an MRI during the first week of life.[68]

Treatment

There is no specific treatment for IP's neurological symptoms. The treatment of seizures is only symptomatic.

Treatment of seizures in newborns is usually done with phenobarbital. If necessary, a benzodiazepine may be added, except in premature infants with birth weight lower than 1800 g. In refractory cases, lidocaine continuous infusion may be employed.[69] The use of antiplatelet drugs in a patient with IP did not decrease the episodes of recurrent CVA.[42] The administration of corticosteroids in one patient with acute disseminated encephalomyelitis resulted in clinical improvement.[65] Spontaneous improvement of epilepsy is customary.

DENTAL FINDINGS

Some alterations of the stomatognathic system (SS) in IP patients, presented as case reports, were found in the literature.[70-74] This system is one of the most complex anatomical and functional units of the human body, consisting of almost all the craniocervical region. Its conjoint or isolated actions are responsible for chewing, speaking, swallowing, breathing, taste and head and neck posture. Among its basic components are the cranial and facial bones, teeth and their supporting elements, the temporomandibular joint (TMJ) and masticatory and facial muscles.[75] Dentofacial deformities are stomatognathic disorders associated with IP described in the literature.[70] This makes the study of patients with this disease very important for orthodontics because IP is a congenital etiologic factor of malocclusion.[76]

Among the reported skeletal problems are: transverse maxillary deficiency associated with oligodontia in the maxilla and mandible, prominent chin on clinical examination and facial asymmetry, such as facial hemiatrophy and hemifacial hypoplasia.[71,72,74,76,77]

Amongst dental problems, missing teeth, conoid teeth, additional cusps in posterior teeth and delayed tooth eruption may be cited, with the lack of teeth being the most frequently found abnormality.[78] Dental anomalies affect both the primary as well as the permanent dentition, though the latter is usually more affected (Figures 8 and 9). Additionally, there may be poor dental positioning and loss of the vertical occlusion dimension, associated with the lack of teeth, disruption of dental enamel formation, and cavities.[71,79,80] Some reports suggest that abnormalities found in maternal dentition can act as a sensitive indicator of the nature of problems expected in the offspring.[81]

Dental features in IP may be mistaken for other diseases such as congenital syphilis or ectodermal dysplasia. Although there are subtle differences in tooth morphology distinguishing these disorders, cutaneous lesions associated with systemic manifestations and laboratory findings are useful to establish the correct diagnosis.[81] Other changes, such as high-arched palate, soft palate hypoplasia, cleft palate and cleft lip are also present in many of these individuals,[7,79] as are swallowing and voice disorders, also common in patients with genetic syndromes.[82]

Therefore, there is an evident need for dental assessment along with attention to other areas, to be able to get a proper diagnosis and treatment, in order to ensure a better quality of life for patients with IP.

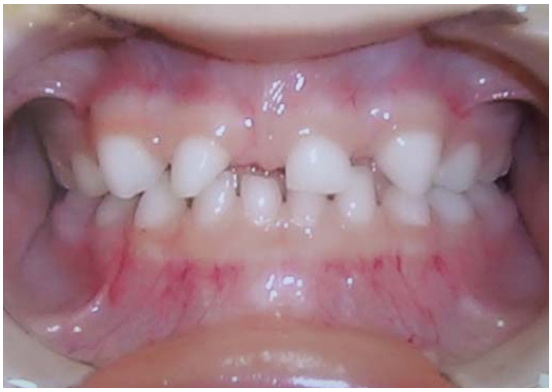

Figure 8: Deciduous dentition with increased overbite, cone-shaped maxillary right central incisor, malformed lower anterior teeth and dental agenesis

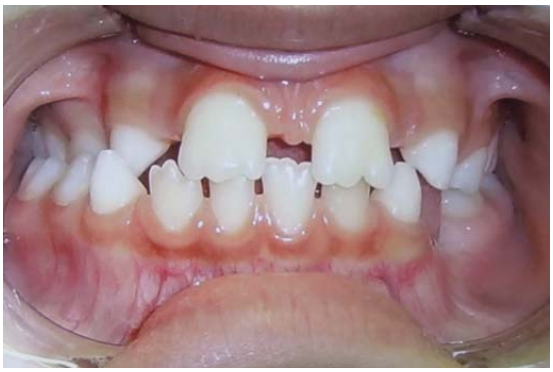

Figure 9: Mixed dentition with atresic maxilla, posterior crossbite on the right side, presence of irregularities on incisal margins of upper and inferior incisors and dental agenesis

OTHER ABNORMALITIES

Other findings have been reported in patients with IP. Breast abnormalities may occur in 1% of affected patients and include supernumerary nipples, hypoplastic nipples, breast hypoplasia and abnormal nipple pigmentation. Skeletal deformities affect up to 20% of patients and include scoliosis, hemivertebra, spina bifida, syndactyly, ear defects, and increased number of ribs, chondrodystrophy, clubfoot, short stature and dwarfism.[18] Oral anomalies include ogival palate, soft palate hypoplasia, cleft palate and cleft lip.[83] More rarely, cardiac malformations can occur as ventricular endomyocardial fibrosis, tricuspid insufficiency and pulmonary hypertension.[68]

Eosinophilia (as high as 65%) in the blood count may be present in up to 88% of patients with IP. In the study of Hadj-Rabia, 23 of 26 patients had eosinophil levels between 550/µL and 15400/µL.[18]

SPEECH THERAPY CONTRIBUTION IN THE ASSISTANCE OF IP PATIENTS

Patients with IP, as described above, may present dental abnormalities, oral malformations, CNS alterations, delayed neuro-psychomotor development and hearing loss. All of these conditions are directly related to the development of speech, language, hearing and swallowing functions. In general, these findings persist throughout the patient's life. Therefore, speech therapy has an important contribution at the time of the diagnosis and management of patients with IP.[6,7,17,18]

Speech and language disorders in patients with IP, as well as their impact on the future development of children affected by this syndrome have not been described in details yet. It is however assumed that, interference with the development of speech, chewing, craniofacial growth, coordination of the swallowing process and language development may occur on a large scale in this group of patients.[84]

In particular, children with IP may even have difficulties in the development of learning skills such as reading and writing, since cognitive, auditory and neurological disorders may occur.[18,84]

After this review, it becomes clear that IP is a multisystem syndrome in which a multidisciplinary approach is very important. There is no doubt that the cutaneous manifestations are characteristic and definitive for the diagnosis and, therefore, should be known to all dermatologists.[85] During routine outpatient visits, identification of possible interfaces with genetics, dermatology, ophthalmology, neurology and dentistry generates a multidisciplinary, comprehensive and better quality care for patients with IP. ❑

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QUESTIONS

1. Most cases of incontinentia pigmenti are caused by wich type of mutation?
a) Small insertions on NEMO gene
b) Point mutations throughout NEMO gene
c) Large deletions on NEMO gene
d) Mutations on the promotion region of NEMO gene

2. On the inheritance pattern of pigmentary incontinence, it is incorrect to state that:
a) Women are more often affected, since the pattern of inheritance is X-linked dominant
b) The disease is usually lethal in males.
c) There is no difference in the expression of the disease when men and women are compared.
d) The penetrance of the disease is 100%

3. The survival of some men with pigmentary incontinence can be explained by:
a) Mosaicism in men 47, XXY
b) Protection by the non-expression of the mutated gene in men 46, XY
c) Non-penetrance of the disease in men
d) Non-random inactivation of the X

4. About the function of the protein encoded by NEMO gene, it can be stated that:
a) Increased expression of NEMO is responsible for the presence of the observed clinical phenotype
b) It is a subunit of a complex multi-protein kinase, which is essential for the activation of the transcription factor NF-kappa B in response to a variety of stimuli, including proinflammatory cytokines
c) The presence of NEMO mutations leads to changes in cytokine production after the onset of puberty
d) The alteration NEMO expression and hence the non-activation of NF-kappa-B is not associated with inflammatory manifestations in the morphology of the skin

5. Cutaneous involvement in IP occurs in four stages. In chronological order, the names of the stages are:
a) Vesicular, atrophic, hyperpigmented, verrucous
b) Verrucous, vesicular, atrophic, hyperpigmented
c) Atrophic, hyperpigmented, vesicular, verrucous
d) Vesicular, verrucous, hyperpigmented, atrophic

6. IP skin lesions usually occur on:
a) The lines of Blaschko
b) Areas of trauma
c) In mucosae
d) On knees and elbows

7. The following symptoms may occur in the IP, except:
a) Onychodystrophy
b) Alopecia on the vertex
c) Ichthyosis
d) Brittle and dull hair

8. Which skin lesions can occur in adults with IP?
a) Linear hypertrophic plaques
b) Linear hypopigmented macules
c) Hyperpigmented macules
d) Hypochromic spots with altered sensitivity

9. The prevalence of neurological involvement in IP is about:
a) 5%
b) 30%
c) 50%
d) 95%

10. The most common neurologic manifestation is:
a) Seizure
b) CNS tumor
c) Intracranial hypertension
d) Brain atrophy

11. The severity of neurologic symptoms in IP relates to the degree of which involvement?
a) Ophthalmological
b) Dental
c) Dermatological
d) Hematologic

12. In IP, the following neurologic findings may be present, except:
a) Microcephaly
b) Bulging fontanelle
c) Hypoplasia of the corpus callosum
d) Mental retardation

13. Regarding the ophthalmologic involvement in Incontinentia Pigmenti Syndrome it can be affirmed that:
a) It is usually severe and disappears over the years
b) It usually occurs bilaterally
c) It is usually associated with neurological disorders
d) It occurs in up to 15% of the cases

14. Among the conditions below, which is not related to IP?
a) Retinal detachment
b) Strabismus
c) Cataract
d) Iris cyst

15. The physiopathological process that determines ocular manifestations in Bloch Sulzberger syndrome is still poorly elucidated. However, some observations about it are described:
I) The ischemic process and the angiogenic response are similar to those of prematurity retinopathy
II) Strabismus is usually secondary to retinal pathology
III) Retinal detachment is secondary to the presence of transverse vessels in the macula
According to the statements above, it can be said that:
a) I and II are correct
b) II and III are correct
c) I and III are correct
d) All are correct

16. In a 30 days-old patient diagnosed with Incontinentia Pigmenti, it is recommended:
I) Ophthalmological examination as soon as possible
II) Ophthalmologic examinations monthly until about 4 months
III) Ophthalmologic examinations with six-month intervals until one year old
Among the statements above it is correct to say that:
a) I and III are correct
b) II and III are correct
c) I and II are correct
d) All are correct

17. Regarding ophthalmologic treatment and visual prognosis in patients with IP, we cannot affirm that:

a) Laser photocoagulation or cryotherapy have shown satisfactory results
b) Retinal detachment surgery has good results.
c) Visual prognosis is usually good for a child with no ophthalmologic findings up to 1 year of age
d) Treatment, when necessary, should be instituted early

18. The following may be skeletal problems of the stomatognathic system, associated with Incontinentia Pigmenti syndrome:

a) Transverse maxillary atresia associated with oligodontia in the maxilla and mandible
b) Alternatives a and c are correct
c) Facial asymmetry as hemifacial hypoplasia
d) None of the alternatives are corrects

19. Select the wrong alternative. The following are dental problems commonly associated with Incontinentia Pigmenti syndrome:

a) Missing teeth
b) Conoid teeth
c) Giant anterior teeth
d) Delayed tooth eruption

20. Because of its dental characteristics, Incontinentia Pigmenti syndrome can be confused with other congenital diseases. Among these are:

a) Syphilis
b) Mandibular Congenital Dysplasia
c) Ectodermal Dysplasia
d) Alternatives a and c are correct

Answer key

Patch test. An Bras Dermatol. 2013;88(6):863-78.

1) D	6) C	11) D	16) D
2) D	7) B	12) B	17) D
3) A	8) A	13) C	18) B
4) D	9) A	14) D	19) B
5) C	10) C	15) B	20) A

Papers

Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.