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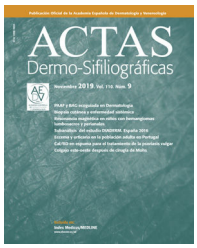

RESIDENT'S FORUM

[Translated article] RF – Diagnosis and Management of Incontinentia Pigmenti: An Update

FR – Actualización en el diagnóstico y manejo de la incontinentia pigmenti

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Incontinentia pigmenti (IP) is a multisystem ectodermal dysplasia, with an X-linked dominant inheritance pattern, although up to 75% of cases occur de novo. Given its inheritance pattern, it predominantly affects girls: in males the mutation is usually lethal in utero. Knowledge of the natural history and management of this disease requires an understanding of 2 key concepts: first, the pathogenic mutation, which occurs in the *IKBKG* gene (formerly *NEMO*), increases cell sensitivity to apoptosis mediators; and second, a phenomenon of progressive selective inactivation of the mutated X chromosome (not random, in contrast to Lyon phenomenon) begins in the intrauterine phase and normally results in inactivation of 100% of mutated X chromosomes by early ages. The genotypic and phenotypic variability is due to the fact that at the moment of diagnosis it is not possible to determine the extent of X chromosome inactivation (and therefore how many vulnerable cells persist). It has been postulated that the stress of childbirth, microbial colonization of the skin and digestive tract at birth, and other factors may trigger the release of pro-apoptotic mediators that target these vulnerable cells, resulting in a neonatal clinical presentation with the typical skin lesions, which are of great diagnostic value. Ocular and neurological involvement are less frequent than dermatological lesions, but of greater importance given the potential severity of sequelae, and are sometimes already present in neonates. It is therefore essential to recognize the clinical signs of the disease as soon as possible in order to establish early treatment and prevent serious sequelae (blindness, paralysis, cognitive deficits, and others).[1,2]

European IP experts recently reviewed the diagnostic criteria and practical management of IP and published a series of consensus recommendations.[3] Diagnostic criteria have been revised 3 times since IP was first described by

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Table 1 Update of Diagnostic Criteria for Incontinentia Pigmenti Proposed by Bodemer et al.

Major criteria	Minor criteria
- Neonatal erythematous, vesicular rash with Blaschkoid distribution (stage 1) - Verrucous papules or plaques with Blaschkoid distribution (stage 2) - Typical hyperpigmentation that fades in adolescence with a Blaschkoid distribution (stage 3) - Linear atrophic lesions with loss of cutaneous adnexa on the extremities with Blaschkoid distribution, or cicatricial alopecia on the vertex (stages 3 and 4) - Dental abnormalities: tooth agenesis (hypodontia or oligodontia), morphological abnormalities (peg incisors, conical teeth, altered molar cusp pattern), and late eruption - Common genomic rearrangement in *IKBKG* (deletion of exons 4–10)	- Eosinophilia (cutaneous stage 1) - Hair: alopecia or wooly hair - Nails: punctate depressions, onychogryphosis - Breast involvement (hypoplasia, asymmetry, hypogalactia) and/or nipple involvement (inverted nipple, supernumerary nipples, difficulty breastfeeding) - Characteristic histology (skin lesions) - Retina: peripheral neovascularization

Table 2 Summary of the Multidisciplinary Management of Incontinentia Pigmenti Patients Proposed by Bodemer et al.

Dermatology	- Quarterly evaluation during first year - Annual evaluation up to 5 y - Subsequent evaluation according to clinical signs - Annual visit to reference center, with multidisciplinary evaluation if necessary, until adulthood - Increased frequency of visits in case of sustained and extensive inflammatory lesions, or disabling verrucous lesions
Ophthalmology	At moment of diagnosis: - Clinical examination of the peripheral retina - In cases of peripheral vascular disease: examination under general anesthesia, argon laser treatment During follow up: - In cases of early laser treatment: clinical examination on days 15, 30, 45, 60, and 90 post-treatment. Subsequent follow-up as in patients without retinopathy - In untreated patients: clinical examination at age 1, 2, 3, 6, 12, 18, and 24 mo - Yearly examination thereafter, for life
Neurology	At moment of diagnosis: - Neurological clinical examination → 2 scenarios: ○ No neurological manifestations at birth: ■ Neurocognitive evaluation at 9 and 24 mo ■ Brain MRI at 2.5 y ○ Neurological manifestations present at birth: EEG: in neonatal period, at 4 and 24 months Brain MRI: during neonatal period and at 2.5 y During follow-up: - Regular neurological and EEG follow-up at least every 6 mo during the first 3 y - Neurocognitive assessment at 5 y of age, before starting school. According to clinical presentation: ○ Neuropsychological evaluation ○ Evaluation of psychomotor capacity, speech, and orthoptic status, and assessment of need for occupational therapy ○ Detailed assessment of memory, executive function, attention, spatial and visual skills, praxis, language (oral and written), math skills, social skills - Rehabilitation with physiotherapy, psychomotor therapy, and speech therapy, if necessary - Psychological management
Odontology	- At 2–3 y: clinical examination of the oral cavity - Subsequent examinations every 2–3 y Assessment of need for early prosthetic treatment in case of inability to eat or speak properly - Consider definitive prosthetic treatment once teeth have stopped growing (from age 12 y) - In adulthood, if necessary: multidisciplinary evaluation by periodontists, implantologists, orthodontists, and specialists in dentofacial orthopedics
Other	Management dictated by other specialists in case of rare anomalies (cardiovascular, pulmonary, etc.)

Abbreviations: EEG, electroencephalogram; MRI, magnetic resonance imaging.

Bloch and Sulzberger almost a century ago: in 1993 by Landy and Donnai[4]; in 2013 by Minić et al.[5]; and in the aforementioned 2020 publication by Bodemer et al.[3] These successive updates are justified based on the growing number of publications on IP and the consequent increase in knowledge of the disease at both the clinical and genetic level. Since 2013, diagnosis of IP has been based on the presence of a series of clinical findings, classified as major and minor criteria, the results of a genetic study, and the presence of relatives with the disease.[5] The latest revision of the diagnostic criteria has added new major criteria to those proposed in the 2013 revision, which grouped classic skin lesions into 4 categories. These new major criteria include dental anomalies (previously a minor criterion) and mutation in the *IKBKG* gene (previously considered separately from major and minor criteria) (Table 1). Key changes to the minor criteria include the addition of eosinophilia in peripheral blood (in the presence of skin lesions of the first classic stage) and the exclusion of anomalies of the central nervous system and palate and of a family history of miscarriage of male fetuses.[3]

To establish diagnosis of IP, at least one major criterion must be fulfilled in the absence of a family history, or one minor criterion fulfilled if the patient has a first-degree female relative with IP.[3]

Another important feature of the Bodemer et al. paper is the proposed management strategy for IP patients. The authors emphasize the need for multidisciplinary management of these patients and the coordinating role of the dermatologist (Table 2). Finally, they suggest that the proposed follow-up guidelines should be interpreted dynamically, always in the context of the patient's clinical presentation.[3]

In conclusion, this publication represents an important contribution to the diagnosis and management of IP, following the same line as previous updates. It is essential to recognize the manifestations of the disease early, either in the neonatal period or during follow-up, in order to detect and treat incipient processes that can cause serious sequelae, especially at the ocular or neurological levels. To this end, a new diagnostic system is proposed based on the latest available data about the disease, as well as a multidisciplinary management plan in which the dermatologist plays a coordinating role.[3]

References

1. Greene-Roethke C. Incontinentia pigmenti: a summary review of this rare ectodermal dysplasia with neurologic manifestations including treatment protocols. J Pediatr Health Care. 2017;31:e45–52.
2. Abe S, Okumura A, Hamano S, Tanaka M, Shiihara T, Aizaki K, et al. Early infantile manifestations of incontinentia pigmenti mimicking acute encephalopathy. Brain Dev. 2011;33:28–34.
3. Bodemer C, Diociaiuti A, Hadj-Rabia S, Robert MP, Desguerre I, Manière MC, et al. Multidisciplinary consensus recommendations from a European network for the diagnosis and practical management of patients with incontinentia pigmenti. J Eur Acad Dermatol Venereol. 2020;34:1415–24.
4. Landy SJ, Donnai D. Incontinentia pigmenti (Bloch-Sulzberger syndrome). J Med Genet. 1993;30:53–9.
5. Minić S, Trpinac D, Obradović M. Incontinentia pigmenti diagnostic criteria update. Clin Genet. 2014;85:536–42.