Pomeranian J Life Sci 2021;67(2):18-20 doi: 10.21164/pomjlifesci.692

Incontinentia pigmenti (Bloch–Sulzberger syndrome) – a diagnosis valid from birth

Ewa Nurska[1, A] ✉, Agata Jankowska[1, B], Beata Łoniewska[1, C], Agnieszka Kordek[2, D]

[1] Pomeranian Medical University in Szczecin, Neonatal Pathology Clinic, Powstańców Wlkp. 72, 70-111 Szczecin, Poland
[2] Pomeranian Medical University in Szczecin, Neonatology Clinic, Siedlecka 2, 72-010 Police, Poland

[A] ORCID: 0000-0003-1108-7298; [B] ORCID: 0000-0001-6816-6590; [C] ORCID: 0000-0002-0482-9014; [D] ORCID: 0000-0002-2881-9769

✉ eva.nurska@gmail.com

ABSTRACT

Incontinentia pigmenti (IP, dye incontinence), or Bloch–Sulzberger syndrome, is a rare genodermatosis (1:40,000 to 1:50,000 births), inherited through a dominant X-linked conjugate, caused by mutations in the *IKBKG/NEMO* gene located on Xq28, often with eosinophilia. In most cases, the disease affects the female sex. In male fetuses, it is usually lethal.

Incontinentia pigmenti is a multi-system disease. Changes occur in tissues and organs derived from the ectoderm and neuroectoderm and may affect the skin and appendages, eyes, central nervous system, skeleton, and teeth. It is usually diagnosed neonatally or during infancy when a characteristic 4-stage evolution of skin lesions materializes – accompanied by abnormalities in other organs. Skin defects can occur in utero, in which case they are visible at birth.

The only treatment is symptomatic and involves proper skin care and prevention of secondary infections. The patient should have interdisciplinary care (dermatologist, neurologist, ophthalmologist, dentist) for the early diagnosis and treatment of possible disorders within other organs.

The low incidence of the syndrome may delay diagnosis.

The aim of this study is to present the characteristic symptoms of the disease, help clinicians make the right diagnosis and to emphasize the legitimacy of multi-specialist care.

Keywords: incontinentia pigmenti; genodermatosis; X-linked; skin.

INTRODUCTION

Incontinentia pigmenti (IP) was 1st described by the German dermatologist Bruno Bloch in 1926 and the American dermatologist Marion Sulzberger in 1928 – hence the name 'Bloch–Sulzberger syndrome'. It is a rare neuroectodermal dysplasia, inherited dominant linked to the X chromosome, caused by mutations in the *IKBKG/NEMO* gene. The gene is located at the Xq28 *locus* and encodes a kappa light polypeptide gene enhancer in B cells, gamma kinase, which has a key role in modulating the nuclear transcription factor kappa B (NF-κ B). Nuclear transcription factor kappa B is involved in many inflammatory, apoptotic and immune response processes [1, 2, 3, 4].

This disorder is observed almost exclusively in women, however, it can also occur in men with karyotype XXY (Klinefelter syndrome) or somatic mosaicism [5, 6, 7].

EPIDEMIOLOGY

The incidence rate of IP is 1:40,000 to 1:50,000 births. Most cases, as much as 65–75%, are caused by spontaneous mutations whilst others are hereditary [1, 4].

CLINICAL PICTURE

The clinical picture of the disease consists of changes occurring in various tissues and organs, however, the most characteristic manifestations are in the skin along the Blaschko lines (Fig. 1), occurring in 4 stages that can overlap.

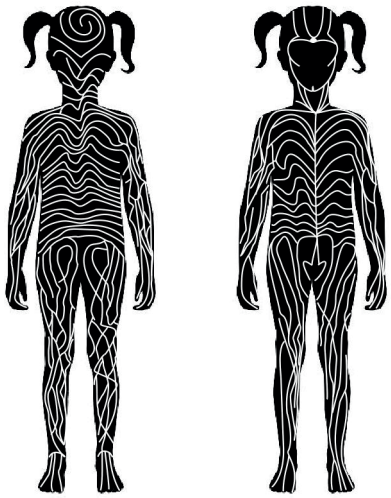

FIGURE 1. Blaschko lines

Stage I – bullous – presence of follicles, papules and pustules on the erythematous base forming along the Blaschko line, on the limbs, trunk, and head (Fig. 2). This stage manifests in 90% of patients and may occur from birth or within the first 2 weeks of life, usually disappearing by the 4 month [8, 9]. There are cases where it has developed after the 1st year of life. There may be episodes of recurrent bullous lesions in older children in the event of acute fever and stress. At this stage, eosinophilia is

common in blood tests. The histopathological picture is endothelial inflammatory infiltrate with eosinophils, neutrophils and (rarely) basophils as well as large dyskeratotic cells [1, 2, 3].

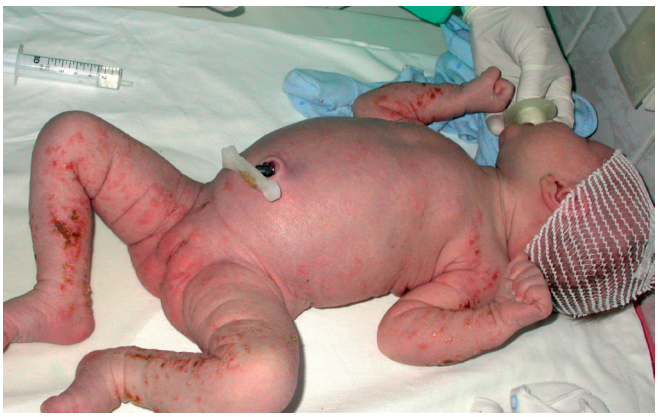

FIGURE 2. Skin manifestation

Stage II – papillary – hyperkeratotic papules forming a line or crust mainly on the limbs and trunk. This occurs in about 70% of patients. They develop 2–6 weeks after birth and usually disappear before the age of 6 months. There are cases, however, where the papules may persist until adulthood or appear later as linear, striated stretch marks that mainly affect the hands and feet. The papillary stage may overlap the bullous stage (Fig. 2). The histopathology of the lesion shows acanthosis, hyperkeratosis and papillomatosis with the presence of eosinophils [1, 2, 3].

Stage III – hyperpigmentation – brown or gray-brown linear changes in skin folds, which may be accompanied by atrophy of the trunk and limbs. This stage occurs in all patients. The location of the changes does not necessarily occur in areas of the skin that were involved in earlier stages. They appear after 6 months of age and slowly disappear during puberty but can also be persistent. Biopsies show a lack of melanin in the dermis and many melanophages [1, 2].

Stage IV – hypopigmentation/atrophic – linear discoloration, atrophy, scarring most commonly on the lower limbs. In the affected areas, hair follicles and sweat glands disappear. These changes usually develop during puberty, persist in adulthood, and may be permanent. Most patients do not have this stage. Histopathologically, this phase is characterized by a lack of pigment in the epidermis and a lack of ecrine glands [1, 2, 10].

ANOMALIES OF APPENDAGES

Hair may also be involved in the process of the disease and affects between 28–38% of patients. The most common symptom is alopecia, but the hair can also be 'woolly' – i.e. dull and brittle. Eyebrows and eyelashes may also be missing or underdeveloped.

In about 40% of patients, the lesions are also visible on the nails. This may affect 1 or several finger- and toe-nails. They present as yellowish plaque, koilonychia, dystrophy, hyperkeratosis or onycholysis [1, 2, 4, 5].

Approximately 11% of patients experienced changes in the mammary glands in the form of breast aplasia, additional nipples or asymmetry of the nipples [1].

ANOMALIES OF THE TEETH AND MOUTH

Changes in teeth were observed in 17–34% of patients, namely hypodontia or anodontia, microdontia and abnormal tooth shape. In addition, there may be a cleft or gothic palate and reduced salivation. For this reason, it is advisable to provide the patient with dental and orthodontic care at the time of the 1st teeth erupting or at the age of 6 months [1, 2, 4].

OPHTALMOLOGIC FINDINGS

Ocular involvement is estimated to occur in 20–80% of cases. When this happens, the consequences can be serious. The most characteristic symptoms are retinal disorders that result from neovascularization and abnormal development of retinal pigment epithelium in the 1st month of life. There is a proliferation of blood vessels, exudate, pre-retinal gliosis and ischemia – which results in retinal detachment. This process can be self-limiting or stopped at any stage. In addition to the above changes, patients can also have cataracts and strabismus [1, 2, 4, 7, 8].

Due to the possibility of significant defects in the organ of vision, it is important to conduct ophthalmologic examinations of newborns with a suspected diagnosis of IP in their first days of life. This examination should be repeated as follows: every month until the 4th month of life, then every 4 months until the 1st year of life, every 6 months up to the age of 3 years and then once a year. Ophthalmologic diagnosis is important because many changes can be prevented with early detection.

CENTRAL NERVOUS SYSTEM FINDINGS

Central nervous system disorders occur in approx. 30% of patients. Symptoms are varied and most likely result from disorders in the microcirculation of the brain – in small and medium sized arteries. The most common neurological symptoms are seizures, which have been observed in some patients from 12 h of age and most often occur in the 1st week after birth. Focal clonic seizures usually occur but may be partial or generalized; singular or recurrent [1, 2, 9].

In addition to the most common neurological disorders, stroke, motor and mental impairment and microcephaly have been reported [8, 10].

In many cases, changes in the central nervous system correlate with changes in the organ of vision.

Regular neurological observation is important to quickly detect and correct any central nervous system disorders [10].

DIAGNOSIS

Current diagnostic criteria were developed in 2014 and include large and small criteria. The diagnosis requires the presence of 2 or more large criteria or 1 large and 1 small criterion or many small criteria. The diagnosis can also be confirmed by a mutation in the *IKBKG* gene and 1 large or 1 small clinical criterion [2, 4].

Large diagnostic criteria which are typical in the evolution of skin lesions:

1) bullous stage,
2) papillary stage,
3) hyperkeratotic stage,
4) hypokeratotic stage.

Small diagnostic criteria include extracellular symptoms:

1) anomalies in the central nervous system (CNS),
2) abnormalities in the eye,
3) teeth anomalies,
4) defects of the palate,
5) nail defects,
6) changes in the mammary glands,
7) irregularities in the hair, eyebrows and eyelashes,
8) incorrect nails,
9) history for miscarriages of male fetuses,
10) typical histopathological results of skin biopsy.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should include Herpes or staphylococcal infections, Varicella zoster, X-chromosome retinal dissection, Ito hypomelanosis and Naegeli–Franceschetti–Jadassohn syndrome [4, 5].

In the neonatal period, skin lesions may be confused with a bacterial superinfection of a papulo-follicular rash and unnecessary treatment with antibiotics may be prescribed.

TREATMENT

Treatment is only symptomatic. This includes proper skin, hair and nail care. In the case of exacerbated inflammation, topical corticosteroid treatment is effective. Secondary skin infections may occur, in which case local or systemic antimicrobial therapy is required. Second stage changes may require topical retinoids [1, 2, 5, 10].

PROGNOSIS

In the absence of non-cutaneous symptoms, the prognosis is usually good. In patients with central nervous system or eye involvement, the clinical course depends on the type and extent of the abnormality [1, 2, 10].

In addition, patients with IP have an increased risk of cancer such as leukemia, retinoblastoma, Wilms' tumor and rhabdomyosarcoma [5].

SUMMARY

Erythematous bullous changes, which are common in newborns, may be the result of a rare genetic disease and special attention should be paid to the distribution and evolution of skin manifestations.

If IP is diagnosed, it is recommended to provide the patient with interdisciplinary care (dermatologist, ophthalmologist, neurologist, dentist, geneticist) ensuring the possibility of early diagnosis and correction of organ disorders in order to improve the patient's health and quality of life.

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(6):e45-e52.
2. Poziomczyk CS, Recuero JK, Bringhenti L, Santa Maria FD, Campos CW, Travi GM, et al. Incontinentia pigmenti. An Bras Dermatol 2014;89(1):26-36.
3. Iguchi A, Aoki Y, Kitazawa K. Progressive skin rashes of incontinentia pigmenti during infancy. Pediatr Int 2019;61(10):1065-6.
4. Cammarata-Scalisi F, Fusco F, Ursini MV. Incontinentia pigmenti. Actas Dermosifiliogr 2019;110(4):273-8.
5. Kordek A, Rosińska Z, Maleszka R, Różewicka M, Łoniewska B, Rudnicki J, et al. Nietrzymanie barwnika (IP) u noworodka powikłane noworodkowym zapaleniem wątroby. Post Neonatol 2010;2(16):153-6.
6. Batson R, Keeling B, Diaz L. Incontinentia pigmenti. J Pediatr 2016;176:218.
7. Ardelean D, Pope E. Incontinentia pigmenti in boys: a series and review of the literature. Pediatr Dermatol 2006;23(6):523-7.
8. Zafeiriou D, Vargiami E, Hatzidimitriou V, Kyriazi M. Incontinentia pigmenti: a skin, brain, and eye matter. J Pediatr 2013;163(5):1520.
9. Gottimukkala SB, Jagalasar M, Sethuraman G, Kitchanan S. Incontinentia pigmenti in a term neonate: an atypical presentation. Res Rep Neonatol 2018;8:65-7.
10. Lioce E, Milani P, Bistolfi A, Capacchione P, Nascimbeni A, Massazza G. Incontinentia pigmenti: a rare pathology with complex rehabilitative aspects. Disabil Rehabil 2014;36(21):1830-3.