

KLINIKINIS ATVEJIS

Incontinentia pigmenti (Bloch-Sulzberger syndrome) in neonates

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Key words: incontinentia pigmenti, female, neonatal period, skin alterations, eosinophilia.

Summary. A female newborn presented with emerging skin lesions, systemic eosinophilia, and eosinophilic reaction in the skin, liver, lungs, spleen, lymphatic nodes, porencephalia, convulsions, and disorders of thermoregulation. In addition to that, respiratory and heart failure, as well as brain edema were progressing. The suspected diagnosis of incontinentia pigmenti (Bloch-Sulzberger syndrome) was confirmed postmortem by skin biopsy.

Introduction

Incontinentia pigmenti (IP) type 2 is a rare genetic disease that affects skin, eyes, hair, teeth, and central nervous system (CNS), and manifests itself during early neonatal period. Synonyms of IP type 2 are: Bloch-Sulzberger syndrome, Bloch-Siemens syndrome, familial incontinentia pigmenti (pigment incontinence) (1). The incidence of the disorder is 1 case per 40,000 population. The name of the disease reflects morphological changes of the skin seen under a microscope.

This disease was first described in 1903 by Garrod, its pathogenesis – in 1926 by Sulzberger, and localization of rash – in 1985 by Happel (2).

Transmission. The damaged gene is called NEMO (NF-kappaB essential modulator). IP type 1, or hypomelanosis, may be transmitted sporadically via Xp11.21; IP type 2 may be transmitted, following a dominant pattern, through the X chromosome Xq28 (3, 4).

Pathogenesis. Changes occur in cells with the altered X chromosome (1, 3). Due to acute inflammation at the blister site the epidermic cells of the basal layer fail to contain the pigment melanin. Melanin accumulates in the dermis or melanophages. The rash is located along the Blaschko lines that reflect the migration ways of melanoblasts in embryogenesis. After the birth, melanoblasts become melanocytes (5, 6). The manifestation of the disease begins after the birth. Only females fall ill with the diseases; males (with one X chromosome) do not survive. The ratio of transmission to the children is 2:1 (F:M). Mortality is re-

lated to malignant tumors, myelogenic leukemia, Wilms's tumor, and retinoblastoma.

Clinical features manifest themselves through the changes in the skin, eyes, hair, teeth, central nervous system, and other organs (2, 7, 8).

- **Skin:** 4 stages are differentiated according to the changes in the skin (Table 1). Nail dysplasia is found in 40–60% of cases;
- **Eye changes** are observed in 1/3 of patients: speckled diffuse hypopigmentation in the retina (a pathognomic feature), microphthalmia, lenticular hemorrhage, retrolental fibroplasia, cataract, atrophy of the optical nerve, and reticular split-off (rare);
- **Teeth and jaws:** in 65–90% of cases – delayed eruption, changes in dental contour (circular or conical shape) hypodontia/microdontia, micrognathia/prognathia;

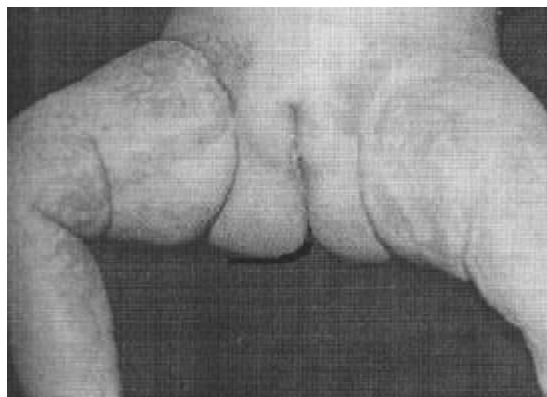


Fig. Incontinentia pigmenti (rash along Blaschko lines) in a female newborn

Table. Stages of the disease according to the changes in the skin (2, 7)

Stage	Clinical features	Time of manifestation
Stage 1 Vesicular	Linear vesicles, pustules, or blisters with erythema along Blaschko lines	During infancy, possible in childhood during fever
Stage 2 Verruciform	Keratotic papules or plaque	At the age of 2–8 weeks
Stage 3 Pigmented	Hyperpigmented macules along Blaschko lines in the mastoid, axillary, and inguinal sites; the localization of secondary rash may not coincide with that of the primary rash	At the age of 12–40 weeks
Stage 4 Depigmented	Brownish macules begin to disappear; hyperpigmentation becomes more apparent during the examination under Wood's lamp; in the site of the lower limbs, there remains linear hypopigmentation, and skin atrophy, hair follicles disappear.	Continues from infancy to adulthood

- **Hair:** sparse and thin, partial baldness in 35–70%;
- The symptoms of the changes in the *central nervous system* in 10–40% of cases are highly miscellaneous – microcephaly, mental retardation, spastic paralysis, convulsions, epilepsy, etc.
- **Structural anomalies** are most frequently related to neurological symptoms – 14% (body asymmetry, scoliosis, spina bifida, syndactylia, ear anomalies, additional ribs, and skull deformations);
- **Breast anomalies** – 1% (hypoplasia, additional nipples).

In more than 95% of cases the disease is detected in female individuals; however, it may also occur in males (9). Carriers of the pathological gene may have only stage 4 indications and dental anomalies; the manifestation of the disease is possible in male individuals with XXY chromosomes (e. g. Klinefelter syndrome). Other rarely surviving males (only 32 cases have been described) have early somatic mutation or a partial mutation of the X chromosome (gene change). All females with IP have X chromosome defect, and, therefore, the disease may manifest itself at any moment of life in spite of the absence of the changes during infancy.

Differential diagnostics. The acute stage of the disease is differentiated from other vesicular-bullous eruption and infection caused by Herpes simplex virus, impetigo, candidosis, and other autoimmune diseases (During's herpetiform dermatitis, bullous pemphigoid), and epidermolysis bullosa congenita (10).

Diagnostic studies

- Testing of peripheral blood – neutrophilia, eosinophilia (in the acute phase – up to 50% of eosinophils);

- Microbiological studies – for the differential diagnostics of infectious skin diseases. Most frequently the content of blisters or vesicles is found to be sterile;
- Cytological study – typical eosinophilia of the content of blisters or vesicles;
- Radiological studies (neurosonography, magnetic resonance imaging, computed tomography (CT)) help to determine structural anomalies, infarctions, cerebral areas of decreased intensity, and pathological changes in the eyes; CT angiography helps to determine decreased speed of blood circulation (11);
- Electroencephalogram may reveal multiple spiked and sharp waves;
- Male individuals with IP require the determination of the karyotype, in order to determine the Klinefelter syndrome (i. e. the XXY syndrome);
- Skin biopsy and histological studies. Typical pronounced eosinophilia of the epidermis and the content of blisters.

Treatment

- The vesicles should not be touched, and the skin must be kept clean in order to avoid bacterial infections. Local antiinflammatory treatment with glucocorticoids may be applied (8);
- Convulsions are treated with anticonvulsants.

Prognosis

IP is a genodermatosis, and thus may be related to malignant processes in the organism (chromosome instability syndrome manifesting itself through acute myelogenic leukemia, Wilms's tumor, or retinoblastoma). Infant mortality is associated with bacterial infection, and malfunction of the central nervous system.

People with IP may experience the following health

disorders at older age:

- Slowing down of the motor function;
- Muscular weakness;
- Mental retardation;
- Convulsions, epilepsy.

In general, it can be stated that incontinentia pigmenti is a genetic disease that is inherited through the X chromosome following a dominant pattern, and manifesting itself not only through visible changes in the skin, but also convulsions and other malfunctions of the central nervous system that can minimize the newborn's ability to survive. For this reason, timely diagnosis of IP prior to pregnancy and early genetic consultation of pregnant women with IP in order to evaluate the risk of damage for the children of such women are essential.

Clinical case report

A full-term female newborn of a mother who had had syphilis was admitted to the Neonatal Intensive Care Unit (NICU) of Kaunas University of Medicine Hospital (KUMH) at the age of 7 hours; the patient presented with progressing respiratory failure. It was the first pregnancy and the first delivery for the mother. The infant was born in 2004 after 42 weeks of pregnancy, weighed 3952 grams, and had signs of post-maturity (peeling skin on the soles and the palms). The evaluation according to the Apgar scale was 7–8 points. In 2001 the mother was diagnosed with and treated for syphilis. During the pregnancy protective penicillin therapy was not administered to the mother due to allergy to penicillin (according to the mother). Specific serological studies of the newborn: *Treponema pallidum* hemagglutination assay (TPHA) – positive 4+, rapid plasma reagin (RPR) titre – negative, cerebrospinal fluid Venereal Disease Research Laboratory (VDRL) test – negative; serological examination for HIV infection – negative; blood test revealed leucocytosis. Due to suspected congenital infection, treatment with penicillin and gentamycin was prescribed.

On the 3rd day of life the girl experienced an attack

of clonal convulsions; the convulsions repeated twice within 7 hours. Treatment with luminalis was prescribed, while continuing with antibiotic therapy. On the 4th day of life a rash on the body and the extremities appeared. Due to suspected allergy to penicillin, antibacterial treatment was discontinued, and antihistamine medications were prescribed. The dynamics of the rash was waveform. On the 15th day of life, fever reached 38.6°C, blood tests revealed increasing leucocytosis – $37\text{--}50 \times 10^9/\text{l}$, eosinophils – 5–37%, and C reactive protein level was normal. Neurosonography showed hyperechogenic foci in the periventricular position, the dynamic picture showed the formation of small cysts in the brain. Eyes and echoscopy of abdominal organs revealed no changes. Microbiological studies of the blister contents were negative.

The differentiation was between allergic drug-induced dermatitis (the mother's allergy to penicillin indicated in the anamnesis) and incontinentia pigmenti: specific IgE C2 for penicillin 0.10 kU/l, blood tests revealed leukemoid reaction, polymorphic granularity in cytoplasm (with occasional intermixture of eosinophilic granules and vacuolization). Skin biopsy: dermis showed an inflammatory infiltrate consisting of eosinophils, and apoptosis of individual keratinocytes was observed in epidermis.

During the course of the treatment, weeping skin rash remained on the trunk and the extremities, blisters with erythema situated along Blaschko lines, later – secondary verruciform hyperpigmentation, progressing respiratory failure, instability of thermoregulation, hypothermia up to 35.9°C; blood tests showed leucocytosis $87.3 \times 10^9/\text{l}$, and eosinophils – 61%. Despite the applied therapeutic measures, cardiac failure was progressing, cerebral edema was developing, and the newborn died after 26 days of life. Autopsy showed the following changes: eosinophilic reaction in the skin, liver, lungs, spleen, and lymph nodes, and small cysts and proliferation of glia in cerebral hemispheres; these changes as well as epilepsy bouts (according to clinical data) confirmed the diagnosis of incontinentia pigmenti (Bloch-Sulzberger syndrome).

Pigmento nelaikymas (*Bloch-Sulzberger* sindromas) naujagimystėje

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Raktažodžiai: pigmento nelaikymas, moteriškoji lytis, naujagimystė, pokyčiai odoje, eozinofilija.

Santrauka. Moteriškosios lyties naujagimei išryškėjo odos pažeidimas, sisteminė eozinofilija, rasta eozinofilinė reakcija odoje, kepenyse, plaučiuose, blužnyje, limfmazgiuose, traukuliais, termoreguliacijos sutrikimai,

progresavo kvėpavimo ir širdies veiklos nepakankamumas bei smegenų edema. Pigmento nelaikymo (Bloch-Sulzberger sindromo) diagnozė patvirtinta atlikus odos biopsiją patologoanatominio tyrimo metu.

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