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Incontinentia Pigmenti (Bloch-Sulzberger Syndrome): A Systemic Disorder

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Incontinentia pigmenti (IP) is a rare inherited multisystem disorder characterized by a distinctive swirling pattern of the skin; defects of teeth, hair, and nails; and ophthalmic, central nervous system, and musculoskeletal abnormalities. It progresses through several well-defined stages. IP is transmitted as a dominant X-linked trait with variable expressivity, but many—if not most—cases are sporadic. IP has been shown to result from mutations in the NEMO *gene that completely abolish expression of NF-κB essential modulator. The diagnosis of IP typically is made based on characteristic clinical findings. Molecular analysis of the* NEMO *gene is now possible, as is analysis of skewed X-chromosome inactivation, which can further reduce diagnostic confusion. A number of disorders, including hypomelanosis of Ito, should be considered in the differential diagnosis. The considerations vary according to the stage of IP. Careful head-to-toe clinical evaluation is critical in the evaluation of a child with suspected IP given the frequent multisystem involvement. A multidisciplinary approach including dermatology, ophthalmology, neurology, and dental consults is typically warranted. The skin manifestations of IP do not require specific treatment other than reassurance; spontaneous resolution of the lesions usually occurs.*

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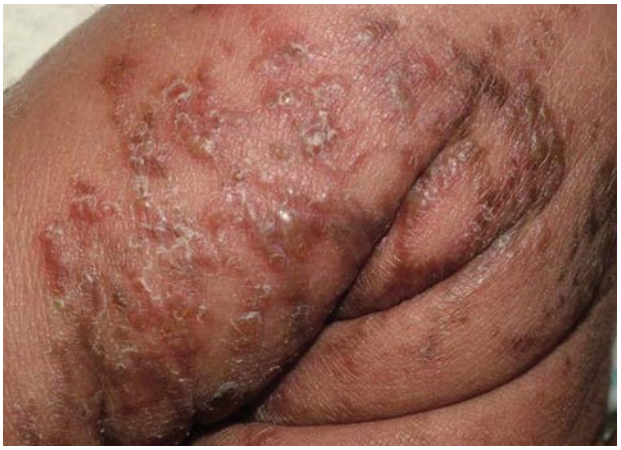
Incontinentia pigmenti (IP) (*Mendelian Inheritance in Man* 308300) is a rare inherited multisystem disorder characterized by distinctive swirling pattern of the skin; defects of teeth, hair, and nails; and ophthalmic, central nervous system, and musculoskeletal abnormalities.[1] To emphasize the systemic nature of the disease, it has been proposed that it be renamed *systemic neonatal eosinophilic vasculitis* or *perinatal ischemia with eosinophilia*.[2] A clinical case fitting the description of IP was reported by Garrod[3] in 1906, but the formal description usually is attributed to Bloch,[4] professor and chairman of dermatology at the University of Zürich.[5,6] In 1926, Bloch[4] provided the following description of a 2-year-old girl with this disorder: "The whole picture has something capricious and artificial about it, as if someone had painted completely irregular patterns on the skin." Following a presentation by Bloch to the Swiss Dermatologic Society in 1925, Sulzberger reported on the patient in more detail and later published a description in the English language literature.[6] Therefore, the disorder also is known by the eponym Bloch-Sulzberger syndrome. The familial form of the disease, or classical IP, has historically been referred to as IP2. It maps to Xq28 and is caused by mutations in the *NEMO* gene. The sporadic form of the disease maps to Xp11 and was in the past referred to as IP1. It is now more properly categorized as hypomelanosis of Ito.[7-11]

Epidemiology

IP is a rare genodermatosis, occurring in 1 in 50,000 newborns.[12] It is transmitted as an X-linked dominant trait with variable expressivity, but many—if not most—cases are sporadic.[13,14] Germline paternal mutations account for 80% of sporadic cases.[15,16] Affected females typically show highly skewed patterns of X-chromosome inactivation[17,18]; selective inactivation of the mutant X chromosome (lyonization)



The second stage of incontinentia pigmenti with linear verrucous clusters of papulonodules.

results in a wide range of phenotypes and can even result in phenotypically normal carrier females.[19] Affected males typically expire in utero, resulting in the observed female-male ratio of 37:1.[20] However, sporadic cases of males with IP have been reported,[14,15,21-24] either in association with Klinefelter syndrome[25-27] or caused by genetic mosaicism in males with normal karyotype.[28]

NEMO, located on Xq28, codes for the 48 kDa NF-κB essential modulator and is believed to be responsible for the IP phenotype. Loss-of-function *NEMO* mutations lead to susceptibility to tumor necrosis factor (TNF) α–induced apoptosis, resulting in skewed X-chromosome inactivation and male lethality.[12]

Clinical Manifestations

IP is marked by defects in ectoderm-derived structures, including skin, teeth, hair, nails, and ophthalmic and nervous tissue. Musculoskeletal anomalies also can occur. Symptoms vary considerably, even within affected families and between identical twins,[29] and are most likely due to variable X-chromosome inactivation. In a global literature review of 653 cases of IP, systemic manifestations such as teeth, hair, eye, CNS, and structural development abnormalities were found to occur in 79.8% of patients.[20]

Skin—Three clinical stages of IP have been described.[30] The first stage, presenting at birth or shortly thereafter, is characterized by linear arrangements of erythema, vesicles, and pustules, and occasional bullae that follow lines of Blaschko.[31] Skin lesions are present in 90% of patients by 2 weeks of age, with the limbs and trunk being most affected. The lesions usually clear by 4 months of age.[14] Late reactivation of these lesions, typically following infectious events, has been reported.[14,32-34] Delayed presentation also can occur.[35] The second stage, beginning at approximately 2 months of age, is heralded by a linear verrucous cluster of papulonodules (Figure). As this stage resolves, the characteristic irregular hyperpigmented whorls become evident, primarily on the trunk (stage III). Some researchers recognize a fourth stage of atrophy and hypopigmentation, typically seen in adults, and possibly so subtle as to only be recognized when investigating the parent of a child with IP.[36,37] In adults, it is possible that there are no residual skin manifestations to aid in the diagnosis of IP.

Teeth—Delayed dentition, anodontia, hypodontia, and misplaced and deformed teeth are common, especially conical forms, impaction, accessory cusps, and pegged teeth. Dental abnormalities occur in 80% of cases.[30]

Hair—Diffuse scarring alopecia, often on the vertex, is a typical finding, reported to occur in 28% to 38% of patients.[14,20,30] Whorled scarring, corresponding to lines of Blaschko on the scalp, also has been described, which is a phenomenon attributed to lyonization.[38]

Nails—Onychodystrophy can involve all of the fingernails and toenails or only specific nails. Koilonychia and a yellow discoloration also may occur. In one case series of 40 patients, nail changes were reported in only 10% of patients, but data were assessed retrospectively and not collected in an organized fashion.[14] The rate of nail involvement usually is reported to be approximately 40%.[20] Rarely, in mild cases, nail changes can be the only manifestation of IP.[39] Benign subungual dyskeratotic tumors have been reported as a late complication, which can be quite painful and lead to destruction of the underlying bone.[40-45]

Ocular Manifestations—Ocular abnormalities often are the most devastating aspects of IP, with an estimated 25% to 77% of patients being affected.[46] Strabismus is the most common finding,[14] but defects leading to blindness are the most serious, occurring in approximately 8% of cases.[14,20] Findings include retinal detachment, peripheral retinal avascularity, and preretinal fibrovascular proliferation with vitreous hemorrhage.[47] Retinal ischemia is believed to be the initiating event, leading ultimately to vascular proliferation.[48] Pigmentation of the conjunctivae, nystagmus, neovascular changes, cataracts, retinal pigment epithelium hypopigmentation, foveal anomalies, keratitis, and optic atrophy are additional complications.[47,49-54] Cortical blindness also occurs.[55]

Neurologic Manifestations—Neurologic manifestations occur in approximately one third of cases.[14,20] Seizures may be the dominant feature,[14] reported to occur in 13% of patients.[20] Spastic or paralytic

quadriplegia, hemiplegia, and diplegia are relatively common.[14] Findings[14] include cerebral atrophy; ischemic[56,57] or hemorrhagic infarcts,[58] which sometimes occur bilaterally[14,59]; periventricular leukomalacia[56]; porencephalia; enlargement of lateral ventricles; and hypoplasia of the corpus callosum.[60] Some investigators have postulated that primary encephalopathy is the underlying etiology, but a specific infectious or inflammatory cause has not been identified.[61] Hydrocephalus, microcephaly, and mental retardation often are present; therefore, IP should be considered in the differential diagnoses of neonatal seizures[62] and cerebrovascular accidents.[59] Seizures can be the presenting symptoms of the disease.[63,64]

Immunologic Manifestations—It has been suggested that immunologic derangements are more common in IP than in the general population. Cutaneous and pulmonary tuberculosis has been reported in association with IP, which may have resulted from immune derangement.[65] Immunologic dysfunction has been reported to be associated with rare male cases of IP and the related syndrome of ectodermal dysplasia and immunodeficiency (EDA-ID).[66] A defect in polymorphonuclear chemotaxis has been reported.[67]

Cardiovascular Manifestations—Cardiovascular manifestations are not typical, but case reports describe pulmonary hypertension and other cardiac abnormalities.[68-70] An associated atrial septal defect[71] and ventricular endomyocardial fibrosis also have been reported.[72]

Musculoskeletal Manifestations—Hemivertebra, syndactyly, hemiatrophy, short limbs, supernumerary ribs, unilateral acheiria,[69] and kyphoscoliosis can be present.

Other—Supernumerary nipples have been noted to occur more frequently in patients with IP than the general population. Their presence has been proposed as a minor criterion for diagnosis.[14] Cleft lip and palate rarely are associated with the disorder.[73]

Pathogenesis

NEMO, located on the X chromosome, codes for the 48 kDa NF-κB essential modulator, which along with other proteins forms the regulatory subunit of the IκB kinase (IKK) complex. IKK, in turn, is responsible for deactivating, by dephosphorylation, the IκB proteins, which are inhibitors of the NF-κB family of transcription factors.[13,74,75] Free of IκB, NF-κB is able to shuttle to the nucleus and activate transcription of various genes. *NEMO* mutations therefore abolish NF-κB activity. NF-κB activity can be induced by a dizzying array of stimuli, including bacteria, fungi, and viruses, and their protein and polysaccharide products; eukaryotic parasites; cytokines and cytokine receptors, including TNF-α, TNF-β, interleukin (IL)–1, IL-2, IL-4, IL-12, IL-15, IL-17, and IL-18, among many others; physiologic, physical, and oxidative stress; environmental hazards such as cigarette smoke; therapeutically used drugs; modified proteins; overexpressed proteins; receptor ligands; apoptotic mediators; mitogens, growth factors, and hormones; physiologic mediators; and chemical agents.[76]

Mutations in the *NEMO* gene that completely abolish protein expression result in IP.[16] Mutations that allow for residual expression can lead to ectodermal dysplasia and immunodeficiency in males,[77,78] a condition termed X-linked recessive anhidrotic EDA-ID. It has been suggested that EDA-ID is a mild variant of IP.[66] It is associated with deletions in exon 10 and is not connected with skewed X inactivation. A specific stop codon mutation (X420W) results in EDA-ID with osteopetrosis and lymphoedema, a more severe phenotype that occurs in males.[77,79-81]

Approximately 80% of patients with IP harbor a deletion of exons 4 to 10 of *NEMO* that results in a complete absence of *NEMO* activity.[13,77] The balance of mutations is various point mutations that do not correlate clearly with the severity or phenotype of IP.[13] *NEMO* mutations were found in 68% of 122 unrelated patients with IP, of which 88% harbored a deletion of exons 4 to 10. Another series reported the identification of 277 mutations in 357 patients with IP, of which 90% harbored a deletion of exons 4 to 10 of *NEMO*.[12] The balance was small nucleotide changes, such as deletions, substitutions, and duplications. Paternal germ line rearrangement was identified as the source of the deletion in most cases. In a mouse model, *NEMO* disruption resulted in embryonic lethality in males, while heterozygous females developed patchy skin lesions similar to IP.[82,83]

The early lesions of IP eventually heal, leading to hyperpigmented lesions resulting from incontinence of melanin. Melanin eventually is scavenged by macrophages, leading to the hypopigmented atrophic fourth stage of the disease. The disease progression is believed to be caused by selective death of cells carrying the mutation.[84,85]

Histopathology

Stage I of the disease, marked by linear arrangements of erythema, vesicles, and pustules, and occasional bullae, is histologically associated with eosinophilic spongiosis and dyskeratotic keratinocytes.[86] Eosinophils also are increased in the peripheral blood, possibly due to upregulation of the NF-κB–activated cytokine, eotaxin.[87] Extracellular deposition of eosinophil major basic protein further implicates eosinophils in the disease.[88] Eosinophilic proteases may

degrade tonofilaments and desmosomes, ultimately resulting in bullae formation. Stage II, heralded by a linear verrucous cluster of papulonodules, is marked by hyperkeratosis, acanthosis, papillomatosis, and dyskeratotic keratinocytes related to keratinocyte apoptosis.[14,19] Vacuolar changes in the basal layer may occur. Stage III, characterized by irregular hyperpigmented whorls, is associated with the finding of numerous melanophages in the upper layer of the dermis. A finding of free melanin in the dermis is characteristic of late lesions and suggestive of IP but is not diagnostic by itself, as it may be observed in other disorders.[89]

Diagnosis

The diagnosis of IP typically is made based on characteristic clinical findings using the criteria of Landy and Donnai.[30] But not all cases are clear-cut. Stages may overlap or not occur at all in any one patient. Other disorders also manifest as hyperpigmentation that follows lines of Blaschko, possibly confusing the diagnosis. In an analysis of 47 patients previously diagnosed with IP who were reevaluated using the Landy and Donnai[30] clinical criteria, it was found that 7 patients had been incorrectly diagnosed (3 patients had hypomelanosis of Ito, 1 patient had orofaciodigital syndrome, and 3 patients remained undiagnosed).[14]

The addition of histologic findings of eosinophilia and apoptosis can help clarify the diagnosis when necessary. Molecular analysis of the *NEMO* gene is now possible, as is analysis of skewed X-chromosome inactivation, which can further reduce diagnostic confusion. The presence of a pseudogene, *delta NEMO,* may lead to misdiagnosis using conventional polymerase chain reaction approaches.[90]

Differential Diagnoses—A number of disorders should be considered in the differential diagnosis of IP, and the considerations vary according to the stage of IP.[91] The first stage occasionally can be confused with herpes simplex,[92] as well as with other blistering disorders, such as epidermolysis bullosa, bullous impetigo, varicella, dermatitis herpetiformis, bullous systemic lupus erythematosus, linear immunoglobulin A bullous dermatosis, bullous pemphigoid, pemphigus vulgaris, and bullous mastocytosis. Importantly, neonatal herpes and IP can coexist; therefore, a diagnosis of herpes should always be excluded.[93,94] IP has infrequently been confused with child abuse.[95] The second stage has a much more narrow differential diagnosis, including verruca vulgaris and linear epidermal nevus. The differential diagnosis for the third stage includes linear and whorled nevoid hypomelanosis, dermatopathia pigmentosa reticularis, Naegeli syndrome (also known as Franceschetti-Jadassohn syndrome), X-linked dominant chondrodysplasia punctata, and pigment mosaicism.

Hypomelanosis of Ito, a variant of systematized depigmented nevus, also can be confused with IP. Both disorders are characterized by linear or whorled pigmentary patterns and are associated with similar ocular, dental, and central nervous system findings. Ectodermal dysplasia of Zonana (*Mendelian Inheritance in Man* 300291[96]) also may evidence linear hyperpigmentation in female carriers.[78] Atypically presenting cases may be suspicious for skin malignancy.[97] Subungual tumors can be confused with paronychia[42] and cancerous lesions.[44]

Genetic Counseling and Prenatal Diagnosis—IP has traditionally been considered a dominant X-linked trait, with embryonic male lethality. Prior to the implication of *NEMO* as the gene responsible for IP, linkage analysis was the only tool available for prenatal diagnosis. However, molecular analysis using PCR and analysis of X chromosome inactivation patterns[98] are now possible and may be used in combination to improve sensitivity.[99] Clinical severity cannot be predicted with certainty based on prenatal diagnosis. Importantly, males also may be affected with a less severe phenotype and should not necessarily be presumed to be destined for embryonic lethality without first identifying the specific mutation.[66] Preimplantation diagnosis is possible in cases of in-vitro fertilization.[100] Determining if the case is sporadic or familial is essential for proper counseling. Parents, particularly the mother, should be carefully examined for subtle signs of the disease, such as hypochromic streaks and atrophy.[37] Distinction from hypomelanosis of Ito, which is often associated with chromosomal abnormalities,[101] must be made.

Treatment

Careful head-to-toe clinical evaluation is critical in the evaluation of a child with suspected IP given the frequent multisystem involvement. An ophthalmologist should be consulted immediately[51] and follow-ups should be conducted regularly. Retinal vascular anomalies are best detected with flurescein angiography with the child under anesthesia.[49] The first successful surgical retinal reattachment in IP was reported in 1993 by Wald et al.[102] More recently, retinal detachment has been treated successfully with indirect diode laser coagulation and pars plana vitrectomy,[47] and with laser photocoagulation.[49,103] Not all cases of peripheral vascular lesions will progress to retinal detachment, and some patients' lesions may remain stable for many years. In less severe cases, the threshold for treatment is not well-defined.[104] Some physicians have used laser photocoagulation at the

preproliferative stage.[103] Cryotherapy also has been used to arrest retinopathy.[105] Changes to retinal vasculature may be markers for more severe intracranial pathology. If neurologic involvement is suspected, computed tomography, magnetic resonance imaging, and transfontanellar ultrasound can reveal the location and nature of the lesion.[14,106] Magnetic resonance angiography is a useful modality to delineate vasculopathy in the central nervous system.[58] It is advisable for patients with IP to be seen regularly by a neurologist, at least during the first few years of life. A dentist should be consulted as teeth erupt if there is any suspicion of irregularity. Orthodontics and dental prostheses are the preferred treatment.

The skin manifestations of IP do not require specific treatment other than reassurance; spontaneous resolution of the lesions usually occurs. Because subungual tumors can lead to bone destruction, treatment is necessary, typically excision or curettage. Oral etretinate, a retinoid, also has been used for the treatment of subungual tumors, leading to resolution without recurrence at 37-month follow-up.[107]

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