Hypomelanosis of Ito

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Introduction

This article includes discussion of hypomelanosis of Ito, Ito's disease, Ito syndrome, Ito's syndrome, Ito hypomelanosis, Ito's hypomelanosis, pigmentary dysplasia, mosaic dyspigmentation, pigmentary mosaicism, pigmentary mosaicism of the Ito type, hypopigmentation along the lines of Blaschko, nevus depigmentosus, linear and whorled nevoid hypermelanosis, and phylloid hypomelanosis. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

The term "hypomelanosis of Ito" encompasses a heterogeneous group of disorders characterized by hypopigmented skin lesions arranged in whorls, streaks, or both, along the lines of Blaschko (a nonrandom developmental system of cutaneous markings characterizing the distribution of various linear and segmental skin disorders). Even though Ito's original report in 1952 described a purely cutaneous disease, subsequent case reports and case series have recorded a significant association with multiple extracutaneous manifestations, including musculoskeletal and neurologic abnormalities. For hypomelanosis of Ito several models of inheritance have been proposed but not proved, and a number of cytogenetic studies have revealed a wide variety of mosaic chromosomal abnormalities, hence, the heterogeneity of associated systemic features. Thus, it has been suggested that this group of conditions is rather a nonspecific manifestation (ie, a phenotype) reflecting genetic mosaicism. These mosaic phenomena likely disrupt expression or function of pigmentary genes. The author includes updates on the occurrence of hemi-overgrowth in patients with hypomelanosis of Ito.

Key points

- Hypomelanosis of Ito is a sporadic neurocutaneous disorder characterized cutaneously by hypopigmented skin lesions arranged in whorls and streaks along the lines of Blaschko.
- Though multisystem involvement is common, it is heterogeneous in presentation and commonly manifests with involvement of the neurologic and musculoskeletal systems.
- The most common neurologic manifestations include cognitive and behavioral problems in up to 70% and epilepsy in up to 50%.
- Neuroimaging findings can include cerebral or cerebellar atrophy, cerebral dysgenesis, or migrational abnormalities.

Historical note and terminology

Lines of Blaschko. Alfred Blaschko (1858 to 1922) was a private practitioner of dermatology in Berlin whose interests ranged from leprosy to occupational skin diseases (Bologna et al 1994). A composite diagram of these distribution patterns was then drawn that has subsequently been referred to as the lines of Blaschko. In 1976, Jackson introduced the concept of the lines of Blaschko into the English-language literature, although it had been well known in the European community for decades (Bologna et al 1994). Happle added to Blaschko's original diagram lines (confined to the trunk and limbs) localized to the posterior scalp (Happle 1985; Bologna et al 1994; Happle 2006).

Hypomelanosis of Ito. In 1952 Minor Ito described a 22-year-old Japanese girl whose skin of the upper half of her body looked as “if the normal pigment was brushed off.” The depigmented skin lesions were widespread and symmetric, arranged in irregular shapes with “zigzag borders and splash-like spots” on the trunk and in a “linear pattern” down her arms. He defined these lesions as “nevus depigmentosus systematicus bilateralis” (Ito 1952). No other physical abnormality was reported apart from asymmetry of breast size. At that time, Ito coined the term incontinentia pigmenti achromians (Pascual-Castroviejo and Ruggieri 2007) because the pattern of color loss was
similar to that of the hyperpigmented changes seen in incontinentia pigmenti of the Bloch-Sulzberger type (OMIM #308300). Subsequent observations expanded the phenotype and the name hypomelanosis of Ito was proposed to avoid confusion with incontinentia pigmenti (Jelinek et al 1973). However, this term was criticized because Ito's original patient was described as having “depigmented,” not hypopigmented lesions (Ito 1952; Sybert 1990; Sybert 1994; Ruggieri and Pavone 2000). Possibly, the original patient by Ito may have had incontinentia pigmenti, as the author himself believed (Ito 1952). Further terms have been used such as Ito disease, Ito syndrome, and Ito hypomelanosis. Proposed changes in terminology included the terms pigmentary dysplasia, mosaic dyspigmentation, pigmentary mosaicism, pigmentary mosaicism of the Ito type, or hypopigmentation along the lines of Blaschko to reflect the disease pathogenesis or recall the cutaneous patterns (Donnai 1996; Sybert 1990; Editorial 1992; Moss et al 1993; Sybert 1994; Ruggieri and Pavone 2000; Pascual-Castroviejo and Ruggieri 2007). Despite these criticisms the term hypomelanosis of Ito is still used.

**Clinical manifestations**

**Presentation and course**

Hypomelanosis of Ito is a multisystem disorder in which most organs of the body may show anomalies in addition to the skin. The most frequent alterations are found in the musculoskeletal and central nervous systems.

The main features that define hypomelanosis of Ito are the cutaneous anomalies. In many instances, patients present with skin hypopigmentation following the lines of Blaschko without any other associated anomaly (Nehal et al 1996; Ruggieri and Pavone 2000). The frequency of cutaneous or extracutaneous abnormalities in published articles and reviews may reflect the detail of the investigation in the series or the population studied. For example Metzker and colleagues did not find extracutaneous involvement in an analysis of 30 children with hypomelanosis of Ito (Metzker et al 1983). Nehal and colleagues and Ruggieri and Pavone recorded low frequencies of extracutaneous abnormalities (30%) whereas Ruiz-Maldonado and colleagues reported nearly 100%, Pascual-Castroviejo and colleagues 94%, Glover and colleagues 79%, and Zvulunov and Esterly 75% (Pascual-Castroviejo et al 1988; Grover et al 1989; Ruiz-Maldonado et al 1992; Zvulunov and Esterly 1995; Nehal et al 1996; Ruggieri and Pavone 2000).

**Skin manifestations.** The pigmentary lesions in hypomelanosis of Ito are either recognizable at birth or become visible during early childhood. Unilateral or bilateral areas of hypopigmentation with irregular borders characterize the typical phenotype with lesions arranged in whorls, patches, or linear patterns along the lines of the Blaschko (Happle 1993; Happle 2006). The lines of Blaschko are always associated with mosaicism (Happle 1993; Bologna 1994). Pigmentary anomalies associated with human mosaicism may show several patterns of distribution in the skin: (1) type 1, typically following the lines of Blaschko (either narrow band, type 1a, or broad band, type 1b); (2) type 2, checkerboard pattern; (3) type 3, phylloid pattern; (4) type 4, patchy pattern without midline separation (Happle 1993); and (5) type 5, spiral pattern (Ruggieri 2000; Pascual-Castroviejo and Ruggieri 2007). Accordingly, other types of cutaneous pigmentary patterns such as the zosteriform or dermatome or plaque-like arrangement have likewise been observed in hypomelanosis of Ito. All of these cutaneous changes are associated with mosaicism, but not all are hypopigmented zones and not all correspond to hypomelanosis of Ito skin patterns other than those following Blaschko lines.

The hypopigmented zones in hypomelanosis of Ito can be seen in any part of the body: head, face, neck, trunk, or extremities (they also have been observed in the iris) (Schwartz et al 1977; Ruiz-Maldonado et al 1992; Pascual-Castroviejo et al 1998). Areas of hyperpigmentation following the lines of Blaschko may also be seen as a counterpart to areas of hypopigmentation. In many patients, determination that the lighter areas of skin were hypopigmented rather than the darker areas hyperpigmented has been arbitrary (Sybert 1994). Areas of hypomelanosis are more easily detected in ethnic groups with increased skin pigmentation, such as Asians, Hispanics, or Africans. Inspection with a Wood (ultraviolet) lamp could help in distinguishing hypochromic zones, especially in Caucasians with fair skin (Schwartz et al 1977). The extent of the hypopigmented cutaneous lesion does not always correlate either with the severity of neurologic disease or with the neuroimaging or histological findings (Ruggieri et al 1996). It is a necessary prerequisite that hypopigmented skin is not preceded by vesicular or verrucous stages because cutaneous lesions in the stage IV of incontinentia pigmenti are indistinguishable from those of hypomelanosis of Ito (Happle 1993; Happle 2006).

Sweat glands and fingernails also may be abnormal (Pascual-Castroviejo et al 1988; Ruiz-Maldonado et al 1992). Hypohidrosis corresponds to hypopigmented areas, which may represent a pathological cell line. This feature,
however, has been found in about one third of patients with hypomelanosis of Ito (Kuster and Konig 1999). Absence of sweating with absence of glands in a skin biopsy has been reported, and this may be an argument in favor of the heterogeneity of hypomelanosis of Ito.

Other types of cutaneous lesions associated with hypomelanosis of Ito include café-au-lait spots, nevus marmorata, angiomatous nevi, nevus of Ota, and slate gray spots.

**Scalp and hair.** Scalp alterations mainly include changes in hair color, diffuse alopecia, and hair with trichorrhexis and white-grayish color (Pascual-Castroviejo et al 1998; Ruggieri and Pavone 2000). Some patients show alopecia in areas of the scalp until 3 to 5 years of age, at which time trichorrhexis and grey-white hair may appear (Pascual-Castroviejo et al 1988; Pascual-Castroviejo et al 1998). Patients with hair anomalies (mostly color changes) may show an increased frequency of systemic anomalies (including macrocephaly, hemicranial or hemifacial hypertrophy, ocular, nasal, or oral abnormalities, cerebral malformations, asymmetry of the trunk or extremities, and others) than patients without hair changes. Hypochromic hair may appear as areas of patches, streaks, or extending over the entire scalp, associated with achromic or hypochromic skin. Focal hypertrichosis of the genital area without signs of precocious puberty has been observed.

**Eye manifestations.** Ocular alterations are rarely reported and they are not specifically related to hypomelanosis of Ito. These include strabismus, nystagmus, dacryostenosis, hypertelorism, ptosis, symblepharon, nonclosure of the upper lid, myopia, amblyopia, iridal heterochromia, scleral melanosis, cataracts, striated patchy hypopigmented fundi, atrophy of the choroid, corneal opacity, micro-ophthalmia, macro-ophthalmia, optic nerve hypoplasia, and retinal degeneration (Jelinek et al 1973; Schwartz et al 1977; Pascual-Castroviejo et al 1988; Ruiz-Maldonado et al 1992; Ruggieri et al 1996; Ruggieri and Pavone 2000; Pascual-Castroviejo and Ruggieri 2007).

**Oral manifestations.** Oral anomalies are of a wide variety and consist of defective dental implantation, partial anodontia, dental hypoplasia or dysplasia, conical teeth, and defective enamel (Pascual-Castroviejo et al 1998). Hamartomatous cuspids protruding from the dental crowns of permanent teeth might be histologically reminiscent of odontoma. Bifid uvula and submucosal cleft palate are other unusual anomalies.

**Musculoskeletal manifestations.** Musculoskeletal disturbances are usually observed in more severe phenotypes (Pascual-Castroviejo et al 1988; Ruiz-Maldonado et al 1992; Pascual-Castroviejo et al 1998). Skeletal defects include short stature, asymmetry with hemihypertrophy or hemihypotrophy of a part or of an entire side of the body (Ruggieri and Pavone 2000; Pascual-Castroviejo and Ruggieri 2007), scoliosis, thoracic deformities (pectus carinatum or excavatum), various finger and toe anomalies (clindodactyly, polydactyly, syndactyly, brachydactyly), and foot deformities (pes cavus, talipes equinovarus) (Jelinek et al 1973; Pascual-Castroviejo et al 1988; Pascual-Castroviejo et al 1998; Ruggieri and Pavone 2000; Tragardh et al 2014).

Hypertrophic or hypotropic areas are usually seen on the same side as the hypomelanotic skin. Unilateral hypertrophy, also referred to as hemi-overgrowth, occurs in 7% of patients and is associated with a higher prevalence of extracutaneous manifestations (Pavone et al 2016). Bilateral hypertrophy is found in some cases with generalized hypomelanotic skin. The patients usually show coarse facies and macrocephaly (Schwartz et al 1977, Pascual-Castroviejo et al 1988; Schwartz et al 1977, Pascual-Castroviejo et al 1998). All these defects are likely related to the age-dependent effect of the genetic mosaic abnormality (Ruggieri 2000; Ruggieri and Pavone 2000).

**Nervous system manifestations.** Anomalies of the CNS may include microcephaly or macrocephaly, cognitive and motor retardation, seizures, ataxia, hyperkinesias, and hypotonia (Jelinek et al 1973; Pascual-Castroviejo et al 1988; Ruiz-Maldonado et al 1992; Ruggieri et al 1996; Pascual-Castroviejo et al 1998; Ruggieri and Pavone 2000). They represent the most severe complications of hypomelanosis of Ito and there is a consistent discrepancy between the reported prevalence figures; by literature review, the incidence of associated neurologic disease was as high as 100% (Hara et al 1989), 94% (Pascual-Castroviejo et al 1988), or 80% (Hamada et al 1979), or as low as 61% (Rosemberg et al 1984), 50% (Hamada et al 1967), 40% (Ortonne et al 1979), or 30% (Nehal et al 1996; Ruggieri and Pavone 2000).

**Cognitive and behavioral problems.** These are the most frequent neurologic problems in individuals with hypomelanosis of Ito. An IQ below 70 has been reported in 30% (Nehal et al 1996; Ruggieri and Pavone 2000), 57% (Pascual-Castroviejo et al 1998), and 70% (Ruiz-Maldonado et al 1992) of cases, likely depending to ascertainment bias in tertiary referral centers (Ruggieri and Pavone 2000). Patients with mental retardation have been reported to exhibit autism spectrum disorders (Pascual-Castroviejo et al 1988; Glover et al 1989; Akefeldt and Gillberg 1991; Ruiz-
Maldonado et al 1992; Zappella 1993), but again the highest prevalence figures for autism in hypomelanosis of Ito (8% to 10%) are likely due to a bias toward child neuropsychiatry referrals (Akefeldt and Gillberg 1991; Zappella 1993). Most patients with mental retardation, autism spectrum disorders, or both previously suffered infantile spasms or severe seizures (Pascual-Castroviejo 1989; Ruiz-Maldonado et al 1992; Pascual-Castroviejo et al 1998). The association of mental retardation with seizures is seen in 65% of cases (Ruiz-Maldonado et al 1992; Ruggieri et al 1996; Pascual-Castroviejo et al 1998).

Epilepsy. This is the second most frequent neurologic manifestation of hypomelanosis of Ito. Seizures may occur in 11% (Nehal et al 1996) to about 50% (Pascual-Castroviejo et al 1988; Pascual-Castroviejo et al 1998) of cases. Seizures commonly appear early, within the first year of life and are mostly associated with cognitive deficits. Seizures can be refractory but are controlled with antiepileptic drugs in 70% (Pascual-Castroviejo et al 1998). Epilepsy surgery can be successful in the carefully chosen candidate with medication-refractory epilepsy (Placantonakis et al 2005; Manjila et al 2014). Seizure semiology is heterogeneous; of those patients with epilepsy, about 50% manifest as generalized tonic-clonic seizures, 25% as partial seizures, 15% as infantile spasms, and 8% as myoclonic seizures (Pascual-Castroviejo et al 1998; Assogba et al 2010; Pavone et al 2015). There is no consistent EEG pattern in hypomelanosis of Ito. The EEG can yield normal results or show a wide range of abnormalities, with both focal and generalized epileptiform discharges (Esquivel et al 1991; Ogino et al 1994; Pavone et al 2015).

Other neurologic alterations found in isolated cases include muscular hypotonia, ataxia, neurosensorial deafness, and cortical visual impairment (Ruggieri and Pavone 2000; Scott et al 2008).

Imaging findings. There are no constant findings in hypomelanosis of Ito, as expected. Most hypomelanosis of Ito cases (and likely almost all cases with no clinical neurologic signs or symptoms) display normal neuroimaging studies (Barkovich 2005; Edelstein et al 2005) or only show enlarged perivascular spaces (Ruggieri et al 1996). In the remainder, abnormalities may be grouped into white matter alterations and structural malformations (Edelstein et al 2005). Nonprogressive white matter abnormalities on MRI (thought to be pathologically related to dilated Virchow-Robin spaces and/or altered/delayed myelination) may appear as early as a few months of age, and on T2-weighted and FLAIR sequences show multifocal, symmetric, high-signal foci in the periventricular and subcortical white matter, particularly in the centrum semiovale. CT shows the same features as multiple low-density areas in the deep white matter of the hemispheres or as diffuse low density in the white matter (when a large number of lesions are present) (Edelstein et al 2005). White matter lesions are static over time (Fryburg et al 1996) and show no correlation between the extent of the lesions and the patient age (Ruggieri et al 1996). The most frequent structural anomalies are cerebellar hypoplasia or atrophy, focal cerebral atrophy or generalized cerebral atrophy, cerebral dysplasias, or other migrational abnormalities rarely associated with hemimegalencephaly. Other anomalies include gray matter heterotopia, blurred gray/white matter junction, agryria, polymicrogyria, porencephaly, and periventricular cysts (Ruggieri and Pavone 2000; Barkovich 2005; Edelstein et al 2005; Pascual-Castroviejo and Ruggieri 2007). Rare cases have also been reported of hypomelanosis of Ito with Sturge-Weber syndrome-like unilateral leptomeningeal angiomatoses (García Muret et al 2002; Degerliyurt et al 2009).

Other systemic anomalies. These can include congenital cardiac disease (Pascual-Castroviejo et al 1988; Ruiz-Maldonado et al 1992; Pascual-Castroviejo et al 1998), renal disease including single kidney or ureteral duplication, focal segmental glomerulosclerosis with end-stage renal disease, or glomerulocystic kidney disease (Gatter et al 2007; Vergine et al 2008), and genitourinary anomalies including cryptorchidism, microopenis, or macrogenitosomia (Pascual-Castroviejo et al 1988; Ruiz-Maldonado et al 1992; Pascual-Castroviejo et al 1998). Asymmetric breast development (Ito 1952; Pascual-Castroviejo et al 1998), gynecomastia in either boys or prepubertal girls (Pascual-Castroviejo et al 1988), and precocious puberty (Park et al 2011) have all been reported. Hypomelanosis of Ito occasionally is associated with vascular anomalies such as moyamoya disease (Echenne et al 1995), aortic malformations (Vivas et al 2009), intracranial arteriovenous malformation, or intestinal lymphangiectasia. Finally, lung involvement with segmental pulmonary hypoplasia has also been reported (Bhat et al 2014).

Hypomelanosis of Ito and tumors. A limited number of hypomelanosis of Ito cases are occasionally associated with tumors, including cystic teratoma in association with diploic epidermoid cyst, complex mature sacrococcygeal dysembryoma tumor, choroid plexus papilloma, and dental hamartomatous tumor (complex composite odontome-like).
Rarely, malignancies such as acute lymphoblastic leukemia, medulloblastoma, neuroblastoma, and retinoblastoma have been reported (Ruggieri et al 2001; El-Sawy et al 2011).

**Prognosis and complications**

Approximately one third (or fewer) of patients with hypomelanosis of Ito and related disorders (depending on the reported series) have psychomotor delay in infancy and present with cognitive or behavioral deficits later in childhood. Approximately the same percentage presents some type of seizure. Seizures in these disorders may be refractory (Pascual-Castroviejo et al 1988; Ruggieri et al 1996), especially because of disordered neuronal migration (Esquivel et al 1991). However, control of seizures in 70% of patients with hypomelanosis of Ito has been reported in series of Pascual-Castroviejo and colleagues and Ruggieri and Pavone (Pascual-Castroviejo et al 1998; Ruggieri and Pavone 2000). Autistic spectrum disorders, even rarely, must be taken into consideration. Musculoskeletal and other systemic abnormalities are congenital and, thus, are not progressive.

**Biological basis**

**Etiology and pathogenesis**

*Mendelian transmission.* There have been a number of single case reports claiming familial occurrence and supporting single gene inheritance (Donnai 1996; Ruggieri 2000; Ruggieri and Pavone 2000; Pascual-Castroviejo and Ruggieri 2007).

Two families were reported with a mother and her daughter and 1 family with a brother and sister affected by hypomelanosis of Ito (Amon et al 1990; Vormittag et al 1992; Ruggieri 2000). Members of the same family having hypomelanosis of Ito have been mentioned in other series (Pascual-Castroviejo et al 1998). Paradominant inheritance has been claimed to be a possible mechanism in these families as well as in some non-Mendelian recurrences of hypomelanosis of Ito phenotypes running in families (Happle 2006).

There have been reports on daughters from mothers with balanced X;autosome translocations with breakpoint above the juxtacentromeric X region with phenotypes overlapping with hypomelanosis of Ito (Hatchwell 1996).

**Chromosome studies.** The recognition of a variety of chromosomal mosaicsisms (to include associations with trisomies such as trisomy 2 and 21) (Gupta et al 2007; Okanari et al 2014), and ring chromosomes, such as ring chromosome 20 (Cappanera et al 2011), as the pathogenic basis of many cases of hypomelanosis of Ito was a clue to explain the protean clinical manifestations of this condition and their often asymmetrical expression (Sybert 1990; Donnai 1996; Ruggieri 2000; Ruggieri and Pavone 2000). The primary question addressed is how such disparate genotypes could produce the common cutaneous phenotype of patchy pigmentation. By cross-comparing karyotype abnormalities in hypomelanosis of Ito and in cases with demonstrated pigmentary mosaicism with 76 pigmentary and candidate pigmentary gene loci, either in humans or animals, Taibjee and colleagues showed extensive (88%) overlaps between cytogenetic abnormalities and 1 or more pigmentary genes as well as significant (74%) overlaps between pigmentary genes and 1 or more karyotype abnormalities supporting the hypothesis that the pigmentary phenotype could arise through karyotype abnormalities specifically disrupting either expression or function of pigmentary genes (Taibjee et al 2004; Pascual-Castroviejo and Ruggieri 2007).

In hypomelanosis of Ito the pigmentary phenotype could arise through karyotype abnormalities specifically disrupting either expression or function of pigmentary genes. Likely mechanisms to explain the disruption are (Taibjee et al 2004; Pascual-Castroviejo and Ruggieri 2007): (1) parallel comigration of genetically different but not necessarily abnormal cell clones; (2) X-chromosome functional disomy; (3) “spreading” of X inactivation to autosomes; (4) transposons (transposable elements of retroviral origin) regulating gene activation and silencing and modulating the activity of pigmentary genes; (5) genetic imprinting; and (6) phenotype reversion. None of these, however, has so far been demonstrated as the likely mechanism to explain hypomelanosis of Ito. The various processes controlled by the (disrupted) pigmentary genes are: (1) melanoblast migration from the neural crest in fetal life; (2) melanocytes function including synthesis, transport, and degradation of melanosomes; and (3) physiology of the surrounding melanocytes milieu that include keratinocytes, intercellular matrix, growth factors, etc. It is unknown, however, at which level the process is disrupted. Sarnat and Flores-Sarnat hypothesized that the lines of Blaschko and hypomelanotic whorls and patches may represent a disorder of neural crest migration and terminal differentiation of melanocytes (Sarnat and Flores-Sarnat 2005).
Epidemiology

For hypomelanosis of Ito a frequency of 1 in every 7805 general pediatric outpatients, 1 in every 790 general pediatric dermatology outpatients, 1 in every 2983 general pediatric inpatients, and 1 in every 63 pediatric dermatology inpatients was reported by Ruiz-Maldonado and colleagues. A prevalence of about 1 per 600 to 700 new patients referred to a pediatric neurology service at a large National Children's Hospital was reported by Pascual-Castroviejo (Pascual-Castroviejo 1988; Ruiz-Maldonado et al. 1992).

The calculated incidence and prevalence data in the area of Catania, Italy (800,000 inhabitants with approximately 13,000 births per year) were 1 in 7540 births (0.013%) and 1 in 82,000 individuals in the general population (0.0012%) (Ruggieri and Pavone 2000).

The female: male ratio is 1:1 (Ruiz-Maldonado et al. 1992; Pascual-Castroviejo et al. 1998).

Prevention

Affected adults should be reassured that the risk of the same condition in their offspring is low. Peripheral blood karyotyping is warranted, however, in the affected child and his or her parents before considering further pregnancies. Paradominant inheritance is a remote but possible mechanism.

Because of the reports on families with balanced X;autosome translocations with breakpoint above the juxtacentromeric X region whose phenotypes overlapped with hypomelanosis of Ito (Hatchwell 1996; Ruggieri 2000), one should consider an “unfortunate” X inactivation resulting in a severe hypomelanosis of Ito phenotype. Conversely, reassurance can be given to a phenotypically normal mother with a balanced X;autosome translocation having a male offspring with the same translocation that her son would be phenotypically normal, although male infertility would be expected (Hatchwell 1996; Ruggieri 2000).

Differential diagnosis

Hypomelanosis of Ito presents many similarities with other diseases with hypopigmented spots on the skin. These diseases are incontinentia pigmenti of Bloch and Sulzberger (OMIM #308300), tuberous sclerosis (OMIM #191100), vitiligo, and skin fungal infections.

Identical to hypomelanosis of Ito, incontinentia pigmenti shows the streaky pigmented changes and the frequent occurrence of extracutaneous abnormalities. Hypomelanosis of Ito also differs from classical incontinentia pigmenti in the absence of preceding inflammatory or verrucous lesions and the occurrence of a much wider spectrum of associated abnormalities. Furthermore, hypomelanosis of Ito occurs as a sporadic trait (Ruggieri 2000; Taibjee et al. 2004), whereas incontinentia pigmenti is X-linked and now known to be due to mutations of the IKBKG (NEMO) gene (Smahi et al. 2000). Incontinentia pigmenti is also characterized by affecting almost only females, and by a dynamic course of distinct cutaneous lesions that appear successively soon after birth, which include: (1) linear dermatitis with vesicles and erythema, (2) linear verrucous anomalies, (3) hyperpigmented streaks, and (4) hypochromic or achromic lesions similar to those of hypomelanosis of Ito. In contrast to incontinentia pigmenti, the hypopigmentation in patients with hypomelanosis of Ito is either recognized at birth, during the neonatal period, or in early childhood and remains unchanged during many years or for the entire life.

Cutaneous lesions in tuberous sclerosis present as multiple independent spots, irregularly bordered, and frequently have the characteristic ash-leaf configuration. In addition, brain MRIs in tuberous sclerosis have specific characteristics (ie, cortical-subcortical tubers, subependymal nodules, radial white matter abnormalities, calcifications, and more rarely subependymal cell astrocytoma).

Vitiligo is a straightforward diagnosis for dermatologists.

Skin fungal lesions are local problems of the skin that do not involve the CNS and can disappear after a variable period of time, whereas cutaneous lesions of hypomelanosis of Ito do not disappear. Wood lamp examination and superficial skin biopsies could help the differential diagnosis.

Misdiagnosis of hypomelanosis of Ito. In the absence of a recognized diagnosis, the label of hypomelanosis of Ito
has been often used for individuals having diffuse or patchy, generalized or limited, linear or spotty skin
dyspigmentation or hypopigmentation in many patchy or streaky configurations. This has caused great confusion and
has expanded the phenotype of hypomelanosis of Ito, melting under the same rubric several conditions of different
etiologies solely because of the presence of hypopigmented skin lesions. Often, in such cases, the presumptive
diagnosis of a child having CNS or musculoskeletal abnormalities associated with cutaneous anomalies has been based
only on a single or a pair of pigmented skin lesions that could ultimately have been merely a presenting symptom of
other diseases (Ruggieri 2000; Ruggieri and Pavone 2000). Notably, in the London Dysmorphology Database there are
more than 70 different syndromes (including hypomelanosis of Ito) under the same entry “patchy depigmentation of
skin” (Winter and Baraitser 2006). Thus, we would favor the use of the term hypomelanosis of Ito (and related
disorders) only in cases with “overt” and “widely distributed” pigmentary abnormalities, with or without associated
extracutaneous manifestations.

**Linear and whorled nevoid hypermelanosis.** Linear and whorled nevoid hypermelanosis is a sporadic disorder
categorized by (Quecedo et al 1997): (1) asymmetrically distributed linear and whorled hyperpigmentation following
Blaschko lines as well as reticulated hyperpigmentation; (2) coexistence (in some cases) of hyper- and hypopigmented
lesions in the same patient; (3) skin lesions noted at birth or within the first 2 years of life; (4) no preceding
inflammatory event or palpable lesion; (5) gradual increase (spread) of involvement during the first 2 years of life and
subsequent stabilization or gradual fading; (6) sparing of mucous membranes, palms, and soles; (7) sporadic male and
female (equal) incidence; (8) increased pigmentation of the basal layer and prominence or vacuolation of melanocytes,
with no pigment incontinence or dermal melanophages on histological examination; and (9), in approximately 30% of
cases (Bologna et al 1994; Nehal et al 1996), associated systemic anomalies consisting in atrial septal defects,
dextrocardia, mild hypereosinophilia, cerebral palsy, psychomotor delay, seizures, and deafness.

Under the term linear and whorled nevoid hypermelanosis 2 different clinical presentations may be included
corresponding to the same spectrum: (1) the classical generalized pattern with onset within the first 2 weeks of life;
and (2) unilateral cases involving only 1 quadrant of the body, with a later onset at about the second decade of life.

**Phylloid hypomelanosis.** The so-called phylloid hypomelanosis (previously regarded as a hypomelanosis of Ito-
related disorder) appears to be constantly associated to trisomy 13 mosaicism (Schepis et al 2001) and, therefore, is
ruled out on cytogenetic basis.

**Diagnostic workup**

Patients who exhibit pigmentary anomalies (hypopigmentation or depigmentation or hyperpigmentation) along the
lines of Blaschko, in a patchy or linear distribution, unilaterally or bilaterally, should be fully evaluated for structural
systemic abnormalities. Laboratory or imaging tests, including EEG and neuroimaging, should be only oriented by the
abnormal findings on clinical examination. Karyotyping of peripheral blood, and if this is normal, skin fibroblasts or
better keratinocytes or melanocytes obtained from biopsies taken from affected and unaffected areas, should be
performed in affected individuals to support the diagnosis.

**Histopathology.** Regarding follow-up controls, each case should be examined individually and further evaluated to
the extent that the history, careful clinical examination, and investigations dictate with more frequent re-evaluations in
children with unusual symptoms or complications requiring special care. Parents should be reassured that serious
complications, if present, are congenital and, thus, typically evident clinically early in infancy. The chance occurrence
of a tumor in an affected patient should be almost the same as in the general population.

The routine or screening use of brain MRI does not improve hypomelanosis of Ito prognosis because the majority of
CNS abnormalities are either unspecific or not treatable and overall do not predict a poor outcome. Conversely, a full
brain MRI study is warranted if and when seizures ensue because some patients could have underlying neuronal
migration anomalies.

**Management**

No special treatment is indicated for the skin lesions and no precaution has to be taken with regard to sun exposure or
cream applications. Malignant transformation was never recorded in the skin lesions in the largest series so far
reported, including ours. No data are available in the literature about pregnant mothers with pigmentary mosaicism
who suffered complications or about children of affected mothers who suffered complications during gestation or
Convulsive episodes should be treated similarly to seizures of other etiologies. Motor disturbances may be minimized with good physiotherapy and orthopedic care.

Mental retardation is approached educationally and special vocational training should be appropriate to each patient's individual capabilities.

Ocular, oral, urogenital, and other disturbances must receive appropriate individual treatment.

Special considerations

Pregnancy

Affected adults should be reassured that the risk of the same condition in their offspring is low. Peripheral blood karyotyping is warranted, however, in the affected child and in his or her parents before considering further pregnancies. The risk for a pregnant woman affected by hypomelanosis of Ito is related to the complications or systemic manifestations of the disorder.

Anesthesia

Special precautions are needed as in other individuals affected by genetic conditions associated with systemic complications and are related to the underlying abnormalities (eg, neurologic, urologic, cardiac complications, etc.).

Acknowledgements

The views expressed are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.

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**References especially recommended by the author or editor for general reading

**Former authors

Ignacio Pascual-Castroviejo MD (original author), Martino Ruggieri MD PhD, and Lorenzo Pavone MD

**ICD and OMIM codes

**ICD codes

ICD-9:
Other specified anomalies of skin: 757.3

ICD-10:
Other congenital malformations of the skin: Q82
OMIM numbers
Hypomelanosis of Ito: *300337

Profile

Age range of presentation
0-01 months
01-23 months
02-05 years
06-12 years

Sex preponderance
female>male, 1:1

Family history
family history may be obtained

Heredit
heredity may be a factor
paradominant heredity

Population groups selectively affected
none selectively affected

Occupation groups selectively affected
none selectively affected

Differential diagnosis list
incontinentia pigmenti of Bloch-Sulzberger
tuberous sclerosis
vitiligo
skin fungal infections
linear and whorled nevoid hypermelanosis
phylloid hypomelanosis

Associated disorders
Chromosomal mosaicism

Other topics to consider
Epilepsy
Hemimegalencephaly
Incontinentia pigmenti
Mental retardation
Neurocutaneous syndromes