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Neurocutaneous disorders identified in the neonatal period and infancy: Hypomelanosis of Ito

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ABSTRACT

Hypomelanosis of Ito is a rare neurocutaneous disorder named after the Japanese dermatologist Minoru Ito who in 1952 described the condition. Characteristically, the hypopigmented lesions in this condition follow Blaschko lines. Extracutaneous manifestations of the disease include neurological, musculoskeletal, cardiac, endocrine, and renal signs and symptoms. The most common neurological manifestation is cognitive impairment. Seizures, developmental delay, and abnormal tone can also be present. In this review we discuss the condition's clinical presentations, its diagnostic criteria, and consensus recommendations.

Introduction

Hypomelanosis of Ito (HI) is one of the most common neurocutaneous diseases after neurofibromatosis and tuberous sclerosis complex and was first described by the Japanese dermatologist Minoru Ito in 1952.[1] Much like other neurocutaneous diseases, it encompasses a wide array of phenotypes involving dermatological, neurological, musculoskeletal, cardiac, endocrine, and renal symptoms. While multisystem involvement is common, HI is heterogenous in its presentation due to the proposed mosaic mode of inheritance.

In the initial description, Ito thought the condition was a cutaneous disorder.[1] HI was later found to have strong associations with neurological manifestations of developmental delay and epilepsy.[2,3] Several modes of inheritance have been proposed in the past,[4,5] but it is now considered to be the result of somatic mosaicism as multiple mosaic chromosomal anomalies have been reported.[6,1]

Clinical presentation

Cutaneous manifestations

Skin findings are often the primary presentation of HI and are required for the diagnosis. The hallmark cutaneous manifestation of the disease involves hypopigmented lesions resulting from genetic mosaicism of cells migrating along Blaschko lines. Blaschko lines are developmental lines that follow the path of ectodermal cell migration (Fig. 1) and are hypothesized to result from mutations in genes expressed in epidermal cells (keratinocytes and melanocytes).[7] These lines are visible because of variation in melanin production due to mosaic gene expression with hypopigmented areas having fewer melanocytes. The remaining melanocytes have fewer premelanosomes and fewer melanosomes which are also unusually small, and have decreased melanin production.[8]

The whorls and linear patterns of Blaschko lines can be a classic finding of cutaneous mosaicism (Fig. 2) seen in various congenital skin disorders. Many documented cases of HI reveal bilateral hypopigmented streaks and whorls most visible on the upper trunk and upper extremities.[11,12] These lesions typically spare mucous and volar surfaces. Linear cutaneous patterns are often noted at birth or early infancy as the skin becomes exposed to sunlight, thereby leading to greater contrast between affected and unaffected areas.[13] These lines can be limited to one area of the body or occur in a more widespread pattern and can often fade in childhood or adulthood due to the age-dependent reduction of melanin in the epidermis.

Other cutaneous manifestations, found in approximately 40% of cases of HI, include café-au-lait spots, cutis marmorata, angiomatous nevi, nevus of Ota, dermal melanocytosis, abnormal sweating, ichthyosis, and morphea.[14] Findings involving scalp and hair abnormalities have been reported including alopecia, hypertrichosis, depigmentation of hair, and nail dystrophy.[2]

It is believed that different chromosomal aberrations can affect the locations of genes involved in pigmentation as described above.

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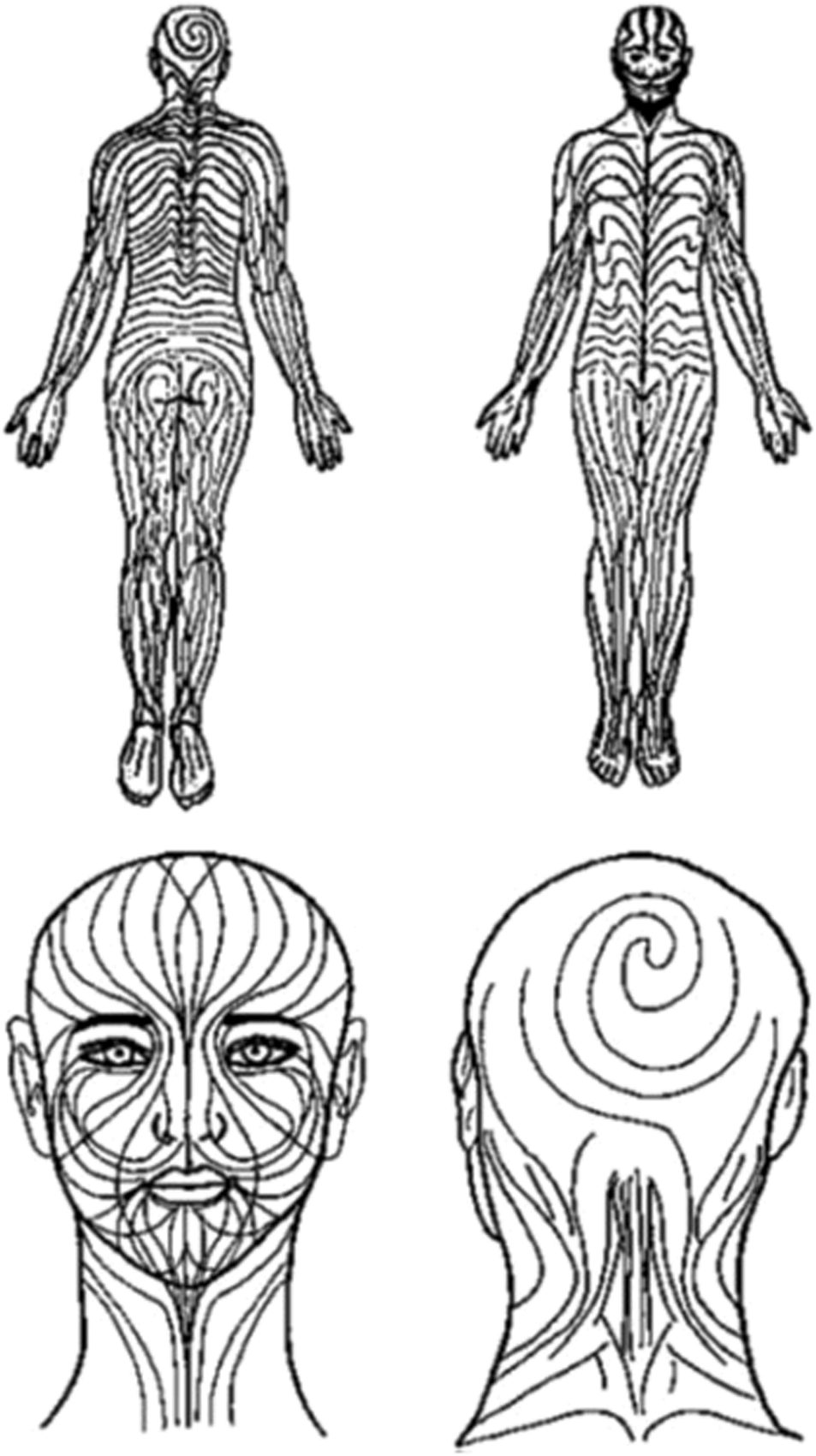

Fig. 1. Blaschko lines.
Blaschko lines are shown over the body. Adapted from "Molho-Pessach and Schaeffer".[9]

Similarly, extracutaneous manifestations are hypothesized to be caused by the presence of different genetic alterations in cells following this pattern of embryonic cell migration but differentiating into extracutaneous cells. Despite this mechanism, the degree of hypopigmentation and cutaneous findings do not correlate with the severity of the disease and extracutaneous symptoms.[14]

Neurological manifestations

Nervous system abnormalities are the most common extracutaneous manifestation of HI with a prevalence between 30% to 90% in affected individuals.[2,14,15] The most common manifestations include intellectual disability and seizures.[15] Intellectual disability occurs in as many as 80% of patients, with 60% having an IQ < 70. Seizures occur in up to 50% of patients.[15] Seizure types include generalized tonic-clonic, focal, myoclonic, and infantile spasms.[15] Treatment for these conditions varies case by case depending on the frequency and seizure type. The epilepsy of children with focal seizures secondary to brain malformations is more pharmacoresistant and requires non-pharmacological interventions for seizure control.[14,16]

Despite the incidence of neurological manifestations, most patients with HI have normal neuroimaging or only show enlarged perivascular spaces.[17] When present, neuroimaging findings of HI include abnormal white matter such as T2 and FLAIR hyperintensities in deep periventricular white matter and migration defects including dilated Virchow-Robin spaces, gray matter heterotopia, pachygyria, microgyria, generalized cerebral or cerebellar atrophy or other white matter migration abnormalities leading to hemimegaloencephaly (Fig. 3).[14,15,17] These white matter abnormalities develop during the first year of life and do not change with the age of the patient.[18] Rare cases of Sturge-Weber syndrome-like leptomeningeal angiomatosis[19] have also been observed in HI. While some authors reported that the extent of the

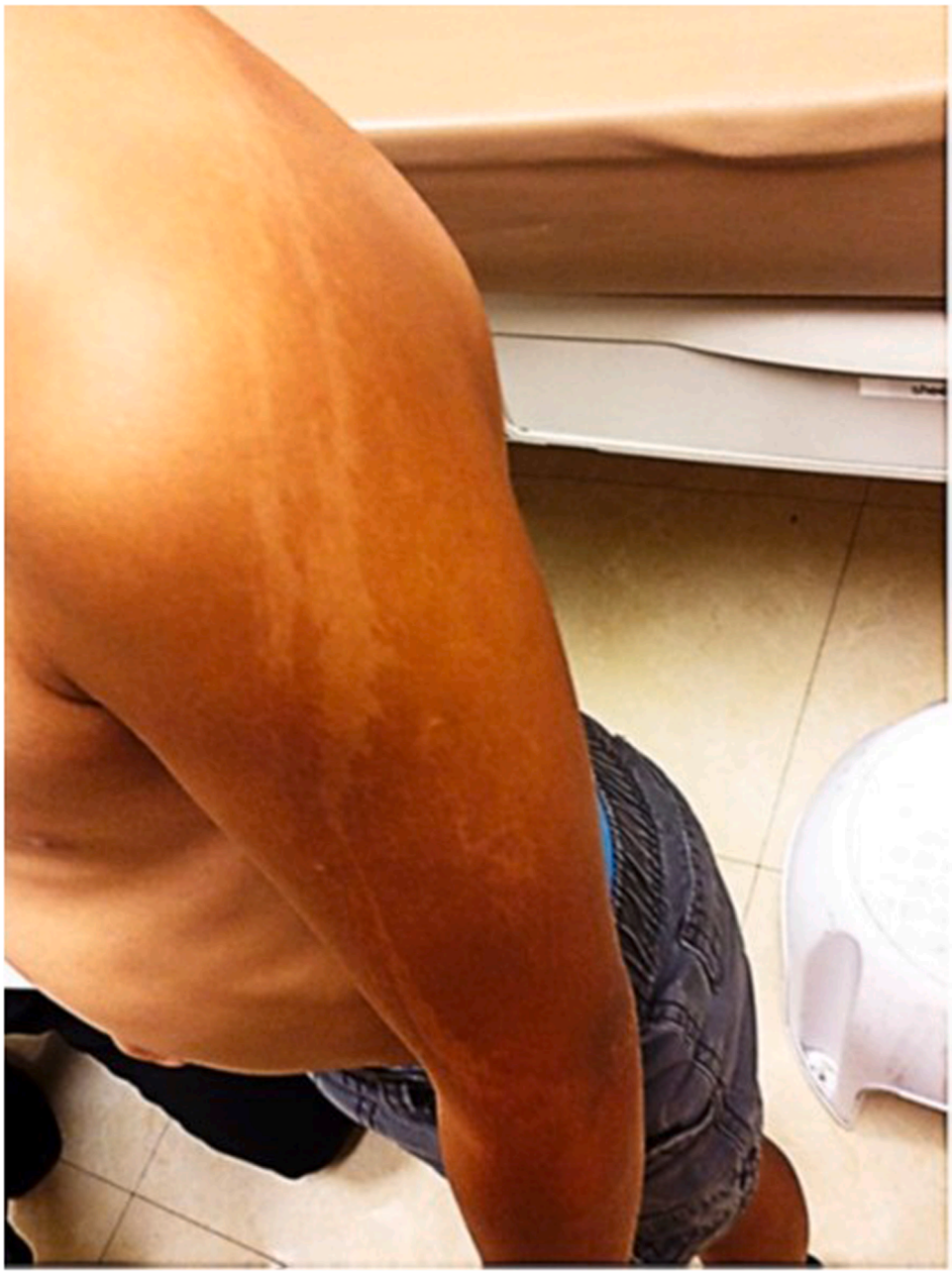

Fig. 2. Cutaneous findings of hypomelanosis of Ito.
Patient with hypomelanosis of Ito showing the lesions characteristic of the disease over his left arm. Adapted from "Albuja, Shrivastava, and Khan".[10]

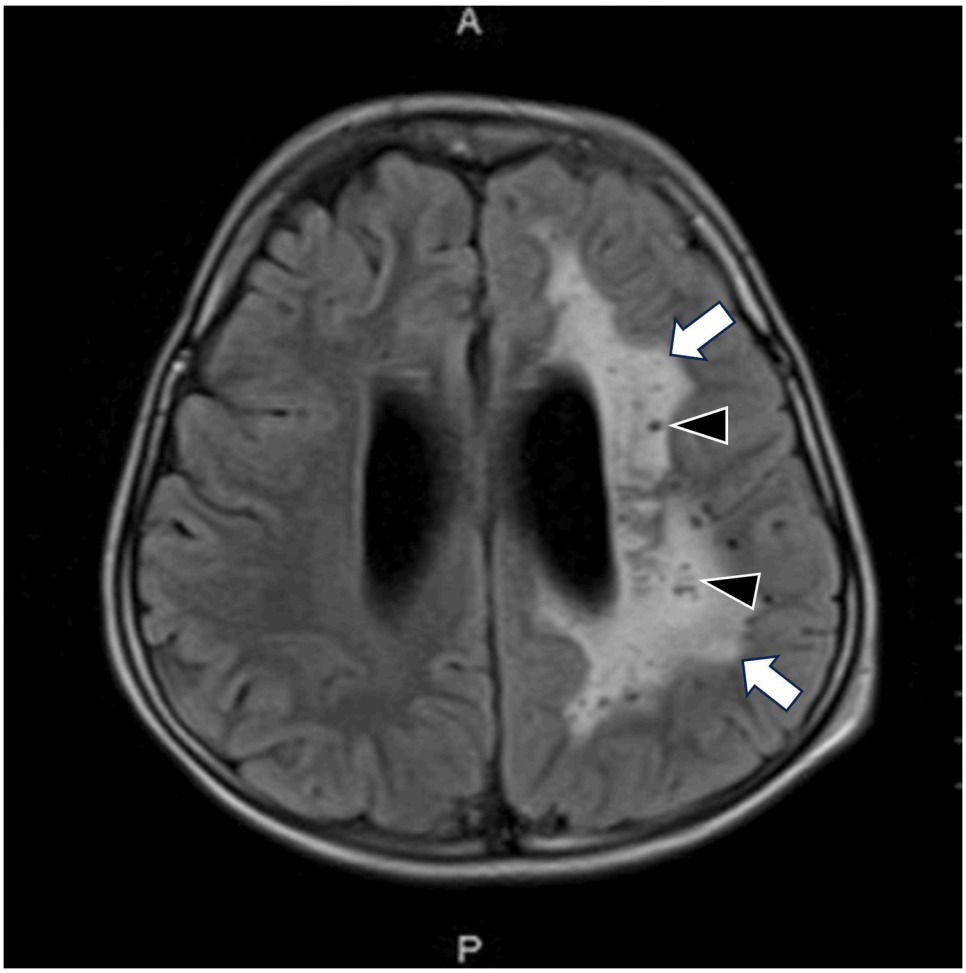

Fig. 3. MRI Findings in hypomelanosis of Ito.
Brain FLAIR MRI shows hyperintense signal predominantly in the white matter of the left hemisphere (white arrows). There are several small cystic dilations of the perivascular space (black arrowheads). Adapted from "Albuja, Shrivastava, and Khan".[10]

white matter's lesions may correlate with the severity of the cognitive delay and seizures,[3,14,15] there are rare cases of children who have extensive white matter changes and yet have normal intellect and a normal neurological exam. neurological.[20]

Other manifestations

Musculoskeletal abnormalities are the second most common extracutaneous manifestations of HI. They are observed in approximately 70% of all cases. Patients may present with skeletal defects including hemihypertrophy or hemihypotrophy of limbs often ipsilateral to the more severe cutaneous findings.[15] Other common findings include scoliosis, chest wall deformity, and finger abnormalities such as polydactyly, clinodactyly, syndactyly, or brachydactyly.[2,21] Almost all cases of HI and musculoskeletal manifestations also have neurological manifestations.

Approximately 25% of patients with HI also have ocular manifestations, with hypopigmentation of the iris being the most common. These pigmentary changes are often static. Despite involvement of pigment cells, they do not interfere with vision.[22] Other eye manifestations include strabismus, nystagmus, cataracts, amblyopia, and myopia.[23,24]

Oral anomalies often involve defective dental implantation with dental hypoplasia or dysplasia and defective enamel.[25]

Cardiac anomalies occur in fewer than 10% of cases. Congenital heart disease can include congenital anomalies such as tetralogy of Fallot, atrial septal defect, and congenital heart block.[2,15]

Structural renal anomalies have been reported in children with HI including glomerulocystic kidney disease[26] and focal segmental glomerulosclerosis with end-stage renal disease.[27]

In three cases, HI was associated with precocious puberty. One of those patients had severe epilepsy, autonomic symptoms, and global delay. The neurological manifestations caused the child's early demise.[28]

A few cases of HI with associated malignancies have been reported with cases of acute lymphoblastic lymphoma, medulloblastoma, and retinoblastoma.[2,29] While many tumor types associated with HI are postulated to be due to abnormal neural crest formation, routine screening for tumors is not recommended.[21]

Diagnosis

The diagnostic criteria of HI is based on the clinical examination with findings of hypopigmented lesions along the lines of Blaschko. If the disease is suspected, careful examination with a Wood's lamp - long wave ultraviolet light - can enhance the hypopigmentation and assist in confirmation of the clinical findings.[30]

In 1992, the following diagnostic criteria were established by Ruiz-Maldonado et al. The diagnosis of HI requires *either* one major and one minor criterion *or* two minor criteria.[2]

Major criteria

- Non-hereditary cutaneous hypopigmented linear streaks or patches involving more than two body segments, appearing at birth or in the first months of life
- One or more neurological or musculoskeletal manifestations

Minor criteria

- Chromosomal anomalies (mosaicism in biopsied fibroblasts)
- Two or more congenital malformations, excluding nervous and musculoskeletal systems

While the diagnosis of HI relies heavily on the skin manifestations, it is important to differentiate this disease from other conditions that manifest with cutaneous lesions. HI can often be distinguished from other conditions based on the age at which the skin lesions become evident. Specifically, the lesions of HI are either present at birth or in early childhood, and become more evident when the skin is exposed to sunlight.[16]

Differential diagnosis

It is important to distinguish HI from Incontinentia Pigmenti (IP) which can present with similar lesions in infancy.[16] While HI lesions are relatively static early in life and may fade over time, IP lesions undergo stages of inflammation with initial hyperpigmentation followed by hypopigmentation. HI, however, is non-inflammatory (Ream, 2015) and is characterized by a decreased number of melanocytes.[31] Other conditions to exclude are Waardenburg syndrome and piebaldism. Waardenburg syndrome is characterized by an association with a white forelock, iris heterochromia, hypertelorism, and depigmented dermal patches. Piebaldism can also present with patches of melanocyte loss, although they do not follow lines of Blaschko, and is associated with a congenital white forelock and leukoderma on the frontal scalp.[32]

Genetics

While several modes of transmission of HI have been proposed, mosaicism remains the most plausible explanation. Genetic mosaicism is defined as the presence of multiple cell lineages with different genotypes in a single individual. This can often be secondary to a mutation or chromosomal disjunction. Mosaicism is thought to lead to the characteristic whorled pattern of pigmentary changes derived from neural crest development.

Other modes of transmission including familial HI have been proposed but have not been proven.[4,23] It has been proposed that familial occurrence is secondary to balanced translocation or other chromosomal abnormalities.[23] While transmission of HI is not commonly seen in families as chromosomal defects generally occur de novo during embryonic development,[12] the diagnostic criteria allow for the diagnosis in the less common occurrence of familial presentation.[2]

Epidemiology

HI is one of the more common neurocutaneous disorders, but remains a very rare condition with an incidence estimated to be from 1/10,000 to 1/8,500 births.[33] The prevalence among the general population is about 1 case per 82,000.[13] While it is not believed to affect one race more than the other, it is more easily diagnosed in darker skinned individuals due to easier recognition of hypopigmentation. Reports of the female to male ratio are inconclusive.[15]

Management

HI is a multi-system neurocutaneous disorder which may require the intervention of multiple specialists as outlined in Table 1. Patients with linear streaks and whorls suspected to be consistent with HI should undergo Wood's lamp testing for confirmation. Karyotyping of blood and if necessary, skin, to detect mosaicism is warranted for all patients with whorled pigmentary changes, either hyperpigmentation or hypopigmentation that cannot be explained by other dermatologic conditions.[4] If patients meet diagnostic criteria, further evaluation is needed due to the outlined risk of associated multisystem involvement.

Cutaneous findings in and of themselves do not require further treatment other than for cosmetic reasons. No extra precautions need to be taken regarding sun exposure or treatment of hypopigmented lesions. There is no known risk of malignant transformation of these lesions.

Neurological manifestations of the disease require close follow up for evaluation and treatment. Once a cutaneous diagnosis is made, MRI of the brain should be done to evaluate for intracranial lesions. Regular follow up visits during the first 3 years of life are recommended to monitor developmental milestones while providing supportive therapies as needed for low tone and developmental delay. Seizures are a common neurological manifestation but, in many cases, respond well to first line treatment, especially in the absence of brain malformations.[3] In the case of pharmacoresitant epilepsy, surgery may provide palliative seizure control.[34]

Other extracutaneous manifestations requiring screening and monitoring include: serial physical examinations to rule out scoliosis and other abnormalities of musculoskeletal development; ophthalmologic evaluation early in childhood with serial annual examinations to ensure no loss of visual acuity; renal ultrasound and kidney function panel are recommended to rule out renal cysts and ensure proper renal function.[35] If precious puberty is suspected, a referral should be made to a pediatric endocrinologist.

Prognosis

HI is a heterogeneous disease and therefore the prognosis and complications associated with the disease differ according to the extent in which the organs and systems are involved. As a general rule, the prognosis for patients who only have cutaneous manifestations is good. Neurological manifestations including developmental and cognitive delay and epilepsy can significantly affect the patient and the patient's family. Systemic involvement including musculoskeletal, cardiac, and renal systems are congenital and non-progressive.

Table 1
Multisystemic management of HI.

	Screening for manifestations	Treatment
Dermatologic	Wood's lamp examination, Dermal biopsy if needed for the diagnosis	Cosmetic only
Neurologic	Brain imaging (MRI) if neurologic involvement is suspected, EEG if seizures are suspected	Supportive therapies for psychomotor delays, Anti-epilepsy medication is often effective, Palliative surgical options for pharmacoresistant cases
Musculoskeletal	Serial physical exams, Radiologic imaging for suspected involvement	Physical therapy, Orthopedic referral for supportive bracing and surgical consideration
Ophthalmologic	Annual ophthalmological exams	Prescription vision correction, Supportive treatment to correct vision loss
Cardiovascular	Routine newborn screening for congenital heart disease	Cardiovascular referral for supportive or surgical treatment of findings
Renal	Renal function panel and renal ultrasound to evaluate cysts following diagnosis	Nephrology referral for abnormalities

Conclusion

Hypomelanosis of Ito is a neurocutaneous disorder that can be associated with a variety of extracutaneous manifestations and it must be distinguished from other neurocutaneous disorders. Early recognition is vital to ensure proper therapy and management of the extracutaneous manifestations.

CRediT authorship contribution statement

George Zakhary: Writing – review & editing, Writing – original draft, Conceptualization. **Margie Ream:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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