Case Report

The neurologic aspects of hypomelanosis of Ito: Case report and review of the literature

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ABSTRACT

The term hypomelanosis of Ito (HI) is applied to individuals with skin hypopigmentation along the lines of Blaschko. Although it was originally described as a purely cutaneous disease, subsequent studies describing HI reported a 33% to 94% association with multiple extracutaneous manifestations, mostly of the central nervous and musculoskeletal systems. This leads to characterization of HI as a neurocutaneous disorder. We report a 10-year-old boy who presented with constellation of multiple congenital anomalies including facial dysmorphism, skin hypopigmentation, musculoskeletal, and nervous system abnormalities. The latter manifested as hypotonia, generalized seizures, and mild mental retardation. Cranial magnetic resonance imaging revealed normal finding initially, however; follow-up diffusion weighted images were suggestive of a possible iron accumulation. The facial phenotype coupled with the bilateral globus pallidi lesions were never been reported in association with HI. Thus, our patient represents a possible novel example of HI.

Key words:

Hypomelanosis of Ito; Brain iron accumulation; Neurocutaneous syndrome

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INTRODUCTION

Hypomelanosis of Ito (IH) or incontinentia pigmenti achromians (Mendelian Inheritance in Man, MIM 146150) is a rare neurocutaneous syndrome, first described by Ito in 1952 as a purely cutaneous disease with skin hypopigmentation [1,2]. It is now known that HI is a systemic disease with other manifestations arising predominately within the central nervous system and the musculoskeletal system [3-7]. Craniofacial, cardiac, renal, and gonadal abnormalities [8 ,9]. McKusick`s catalogue of inherited diseases lists IH as an autosomal dominant disorder, although evidence for this mode of inheritance, or indeed for any genetic etiology, is inconclusive [10, 11]. Current theory suggests that hypomelanosis of Ito is a nonspecific manifestation of chromosomal mosaicism; however, chromosomal alteration have not been demonstrated in every case of HI [5,12,13]. The incidence and prevalence of HI was estimated to be between 1 in 7540 births and 1 in 82,000 in different studies [5].

The clinical manifestations of HI are variable, but the most remarkable clinical markers are distinct patterns of skin involvement along the lines of Blaschko consisting of hypopigmented bizarre macular zones or spots with irregular borders, whorls, patches or linear white streaks with various patterns of distribution and colors, that appear frequently on the trunk, occasionally on the extremities , and seldom on the face and scalp with sparing of the palms, soles, and mucous membranes. Contrary to incontinentia pigmenti, these skin manifestations, are not preceded by inflammatory or degenerative changes, and can be present at birth or develop during childhood. Histopathologically, there is a decreased number and size of melanosomes in the basal layer of the epidermis [5-7,14]. Other manifestations include patchy alopecia, nail abnormalities include ridging, dystrophy, and absence of nails. Dental abnormalities include increased tooth spacing, abnormal number, size, and shape. Craniofacial abnormalities include macrocephaly, low set ears, small nose, and orbital hypertelorism. A wide variation of neurologic involvement is reported in HI including: developmental delay (40-60%), epilepsy with early onset in life (11.5-50%), and autistic behavior. Some patients reported with an early epileptic encephalopathy syndrome such as West syndrome with evidence of asymmetrical hypsarrhythmia on electroencephalogram. Other occasional findings in HI are; muscular hypotonia or hypertonia, hyperkinesias, nystagmus, ataxia, and neurosensory deafness and speech delay. The association of mental retardation and seizures is frequent (60-70%) and is thought to be due to abnormal neuronal migration [5-7,14,15]. Although there are no reported consistent central nervous system lesions demonstrated radiographically in HI, more than half of patients have white matter abnormalities detected with magnetic resonance imaging in the parietal, periventricular and subcortical white matter of both hemispheres. Other types of central nervous system lesions have been demonstrated by computed tomography or magnetic resonance imaging in isolated cases [5,6,14]. There are limited neuropathologic descriptions of HI in the literature [16-18]. Nevertheless, heterotropic gray matter and regional cortical dysplasia have been described [16,17]. Also, HI has been associated with migration disorders such as polymicrogyria, hemimegaloencephaly, intracranial arteriovenous malformation and moyamoya disease [19,20]. To the best of our knowledge the association of bilateral golbus pallidi lesions particularly lesions of iron accumulations and HI has not, hitherto, been reported.

CASE REPORT

A 13 -year-old boy was evaluated in our tertiary care neurology clinic. His pregnancy and delivery were uneventful and he passed through a normal neonatal period. Although his gross and fine motor

milestones were achieved within the normal range, his cognitive and language development were noted to be slower compared with his siblings. Areas of abnormal skin pigmentation were first noted when he was six months old. At age 6 years, he had afebrile seizures consisting of frequent episodes of sudden dizziness, feeling of spinning, and abnormal sound in the left ear followed by weakness of the left leg that caused him to fall. Each episode lasted for less than 2 minutes and ended spontaneously without generalization, loss of consciousness, loss of sphincter control or post ictal sleep. There were no clear precipitatory events, headache, vision problems, paresthesia or post ictal vomiting. His school performance was poor. His general exam showed macrocephaly with head circumference of 53.5 cm (> 98th percentile), short stature with height 141.7 cm (< 5th percentile) and a weight of 29.5 Kg (< 5th percentile) . He had dysmorphic features in the form of high prominent forehead, low set and posteriorly rotated prominent ears, orbital hypertelorism , epicanthal folds, depressed nasal bridge, long nose, anteverted nostrils, high arched palate, tooth spacing with abnormality in size and shape, micrognathia, broad fingers with archanodactyly, mild clinodatyly of 5th finger, broad nails, a gap between big toe and the second one, mild scoliosis with prominent lordosis, joint hyperlaxity and bilateral pes planus. He had normal hair with whorl-like hypopigmented triangular area 10 x 18 cm in diameter, non- blanchable seen on the back extending from midline to lumbar region resembling Blaschko lines (Figure 1) and another similar one, but with small size, seen at the right shoulder. These were non- inflammatory with no history of previous trauma and no family history of vitilligo. His neurological examination revealed poor short-term memory and cognitive delay, especially in the ability to read and to solve mathematical questions. The fundi, extraocular movements, visual fields, and cranial nerve examination were normal. Tendon reflexes, muscular strength and tone were normal. His plantar responses were downgoing bilaterally. Cerebellar signs were absent. There was no stereotypic behavior and no extrapyramidal movement disorder. His initial basic laboratory work-up revealed mild anemia, with normal random blood glucose level, urea and electrolytes, bone profile and liver function tests. His vitamin D level was low (48 nmol/l, normal=75- 120). Full metabolic, endocrinology (including thyroid function test, growth hormone, cortisol, insulin and insulin like growth factor 1, and sex hormones), infection screening including throat swab and antistreptolysin (ASO) titer were normal.

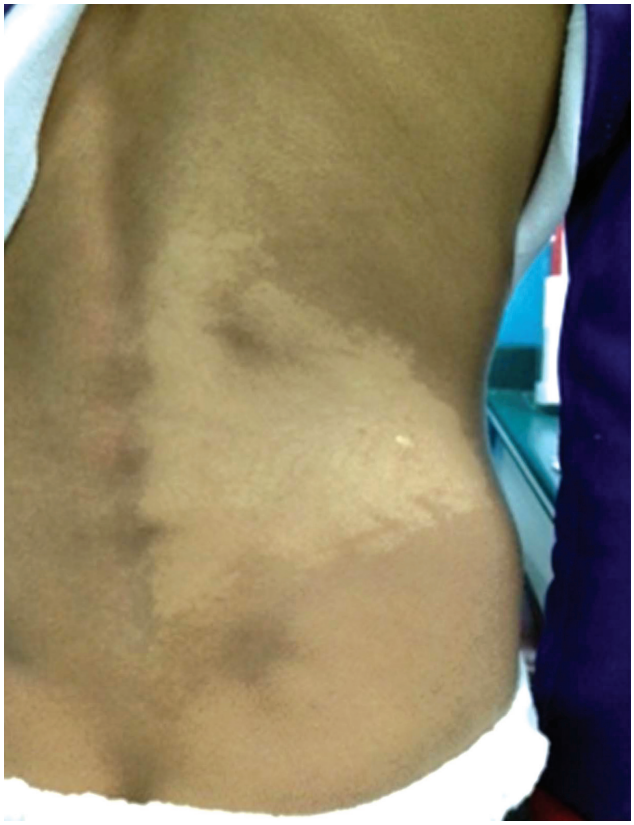

Figure 1 - Hypomelanosis of Ito: Hypopigmentation on the back of trunk on the right side (V- shaped) along the lines of Blaschko. Note the associated kyphoscolosis.

Electrocardiogram (ECG) showed sinus rhythm and wide P wave while echocardiogram (Echo) revealed tricuspid regurgitation with pulmonary pressure of 22 mm Hg with good function. Ophthalmological evaluation as well as full chromosomal analysis revealed normal results. Skeletal survey showed osteoporosis and mild scoliosis. His thyroid function test revealed normal free T4 (17.22 ug/ml, NR=10.3-25,8), high TSH with values between 5.33 and 10.19 mIU/L (NR=0.25-5) consistent with subclinical hypothyroidism. His electroencephalogram (EEG) showed frequent epileptic discharges at the left occipital region with infrequent burst of 2- 3 HZ pike and slow wave complexes / secondary generalization, consistent with partial seizures with secondary generalization. Skin biopsy from the hypopigmented macule showed evidence of reduced number of melanocytes count consistent with depigmented nevous or hypopigmented patches (Figure 2). A cytogenetic study (CTG banding) from the areas with pigmentary changes in our patient revealed a normal 46,XY karyotype. Mutation analysis on peripheral blood lymphocytes and on skin cultured fibroblasts from affected and unaffected skin areas in the child were unrevealing. Molecular linkage study looking for mutation in PLA2G6, common gene mutation associated with iron deposition neurodegenerative disorders, revealed a negative result.

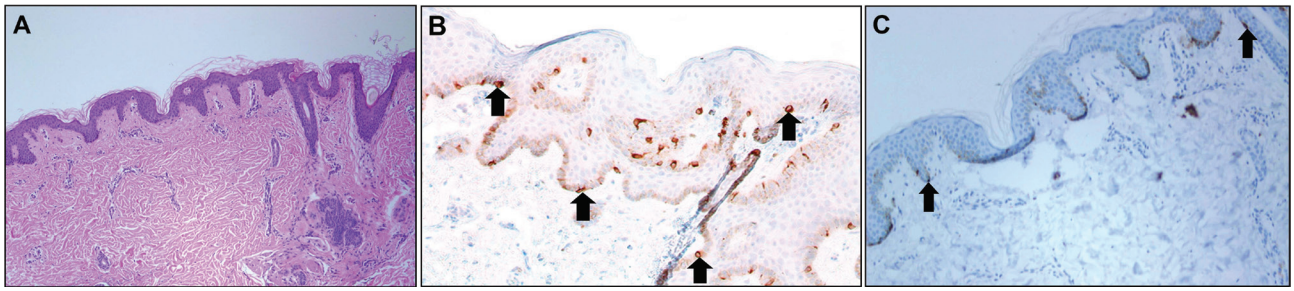

Figure 2 – (A) Skin biopsy shows no significant pathological change on H/E stain (hematoxylin-eosin ×100). (B) Melan A immunohistochemistry of normal skin reveals normal number of melanocytes (arrows) in basal layer of epidermis (1 melanocyte per 10 basal keratinocytes) [immunohistochemistry stain ×200]. (C) Melan A immunohistochemistry of the affected skin reveals decreased number of melanocytes (arrows) in basal layer of epidermis (immunohistochemistry stain ×200).

Metabolic screening including biotindase level was normal. Abdominal ultrasound revealed normal findings. The computed tomographic (CT) scan of the brain, with and without contrast, was normal. The magnetic resonance imaging scan of the brain revealed normal result with no evidence of neuronal migration disorders, cortical dysplasia or hemimegaloencephaly. His brain magnetic resonance angiography was normal with no evidence of vessel stenosis or picture similar to moyamoya disease. Brain single photon emission tomography scan (SPECT) revealed focal area of increased perfusion at the left occipital region, consistent with the EEG findings. The patient was treated with carbamazepine. Unfortunately there was poor compliance and he continued to have frequent similar episodes in addition to frequent starring. Furthermore, he developed an allergic skin reactions and, therefore, carbamazepine was switched to levetiracetam (Keppra) that resulted in control of his seizures. He was started on vitamin D and L-thyroxin. He showed progressive improvement in his language skills. His recent MRI evaluation revealed bilateral

low signal intensity within the basal ganglia particularly golbus pallidi as well as in the cerebellar folia on both T2 Weighted images and diffusion weighted images consistent with iron deposition as seen in neurodegenerative disorders with brain iron accumulation (Figure 3).

At the most recent re-evaluation, at the age of 15 years, the child had improved language skills and his intelligence quotient score was 85. His skin, general examination, and neurologic findings were unchanged.

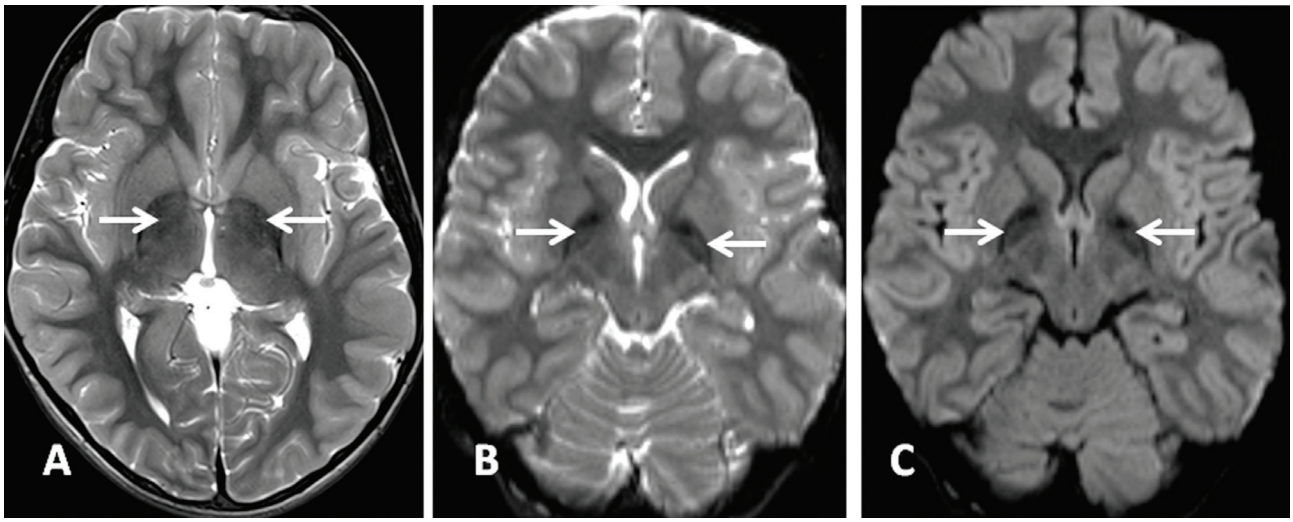

Figure 3 - MRI brain axial T2-weighted sequence (A), axial diffusion sequence b value 0 s/mm2 (B) and axial diffusion sequence b value 1000 s/mm2 (C) showing low/dark signal intensity of bilateral globus pallidus suggestive of excessive iron accumulation (arrows).

DISCUSSION

Nevous depigmentosus is a congenital, non-progressive disorder characterized by hypopigmented spots on the skin [21]. It is associated with decreased melanosome synthesis and the transfer of melanosome to neighboring keratinocytes. The cutaneous lesions are usually evident during infancy [22]. Isolated and widespread clinical forms were reported. Nevus depigmentosus and hypomelanosis of Ito are synonymous. However, there is a tendency to classify cases without extrademal involvement as nevus depigmentosus, and cases with extradermal anomalies as hypomelanosis of Ito [22].

Approximately 75% of the reported cases of hypomelanosis of Ito involved anomalies of the central nervous system, ocular system, musculoskeletal system, cardiac, renal and teeth leading to frequent characterization as a neurocutaneous disorder [23]. The pathogenesis of the disorder is unknown and is likely to be multifactorial. Autosomal dominant inheritance has been seen in some (but not all) cases; with equal frequency among males and females [24]. The variety of clinical findings in hypomelanosis of Ito, the sporadic character, and the karyotype analysis that reveals a variety of chromosomal rearrangements, lead to the belief that this disorder is not a distinct entity but is rather a skin-related symptom of many different genetic disorders associated with disturbed expression or function of pigmentary genes [25-27].

The hypopigmented areas of skin of our patient correspond to the Blaschko lines that was first described in 1901 by the German dermatologist

Alfred Blaschko [28, 29]. These lines are non-random developmental system of linear and/or whorled streaks with V-shaped on the back and S- shaped on the abdomen, and indicate the ectodermal cell migration pathways in the embryologic period. The severity and area of involvement of skin changes are related to the time of development of the mosaic event that causes the pigmentation abnormalities. This involvement may be widespread if caused by an event in the early period, whereas late onset mosaicism may involve smaller regions [30].

The neuropathology findings recorded in hypomelanosis of Ito are limited, and have usually consisted of abnormal cortical morphogenesis with disarray of cortical lamination, heterotopic areas, laminar or band heteropia, pachygyria, cerebral or cerebellar micropolgyria, focal or generalized brain atrophy, brainstem and cerebellum hypoplasia with dysmyelination of the corticospinal tracts, existence of abnormal neurons in the white matter and periventricular areas , and notable astrocytes reaction, resulting from the coexistence of neural cells undergoing a normal migration and cells exhibiting migration arrest or even complete absence of migration [3-5 , 17, 18, 31].

The characteristic skin manifestation of HI are pigmentary patterns with irregular borders, streaks, whorls, and patches. These are usually found in all affected individuals and appear in the first year of life in 70% of cases [23, 31]. Minor abnormalities such as café`-au-lait spots, cutis marmorata, angiomatous nevi, nevus of Ota , mongolian blue spots, abnormal sweating, ichthyosis, and morphea are found in 40% of cases [32]. Alopecia, weather diffuse or localized, variation in hair color and texture as well as facial hypertrichosis have also been reported [14]. Ridging, dystrophy, or absence of nails can be observed. Dental hypoplasia/ dysplasia, in the form of irregularities of teeth spacing, number and size, unusual hamartomtous dental cusps, peg-like incisions, defective dental implantation, and defective enamel have also been reported. Other abdominal manifestations that can be seen in association with hypomelanosis of Ito include umbilical and inguinal hernia, and primary small intestine lymhangiectasia. Anterior eye chamber abnormalities like strabismus, nystagmus, exotropia, myopia, heterochromia of the irides, coloboma of iris, dacryostenosis, corneal asymmetry, pannus, cataract and pinpoint pupils, and microphthalmia are common while the posterior chamber abnormalities like pigementary changes in retina, retinal detachment, and small optic nerve or optic atrophy are less common. Macrocephaly, flat occiput, orbital hypertelorism, low-set ears, small nose, and inner epicanthal folds have been seen in 30% while other craniofacial abnormalities account for 10% like frontal bossing, large philtrum, wide cranial sutures, thin eye brows and retrognathia, or occasionally, microcephaly, brachiocephaly, turricephaly, large fontanels, late closure of fontanels, frontonasal and midface hypoplasia, triangular face, prognathism, or hypotelorism. The commonest skeletal abnormalities which have been observed were asymmetry of length or size of limbs, joint contractures, kyphoscoliosis, pectus excavatum or carinatum rudimentary ribs, small hands and feet, pes valgus or varrus or cavus, genu valgaus, or congenital hip dislocation, polydactyly, or syndactyly, short stature in 20% and delayed skeletal maturation in another 20% [31]. Approximately 10% or less of affected patients has other system involvement. Congenital cardiac defects such as Fallot's tetralogy and atrial or ventricular septal defects have also been reported. Kidney anomalies associated with HI include ureteral and renal agenesis, horse-shoe kidneys, bilateral urethra duplication, and renal tubular acidosis, and genital anomalies such as hypospadias and vaginal skin tags [31, 14]. Interestingly, hypomelanosis of Ito have been reported in association with certain tumors like cystic teratoma of mediastinum in association with

diploic epidermoid cyst of bone, complex mature sacrocoxygeal dysembryonal tumor, choroid plexus papilloma and dental hamartomatous tumor, and rarely malignant tumors such as acute lymphoblastic leukemia, meduloblastoma, neuroblastoma and primary meningeal rhabdomyosarcoma. There is a higher frequency (94-100%) of central nervous system abnormalities reported in association with hypomelanosis of Ito. The commonest of these were developmental delay, mental retardation of various degrees ranging between mild to severe, poor school performance and autistic- like behavior especially in those who suffered from either infantile spasm or drug resistant seizures. Developmental delay is reported in 75% of affected patients and moderate to severe cognitive deficits (IQ <70) in 57%; with only 20% of patients having an IQ above 85% [14] .The association between seizures and mental retardation is frequent and reported in 60-70% of cases. In general, seizures occurred in 50%, commonly appearing early in the first year of life with the most frequent seizures type including generalized tonic or tonic-clonic, complex partial , myoclonic seizures and infantile spasm [31 , 14]. While some patients suffer from generalized seizures that are well controlled with anticonvulasant therapy, many have severe, pharmaco-resistant focal seizures, and of those some patients may benefit from surgery [32 - 34]. The behavior and psychological problems commonly found in HI include autism, Asperger`s syndrome, self-injurious behavior and sever sleep problems especially in the first 3-5 years of age [35, 36]. A non-progressive speech delay have been reported occasionally, mainly in the form of delay in the production of speech sounds, in communication milestones and specific expressive language disabilities according to the diagnostic and Statistical Manual of Mental Disorders-IV [37].

Our patient had a complex constellation of skin, systemic and neurologic features, including mosaic hypopigmentation along the lines of Blaschko [38] facial dysmorphism, joint hypermobility, skeletal dysplasia (including short stature, dental abnormalities, and congenital hip abnormality), hypotonia, seizures and mild mental retardation-all consistent with the diagnosis of hypomelanosis of Ito (or pigmentary mosaicism of the Ito type) [3-5].

Notably, his skin lesions did not fade with age. Cranial imaging studies were normal initially, but a follow-up studies approximately 6 years later, showed changes within the globus pallidi and the cerebellar follia , best seen on both T2-weighted and diffusion-weighted images (Figure 3) Such findings were commonly reported in association with iron deposition in basal gangalia either secondary to acquired causes such as post repeated blood transfusion as in thalassemia, sickle cell disease and G6PD deficiency, or genetically determined as in neurodegenerative disorders (neurodegeneration with brain iron accumulation – NBIA) such as juvenile onset Hallervorden-Spatz disease, and in association with PLA2G6 or PANK2 gene mutation [39- 43].

Our patient had no previous blood transfusion, no family history of hematological illnesses or neurodegenerative disorders, and did not manifest clinical regression of developmental milestones or neurological signs suggestive of evolving neurodegenerative disorders such as extrapyramidal manifestations. He had no headache, paresthesia or symptoms suggestive of transient ischemic attacks (TIAs). His MRI did not show the classic eye-of-the tiger sign, which correlates with pantothenate kinase-associated neurodegeneration (PKAN) [44]. These bilateral basal ganglia changes have never been reported in isolation in cases of HI. In hypomelanosis of Ito, the brain magnetic resonance commonly revealed findings such as:

1. diffuse white matter abnormalities (> 50%) mainly in the parietal, periventricular and

subcortical white matter of both hemispheres, either in the form of cystic-like lesions (isointense to cerebrospinal fluid surrounded by regions of decreased signal intensity) or altered / delayed myelination [31],

2. generalized cerebral, brainstem, or cerebellar atrophy and /or dilatation of cerebral ventricles,
3. hemispheric asymmetry (both hemimegaloencephaly and hemiatrophy) [45-47],
4. cerebellar hypoplasia,
5. agenesis or hypoplastic corpus callosum [47],
6. large, bilateral subcortical bands of grey matter heterotopia (double cortex syndrome due to premature arrest of neuronal migration) [3, 33, 47],
7. lissencephaly [46],
8. polymicrogyri as a part of neuronal migration disorders [31],
9. porencephaly,
10. intracranial arteriovenous malformation,
11. moyamoya disease,
12. leptomeningeal angioma [48] ,
13. absence of normal demarcation between gray and white matter,
14. normal neuroimaging findings or show only enlarged perivascular spaces .

The white matter lesions of our patient presented as early as the first month of life, did not correlate in extension with the age of patients, and were static over time [6]. In contrast, Fryburg et al [49] reported a child with normal intellect and non-neurologic manifestation, but with extensive white matter changes.

Although we could not detect any chromosomal abnormalities in our patient, nevertheless these have been detected only in 50% of reported HI cases so far [4, 26], and the changes within the globus pallidi and the cerebellar folia, documented in this child, could add to the overall phenotype of HI.

In conclusion, given the range of genetic, clinical, and neuroradiological features, it seems that HI is not an isolated entity but a clinical syndrome encompassing multiple cutaneous and CNS disorders as demonstrated by our patient.

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