Hypomelanosis of Ito

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ABSTRACT

Hypomelanosis of Ito (HI) is a rare neurocutaneous syndrome with characteristic whirled hypopigmented skin lesions and neurological manifestations. Less consistently, there may be non-neurological manifestations that include ophthalmic, musculoskeletal, craniofacial, cardiac, genitourinary, and gastrointestinal involvements. We report a case of HI, with typical skin lesions in association with hemimegalencephaly, seizures and mental retardation along with the hitherto unreported repetitive hand movements such as seen in Rett syndrome.

Keywords: Hemimegalencephaly, **hypopigmentations, Ito syndrome, pigmentation disorders**

INTRODUCTION

Hypomelanosis of Ito (HI) was first described by Ito in 1951. [1] Later, Ruiz-Maldonado *et al.* in 1992, established some diagnostic criteria for HI. [2] Currently HI is diagnosed only if there is central nervous system or skeletal anomalies along with dermatological manifestations. The latter usually appear during the first year of life (70%) and may be noticeable at birth (54%), and rarely in mid-childhood. The pathogenesis of HI is complex and not well understood. It is believed to be genetic but includes a range of chromosomal abnormalities including translocations, triploidy, trisomies and mosaicism. [3] We report a case of HI who had typical skin lesions associated with hemimegalencephaly, seizures and mental retardation along with the hitherto unreported repetitive hand movements as seen in Rett syndrome.

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CASE REPORT

A 10-month-old girl was referred to the Paediatric clinic from a district hospital with a history of delayed milestones, macrocephaly and hypopigmented skin lesions.

She was delivered normally at term, is the second of three siblings and her parents are unrelated. Her older brother and younger sister are normal. Her mother previously had two abortions. Apparently, at routine follow

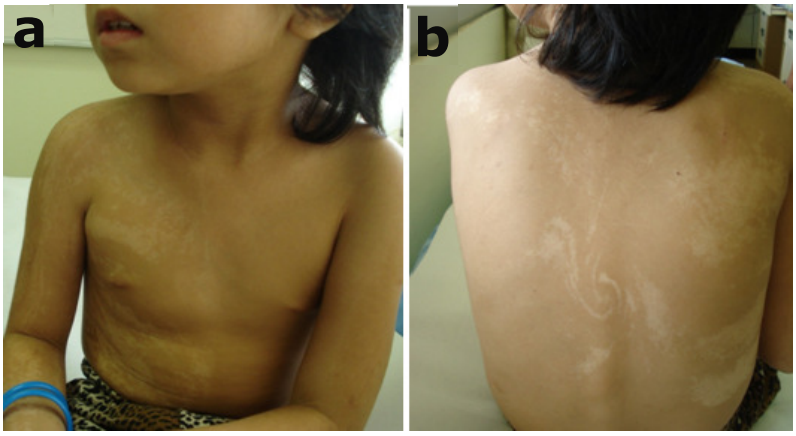

Fig. 1: Hypopigmented lesions of Hypomelanosis of Ito distributed in distinctive patterns in the (a) front on the right side of the body and (b) bilaterally on the back.

up at the age of two months old, the patient was noted to have a large head, but was otherwise normal. However, for reasons not known, there was no further review.

On assessment, she was confirmed to have macrocephaly (head circumference >2 standard deviations), mild generalised hypotonia and moderate global developmental delay. There were hypopigmented skin lesions in distinctive patterns - whirls, patches and streaks - involving the trunk and extremities, confined to the right side of the body anteriorly (Figure 1a) but also extending to the left side posteriorly (Figure 1b). All other systems were normal. Based on the characteristic skin manifestations, associated with neurodevelopmental abnormalities, a clinical diagnosis of HI was made at the initial assessment (at 10 months of age). A magnetic resonance imaging (MRI) brain scan showed left hemimegalencephaly and widening of the

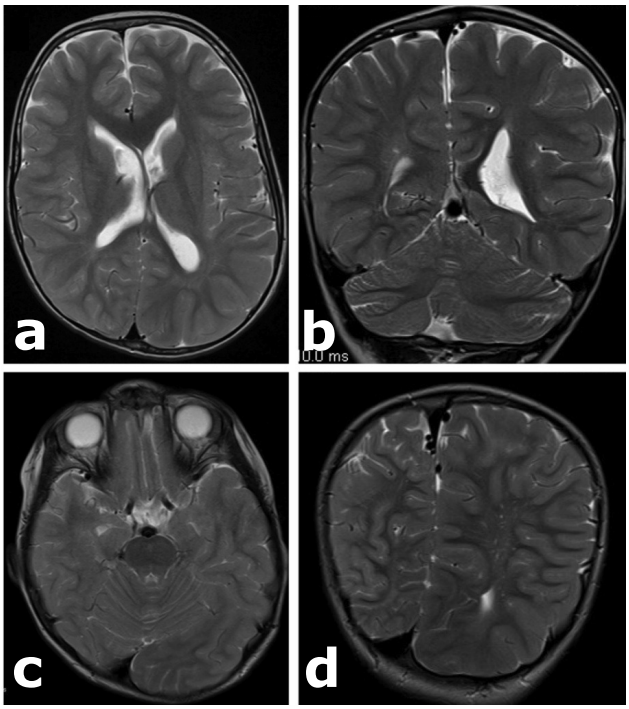

Fig. 2: Axial magnetic resonance imaging views (a and b) and coronal views (c and d) showing left megalencephaly predominantly affecting the parietal and occipital lobes (images b and d) and widening of the posterior horn of the left lateral ventricle (image c).

posterior horn of the left lateral ventricle with no other abnormalities (Figure 2). The MRI findings, contralateral to the distribution of the hypopigmented lesions, further supported the diagnosis of HI. Chromosomal analysis was normal.

The girl has been under regular review since then. Ophthalmologic evaluation has shown no abnormalities. At 3½ years of age she developed a brief generalised tonic clonic seizure and electroencephalography (EEG) showed generalised spike and wave discharges more pronounced in the right temporal region. At about 5 years of age, she developed repetitive symmetric hand clapping movements reminiscent of Rett syndrome. At the last follow up at 5½ years of age, she still had developmental delay, though she was acquiring new milestones. Her epilepsy has been fairly well controlled on carbamazepine, having shown no response to valproate, and is now limited only to momentary twitching of the lips.

DISCUSSION

HI is sporadic in occurrence, and the exact prevalence is unknown although it appears to be the third most common neuro-cutaneous disease, after neurofibromatosis and tuberous sclerosis. [3] Our patient fulfilled the criteria for the diagnosis of HI with distinctive skin lesions (whirls, streaks and patches with irregular borders) associated with macrocephaly, developmental delay and seizures and to our knowledge is the first case to be reported from Brunei Darussalam.

HI may be considered a cutaneous disease with multisystem involvement; skin and neurological manifestations being crucial for diagnosis. Hypopigmented skin lesions may appear in whirls, streaks or patches with irregular borders. They tend to run parallel to one another, following the lines of Blaschko. There may be non-specific skin lesions as listed in Table a. [3] In children with fair skin, the use of a Wood lamp may be needed to demonstrate these hypochromic lesions. Typical skin lesions are demonstrated at birth in 54% of patients and during the first year of life in about 70% of patient. In rare instances, these lesions may not be visible until mid-childhood. [3] In our case it was first noticed at 10 months of age when a diagnosis of HI was made.

The pathogenesis of dermatological manifestations in HI is not exactly known but is probably strongly linked to genetics and chromosomal anomalies as reported in many case reports. [6] Chromosomal mosaic patterns, with two cell lineages, produce patterns of hypopigmented and hyperpigmented skin. Recent evidence points to X-chromosome inactivation, activation, and mosaicism as causes of different patterns of cell behaviour in the skin. Perhaps these can also be found in other tissues, such as the fundus (tessellated or radial pigmentation of the fundi), iris (hypopigmentation), and the brain (areas with abnormal cell morphology and neuroblast migration side by side with normal patterns). Karyotyping was normal in our case: however skin biopsy for fibroblasts may be necessary to detect chromosomal anomalies. [3] A cutaneous ultra-structural study showed abnormal nerve termination in close proximity to basal keratinocytes, degenerated melanocytes, premelanosomes, and Langerhans cells. These findings may be important in the pathogenesis of HI. [7] Another report has highlight–

ed the regulation of cutaneous pigmentation by a complex melanogenic network of cells that secrete growth factors and cytokines with considerable variability in penetrance and expression of the relevant genes. More recently, the central role of the KITLG/c-Kit and Ras/MAPK pathways in controlling pigmentation, with environmental factors further influencing disease phenotype, has been described. [8]

The most common non-dermatological manifestations of HI are mental retardation (67%) and seizures (35%) [4] both of which are present in our case. During the first decade of life, 76% of patients may develop neurological involvements. Seizures are also common and the frequencies of occurrence are generalised tonic-clonic in about 25%, partial seizures in 12%, infantile spasms in 8% and myoclonic seizures in 4%. Although it can occur, Lennox-Gastaut syndrome is rare. [3] Seizures can be difficult to control in patients with HI and only about half of these patients are reported to achieve full seizure control. In our case, seizures were partially controlled.

MRI often shows macrocephaly, neuronal migration disturbances, cortical anomalies and further abnormalities like atrophy or dilated ventricles, [5] but can also be normal. HI is only occasionally associated with hemimegalencephaly and unilateral skin lesions contralateral to the side of brain malformation. [3] Our case belongs to the rare group with this association.

The histopathological basis of the neurological manifestations of HI may include the findings of polymicrogyria, disarray of cortical lamination, and heterotopic neurons in the white matter and giant cells as demonstrated on neuropathological studies. [3]

A wide variety of craniofacial, ocular, musculoskeletal, dental, cardiac, genitourinary, gastro-intestinal and other abnormalities have been reported, [3] (Table) but none of these were detected in our patient.

Presently there is no specific treatment available for HI, but recent developments in understanding the molecular mechanisms of pigmentation may lead to effective therapies in future. [8] However, until then the management will remain focussed on alleviating symptoms like seizures and multidisciplinary support for all forms of disabilities. Early diagnosis of the disease is crucial for planning of symptomatic treatment. Apart from clinical findings, sonography (in newborns) and MRI for detection of brain abnormalities are important tools to confirm the diagnosis. [10]

Parents can be reassured regarding insignificant or non-existent recurrence risks in future pregnancies: HI most commonly being a *de novo* occurrence. [3] Regular follow-up for symptomatic and multi-disciplinary supportive management and counselling should be offered as early as possible. Apart from this, it is also important to be aware that patients with chromosomal anomalies are at higher risk for the development of tumours and counselling and regular follow-ups should be maintained to monitor for these conditions.

In conclusion, we report a rare case of HI and to our knowledge this has not been previously reported in Brunei. Although a relatively rare neurocutaneous syndrome, HI is

Table 1: System abnormalities in Hypomelanosis of Ito.

System abnormalities	Approximate prevalence
Dermatological **Hypochromic lesions** **Nonspecific findings**: hypohidrosis of hypopigmented skin, café-au-lait spots, persistent mongolian blue spots, Nevus of Ota, nevus marmoratus and angiomatous naevi, soft fibroma, pilomatrixoma, aplasia cutis, atopic dermatitis. **Hair abnormalities**: slow growth, diffuse alopecia, trichorrhexis, widow's peak, generalised hirsutism, facial hypertrichosis, coarse and curly hair, low hairline, a zone of alopecia or white hair in the scalp.	100%
Neurological Learning disability, hypotonia, seizures, autistic behaviour, hemimegalencephaly, brain tumours.	90%
Ophthalmologic Retinal pigment abnormalities: tessellated fundus, radial hypopigmented streaks, or geographic areas of hypopigmentation; heterochromic iris, hypopigmentation of the cornea; myopia, hyperopia, astigmatism, megalocornea, opaque corneas, scleral melanosis, strabismus, slow pupillary response, pupillary atrophy or irregularity, nonclosure of the upper eyelid, ptosis, symblepharon, optic atrophy, choroidal atrophy, microphthalmia, macrophthalmia, epicanthal folds, dacryostenosis, and nystagmus.	20%
Musculoskeletal Hemihypertrophy, arm and leg length discrepancy and scoliosis; **Fingers anomalies**: atrophy, syndactyly, polydactyly, clinodactyly, or bifid thumb; luxatio coxae, genu valgus.	20%
Head and face Macrocephaly, microcepahly, hypertelorism, coarse facies, cleft lip and palate, bifid uvula, nose and ear anomalies, coarse faces.	23%
Dental Partial anodontia and dental dysplasia, defective enamel, hamartomatous cuspids.	Rare, unknown %
Cardiac Vetricular septal defect, atrial septal defect, pulmonary artery stenosis, Tetralogy of Fallot, incomplete right bundle branch block, cardiomegaly.	Rare, unknown %
Genito urinary Hypospadias, micropenis, single kidney, urethral duplication, cryptorchidism, sexual precocity, gynaecomastia, asymmetrical breasts, nephritis.	Rare, unknown %
Others Hepatomegaly, segmental dilation of the colon; diaphragmatic, umbilical, and inguinal hernia.	Rare, unknown %

easy to recognize if one is aware of the hypopigmented skin lesions in their characteristic pattern and distribution. Early detection and regular follow-up looking for disease manifestations and disabilities that may appear and evolve over time are of obvious significance in this process. Looking for unusual or unreported findings, like the repetitive hand movements in our case, will enhance the knowledge and understanding of rare syndromes such as HI.

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Medically related International Observance days between April and July

World Autism Awareness Day (April 2)
World Health Day (April 7)
World Haemophilia Day (April 17)
World Malaria Day (April 25)

World Asthma Day (May 1: First Tuesday of May)
International Midwives Day (May 5)
International Nurses Day (May 12)
World AIDS Vaccine Day (May 17)
World No Tobacco Day (May 31)

International Children's Day (June 1)
International Day of Innocent Children Victims of Aggression (June 4)
World Brain Tumour Day (June 8)
World Blood Donor Day (June 14)
World Sickle Cell Day (June 19)

Doctor's Day (July 1)
World Hepatitis Day (July 28)