HYPOMELANOSIS OF ITO. REPORT OF A CASE AND REVIEW OF THE LITERATURE

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Summary:
Hypomelanosis of Ito (HI) is a rare neuro-ectodermal disorder. It was first described as a disorder characterized by unusual unilateral or bilateral cutaneous macular hypopigmented whorls, streaks and patches. Subsequently multiple extracutaneous manifestations mostly of neurologic, ocular and musculoskeletal system were described. This case report presents a five year old girl who was diagnosed as having Hypomelanosis of Ito.

Introduction
Hypomelanosis of Ito or incontinentia pigmenti achromians is a rare neuro-ectodermal disorder first described by Ito in 19521. The most remarkable clinical markers of HI are cutaneous lesions that are observed within first year of age in about 70% patients2. These consists of sharply circumscribed hypopigmented streaks, whorls patch and spot that are usually distributed along then lines of Blaschko on the trunk and occasionally on the extremities and the face. Even though Ito’s original report in 1952 described a purely cutaneous disease, subsequent case reports and case series have included a 33% to 94% association with multiple and sometimes severe extracutaneous manifestations, mostly of central nervous system, musculoskeletal system and ocular system3. Neurological findings include seizure types that have been reported, including infantile spasm, complex partial, myoclonic, and generalized tonic-clonic seizures, often poorly responding to anti-epileptic therapy4. Musculoskeletal abnormalities including hemi hypertrophy, scoliosis arm and leg length discrepancy and bifold thumb may also be found. HI have been reported to be coexist with other neurocutaneous syndromes5,6 cerebrovascular disease7 with cerebral malformation8. Since 1952, when Ito described the syndrome its procten clinical manifestations have been the object of detailed reports. Our objective is to report a case of a girl with hypomelanosis of Ito who presented with neurological and musculoskeletal abnormalities associated to cutaneous involvement. It is also our HI.

Case Report
A five year-old girl, first daughter of healthy and unrelated parents was admitted in our hospital because of epileptic 2-3 times/month. After an uneventful pregnancy she was born normally at term with no natal or postnatal complication. History revealed that her developmental milestones were delayed. She attained neck control at 8 months, was able to sit unaided at 18 months and started walking without support at 3 years. Her speech was also delayed and at present she can only utter 'dada' 'baba'. Physical examination revealed weight of 15 kg and occipito-frontal circumference 51 cm. She had strabismus and nystagmus. Neurological except for hypotonia. The most striking feature was hypopigmented skin lesion on her right side and homolateral hypertrophy of the body side. Skin showed unilateral bizarre hypo pigmented lesions in streaks, patches and whorls with a midline cutoff involving only the right half of the body (Figure 1, 2, 3, 4). The lesions are located on the torso and extremities sparing the sole, palm and mucous membranes. Her right lower limb measured 15 mm more than left, right mid thigh circumference was 15 mm more than then left. All routine laboratory tests were normal as were all craniofacial and ultrasound investigations. CT scan of brain showed mild dilatation of ventricles (Figure 5). For further evaluation we planned a brain MRI, EEG, skin biopsy and cytogenetic study but as the parents did not give consent we could not proceed. So from the history, clinical findings and supportive investigations the girl was diagnosed as a case of Hypomelanosis of Ito, a rare neurocutaneous syndrome.

Discussion:
Hypomelanosis of Ito is perhaps the fourth most common neurocutaneous syndrome6. In 1952, Ito described a 22 year-old Japanese girl with the skin of her upper half of the body looking as "if the normal pigement was brushed off" he used the term incontinentia pigmenti anchromians as it was considered as the negative image of incontinentia pigmenti. Subsequent observations expanded the phenotype, the name hypomelanosis of Ito was proposed, and now it is suggested to drop this term and use a new term which will reflect the disease pathogenesis or recall the cutaneous pattern8.

In a systemic study of the largest series published, Pascual-Castroviejo et al.9 reported a frequency of 1 in every 8,000 to 10,000 new patients in a hospital and 1 in every 1,000 new patients in a pediatric neurology service. Almost all cases of HI are sporadic, suggesting that HI is the result of post-zygotic mutation. Both sexes are affected with an unexplained, approximate 2:1 female predominance. It has

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been hypothesized that HI might be a non-specific expression of chromosomal mosaicism often leading to the generation of two cell lineages, which produce patterns of hypo pigmented and hyper pigmented skin. The variety of aneuploid cell lines include triploidy, trisomies, monosomies, as structural abnormalities with ring chromosomes, inversions and X chromosome or auto some translocations11.

HI is a multisystemic disorder that most frequently involves the cutaneous and central nervous system. Patients usually seek care from a pediatrician, dermatologist or neurologist by the time they are aged 2 years. The skin markings display a varied pattern of lines that is circumferential around the trunk, forming whirls, patches, zig-zag and S-shaped markings over the abdomen and a V shaped pattern over the spine usually stopping in the anterior or posterior midline. In children with fair skin, the use of a Wood lamp is helpful in demonstration the hypochromic lesions. The hypo pigmentation is not preceded by vesicular or varicous lesions. This feature is in contrast to the usual presentation of incontinent pigments. Clinical picture is characteristic enough to make the diagnosis when hörnited pattern is present112 as in our patient. Though the histopathology features of hypo pigmented lesions of hypomelanosis of Ito are nonspecific there is evidence of decreased number of melanocytes and decreased number and size of melanosome in the basal layer of the epidermis with selective decrease in eumelanin113. Minor skin abnormalities like café-au-lait spots, cutis marmorata, angiomatous nevi, nevus of Ota Mongolian blue spots, abnormal sweating, ichthyoids, and morphed may be present, the significance of which, however, is still poorly understood.

Epilepsy represents, along with mental retardation, the most common neurological complication in HI.2 Seizures were reported to occur in 11.5% to 50% of patients in the literature. Most frequently seizure types are gene real time tonic-clonic seizures, partial seizures, myoclonic seizures, and infantile spasms. Seizures commonly appear early within the first year of life and cases refractory to treatment are also reported2. Mental retardation is present and may vary from mild to severe and about 10% of patients show in addition autistic behavior23. Mental retardation can be usually attributed to the underlying brain abnormalities or to severe seizure disorder. Developmental delay is common and delay in speech is common and delay in speech is occasionally reported and both were present in our case. Other neurologic abnormalities found in HI are muscular hypotonic or, hyperkinetism, nystagmus, ataxia, and neurosensory deafness. Although there are no reported constant central nervous system lesions in HI, study showed more than 50% of patients had specific white matter abnormalities demonstrable by MRI14. Other abnormalities revealed by CT and MRI in HI cases are localized or generalized cerebral, brainstem, or cerebral ventricles, hemispheric asymmetry (both hemimegalencephaly and hemiatrophy). Cerebellar hyperplasia, agenesis or dysplasia of the corpus callosum, and arterovenous malformations. There is no consistent electroencephalographic pattern in HI. The electroencephalogram can yield normal results or show a wide range of abnormalities.

Eye abnormalities include strabismus, nystagmus, exotropia, myopia, heterochromia of the irides, coloboma of iris, dacryostenosis, corneal asymmetry, pannus, cataract and pinpoint pupils, microphthalmia and retinal pigment abnormalities. Craniofacial, limb, and skeletal abnormalities are particularly common in patients who have chromosomal mosaicism. Macrosomia, frontal bossing flat occipital, orbital hypertelorism, low -set ears, small nose and inner canthal folds were observed in different reports. Asymmetry of length or size of limbs and body parts along with joint contractures are recorded. One fifth of patients have hemihypertrophy, usually ipsilateral-to-hypomelanotic lesions. Kyphoscoliosis or scoliosis, pes cavus and carpal tunnel are common as are small hands and feet genu valgus or congenital dislocation of hip. Fingers may be abnormal, showing atrophy, syndactyly, polydactyly, clinodactyly or bifid thumb. Other systemic abnormalities reported in different cases include congenital cardiac defects as Fallot's tetralogy and atrial or ventricular septal defects, kidney anomalies or general anomalies as hypospadias and vaginal skin tags.

The different diagnosis includes other disease with hypopigmented spots on the skin. Many other skin pigmentary abnormalities may be associated with systemic and neurological abnormalities. In tuberous sclerosis, the lesions are round oval or in the shape of an ash leaf and do not follow the lines of Blaschko. Incontinentia pigmenti of Bloch-Sulzerer during its fourth stage could be confused with the lesions of HI. However, the natural history of the skin lesions in incontinent pigment passing through different stages and the presence of the disease only in females lead to an easier differential diagnosis. Isolated hypomelanotic (hypo pigmented) nevi (nevus depigmentosus) are characterized by hypochromic lesions in streaks and whorls, which also follow the lines of Blaschko. But the lesions are fixed at birth and usually single and well defined changing little thereafter and systemic abnormalities are rare in nevus depigmentosus. Segmental vitiligo, skin fungi infections may be the other considerations but they appear long after birth.

Patients who exhibit hypo pigmentation or depigmentation along the lines of Blaschko, in a patchy or linear distribution should be fully evaluated for structural systemic abnormalities. Laboratory or imaging tests including electroencephalography and neuroimaging, should be oriented only by the abnormal findings on clinical examination. Karyotyping of peripheral blood or skin fibroblasts or better keratinocytes or melanocytes, obtained from biopsies taken from affected and unaffected areas, may be performed to support the diagnosis.

No special treatment is indicated for the skin lesions and no
precaution has to be taken with regard to sun exposure. Cover-up makeup can be used if the patient desires it. Associated diseases (including seizure, mental retardation, visual or orthopedic problems, tooth deformities) require appropriate specialty care. Affected parents should be fully reassured that the risk of HI in his or her offspring is low, as HI is only rarely familial. The prognosis is determined by the associated abnormalities.

In conclusion, in HI a cutaneous epiphenomenon with a peculiar pattern of distribution usually associated with multisystem disorders. The genetic substrate for HI is not homogenous and only partially understood. It is still unclear how such a wide range of different karyotypes leads to a similar phenotype. Some authors proposed different models of inheritance but none has been proved. These findings, along with the different clinical and neuroradiological features led some authors to state that HI is a descriptive term rather than a true syndrome. Further research is required to shed light on the pathogenesis of HI phenotypes.

References