

# Coexistence of two neurocutaneous syndromes: Tuberous sclerosis and hypomelanosis of Ito

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### ABSTRACT

Tuberous sclerosis complex (TSC) and hypomelanosis of Ito (HI) are two uncommon neurocutaneous syndromes and their coexistence is extremely rare. An epileptic child presented with progressively increasing multiple hypopigmented macules arranged in a linear and whorled pattern along the lines of Blaschko over the trunk and limbs, characteristic of HI. He also had facial angiofibromas, ash-leaf and confetti macules and shagreen patches. Magnetic resonance imaging of the brain showed cortical tubers and subependymal nodules; which are diagnostic of TSC. The TSC defining loci have been mapped to Chromosome 9q34 (TSC1) and 16p13.3 (TSC2). There is no common genetic background for HI, but mosaicism of 9q33 locus has been documented. As per our knowledge, this is the second case of association of TSC with HI in a four-year-old child.

**Key Words:** Hypomelanosis of Ito, Tuberous sclerosis

### INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disease, associated with the development of hamartoma in many different organs and tissues. Prevalence of the disease is approximately 3 to 10 per one lakh.<sup>[1]</sup> The TSC defining loci have been mapped to Chromosome 9q34 (TSC1) and 16p13.3 (TSC2). Hypomelanosis of Ito (HI) is another neurocutaneous disease characterized by hypopigmented whorls, streaks and patches typically distributed along the lines of Blaschko. One or more abnormalities of the central nervous system, eyes, hair, teeth and musculoskeletal system have been described in 70% of cases.<sup>[2]</sup> There is no common genetic background for HI. A wide variety of chromosomal abnormalities have been described in different cases of HI, including mosaicism of 9q33. An association of TSC and HI is extremely rare, reported in only one case previously.<sup>[2]</sup>

### CASE REPORT

A four-year-old boy presented with multiple asymptomatic hypopigmented macules over the trunk and extremities of one year duration which were progressively increasing in size and extent. He also had absence seizures of two months duration.

He was born of a nonconsanguineous marriage, his parents and siblings were normal. The parents had noticed some delay in speech and motor development which had improved gradually. Dermatological examination showed brownish and skin-colored papules over the central part of the face (adenoma sebaceum or angiofibromas) and an irregular skin-colored firm plaque of size 1x1 cm over the right cheek. A hypopigmented oval macule with irregular borders of size 3x2 cm was seen over the left flank (ash-leaf macule). A few

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hypopigmented grouped macules were seen over the lateral aspect of the right thigh (Confetti macules). Thickened raised firm skin-colored plaques, with ill-defined margins were present over the lower back (shagreen patch) [Figure 1]. In addition, he had multiple hypopigmented macules arranged in a linear and whorled pattern along Blaschko's lines distributed bilaterally symmetrically over the sides and back of the trunk, buttocks and posterior aspect of lower limbs [Figure 2]. These lesions were characteristic of HI.

On further evaluation, he was found to have mild mental retardation, with a mental age of less than three years. His anthropometric measurements, systemic and ophthalmologic examination, electroencephalogram, ultrasonogram of abdomen and echo cardiogram were found to be normal. The magnetic resonance imaging scan of brain showed the presence of cortical tubers, calcified subependymal nodules and bands of curvilinear white matter signal abnormalities



**Figure 1: Shagreen patch and ash leaf macule**



**Figure 2: Symmetrical linear and whorled hypopigmented patches on the back of the trunk, buttocks and posterior aspect of lower limbs**

(white matter migration bands) suggestive of TSC. He also had mild cortical atrophy that can be seen in both TSC and HI. Patient was started on carbamazepine 100 mg daily after consultation with neurologist with which he had adequate control of seizures on further follow-up.

## DISCUSSION

Tuberous sclerosis complex was first described by Desiree Magloire Bourneville in 1880 as “tuberous sclerosis of the cerebral convolution”. Tuberous sclerosis complex is an autosomal dominant trait characterized by the development of hamartomatous growths in many organs. As per the diagnostic criteria for TSC proposed by Gomez<sup>[3]</sup> our patient had all the features diagnostic of tuberous sclerosis. Genetic linkage studies have shown mutation in TSC1 and TSC2 gene, each accounting for half of the cases of TSC. TSC1, an 8.6Kb gene maps to 9q34 and encodes hamartin, a 130 KD protein, which is a tumor suppressor gene. TSC2 gene maps to 16p13.3 and codes for tuberlin, a 1784 amino acid protein, which is involved in cell proliferation and differentiation.<sup>[1]</sup> Approximately 50% of TSC cases are thought to result from new gene mutations.<sup>[4]</sup>

Hypomelanosis of Ito was first described by Ito in 1952 as incontinentia pigmenti achromicans of Ito as it was considered as the negative image of incontinentia pigmenti.<sup>[4]</sup> The clinical picture is characteristic enough to make the diagnosis when the whorled pattern is present<sup>[5]</sup> as in our patient. Extracutaneous anomalies are seen in 75% of cases. There are reports of HI associated with tumors like teratoma of the mediastinum and epidermoid cyst of bone<sup>[6]</sup> and Moyamoya disease.<sup>[7]</sup> Ishikawa *et al* called it “Ito syndrome” instead of HI because of its multisystem involvement and tumor formation.<sup>[6]</sup> Several chromosomal anomalies have been associated with HI,<sup>[6]</sup> among which the genomic mosaicism of 9q33 is the most characteristic.<sup>[3]</sup> In our case, the parents and siblings were normal, suggesting a possible sporadic mutation to account for TSC and HI.

Renal cysts are a frequent manifestation of TSC. Major genes for TSC and autosomal dominant polycystic kidney disease (PKD), TSC2 and PKD1 respectively, lie adjacent to each other at Chromosome 16p13.38, suggesting a role for PKD1 gene in the etiology of renal cystic disease in TSC. On review of the literature, there is only a single case report of an association between HI and TSC, in which the patient also had other features like  $\alpha$ -Thalassemia trait, dysmorphic facies and mental retardation.<sup>[2]</sup> His half brother had TSC and died of renal disease which was probably PKD. In that patient PKD1 gene was also

detected. The authors postulated the possibility of contiguous gene syndrome involving deletion of genes in the Chromosome 16p13.3 region. They suggested that the HI gene involved may be between the break point t(8;16) and the PKD1 gene.<sup>[2]</sup> Even though our case does not have all the associations of contiguous gene syndrome involving the distal Chromosome 16 region, we also suggest the possibility of this phenomenon. A detailed gene mapping study will further unmask the reality.

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## Announcement

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