Griscelli Syndrome: Rab 27a Mutation

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An infant with partial albinism was suspected to have Chediak-Higashi syndrome because two of his three elder siblings had albinism and died in childhood following accelerated phase. Detailed investigations of blood, hair and skin of the proband revealed that he had Griscelli syndrome.

Key words : *Griscelli syndrome, Accelerated phase, Mutation study.*

Griscelli syndrome is a rare autosomal recessive disease characterised by pigmentary dilution of skin and hair, variable cellular immunodeficiency and an acute phase of uncontrolled T lymphocyte and macrophage activation leading to fatal hemophagocytic syndrome. It was first described by Griscelli in 1978, and since then only around 60 cases have been reported, mostly from the Turkish and Mediterranean population. To the best of our knowledge this is the first case reported from India, which has been proven by mutation syudy.

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Case Report

A 13-day-old male baby born of second degree consanguineous parentage was brought for evaluation of excessively fair skin and silvery gray hair. His birth weight was 3.25 kg. The mother had conceived five times, resulting in one abortion, a normal female child who is now 4 years old, and two elder male siblings who had the same clinical features as the proband and in addition had photophobia and delay in motor and mental milestones. They both expired at around 15 months of age after developing hepatosplenomegaly, neutropenia, seizures and developmental regression. One child was investigated in detail for metabolic problems and his peripheral smear failed to show any abnormal granules in the granulocytes. There was no history of any relatives affected by similar clinical presentation.

On examination the child had generalized excessively fair skin when compared with his parents and living sibling. He had silvery gray scalp hair, white eyelashes, eyebrows and body hair (*Fig. 1*). All other systems were within normal limits.

Fig. 1. Typical silvery gray hair and hypopigmented skin of the proband at 9 months

The possibility of Chediak-Higashi Syndrome (CHS) was considered, with the two siblings dying due to the "accelerated phase". Peripheral smear of the proband failed to show any abnormal granules even after repeated examination. Intracytoplasmic granules were absent on the peripheral smear of one of the elder siblings which was examined while he was terminally ill from old records. Serum copper and ceruloplasmin levels were normal. Microscopic examination of the hair shaft of the proband showed uneven aggregations of large pigment granules, and hypopigmentation in the rest of the hair which is the hallmark of Griscelli syndrome (*Fig. 2*). Light microscopy of skin showed large clumps of melanin granules in melanocytes in the basal cell layer in Masson-Fontana stained sections, which is consistent with the skin changes of Griscelli Syndrome (*Fig. 3*).

Mutation study of the proband and the parents were done at Hospital Necker-Enfants Malades, Paris. Rab27a gene was sequenced from the proband and a homozygous C550T leading to R184X mutation (X is a stop mutation) in Rab27*a* gene was identified.This nonsense mutation is the cause for Griscelli syndrome. Both parents were found to be heterozygous carriers of the same mutation.

The child is on regular follow up. He is 1-year-old now and weighs 9 kg and has normal motor and mental development for his age. He has not yet developed any features of the "accelerated phase". Bone marrow transplantation is being considered.

Discussion

Griscelli Syndrome (GS) is an extremely rare autosomal recessive disorder characterized by partial albinism with silvery gray hair, eyebrows and eyelashes, in association with cellular immunodeficiency, frequent infections, and neurological abnormalities. A fatal outcome occurs in the so-called "accelerated phase" of the disorder, which is caused by uncontrolled T lymphocyte and macrophage activation(1). Thus it is clinically similar to Chediak Higashi Syndrome.

The single most consistent cutaneous expression of albinism in these patients is silvery gray sheen to their hair(2). Microscopic

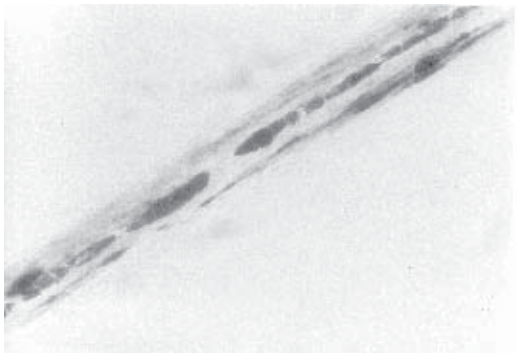

Fig. 2. Microscopic examination of hair showing uneven aggregation of large pigment granules (× 400).

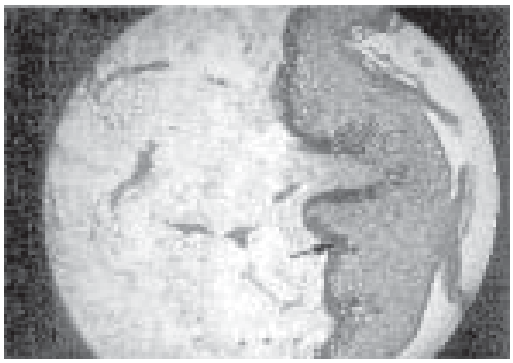

Fig. 3. Skin biopsy showing large clumps of melanin granules in the basal cell layer (Masson-Fontana × 400)

examination of the hair shaft provides strong support for the diagnosis of these syndromes, and allows one to distinguish between them. In both syndromes the hair shaft contains a typical pattern of uneven accumulation of large pigment granules, instead of the homogeneous distribution of small pigment granules seen in normal hair. In GS the clusters of melanin pigment on the hair shaft are six times larger than in CHS.

The hallmark of CHS is the presence of giant intracytoplasmic granules in virtually all granulated cells, which is never observed in GS. Light microscopy of the skin in GS shows hyperpigmented melanocytes with poorly pigmented adjacent keratinocytes, instead of the homogeneous distribution of melanin granules in melanocytes and keratinocytes as seen in normal epidermis(3).

The disease is mapped on chromosome 15q21 locus and mutations of MyoVa or Rab27a gene can lead to GS. Although pigmentary dilution is identical in both groups, only patients with Rab27a mutations have abnormal lymphocyte cytotoxic activity which result in haemophagocytic syndrome. Severe neurological impairment with no immune deficiency is the characteristic feature with MyoVa mutation as this gene regulates organelle transport in melanocytes and in neuronal cells. Impairment of intracellular trafficking and secretion of several lysosomal proteins including melanin from melanocytes and the lytic enzymes from cytotoxic cells occur in GS and CHS. The secretory defect accounts for the hypopigmentation and the cellular immunodeficiency(4). The immunologic abnormalities are restricted to the patients with Rab27a mutation as the capacity of the lymphocytes and NK cells of these patients to lyse target cells is impaired or absent, due to a consistent inability to secrete cytotoxic granules. MyoVa defect does not affect cytotoxic granule secretion and hence they never develop accelerated phase.

Elejalde syndrome or Melanolysosomal neuroectodermal syndrome is another rare autosomal recessive disorder with striking resemblance to GS and they manifest with hypopigmentation, silvery hair and early onset severe psychomotor retardation without immne deficiency strongly suggesting that Elejalde syndrome and GS with MyoVa mutation are allelic(5). Griscelli, Chediak Higashi and Elejalde syndromes are compared in *Table I*.

TABLE I–*Comparison of Griscelli, Chediak-Higashi and Elejalde Syndromes.*

	Griscelli syndrome	Chediak-Higashi syndrome	Elejalde syndrome
Hypopigmentation	+	+	+
Silvery hair	+	+	+
Immune deficiency	+	+	–
Neurological impairment	+ MyoVa – Rab27a	–	++
Intracytoplasmic granules	–	+	–
Clusters of melanin pigments in hair microscopy	++	+	++
Impaired transfer of melanin to keratinocytes in skin biopsy	+	+	+
Mode of inheritance	AR	AR	AR

Same mutation in Rab27a as the one observed in the proband reported here was previously identified in Turkish, Italian, Danish, English and Mauritius patients but ours is the first patient analysed from India (6).

The prognosis for long term survival in GS due to Rab27a defect is relatively poor. This disorder is rapidly fatal during the accelerated phase of the disease. Etoposide was found to be effective in some cases during the accelerated phase(7). Antithymocyte globulin and cyclosporin A have also achieved remission in a few cases(8). Allogenic bone marrow transplantation is the only curative treatment(9). In MyoVa defect the neurological impairment and psychomotor delay do not improve and hence there is no role for bone marrow transplantation.

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