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Case Presentation

A rare pigmentary disorder in two non-identical siblings: Griscelli Syndrome –type 3

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Absract

Griscelli Syndrome (GS) is a rare autosomal recessive disorder characterized by pigmentary dilution of the hair and skin (partial albinism). Three different types (1-3) caused by mutation in three different genes have been described. Patients with GS type 1 have primary central nervous system dysfunction; type 2 patients commonly develop hemophagocytic lymphohistiocytosis and type 3 patients present with partial albinism only. Two siblings discussed here had silvery hair, eyebrows and eyelashes since birth with no features suggestive of immunodeficiency or neurological impairment, making it an even rarer presentation of Griscelli Syndrome, type 3. Diagnosis was confirmed on light microscopy (LM) of hair shafts. Both GS1 and GS2 have been described earlier. However, extensive search of the literature failed to reveal a similar presentation from Indian origin. This is the first ever report of GS-3 in non-identical siblings from India.

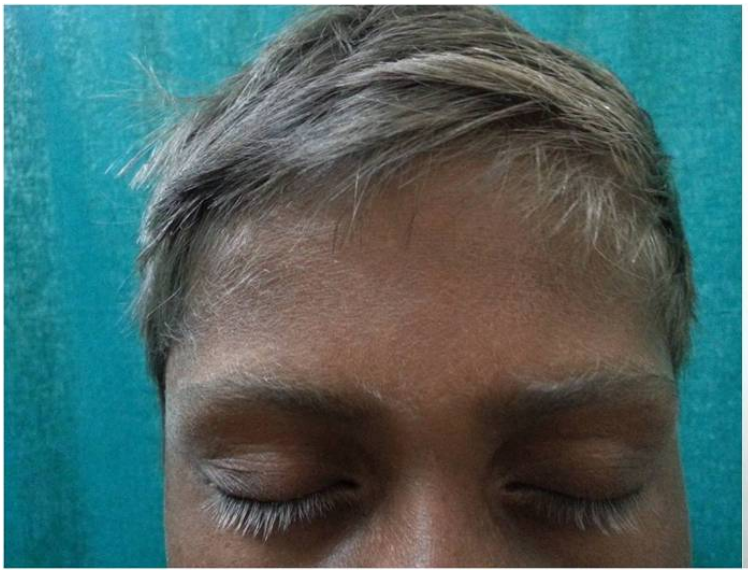
Introduction

GS is a rare autosomal recessive disorder with characteristic pigmentary dilution of the skin and hair. Light microscopy of hair and skin shows the presence of large clumps of pigment in hair shafts and an accumulation of melanosomes in melanocytes [1]. Three different subtypes are caused by mutations in the Myosin Va (MyoVa) (GS1, Elejalde), small GTPase protein RAB27A (GS2), or melanophil MLPH (GS3) genes, respectively. The protein complex formed by these is essential for the capture and movement of melanosomes in the actin-rich cell periphery of melanocytes [2].

Case synopsis

Two non identical siblings (elder male child, eight years of age and younger female child, two years of age) were referred from the department of pediatrics for the evaluation of silvery grey hair. Mother revealed that two out of three siblings were affected. Children were born from a first-degree consanguineous marriage. Both the children had silver grey (leaden) scalp hairs, eyebrows, and eyelashes since birth (Figure1, Figure2). Family history was insignificant. Examination of both children revealed normal vitals; height and weight of elder child was 118cm and 18 kg and younger child was 78cm and 10 kg. Nutritional and developmental status was normal for their age. There was no history of any change in skin color, fever, irritable behavior, pain in the abdomen, jaundice, photosensitivity, mental retardation, seizures, headache, bleeding tendency, or repeated skin infections. Systemic examination was normal. All baseline investigations were within normal limit. Coagulation and lipid profile was within normal limit. Viral markers for hepatitis were negative. Chest roentgenogram and ultrasound abdomen of both patients had no abnormality. Magnetic resonance imaging of the brain was completely normal. Microscopic examination of hair shafts of both the patients showed large discrete clumps of melanin pigment along the length of the shaft (Figure3, Figure4). Clinical features, pigment clumping in the hair shaft, normal laboratory investigations, and absence of neutrophilic inclusions on blood smear differentiated the present case (Griscelli Syndrome type-3) from GS type-1 and GS type-2 and further excluded Chediak Higashi Syndrome (CHS) and Eljalde syndrome (ES). Mother was counseled about the course and prognosis of the disease and was reassured.

Both patients receive yearly follow up and have not yet developed any features suggestive of neurological or immunological impairment.



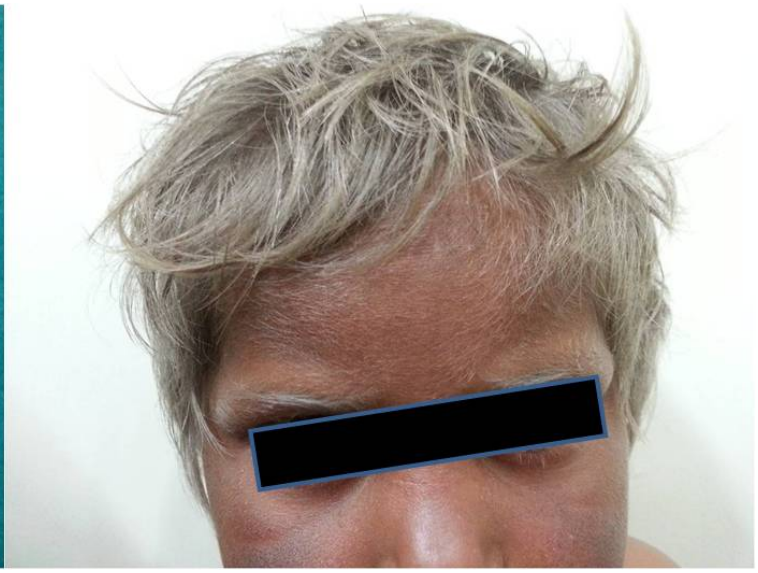
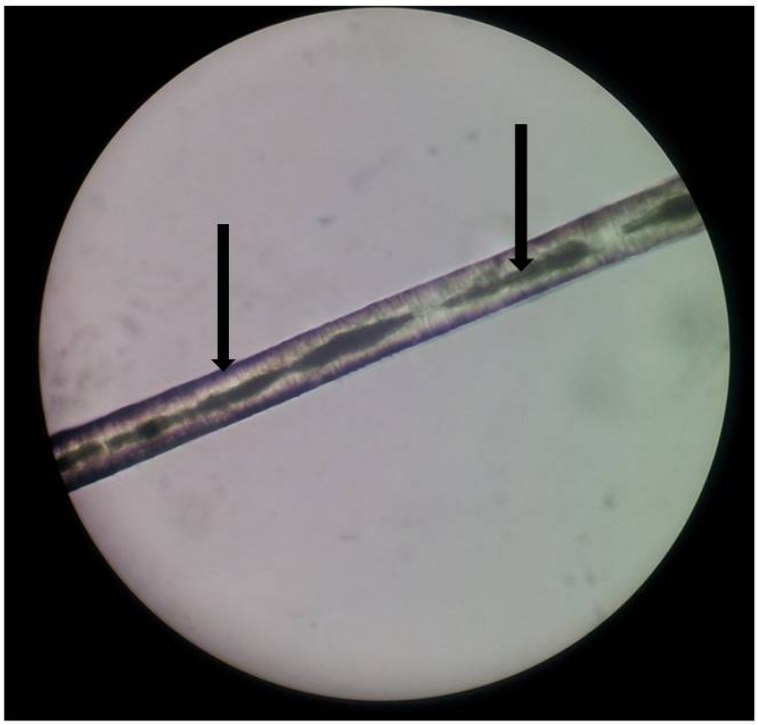


Figure 1. Eight year old male child with silver grey scalp hairs, eyebrows, and eyelashes since birth.

Figure 2. Two year old female child with silver grey scalp hairs, eyebrows, and eyelashes since birth.



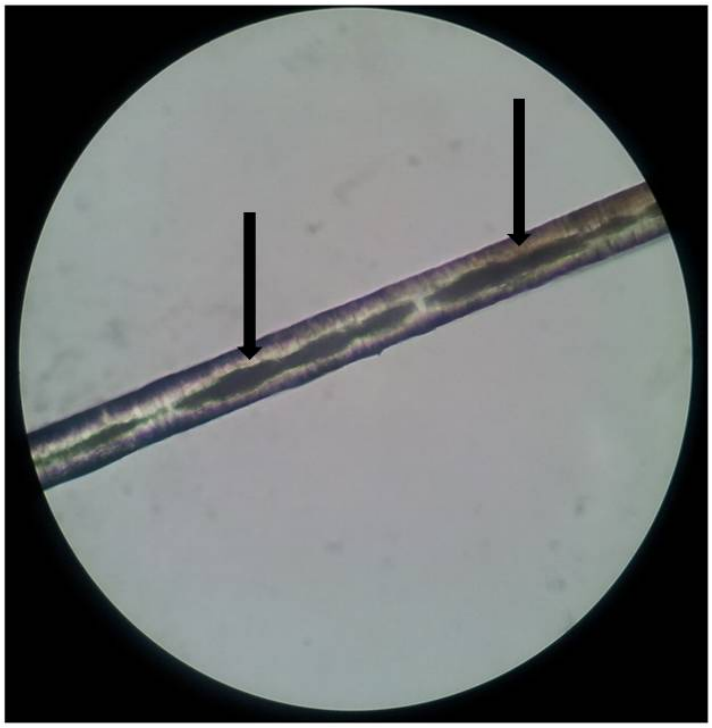


Figure 3. LM- Large clumps of melanin distributed irregularly along the length of hair shaft of eight year old male child.

Figure 4. LM- Large clumps of melanin distributed irregularly along the length of hair shaft of two year old female child

Discussion

Claude Griscelli and Michel Prunieras in 1978 described Griscelli Syndrome in two girls with partial albinism and immunodeficiency [3]. It was differentiated from Chediak-Higashi Syndrome on the basis of differences in light and electron microscopic examination of skin and hair. Since then, a little over than 60 cases of GS have been reported in the medical literature, mostly from the Turkish and Mediterranean populations [4]. A few cases have been reported from different regions of India. Literature revealed three case reports from South India [5,6,7], two from Mumbai [8,9], and one case from New Delhi [10].

The common pigmentary defect observed in the three types (GS1, GS2 and GS3) results from a defect in the interaction of three encoded proteins for melanosome transport [1]. Most patients are diagnosed between 4 months and 7 years of age [4]. GS1 has characteristic albinism with severe neurological impairment. The second type (GS2) is associated with albinism and a primary immunodeficiency owing to an impairment of T cell and natural killer cytotoxic activity, which culminates in a life-threatening condition known as hemophagocytic syndrome or hemophagocytic lymphohistiocytosis (HLH).

The third type of GS, caused by a mutation in the melanophilin gene (MLPH), is restricted only to hypopigmentation defects [11]. The main differential diagnoses in our patient were the Griscelli Syndrome type 1, 2 and 3, Chediak-Higashi Syndrome, and Elejalde Syndrome (Discussed in detailed in Table 1[1,11,12]). A retrospective study by VV smith et al [13] of 322 hair samples suggested that light microscopic examination of scalp hair is an inexpensive, rapid, non-invasive, and first line investigation, which can provide valuable diagnostic information in silvery hair syndromes. It is important to examine as many strands of hair as possible because every hair may not demonstrate morphological abnormalities in the lengths examined. The various other investigations to diagnose GS are electron microscopy of hair shaft and skin, polarized microscopy (shaft looks bright with a monotonously whitish appearance), skin biopsy, and genetic study. Although gene study is helpful to confirm the syndrome, the clinical findings and light microscopy of hair is distinctive [14].

Conclusion

To the best of our knowledge this is the first ever report of GS3 in two non identical siblings from India. Any patient presenting with silvery hair must undergo light microscopic examination before initiating an exhaustive work up. GS3 should be differentiated from Type 1 and type 2 GS, Chediak Higashi syndrome, and Elejalde Syndrome. GS type 3 needs no active intervention except for regular follow up.

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Differentiating features of silvery hair syndromes [1,11,12].

	ES	CHS	GS
Mode of inheritance	AR	AR	AR

Hair shaft under LM	Small &large clumps of melanin in irregular pattern	Small clumps of melanin regularly distributed	Large clumps of melanin irregularly distributed. Clusters of melanin pigment are six times larger than in CHS.		
LM of blood smear	No detectable alteration	Giant lysosomes inclusion bodies in neutrophilis	No detectable alteration		
EM of skin	Melanosomes at different stages of formation in the melanocytes	Giant melanosomes within melanocytes and kerattinocytes	Melanocytes with a massive accumulation of mature melanosomes and to some extent in keratinocytes		
Histopathology of skin	Irregular sized melanin granules dispersed in basal layer	Large melanosomes in both melanocytes and keratinocytes	Excess pigmentation of melanocytes at basal layer and scanty pigmentation in skin surrounding the pigmented areas		
Brain MRI	Cerebellar atrophy	Hypersignal; encephalitis secondary to HLH	GS-1	GS-2	GS-3
			Cerebellar atrophy	Same as CHS	No alteration
Clinical features	Neuroectodermal-melanolysosomal disease, silvery hair, intense tanning, Neurological & ophthalmological abnormalities. Related to or	At early childhood Immune deficiency: repetitive infections, HLH syndrome	Primary neurological deficiency at birth	Same as CGS	Pigmentary alteration only

	allelic to GS1				
Gene sequencing	MyoVa	LYST 1q42.1-q42.2	MyoVa 15q21), (myosin-Va has a determining role in neuron function)	RAB27A 15q15-q21.1 (Rab27a required for exocytosis of cytolytic granules in cytotoxic T lymphocytes and natural killer cells)	MLPH 2q37.3 or MyoVa-exon F
Treatment	Palliative treatment and support to family	Bone marrow transplantation	Palliative treatment and support to family	Same as CHS	No treatment required