



Griscelli Syndrome Type 3: A Case Report

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Abstract

Griscelli syndrome (GS) is a rare autosomal recessive multisystem disorder of pigmentary dilution of skin, silver gray hair, variable immunodeficiency, neurological impairment and abnormal accumulation of melanosomes in melanocytes. The three different types of GS are caused by mutations in three different genes. Griscelli type 3 is due to mutations in the Mlph gene, characterized by hypomelanosis with no immunological and neurological manifestation. We report a 19 years old male with type 3 GS having only pigmentary dilution; silvery gray hair, eye brows, and eyelashes.

Introduction

GS was first described in 1978 by Claude Griscelli and Michel Prunieras^[1]. GS is characterized by a silver-gray sheen of the hair and the presence of large clusters of pigment in the hair shaft and the occurrence of either a primary neurological impairment or a severe immunological disorder. Three types of this disorder are distinguished by its genetic cause and pattern of signs and symptoms^[2,3]. GS type 1 is caused by mutation in the Myo5A gene, causing severe neurological impairment such as developmental delay, mental retardation, seizures, hypotonia and vision abnormalities in addition to the distinctive skin and hair colouring. Patients with GS type 2 caused by mutation in Rab27A gene associated with a primary immunodeficiency due to an impairment of T cell and natural killer cytotoxic activity, that leads to susceptibility to recurrent

infections and may develop an immune condition called hemophagocytic lymphohistiocytosis (HLH) in which the immune system produces too many activated immune cells called T-lymphocytes and macrophages. Over activity of these cells can damage organs and tissues throughout the body, causing life-threatening complications if the condition is untreated. Neurological involvement in GS2 is secondary to lymphohistiocytic infiltration^[4,5]. Light skin and hair colouring are the only features of GS type 3. People with this form of the disorder do not have neurological abnormalities or immune system problems.

Light microscopy examination of the hair shaft is an easy way to diagnose GS, typically with a large cluster of pigment unevenly distributed in the hair shaft predominantly in the medulla^[6,7].

Case Report

A 19-year-old boy came to skin department with the complaint of lightening of skin and hair since infancy. The patient is born by spontaneous vaginal delivery and normal birth weight. He was born to consanguineous healthy parents (first degree cousins) with no history of similar condition in the family. He had silvery-gray hair including the eyebrows and eyelashes. General physical examination was normal. There was no lymphadenopathy or hepatosplenomegaly. The patient had no history of recurrent infections. CNS examination and routine blood investigations were normal. On light microscopic examination of hair, uneven clusters of aggregated melanin pigment, accumulated mainly in the medullary area of the shaft was seen instead of the homogeneous distribution of small pigment granules as seen in normal hair. On the basis of clinical presentation, absence of neurological and immunological abnormality, and characteristic microscopic findings of hair shaft and skin, patient was diagnosed as Griscelli syndrome type 3.



Figure 1: Silver-Grey sheen of hairs, eyebrows



Figure 2: Silver-grey hairs

GS is classified into 3 types based on mutations in genes; Myo5A (GS1), Rab27A (GS2) or Mlph (GS3). The transport of melanosomes from the cell center to cell periphery involves a bidirectional transport. This transport takes place along microtubule tracks with the help of the motor proteins, dyneins, and kinesins. Myosin Va (Myo5a), which is a motor protein, attaches to melanosomes through interaction with Mlph and Rab27a. The tripartite complex, which is composed of Rab27a, Mlph, and Myo5a, has roles in vesicle transport and membrane trafficking processes^[8]. If any member of the tripartite complex is defective, melanosome transport is impaired. Melanosomes are not captured in the periphery, not transferred from melanocytes to keratinocytes and perinuclear accumulation of melanosome occurs. This results in skin hypopigmentation and silvery gray hair. In cytotoxic T lymphocytes, Rab27A does not interact with either Mlph or Myo5A. Rab27A deficient cells have normal granule content in perforin and granzymes, but defective release. Whereas Myo5A or Mlph deficient T cells are normal^[9,10]. Only Myo5A is expressed in brain and plays a role in secretion of neurotransmitters. This selective tissue expression is the basis for phenotypic differences between subgroups^[1,9]. Type 1 GS presents with severe primary neurological impairment in the form of severe developmental delay, muscular hypotonia, and mental retardation occurring early in life^[11]. It

results from mutations of the myosin 5A gene (Myo5A) which encodes an organelle motor protein myosin 5A (MyoVa) and has a determining role in neuron function. GS2 is caused by mutations in the gene encoding the small GTPase Rab27A. Rab27A deficiency causes defects in the exocytosis of cytotoxic granules from T cells and natural killer (NK) cells and melanosome exocytosis. A history of severe infections, absence of delayed type cutaneous hypersensitivity, hypogammaglobulinemia are all characteristic features of type 2 GS. Hemophagocytic lymphohistiocytosis (HLH), an accelerated form, is characterized by overwhelming T cell and macrophage activation that leads to fever, splenomegaly, cytopenia, hypofibrinogenemia, and/or hypertriglyceridemia and hyperferritinemia. It can prove fatal if not treated promptly. Chemotherapy can be given to achieve remission; however, allogeneic hematopoietic stem cell transplantation is the only currently available curative treatment for GS2^[12]. Mlph gene defect responsible for type 3 GS presents with hypopigmentation of skin and hair without any systemic involvement^[13]. The prognosis for patients with GS3 is good, and these patients do not require any treatment. Similarly as in our case patient was otherwise healthy but had silvery-gray hair including the eyebrows and eyelashes. A very close differential diagnosis of GS is Chediak–Higashi syndrome, which also presents with partial albinism and recurrent infections. Differentiation of GS from Chediak–Higashi syndrome (CHS) can be made on the basis of abnormal vacuolation in the granulocytes in peripheral blood film, associated with decreased nitroblue tetrazolium test with biopsies of skin, hair, and Schwann cells showing abnormal membrane-bound lysosome-like organelles in CHS^[14]. The hair shaft also contains a typical pattern of uneven accumulation of large pigment granules but in GS the clusters of melanin pigment on the hair shaft are six times larger than in CHS

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