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Case Report

Griscelli Syndrome with hemophagocytosis: a case report

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ABSTRACT

Griscelli syndrome is a rare autosomal recessive disorder characterized by pigmentary dilution of the skin and the hair (silver hair), the presence of large clumps of pigment in hair shafts, and an accumulation of melanosomes in melanocytes. In one variant, hepatosplenomegaly, lymphohistiocytosis, and a combined T-cell and B-cell immunodeficiency are pronounced. The associated immunodeficiency often involves impaired natural killer cell activity, absent delayed-type hypersensitivity, and a poor cell proliferation response to antigenic challenge. Occasionally, impaired lymphocyte function and an inability to produce normal levels of immunoglobulins have also been described. In another variant, neurologic signs are most prominent. We present a case of 1 year male who presented with fever, jaundice, silver hair, heptoslenomegaly, and pancytopenia.

Keywords: Griscelli syndrome, Pancytopenia, Grey hair, Lymphohistiocytosis

INTRODUCTION

Griscelli syndrome was first described by Griscelli and Siccardi in 1978 in a hospital in Paris.[1] It is a rare autosomal recessive disorder resulting in pigmentary dilution of the skin and hair, presence of large clumps of pigment in hair shafts and an accumulation of melanosomes in melanocytes.[2] It results in silver-grey hair along with variable cellular immunodeficiency or severe neurological impairment or both.[2] The condition is rare in all countries and up to January 2003 only 60 cases had been described in the world medical literature .[2] In most cases diagnosis occurs between the ages of 4 months to 7 years.[2] The boy discussed here had silvery hair, eyebrows and eyelashes and was admitted at the age of five months to hospital with fever, jaundice, hepato-splenomegaly and ascitis.

CASE REPORT

A 1 year old boy born out of second degree consanguineously married couple admitted in our hospital with complaints of fever, abdominal distension, jaundice which the mother notice since past 5 days, also had silvery greyish discolouration of hair since birth .

The physical examination revealed severe pallor, icterus, hepatomegaly, splenomegaly and ascitis. Developmentally appropriate for age and neurologically unremarkable.

The Initial investigations revealed pancytopenia (Hb-5.1, Total count-10.230, Plt count-0.48, MCH-28, MCV-65, MCHC-28) biochemical tests of liver function showed TB-4.40, DB-3.73, Total protein-4.5, Albumin-2.1, SGOT-78, SGPT-44 and abnormal blood coagulation profile (Pt-30, Aptt-42, INR-2.31).

A raised serum triglyceride (1314), LDH (326), serum ferritin (347.9), low serum fibrinogen (80mg/dl) supported the diagnosis of haemophagocytic lymphohistiocytosis.[3]

MRI brain

Mild diffuse cerebral parenchymal atrophic changes are seen with widened CSF spaces.

Mild passive dilation of entire ventricular system.

USG Abdomen - Hepatomegaly with no change in echo texture, Splenomegaly with moderate ascitis. Bone marrow-reactive bone marrow, no hemophagocytes.

Treated with broad spectrum antibiotics, fresh frozen plasma transfusion, packed cells transfusion following which child improved. Refer to paediatric Hemato-Oncologist for further management.

DISCUSSION

Griscelli and Siccardi first described the Griscelli syndrome in 1978.[1] It is an autosomal recessive disorder resulting in pigmentary dilution of the skin and hair with the presence of large clumps of pigment in hair shafts as a result of the accumulation of melanosomes in melanocytes. More significantly the inherited metabolic defect can also be associated with haemophagocytic lymphohistiocytosis and/or severe neurological impairment early in life. Our patient presented with the pigment disorder and immune dysfunction resulting in partial albinism and haemophagocytic lymphohistiocytosis.

In most cases diagnosis is made between the ages of 4 months to 7 years.[2] Three main types of Griscelli syndrome are recognized and classified according to the mutation involved and the clinical presentation. The common pigmentary defect observed in the three types (GS1, GS2 and GS3) results from the absolute requirement and interaction of three encoded proteins for melanosome transport. GS1 associates characteristic albinism with a severe primary neurological impairment. Patients exhibit severe developmental delay and mental retardation occurring early in life. These patients carry mutations of the myosin 5A gene (MYO5A), which encodes an organelle motor protein, Myosin 5A (MyoVa), and has a determining role in neuron function.[4,5]

The second type of Griscelli syndrome (GS2) is characterized by the same hypopigmentation associated with an immune defect, leading to episodes of life-threatening uncontrolled T lymphocyte and macrophage activation that are the hallmark of haemophagocytic lymphohistiocytosis (HLH).[6] During HLH activated T cells and macrophages infiltrate various organs (including the brain), leading to massive tissue damage, organ failure, and death in the absence of treatment.[6] The immune dysfunction can initially be controlled with immunosuppressive treatment but haematopoietic stem cell transplantation is the only definitive curative treatment for this condition.[6]

Mutations in RAB27A, a gene that encodes a small GTPase protein (Rab27a) and is involved in the function of the intracellular-regulated secretory pathway, cause GS2.[7] The immune deregulation observed in GS2 patients is accounted for by the absolute requirement of the Rab27a protein function for lymphocyte cytotoxic granule release and underlines the determining role of this cytotoxic pathway in immune homeostasis.[7]

Therefore in GS2 patients the ability of lymphocytes and natural killer cells to lyse target cells is impaired or absent due to a consistent inability to secrete cytotoxic granules. This inherited defect therefore accounts for the severe immunologic disorder characteristic of this syndrome, namely haemophagocytic lymphohistiocytosis.

Both genes (MYO5A and RAB27A) map to the same chromosome 15q21.1 region and are distant from each other by less than 1.6 cM.[8] Homozygous missense mutation in human melanophilin (MLPH), leading to defective Rab27a - Mlph interaction, results in a third form of GS (GS3), the phenotype of which is restricted to hypopigmentation only.[9] Slac2/melanophilin is the link between myosin Va and GTP-Rab27a. In the absence of the tripartite protein complex (Rab27a-Mlph-MyoVa) formation in melanocytes, melanosomes cannot be connected to the action network and thus transported toward the melanocytes tips.[9,10]

Our patient, MS, probably has the GS2 form of Griscelli syndrome. The main differential diagnoses in our patient were the Chediak-Higashi syndrome (CHS) and Elejalde syndrome (ES). Both disorders can present with the characteristic silvery grey hair. An important clue to the diagnosis of the Griscelli syndrome is from the histological examination of the hair shaft of the patient. Examination of the hair shaft from our patient showed large discreet clumps of melanin pigment along the length of the shaft, instead of the homogeneous distribution of small pigment granules seen in normal hair. In Chediak-Higashi syndrome, 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.[11]

CONCLUSION

We present the first documented case of Griscelli syndrome. The characteristic phenotypic appearance, especially the pigment disorder of the patient's hair, is emphasized so that it is quite possible to suspect the diagnosis at the bedside. The underlying defects of the condition are also presented and these serve to shed important light on the importance of the secretory pathways required for normal lymphocyte cytotoxicity, melanosome transfer and neurotransmission.

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