Griscelli syndrome type-2 with haemophagocytic lymphohistiocytosis in an infant

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Introduction

Griscelli syndrome (GS) is an autosomal recessive disorder first described in 1978 by Claude Griscelli and Michel Prunieras.[1] Based on the genes involved and the phenotype, it is of three types: GS1, GS2, and GS3. The common feature is pigmentary dilution caused by defective melanosome transport. Up to 160 cases of GS have been reported in the literature, mostly from Turkish and Mediterranean regions.[2] GS2 is the commonest with 13 cases reported in Indian literature.[3-5] GS flares up due to macrophage and T lymphocyte activation.[6] It is usually diagnosed between 4 months and 7 years of age.[7]

Case report

A 5-month-old boy, born to parents with third degree consanguinity, and an uneventful full-term pregnancy presented to us with fever, cough and cold for one week. He had 2 similar febrile episodes without respiratory symptoms at 3 and 4 months of age, and received blood transfusion on both occasions. Previous reports showed moderate anaemia with raised C-reactive protein and sterile blood cultures. For these episodes, considering sepsis, he was treated with intravenous antibiotics for 5-7 days and discharged on oral antibiotics.

Based on records, he weighed 2.8 kg, measured 51 cm in length, and had a head circumference of 34.4 cm at birth. The parents did not vaccinate him at 14 weeks due to apprehension about fever. Compared to his parents, he had very fair skin, silvery grey scalp hair, eyebrows, and eyelashes (Figure 1). The infant successfully attained his early developmental milestones at the appropriate times. Notably, he recognises his parents, responds with smiles, exhibits commendable neck control, and actively engages in interactions. He has an older male sibling, aged 3 years, who also had similar fair skin and silvery scalp hair but is healthy. The colour of his skin and hair improved over time, so the parents did not consult any clinician.

His current anthropometric measurements are normal for his age: weight 6.5 kg, length 66 cm, and head circumference 42 cm. On examination, he had moderate pallor and moderate hepatosplenomegaly, while the central nervous system (CNS) examination was normal.

Figure 1: *A 5-month-old infant having silvery grey hair and eyebrows*

Investigations showed a haemoglobin level of 8.4 g/dL, a total leucocyte count of 5200/mm³ with an absolute neutrophil count of 618/mm³, and a platelet count of 68,000/mm³. The peripheral blood smear showed normocytic normochromic red blood cells without evidence of characteristic giant granules in neutrophils, eosinophils, and granulocytes, ruling out Chediak-Higashi syndrome. Given the silver-grey hair, hepatosplenomegaly, and absence of neurological manifestations, a diagnosis of Griscelli Syndrome type 2 (GS-2) was considered. Light microscopy of the scalp hair shaft revealed large irregular clumps of pigment, supporting the diagnosis of GS-2 (Figure 2B). Laboratory findings also indicated haemophagocytosis, hyper-triglyceridaemia of 315 mg/dL (normal <150 mg/dL), hypofibrinogenaemia of 132 mg/dL (normal: 150–450 mg/dL), and hyperferritinaemia of 1749 ng/mL (normal: 50–200 ng/mL).

Figure 2A: *Light microscopic image of normal hair*

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Figure 2B: *Light microscopic image of patient's scalp hair shaft showing large irregular clumps of melanin pigment*

A bone marrow biopsy for haemophagocytosis was found to be normal at present. Cerebrospinal fluid examination and magnetic resonance imaging of the brain were done to check for CNS involvement and both were normal. Serum IgG, IgA, and IgM levels were measured to assess humoral immunodeficiency and were normal for his age. However, assessment of cellular immune deficiency by flow cytometry was not available at our centre, and genetic analysis was also not performed for similar reasons.

Discussion

We considered a few differential diagnoses in our case, such as Chediak-Higashi syndrome, Griscelli syndrome, Elejalde syndrome, and Hermansky-Pudlak syndrome. The absence of giant granules in granulocytes and other leucocytes disfavoured Chediak-Higashi syndrome. Additionally, the absence of a bleeding diathesis with a normal coagulation profile, no visual abnormalities in the baby argued against Hermansky-Pudlak syndrome. Researchers have identified three types of GS which are distinguished by their genetic causes and pattern of signs and symptoms. Three genes on 15q21 are responsible for GS manifestations.[8]

Griscelli syndrome type 1 (GS1) and Elejalde disease share similar clinical features, particularly severe neurological involvement, and pigmentary dilution, leading some researchers to suggest that they may be the same disorder.

Griscelli syndrome type 2 has hypopigmentation of skin and hair as well as immune system abnormalities and affected individuals are prone to recurrent infections. GS2 is strongly associated with haemophagocytic lymphohistiocytosis (HLH) in which there is overactivity of T-lymphocytes and macrophages (histiocytes) and which can damage organs and tissues throughout the body, causing life-threatening complications if the condition goes untreated. The secondary CNS involvement in GS-2 is caused by the infiltration of lymphocytes and histiocytes because of haemophagocytic syndrome. Temporary remission of the accelerated phase seen in GS-2 can be achieved with chemotherapy or immunotherapy[9].

In Griscelli syndrome type 3, there is primarily pigmentary abnormality without significant immunodeficiency or neurological impairment.

The long-term prognosis of GS-2 is poor due to its strong association with HLH and survival of patient is difficult. Patient usually succumbs to severe infection or CNS infiltration at an average age of 5 years without BMT[10]. Thus, prompt diagnosis is vital in the prognosis of GS-2.

In our patient, recurrent fever with bicytopenia, hepatosplenomegaly, and laboratory evidence of haemophagocytic syndrome without CNS involvement, along with characteristic scalp hair microscopy findings, was suggestive of GS-2 with primary HLH. The diagnosis of GS-2 is crucial because bone marrow transplantation (BMT) is the only definitive treatment for GS-2 and has no role in GS-1. We referred the patient to a centre where genetic analysis and BMT can be performed to potentially save the child's life.

Informed consent: Written informed consent was obtained from the parents of the infant for the publication of the images and case report.

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