ejpmr, 2015,2(3), 674-680

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Case Report

ISSN 3294-3211

EJPMR

GRISCELLI SYNDROME WITH FEATURES OF HEMOPHAGOCYTOSIS; A RARE PRESENTATION

Dr. Sudhir Mehta*

Department of Pediatrics, Sri Aurobindo Medical College and PG Institute, Indore, Madhya Pradesh, India.

Article Received on 29/03/2015 **Article Revised on 20/04/2015** **Article Accepted on 10/05/2015**

***Correspondence for Author**

Dr. Sudhir Mehta

Department of Pediatrics, Sri Aurobindo medical college and PG Institute, Indore, Madhya Pradesh, India.

ABSTRACT

Griscelli syndrome is a rare genetic immunodeficiency disorder characterized by pigment dilution, recurrent cutaneous and pulmonary infections, splenohepatomegaly, neurological deterioration, hypogammaglobulinemia, pancytopenia and defective cell-mediated immunity. Mutations of three distinct genes have been described in Griscelli syndrome with different phenotypes. The disease is usually fatal by the first decade of life. Only few cases are reported from India. We report a 3 year-old male child of Griscelli syndrome with diffuse pigment dilution with silvery hairs, recurrent infections, splenohematomegaly with features suggestive of hemo phagocytic -lymphohistiocytosis syndrome.

KEYWORDS: Griscelli syndrome, Hemo- phagocytosis, Silvery hair.

INTRODUCTION

Griscelli syndrome (GS) is a disorder of defective neutrophilic function with autosomal recessive inheritance.[1] It was first described by Griscelli in 1978.[2] and since then many cases have been reported but, mostly from the Turkish and Mediterranean population. Only few cases are reported from India. There is a characteristic pigmentary dilution of the skin and the hair, with the presence of large clumps of pigment in hair shafts and an abnormal accumulation of end-stage melanosomes in the center of melanocytes. The albinism is present at birth and patients with immunodeficiency develop accelerated phases of hemophagocytic lymphohistiocytosis. It is multisystem disorder with three subtypes (GS1, GS2, GS3), based on genetic loci (Myosin VA, Ras related protein Rab-27A, melanophilin). GS1 presents with

primarily neurologic impairment with no immunologic involvement while GS2 presents with immunological dysfunction and multisystem involvement, whereas GS3 have only hypomelanosis. GS2 is the most common among three types. The differential diagnosis of GS includes disorders of pigment dilution such as Chediak-Higashi syndrome and Hermansky-Pudlak syndrome as well as disorders of neutrophilic function such as chronic granulomatous disease of childhood (CGC), myeloperoxidase deficiency, hyper-IgE syndrome and Wiskott-Aldrich syndrome. We present a child with classic clinical features along with picture of hemophagocytic lymphohistiocytosis and confirmatory findings of clumped melanosomes on microscopy of hair shaft.

CASE REPORT

A 3-year-old male child born of non-consanguineous parentage with history of recurrent episodes of fever and infections with ear discharge off and on since birth. This time, he presented with jaundice, pallor and abdominal distension for last three weeks. He was third born to healthy parents by normal vaginal delivery at term with normal birth weight. He had history of global developmental delay with development age corresponding to one and half years. He was adequately immunized for age. There was no history of prior blood transfusions or bleeding from any site or jaundice in past. He had history of two sibling deaths of two and half-year-old female and another two-year-old male sibling with similar clinical features with repeated episodes of fever and ear discharge and light colored hair. There was no history of any other relatives affected by similar clinical presentation.

At admission, his vitals were stable. He was grossly malnourished with weight for age, height for age and weight for height less than 3 standard deviation as per WHO classification. He had silvery grey sheen hair [figure 1]. The skin, iris and retina had normal pigmentation. He had pallor, icterus with minimal bilateral pitting pedal edema. Abdominal examination revealed firm hepatomegaly of 6 cms and splenomegaly of 9 cms. Other systemic examination was normal.

Investigations revealed pancytopenia with hemoglobin of 7.5 gm/dl, total leukocyte count of 3200/cu.mm with differential count of L60%, N28%, Band forms 10% and myelocytes 2%, platelets 40000 cu.mm and 0.9% reticulocytes. Blood picture did not show azurophil granules. Prothrombin time and activated partial thromboplastin time were prolonged. Serum electrolytes, calcium and creatinine were normal. Liver function test revealed total bilirubin of 3.3 mg%, direct bilirubin of 2.7 mg%, total protein of 3.1 gm%, albumin of 1.3 gm%,

SGOT of 195 U/L, SGPT 167 U/I and alkaline phosphatase 571 U/L. Lipid profile revealed cholesterol 285 mg%, triglycerides 386 mg%, high-density lipoprotein cholesterol 68 mg% and low-density lipoprotein cholesterol 69 mg%. Serum ferritin levels were also elevated. Malarial parasite and Kala Azar serology was negative. Serum ceruloplasmin and 24h urinary copper were within normal limits. Tubercular work-up was negative. Serum immunoglobulin was IgG 556 mg%, IgM 172 mg% and IgA 122 mg%. Viral markers for hepatitis (HAV and HBV) were negative. HIV ELISA, Dengue IgG and IgM were negative. Hemoglobin electrophoresis was normal.Bone marrow examination and culture were normal except for mild erythroid hyperplasia with megaloblastic erythropoiesis. ESR was normal , anti-nuclear antibody and other autoimmune work up was negative. MRI brain was normal. His ultrasonography abdomen revealed spleno-hepatomegaly. Genetic study could not be done because of financial constraints.

His hair examination revealed irregular pigment clumps in hair shaft [figure 2]. His skin biopsy revealed clumped pigment deposition in the basal epithelial layer and pigment in the keratinocytes [figure 3]. With clinical and laboratory findings he was diagnosed as Griscelli syndrome with features suggested of hemophagocytosis.

He was treated symptomatically with IV fluids, oxygen, antibiotics, blood and blood products. During hospital stay he improved with the above measures and was discharged. Allograft bone marrow transplant was deferred in view of no other sibling.

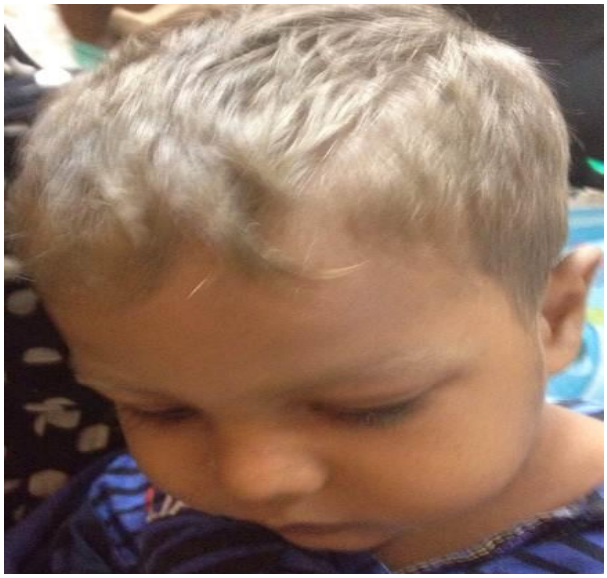

Figure 1- Showing silvery gray sheen hair

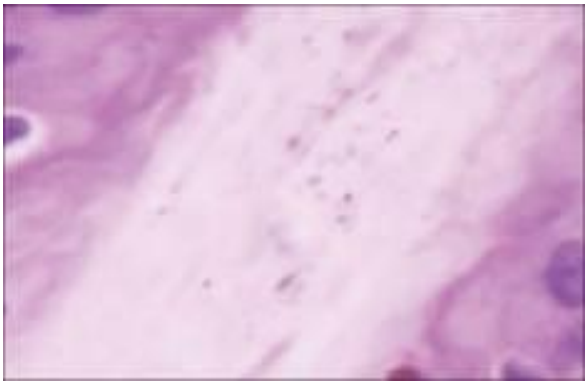

Figure 2- showing irregular pigment clumps in hair shaft

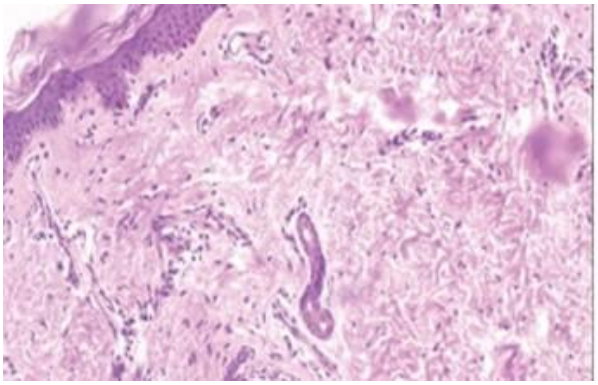

Figure –3 Showing skin biopsy with clumped pigment deposition in the basal epithelial layer

DISCUSSION

Griscelli syndrome is an immunodeficiency disorder characterized by partial albinism, hepatosplenomegaly, progressive neurological deterioration, hypogammaglobulinemia and pancytopenia.[2] In 1978 Griscelli *et al* .[2] first described two patients with partial albinism of hair and skin, frequent pyogenic infections and acute episodes of fever, hepatosplenomegaly, neutropenia and thrombocytopenia. Immunologic abnormalities most often include impaired natural killer cell activity, absent delayed-type hypersensitivity and impaired responses to mitogens. Impaired helper T cell function and hypogammaglobulinemia have also been described.[3] Three different gene loci on chromosome 15q21 are responsible for this rare disease: the myosin Va gene (GS1), the RAB27A (GS2) and the MLPH (GS3) gene.[4] It is clinically characterized by accelerated phases triggered by viral or bacterial infections. Microscopic examination of hair shafts reveals uneven clusters of aggregated melanin pigments, accumulated mainly in the medullary area of the shaft. Histopathological examination of skin biopsy shows hyper-pigmented oval melanocytes with poorly pigmented adjacent keratinocytes. Electron

microscopic evaluation of skin specimens shows epidermal melanocytes filled with numerous stage IV melanosomes arranged in a perinuclear distribution, without giant melanosomes.[5] Neurologic involvement is prominent in many patients with Griscelli syndrome.[5,6] Clinical manifestations include intracranial hypertension, cerebellar signs, bulbar poliomyelitis, encephalopathy, hemiparesis, peripheral facial palsy, hypotonia seizures, and psychomotor retardation.

The differential diagnosis of the disease in the patient presenting with silvery hair includes primarily Chediak-Higashi syndrome (CHS), Griscelli syndrome and Elejalde syndrome. CHS differs from Griscelli syndrome by the presence of abnormal giant cytoplasmic inclusions in leukocytes, most frequent cutaneous pigmentary dilution, aggregates of giant melanolysosomes in melanocytes and keratinocytes, more evenly distributed pigment clumps in hair shafts and more consistently defective granulocyte activity.[5] Elejalde syndrome, also known as neuroectodermal-melanolysosomal disease reveals spotty hair pigmentation similar to Griscelli syndrome with incomplete melanization of melanosomes in skin melanocytes.[7]

The diagnosis of Griscelli syndrome is made by clinical presentation combined with characteristic light and electron microscopic findings in hair shaft and skin and absence of giant cytoplasmic granules in peripheral leukocytes. Prenatal diagnosis has been accomplished by examination of hair from fetal scalp skin biopsies performed at 20 weeks gestation.[8] GS presents with variable phenotype and is categorized in to 3 types. GS1 patients primarily present with neurological involvement without immune dysfunction. Hepatosplenomegaly, recurrent infection, hypomelanosis and silvery gray hair are consistent features of GS2 patients. GS3 is categorized by hypomelanosis with no immunologic or neurologic involvement. Presence of grayish hair is a hallmark of all the three types of GS patients.

The prognosis for patients with Griscelli syndrome is grave. As in other genetic immunodeficiency diseases, bone marrow transplantation is the only hope for a cure and appears to be most successful when performed early in the course of the disease.[9] There are a very few reports of successful BMT in patients of Griscelli syndrome. Schuster F et al.[10] reported the first PBSCT with T cell depletion in a 6-month-old girl with deletion of the RAB27A gene. The donor was her phenotypically HLA-identical mother. Arico M et al.[11] described the first patient with GS cured with an allograft from a compatible unrelated bone marrow donor. In resource-limited situations, management of GS is symptomatic with

counseling, ascorbic acid and non-specific immunostimulators. Systemic corticosteroids, anti-thymocyte globulins and cyclosporine are the treatment options in established cases of lymphohistiocytic histiocytosis.[12]

The constellation of hypopigmented hair, recurrent infection, severe malnutrition and hepatosplenomegaly pose a diagnostic challenge to treating pediatrician in a developing country where malaria, Kala- Azar, thalassemia, leukemia, lymphoma, and tropical splenomegaly syndrome masquerade similarly. We considered the differential diagnosis of silvery gray hair-GS and Chediak Higashi syndrome. The diagnosis of GS was made in presence of following features (silvery gray hair, splenohepatomegaly, recurrent infection) and absence of significant neurologic dysfunction and intracytoplasmic granules in leucocytes. Our diagnosis was further supported by hair shaft microscopy and skin biopsy.

CONCLUSION

In summary, the silvery-greyish hair associated with fever, pancytopenia and hypertriglyceridemia is the clue to early diagnosis of Griscelli syndrome, with hair shaft microscopy and skin biopsy helpful in resource poor countries.

ACKNOWLEDGEMENT: None

CONFLICT OF INTERESTS: None

REFERENCES

1. Piette WW. Hematologic diseases. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. Fitzpatrick's Dermatology in general medicine. 5th ed. New York: McGraw- Hill, 1999; 1868.
2. Griscelli C, Durandy A, Guy-Grand D, Daguillard F, Herzog C, Prunieras M. A syndrome associating partial albinism and immunodeficiency. Am J Med, 1978; 65: 691-702.
3. Klein C, Philippe N, Le Deist F, Fraitag S, Prost C, Durandy A, *et al* . Partial albinism with immunodeficiency (Griscelli syndrome). J Pediatr, 1994; 125: 886-95.
4. Paller AS. Genetic immunodeficiency diseases. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. Fitzpatrick's Dermatology in general medicine. 5th ed. New York: McGraw- Hill, 1999; 1406.

5. Mancini AJ, Chan LS, Paller AS. Partial albinism with immunodeficiency: Griscelli syndrome: Report of a case and review of the literature. J Am Acad Dermatol, 1998; 38: 295-300.
6. Hurvitz H, Gillis R, Klaus S, Klar A, Gross-Kieselstein F, Okon E. A kindred with Griscelli disease: spectrum of neurological involvement. Eur J Pediatr, 1993; 152: 402-5.
7. Elejalde BR, Holguin J, Valencia A, Gilbert EF, Molina J, Margin G, *et al* . Mutations affecting pigmentation in man. Neuroectodermal melanolysosomal disease. Am J Med Genet 1979; 3: 65-80.
8. Durandy A, Breton-Gorius J, Gay-Grand D, Dumez C, Griscelli C. Prenatal diagnosis of syndromes associating albinism and immune deficiencies (Chediak-Higashi syndrome and variant). Prenat Diagn 1993; 13: 13-20.
9. Schneider LC, Berman RS, Shea CR, Perez-Atayde AR, Weinstein H, Geha RS. Bone marrow transplantation for the syndrome of pigmentary dilution and lymphohistiocytosis (Griscelli syndrome). J Clin Immunol 1990; 10: 146-53.
10. Schuster F, Stachel DK, Schmid I, Baumeister FA, Graubner UB, Weiss M, Haas RJ, Belohradsky BH. Griscelli syndrome: report of the first peripheral blood stem cell transplant and the role of mutations in the RAB27A gene as an indication for BMT. Bone Marrow Transplant. 2001; 28: 409-12.
11. Arico M, Zecca M, Santoro N, Caselli D, Maccario R, Danesino C, et al. Successful treatment of Griscelli syndrome with unrelated donor allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2002; 29: 995-8.
12. Bejaoui M, Veber F, Girault D, Gaud C, Blanche S, Griscelli C, et al. The accelerated phase of Chediak-Higashi syndrome. Arch Fr Pediatr. 1989; 46: 733-6.