GRISCELLI SYNDROME; A CASE REPORT AND REVIEW OF THE LITERATURE

B.Sh. Shamsian MD[1]
M.T. Arzanian MD[2]
S. Alavi MD[1]
S. Zareifar MD[3]

Abstract:
Griscelli syndrome (GS) is a rare disease first described in 1978. It is inherited in autosomal recessive pattern. This disease is characterized by partial albinism, pigmentation dilution, cellular immunodeficiency, neurological involvement & uncontrolled phases of macrophage & lymphocyte activation.
We report a 5 months Old Iranian girl presenting with silver-gray hair, eyelashes and eyebrows, hepatosplenomegaly, pancytopenia, hemophagocytosis and progressive neurologic deterioration. Griscelli syndrome can be suggested according to her symptoms. The chemotherapy was not effective for her and she died due to multi organ failure.
Key words: Griscelli syndrome, Hemophagocytosis, Albinism.

1. Assistant professor, Department of pediatric hematology-oncology, Mofid children's hospital, Shaheed Beheshti University of medical sciences
2. Assistant professor ,Cheif of hematology-oncology ward, Department of pediatric hematology-oncology, Mofid children's hospital, Shaheed Beheshti University of medical sciences
3. Assistant professor, Department of pediatric hematology-oncology, Namazi Hospital, Shiraz University of medical sciences
Corresponding author:
B.Sh. Shamsian MD
Tel: +98 2122227020
Fax:+ 98 22220254
E-mail: Shamsianb@yahoo.com

Introduction

Griscelli syndrome (GS) is a rare autosomal recessive disorder characterized by pigmentary dilution of the hair and by abnormal regulation of the immune system in most patients (1, 2).

Primary abnormalities include a silver grayish sheen to the hair, large pigment agglomerations in hair shafts and abundance of mature melanosomes in melanocytes with reduced pigmentation of adjacent keratinoncytes(1,2,3). Immunologic abnormalities are impaired function of natural killer (NK) cells and cytotoxic T cell (CTC). The abnormalities are characterized by absent delayed type cutaneous hyper sensitivity; impaired major histocompatibility complex mediated cytotoxic effects and impaired response to mitogens and sometime hypogammaglobulinemia (1, 2, 3).

Griscelli syndrome affects young children. Clinical onset occurs between 4 months to 4 years (2). Viral and bacterial infections can trigger that (2). The clinical manifestations are silvery hair, recurrent infections, hepatosplenomegaly and progressive neurologic deterioration (1,2,3,4,5,6,7,8,9,10). Laboratory features include pancytopenia, hypofibrinogenemia, elevated level of triglyceride ,high level of the alpha chain of the soluble interleukin II receptor and hemophagocytosis in liver, spleen and bone marrow(3).

Genetic analysis was done in a fraction of GS patients (1, 2). Three different genetic forms have been described in GS. (1, 11, 12, 13, 14). **GS1:** mutation in the genes encoding the molecular motor protein, myosin VA (myo VA) on ch 15q 21(1)

GS2: mutation in the gene encoding the small GTPase Rab 27a (1)

GS3: mutation in the gene that encodes melanophilin (1)

Different mutations cause different clinical presentations of Griscelli syndrome. On the other hand GS1 had neurological symptoms; GS2 had immunological symptoms, and GS3 had hypopigmentation (1). The differential diagnosis of GS includes Chediak-Higashi syndrome (CHS). Presence of giant cytoplasmic granules in leukocytes on peripheral blood smear is the particular abnormality in CHS (11, 12). Patients with Elejalde syndrome (EJ) are also being compared with GS. EJ is a rare autosomal recessive disease characterized by silvery hair and severe dysfunction of central nervous system (1). Griscelli syndrome seems to be invariably lethal without stem cell transplantation (1). The mean age at the time of death is about 5 years (2). So awareness of the clinical symptoms and diagnosis criteria for GS is crucial to starting life saving therapy in time (3).

Case Report

The patient was a 5 months girl of Iranian parents. Her parents were relative as first cousins. She was the fourth child and was delivered at term by normal vaginal delivery (N.V.D) with 2600 gr body weight. Her past medical history was uneventful until the age of 5 months when she was referred to Mofid children's hospital because of fever.

In physical examination she had silvery hair, eyelashes,eyebrows, and hepatosplenomegaly (liver and spleen 7 and 4 cm respectively below costal margin). Laboratory data included: WBC count of 3300 cells/mm3, PMNs 16%, lymphocytes 89%, Hb of 7.1gr/dl, Hct of 23% & platelets of 51×10 9/L. ESR 50 mm/hr, CRP (3 +), reticulocyte 3.3%, Result of direct coombs test was negative.

There weren't any giant cytoplasmic granules in peripheral blood smear of leukocytes. Chemical markers of serum revealed, ALT 247 U/L (10-40), AST 227 U/L (10-40), LDH 1150 U/L (225-400), Total bilirubin 4mg/dl (0/2-1), direct bilirubin 2mg/dl (0-0/2), Total protein 6/2g/dl (5-7/3), serum albumin 3gr/dl (3/8-5/4), PT & PTT were 24" (control of 12") and 48" (control of 43") respectively. Blood sugar was 51 mg/dl (60-100 mg/dl), fibrinogen level was 92% mg (200-400 mg %), Triglyceride was 750 mg/dl (50-200 mg/dl), ferritin was 300 ng/ml (6-140 ng/ml). serum Immunoelectrophoresis was in normal range.

Chest radiography (CXR) was normal. Hepatosplenomegaly was seen in abdominal sonography. Bone marrow aspiration and bone marrow biopsy demonstrated hemophagocytosis without evidence of infiltrative or malignant process. Flowcytometry results included CD56 (21), CD11c (26), CD64 (81), CD14 (10), CD45 (82), CD4 (26), CD8 (31) with CD4/CD8 ratio of 0.83. Examination of the hair showed irregular agglomerations of pigment in hair shafts. According to the above findings, the diagnosis of Griscelli syndrome was suggested in the absence of gene analysis. Immunosuppressive therapy including prednisolone 2mg/kg/day, IVIG 1gr/kg/day for 2 days and cyclosporine5mg/kg/day were initiated. HLA typing with her siblings was done, but it was not compatible. Despite initial remission with Immunosuppressive therapy after two months she developed neurological symptoms including seizure, Ptosis , facial palsy and left hemiplegia. Brain atrophy and diffuse hypodensity in white matter were seen in brain CT results. Brain MRI showed abnormal enhancement in the white matter. The treatment was not effective and the patient died because of multiorgan failure.

Discussion

In this case, the diagnosis was based on family history (parents were first cousins), clinical features, laboratory findings & hemophagocytosis in bone marrow aspiration and biopsy along with light microscopic examination of the hair with absence of giant granule in leukocytes. Unfortunately, molecular gene analysis of this case wasn't possible for us.

Griscelli syndrome is a rare autosomal disorder that was first described in 1978. It has been described in approximately 45 patients. There are many articles in the literature about GS presentation especially neurologic problems during last year.

Ashrafi MR (2006, Iran) reported a 6 years old boy with silvery hair, seizure and previous history of hemiparesis with bilateral frontal cortical and subcortical high signal lesions, dirty white matter and high signal area in the upper pons and both caudate and lentiform nuclei in T2W1 in the brain MRI (5).

Gogus S(1995, Turkey) reported bilateral diffuse involvement of CNS, cranial nerve and spinal cord in two cases of GS besides of other clinical features(7). Brismar J(1992 , Saudi Arabia) reported that GS should be added to the list of demyelinating diseases and should be kept in mind when white matter changes are prominent in posterior fossa (8).

Sarper N (2002, Turkey) reported a 7.5 months old girl with GS who developed neurological symptoms after initial hematological remission with chemotherapy. MRI of the brain revealed an area of increased T2 signal & abnormal enhancement in the white matter (10). Initially, our patient gave a good response to immunosuppressive therapy and her general condition improved noticeably but this was a transient response and after 2 months she developed neurological symptoms including seizure, ptosis, facial palsy and left hemiplagia. Stem cell transplantation was not performed because of lack of an HLA-compatible donor and she died due to multi organ failure.

So in Griscelli syndrome, neurologic problems should be considered besides other clinical manifestations including silvery hair, hepatosplenomegaly, pancytopenia & hemophagocytosis. Awareness of the clinical symptoms and diagnostic criteria is crucial to start life saving therapy in time.

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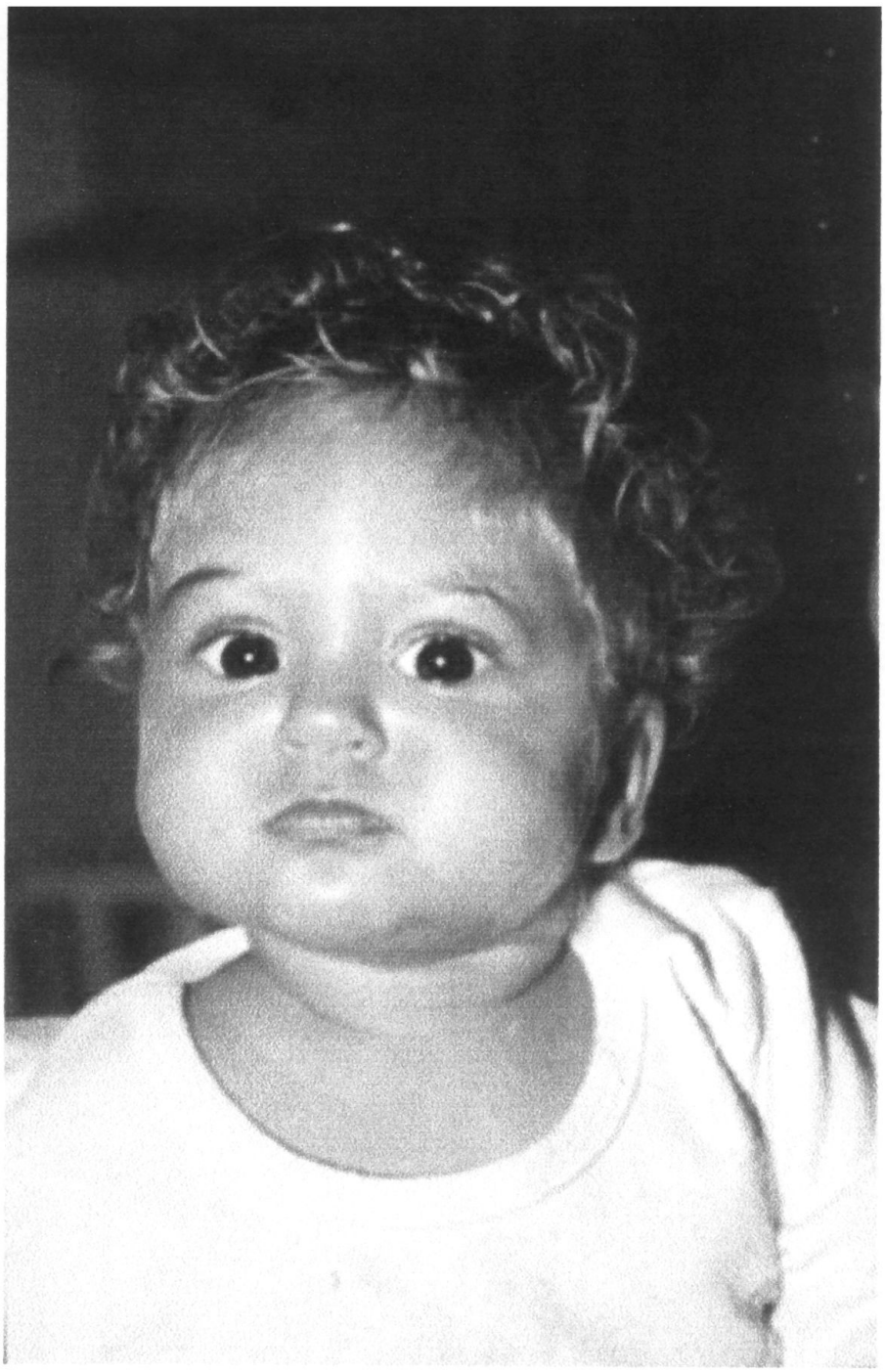
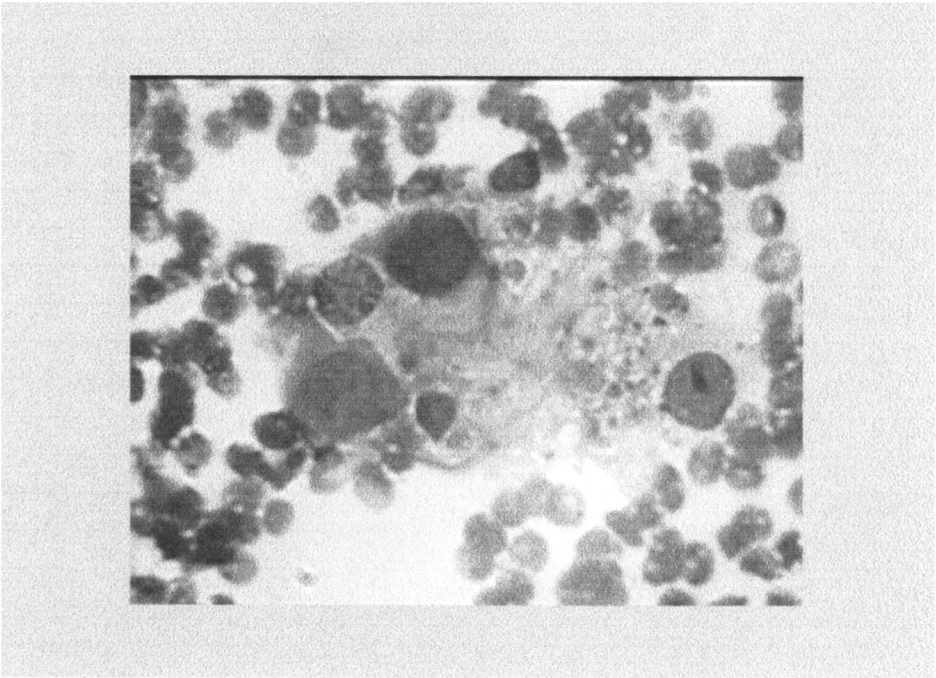
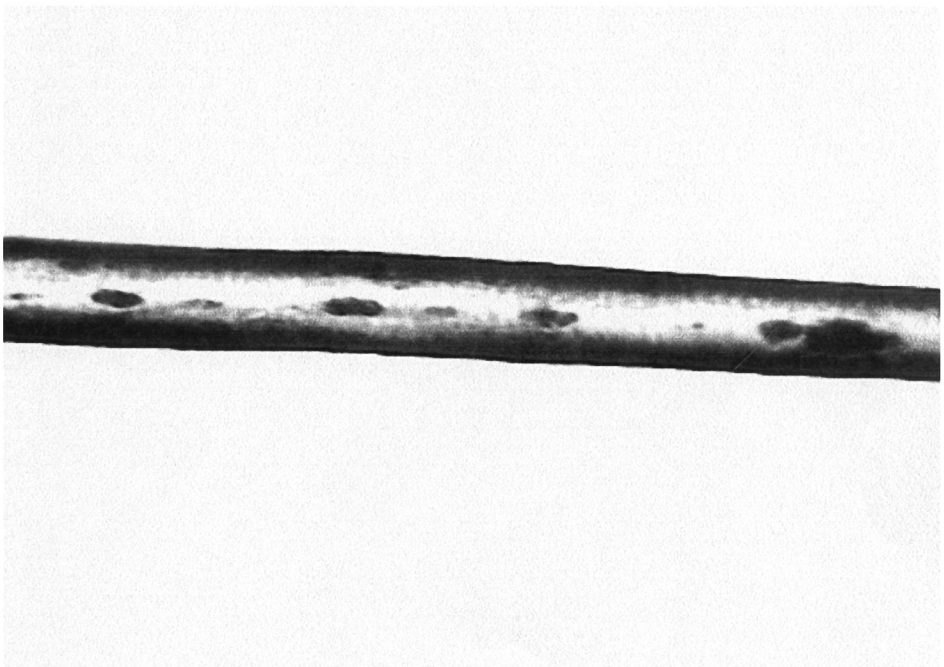


Patient with silver-gray hair and eyebrows



Bone marrow aspiration of patient



Griscelli Syndrome. Hair with giant melanin in granules