

Griscelli Syndrome Type 2: A Rare Case With Apparently Normal Skin and Hair Pigmentation

Ahmad Bahrami^{1,2}, Alireza Nateghian^{2,3}, Shima Salehi^{2,4}, Gholamreza Bahoush⁵, Saeed Talebi⁶, Saeide Ghasemi^{1,2}, Sepideh Razi^{7,8}, Nima Rezaei^{8,9,10}

¹ Department of Allergy & Immunology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

² Ali Asghar Children's Hospital, Iran University of Medical Sciences, Tehran, Iran

³ Infectious Disease Research Center, Iran University of Medical Sciences, Tehran, Iran

⁴ Department of Rheumatology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

⁵ Department of Hematology, Ali-Asghar Children's Hospital, Iran University of Medical Sciences, Tehran, Iran

⁶ Department of Medical Genetics & Molecular Biology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

⁷ Student Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

⁸ Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

⁹ Research Center for Immunodeficiencies, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran

¹⁰ Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Received: 14 Jul. 2019; Accepted: 28 Dec. 2019

Abstract- Griscelli syndrome (GS) is a rare autosomal recessive disease that affects hair, skin, and immune system. Here, we describe an 8.5-month-old infant with multiple admissions due to fever, petechial purpura, and several recurrent vomiting episodes with a presumptive diagnosis of recurrent sepsis. He was born from parents with consanguineous marriage. The initial examinations revealed huge splenomegaly and hepatomegaly without any source of infection. Laboratory tests revealed a hemophagocytic lymphohistiocytosis (HLH) like a picture with a high blood level of ferritin in all episodes, but the bone marrow test result was normal. Although he had normal hair and skin pigmentation on physical examination, the accumulation of melanosomes was found in his hair shafts on microscopic investigations. Eventually, a genetic test revealed a mutation in the *RAB27A* gene, which confirmed GS-II diagnosis. Our case is the first case of GS-II from Iran without any apparent clinical features of GS, such as hypopigmented skin and silvery-gray hair. Therefore, a genetic test, together with the microscopic examination of hair and skin, is necessary for the diagnosis and confirmation of GS-II. Since GS-II is an autosomal recessive disorder and consanguineous marriages are popular in Iran, premarital genetic counseling is recommended for this region.

© 2020 Tehran University of Medical Sciences. All rights reserved.

Acta Med Iran 2019;58(1):38-42.

Keywords: Griscelli syndrome; Pigmentation disorder; Immunodeficiency; Hemophagocytic lymphohistiocytosis

Introduction

Griscelli syndrome (GS) is a rare autosomal recessive disease caused by mutations in *MYO5A*, *RAB27A*, and *MLPH* genes, which are responsible for melanosome transport in melanocytes (1). This disease is generally characterized by light skin and silvery-gray hair initiating in infancy (2). Recent pieces of evidence have identified three subtypes of GS (GS-I, II, and III) based on the pattern of signs and symptoms, as well as

genetic loci involved. GS-I, which is caused by a mutation in the *MYO5A* gene, involves severe dysfunction of the central nervous system (CNS) (3). GS-II is the most common type of the disorder (4). It is induced by mutations in the *RAB27A* gene and is associated with primary immunodeficiency (4). In addition to immunological problems, hypopigmented skin, and silver-colored hair, these patients may suffer from hemophagocytic lymphohistiocytosis (HLH), which is associated with the accumulation of T-

Corresponding Author: N. Rezaei

Research Center for Immunodeficiencies, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 6692 9234, Fax: +98 21 6692 9235, E-mail address: rezaei_nima@tums.ac.ir

lymphocytes and macrophages (5). Overproduction of these immune cells can adversely affect body organs and tissues, causing various life-threatening complications (6). The HLH-2004 guideline for diagnosis of patients with HLH is as follow: 1) cytopenias, 2) fever, 3) splenomegaly, 4) hemophagocytosis in the spleen, bone marrow or lymph nodes, 5) hypertriglyceridemia and/or hypofibrinogenemia, 6) hyperferritinemia, 7) low or absent NK-cell activity and 8) high levels of soluble interleukin-2 receptor (sIL-2r). Five out of eight criteria need to be fulfilled for the diagnosis of HLH. However, these criteria do not need to be fulfilled in patients with a molecular diagnosis compatible with HLH (7). GS-III, caused by mutations in the *MLPH* gene, is characterized by only pigment dilution of skin and hair (6).

The prognosis of GS depends on the type of disease. GS-I prognosis relies on the severity of neurological problems. GS-II can lead to death due to HLH. Therefore, early diagnosis of patients with this syndrome is very important. The prognosis of GS-III is good, and this type does not require any treatment (3). Here, we describe the first case of GS-II from Iran without any apparent clinical features of GS, such as hypopigmented skin and silvery-gray hair. GS-II diagnosis was eventually confirmed based on a mutation in the *RAB27A* gene.

Case Report

An 8.5-month-old boy was brought to our hospital with complaints of fever, petechial purpura, and several times of vomiting. He developed productive cough and conjunctivitis a few days after the admission time. He was phenotypically normal (Figure 1). On physical examination, he had an ill appearance, and abdominal examination revealed huge splenomegaly and hepatomegaly (with a span of 10 cm) without any detected source of infection.



Figure 1. The phenotypic feature of the patients without skin and hair pigmentation under physical examination

The past medical history of the patient showed that he was the third child of the family (III/III). The baby was born as a result of *in vitro* fertilization (IVF) from parents with consanguineous marriage. He had a complete vaccination history and had reached typical developmental milestones. At birth, his weight was 4.1 kg, and the bodyweight was 9 kg at the admission time. He had a history of hospitalization due to fever when he was at 45 days of life. During that time, he developed splenomegaly and thrombocytopenia, which were resolved after antibiotic therapy. He also had a history of unknown prolonged icterus from day 3 to day 40 of his life.

His laboratory exams showed neutropenia (Absolute neutrophil count (ANC): 640) despite leukocytosis, anemia, and thrombocytopenia. Therefore, oncology consultation was performed with the possibility of leukemia due to his lab results and hepatosplenomegaly. On peripheral blood smear, suspicious malignant lymphoblasts were detected. Hence, bone marrow aspiration (BMA) was done, which was normal. Based on these results, leukemia was ruled out. The patient was admitted to an isolated room at the infectious diseases unit, and then empiric antibiotic therapy was started. Laboratory test results were negative for *Epstein-Barr virus* (EBV), *Cytomegalovirus* (CMV), *hepatitis B virus* (HBV), *hepatitis C virus* (HCV) and *human immunodeficiency virus* (HIV), which ruled out the presence of infectious source for hepatosplenomegaly and pancytopenia. Kala Azar serology test was normal. PCR and enzyme-linked immunosorbent assay (ELISA) tests results were negative for adenovirus. Also, The PCR and BK test results were negative for *Mycobacterium tuberculosis*. Induration of 18 mm was measured in purified protein derivative (PPD) test, and consequently, isoniazid prophylaxis therapy was started. A morning sputum sample was collected because of contact history with his grandmother, who had a chronic cough. Additionally, three gastric lavages were performed that showed negative results. The patient had no positive culture from the day of admission. Laboratory test results for the possibility of HLH were as follows: Lactate dehydrogenase (LDH): 80, ferritin: 400 (which was dropped from 1400 at the initial examination), D-dimer: 4.1 (increased from 3.4 at the initial examination), and fibrin degradation products (FDP): 20 (increased from 18 at the initial examination). Since he had a history of positive PPD, prolonged icterus, and the possibility of immunodeficiency, which causes repetitive sepsis and macrophage activating syndrome (MAS), a genetic test for HLH was advised.

Griscelli syndrome type 2

Flow cytometry tests, CD markers, and immunoglobulins were normal. Cardiology consultation was requested due to the possibility of endocarditis. The first echocardiography exam reported mild dyskinesia of left ventricular walls (mainly of the apex) and mitral regurgitation (MR). 48 hours later, the second echocardiography was done, which showed increased severity of MR. Intravenous immunoglobulin (IVIg) therapy and aspirin administration was advised because of the possibility of Kawasaki disease. However, aspirin was replaced by dipyridamole due to thrombocytopenia. Rheumatology consultation ruled out the Kawasaki disease, and then dipyridamole therapy was stopped. Since antibiotic and IVIg therapies caused relative improvement of neutropenia and thrombocytopenia, decreased size of the liver and spleen, reduced blood level of ferritin and C-reactive protein (CRP), HLH following infection could be suspected despite his normal phenotype. Whole exon sequencing was done to evaluate genetic disorders. The patient was discharged and recommended to continue isoniazid prophylaxis therapy. One week after discharge, a *complete blood count* (CBC) test was provided which showed normal results (*White blood cell* (WBC): 6000; neutrophil: 19%; lymphocyte: 68%; *hemoglobin* (Hb): 11.2; platelet (PLT): 239,000; and CRP<1).

One month later, the patient was admitted again with the complaint of vomiting. There was no sign of infectious source, but on further examinations, huge splenomegaly and hepatomegaly were observed. Laboratory test results were as follows: ferritin: 763; *triglycerides* (TG): 195 and fibrinogen: 195. He also had neutropenia (ANC: 564), leukopenia, and thrombocytopenia. The patient was admitted to the hematological unit to rule out the possibility of HLH and storage diseases such as Gaucher's disease. Empiric antibiotic therapy was started, and BMA has performed again, which did not show any abnormal cells. Dried-blood filter paper samples were evaluated for Gaucher's disease. The patient received IVIg therapy for one day. Three to four days later, thrombocytopenia was relatively improved, leukopenia was completely resolved, and the size of the liver and spleen was decreased. Eventually, he was discharged from the hematological unit with a following-up recommendation for the genetic and filter paper test results along with isoniazid prophylaxis therapy.

Two weeks later, the patient was admitted again with a complaint of diarrhea. He had huge splenomegaly and hepatomegaly. In addition, laboratory tests revealed pancytopenia and severe neutropenia without any source

of infection. He was admitted to the rheumatology unit to rule out periodic fevers such as Hyper immunoglobulin D syndrome (HIDS) and MAS. BMA was provided again, which showed a normal result. The mevalonic acid level was normal in a 24-hour urine collection test. Additionally, the bone survey did not detect any abnormalities. The genetic and filter paper test results were followed-up during his admission time. Gaucher's disease was ruled out due to the negative result of the filter paper test, while the genetic test result showed a mutation in the *RAB27A* gene indicating GS-II. Whole exome sequencing (CentoXome® Gold) was done in centogene AG, which is a diagnostic laboratory and is the college of American pathology (CAP) certified and has international standard organization (ISO)-15189. Agilent's sure select human all Exon V6 kit was used for the enrichment of exons. The mean coverage was 138 X, with about 81.67% more than 50 X coverage. Whole exome sequencing revealed a homozygous mutation in the *RAB27A* gene located at exon 5, namely, a single-base substitution (hg19; g.55516126 A>G) leading to an amino acid change (p.Val 143 Ala) from Valine to Alanine. This variant was absent in all population databases, including genome aggregation database (gnomAD), exome aggregation consortium (ExAC), 1000 G, and exome sequencing project (PM2). Nearly all computational prediction software tools (DANN, GERP, FATHMM, LRT, Meta LR, Meta SVM, mutation assessor, mutation Taster, and PROVEAN) evaluated this variant as a leading cause of disease variant (PP3). In addition, the clinical (PP4) and paraclinical (PS3) findings were compatible with the GS. Therefore, according to the sherlock classification, this variant may be classified as a pathogenic variant because of at least 6 pathogenic points (PM2:1 point, PP3: 0.5 points, PP4: 2, and PS3: 2.5).

On microscopic examination, his hair strand was normal in color. However, the accumulation of melanosomes was observed in hair shafts, which indicated GS (Figure 2). Based on the genetic test result and microscopic examination of the hair strand, the diagnosis of GS-II was confirmed, and the patient was admitted to the oncology unit. IVIg therapy was started along with cyclosporine and dexamethasone prescriptions. He became a candidate for the bone marrow transplant (BMT) and received relative treatment after starting the above-mentioned therapies.

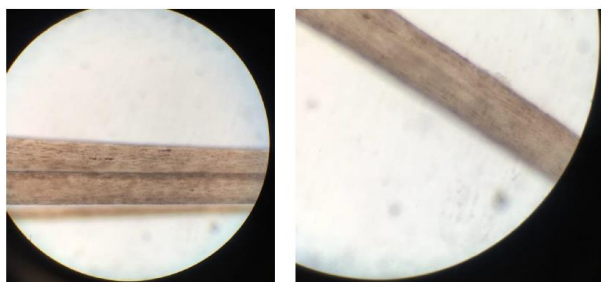


Figure 2. Accumulation of melanosomes was observed in hair shafts which confirmed Griscelli syndrome

Discussion

GS type II is a rare inherited disorder caused by a mutation in the *RAB27A* gene, which affects hair, skin, and immune system (5). The *RAB27A* variant c.428T>C p.(Val143Ala) can cause an amino acid change from Val to Ala at position 143. According to HGMD Professional, this variant has previously been described as disease-causing for HLH (8). In melanocytes, *RAB27A* intervenes in secretion by attaching to the synaptotagmin-like protein melanophilin (Mlph) and plus-end directed motor protein myosin Va. In addition, *RAB27A* can control the release of cytolytic granules from cytotoxic T lymphocytes by binding to Munc13-4. Therefore, the mutation in *RAB27A* can damage attaching to Munc13-4 but not Mlph, which leads to cytotoxic T lymphocytes dysfunction but not melanocytes (9). Patients with GS-II may have variable clinical and phenotypical features. They usually have hypopigmented skin and silver-colored hair. Lipid metabolism deficiency may be occurred in these cases as well (10). Hepatosplenomegaly and recurrent infection are the other clinical features of GS-II patients. They also can develop HLH, a life-threatening condition in which immune cells such as natural killer cells, T cells, and lymphocytes are overproduced and overactivated, which can result in damage to body organs (1). Therefore, early diagnosis and treatment of the disease are very important to prevent mortality. Currently, allogeneic hematopoietic stem cell transplantation (HSCT) is the only therapeutic method that can extend the survival rate among these patients (11).

Here, we reported a GS-II case with normal skin and hair pigmentation on physical examinations. To our knowledge, it is the first report presenting a case of genetically confirmed GS-II with normal pigmentation from Iran. A previous study in Iran reported a one-year-old child with GS-II who suffered from pigmentation disorder and hypogammaglobulinemia (12). In another study in Iran, Shamsian *et al.*, (13) reported a 6-month-

old infant with GS-II who presented with silvery hair, eyelashes, and eyebrows on physical examination. Several lines of studies have reported the accumulation of melanosomes clusters on patients' hair, as well as hypomelanosis with irregular melanin pigmentation in basal melanocytes of their skin (14). In our case, scalp hair microscopy showed an accumulation of melanosomes in hair shafts, which was indicative of GS. Eventually, the results from hair microscopy, along with the genetic and laboratory test results, clinical manifestations such as fever, hepatosplenomegaly, and pancytopenia and lack of CNS involvement confirmed the diagnosis of GS-II with HLH.

Fever, pallor, hepatosplenomegaly, and pancytopenia are also frequently reported among these cases (3). Our patient had complained of vomiting, diarrhea, and sepsis-like symptoms, and he was manifested with hepatosplenomegaly and pancytopenia. He had also suffered from mild dyskinesia of left ventricular walls and MR upon echocardiography examination. The exact mechanism is unknown, and further evaluations are needed to consider the relationship between GS-II and heart failures. Our case had also been admitted several times with repetitive sepsis and MAS. Although these problems were mitigated after IVIg and antibiotic therapies, the severity of these symptoms and attack numbers had been increased along with age. These data have indicated that various symptoms and clinical features with different disease degree can be found in GS-II. Variations in disease severity and the number of clinical features are probably due to different mutations in the *RAB27A* gene in patients with this syndrome. Therefore, further studies are necessary to evaluate the relationship between genotype and phenotype.

Our patient was born from parents with consanguineous marriage. However, there was no evidence of similar conditions in his family. Several studies, especially from the Middle East, reported GS-II cases from parents with consanguineous marriage (3, 10, 12). Since consanguineous marriage is popular in the Middle East, there may be a relationship between the incidence of GS-II and consanguineous marriage, which require further considerations. Therefore, premarital genetic counseling and education may be helpful.

Our patient was born as a result of IVF. Therefore, it can be further considered to find any relationship between IVF and other assisted reproductive technology (ART) methods with the incidence of GS-II.

GS-II is a rare and recessive autosomal disorder that can be presented with a wide range of symptoms. The severity of the disease and its clinical symptoms can be

Griscelli syndrome type 2

different from cases to cases, possibly due to different mutations in the *RAB27A* gene. Our case highlights that GS-II can be presented with normal skin and hair pigmentation under physical examination. Our patient was born as a result of IVF from parents with consanguineous marriage. For as much as consanguineous marriages are popular in Iran and other parts of the Middle East, premarital genetic counseling is essential for these regions. Genetic tests for HLH, together with the microscopic examination of hair and skin, are necessary for the diagnosis and confirmation of GS-II. Currently, BMT is the only treatment that can expand the survival of these patients.

References

1. Durrani S, Chicka M, Afroze B. Griscelli syndrome type 2—A case report and clinical approach to silver blonde hair. *Egyptian J Med Hum Genet* 2016;17:229-32.
2. Rajyalakshmi R, Chakrapani RNB. Griscelli syndrome type 2: A rare and fatal syndrome in a South Indian boy. *Indian J Pathol Microbiol* 2016;59:113-6.
3. Minocha P, Choudhary R, Agrawal A, Sitaraman S. Griscelli syndrome subtype 2 with hemophagocytic lympho-histiocytosis: A case report and review of literature. *Intractable Rare Dis Res* 2017;6:76-9.
4. Singh A, Garg A, Kapoor S, Khurana N, Entesarian M, Tesi B. An Indian boy with griscelli syndrome type 2: case report and review of literature. *Ind J Dermatol*. 2014;59:394.
5. Mishra K, Singla S, Sharma S, Saxena R, Batra VV. Griscelli syndrome type 2: A novel mutation in *RAB27A* gene with different clinical features in 2 siblings: A diagnostic conundrum. *Korean J Pediatr* 2014;57:91-5.
6. Meschede IP, Santos TO, Izidoro-Toledo TC, Gurgel-Gianetti J, Espreafico EM. Griscelli syndrome-type 2 in twin siblings: Case report and update on *RAB27A* human mutations and gene structure. *Braz J Med Biol Res*. 2008;41:839-48.
7. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr blood cancer*. 2007;48:124-31.
8. Ammann S, Lehmborg K, Zur Stadt U, Klemann C, Bode SFN, Speckmann C, et al. Effective Immunological Guidance of Genetic Analyses Including Exome Sequencing in Patients Evaluated for Hemophagocytic Lymphohistiocytosis. *J clin immunol* 2017;37:770-80.
9. Cetica V, Hackmann Y, Grieve S, Sieni E, Ciambotti B, Coniglio ML, et al. Patients with Griscelli syndrome and normal pigmentation identify *RAB27A* mutations that selectively disrupt *MUNC13-4* binding. *J Allergy Clin Immunol* 2015;135:1310-8.e1.
10. Thomas N, Jithendriya M, Prakash A. Griscelli syndrome type 2: A silvery hair syndrome with hemophagocytosis. *Pigment Int* 2015;2:48-50.
11. Pachlopnik Schmid J, Moshous D, Boddaert N, Neven B, Dal Cortivo L, Tardieu M, et al. Hematopoietic stem cell transplantation in Griscelli syndrome type 2: a single-center report on 10 patients. *Blood* 2009;114:211-8.
12. Mansouri Nejad SE, Yazdan Panah MJ, Tayyebi Meibodi N, Ashraf Zadeh F, Akhondian J, Beiraghi Toosi M, et al. Griscelli Syndrome: A Case Report. *Iran J Child Neurol*. 2014;8:72-5.
13. Shamsian BS, Norbakhsh K, Rezaei N, Safari A, Gharib A, Pourpak Z, et al. A Novel *RAB27A* Mutation in a Patient With Griscelli Syndrome Type 2. *J Investig Allergol Clin Immunol* 2010;20:612-5.
14. Khemka P, Kundu R, Niyogi P, Tudu J. A case of silvery hair syndrome: Griscelli syndrome. *Indian J Paediatr Dermatol* 2015;16:72-4.