CASE REPORT

A Novel *RAB27A* Mutation in a Patient With Griscelli Syndrome Type 2

BS Shamsian,[1] K Norbakhsh,[1] N Rezaei,[2,3] A Safari,[1] A Gharib,[4] Z Pourpak,[5] S Alavi,[1] N Parvaneh,[2] MT Arzanian[1]

[1]Department of Pediatric Hematology/Oncology, Mofid Children Hospital, Shahid Beheshti Medical University, Tehran, Iran
[2]Molecular Immunology Research Center; and Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[3]Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Pathology, Mofid Children Hospital, Shahid Beheshti Medical University, Tehran, Iran
[5]Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Griscelli syndrome type 2 is a rare autosomal recessive primary immunodeficiency disease caused by a mutation in the *RAB27A* gene and characterized by oculocutaneous hypopigmentation and variable cellular immunodeficiency.
We report the case of a 6-month-old infant with silvery hair, eyelashes, and eyebrows who was referred to our center because of fever and hepatosplenomegaly. Bone marrow studies indicated hemophagocytosis, whilst microscopic examination of the hair showed irregular agglomerations of pigment in hair shafts. Molecular analysis revealed a novel homozygous mutation in exon 5, namely, a single-base substitution (g.42996 A>G) leading to an amino acid change (S115G) and thus confirming the diagnosis of Griscelli syndrome type 2.
Griscelli syndrome could be more common than thought, especially in regions with high rates of consanguinity. As the prognosis of disease is usually poor, prompt diagnosis and appropriate treatment are vital to avoid complications.

Key words: Griscelli syndrome type 2. Gene mutation. Hemophagocytic lymphohistiocytosis. Immunodeficiency. *RAB27A*.

Resumen

El síndrome de Griscelli de tipo 2 es una inmunodeficiencia primaria autosómica recesiva poco frecuente causada por una mutación del gen *RAB27A* y que se caracteriza por una hipopigmentación oculocutánea y una inmunodeficiencia celular variable.
Se describe el caso de un lactante de 6 meses de edad con cabello, pestañas y cejas canosos que fue remitido a nuestro centro por presentar fiebre y hepatoesplenomegalia. Los análisis de médula ósea indicaron hemofagocitosis, mientras que el examen microscópico del cabello mostró aglomeraciones irregulares de pigmento en el tallo del pelo. El análisis molecular reveló una nueva mutación en homocigosis en el exón 5, en concreto, la sustitución de una única base (g.42996 A>G), que da lugar a un cambio de aminoácido (S115G), lo que confirma el diagnóstico de síndrome de Griscelli de tipo 2.
El síndrome de Griscelli puede ser más frecuente de lo que se había pensado, especialmente en regiones con índices de consanguinidad elevados. Puesto que el pronóstico de la enfermedad suele ser desfavorable, es esencial establecer un diagnóstico inmediato y aplicar el tratamiento adecuado para evitar complicaciones.

Palabras clave: Síndrome de Griscelli de tipo 2. Mutación génica. Linfohistiocitosis hemofagocítica. Inmunodeficiencia. *RAB27A*.

Introduction

Griscelli syndrome type 2 is a rare autosomal recessive primary immunodeficiency disease characterized by oculocutaneous hypopigmentation and variable cellular immunodeficiency. Silvery gray hair is common in this condition, and some patients experience neurological symptoms [1-4]. Hemophagocytic lymphohistiocytosis is a serious complication in this group of patients [1,5].

Mutations in the *RAB27A* gene, which is located on 15q21 and encodes a small GTPase protein, are responsible for Griscelli syndrome type 2 [5,6].

We describe the case of an Iranian infant with Griscelli syndrome type 2 who presented a novel mutation in the *RAB27A* gene.

Case Description

The patient was a 6-month-old boy, the second child of consanguineous parents (first cousins). The first child of the family was a 6-year-old girl with no medical history of interest. The patient's medical history was uneventful until the age of 6 months, when he was referred to Mofid Children's Hospital, a referral center in Tehran, Iran, because of fever and hepatosplenomegaly.

Physical examination revealed silvery hair, eyelashes, eyebrows (Figure 1), and hepatosplenomegaly (liver and spleen span below costal margin 4 cm and 3 cm, respectively). Laboratory data revealed severe neutropenia, anemia, and thrombocytopenia (white blood cell count, 3400/μL; polymorphonuclear cells, <1%; lymphocytes, 98%; monocytes, 2%; hemoglobin, 9 g/dL; and platelet count, 38×103/μL). The erythrocyte sediment rate was 50 mm/h, C-reactive protein was 3+, the reticulocyte count was 0.5%, and the result of a direct Coombs test was negative.

The peripheral blood smear showed no giant cytoplasmic granules in leukocytes. The results of biochemical tests were as follows: alanine aminotransferase, 51 IU/L (normal range, 10-40); aspartate aminotransferase, 41 IU/L (normal range, 10-40 IU/L); lactate dehydrogenase, 360 IU/L (normal range, up to 450 IU/L); total bilirubin, 1.5 mg/dL (normal range, 0.2-1 mg/dL); direct bilirubin, 0.2 mg/dL (normal range, 0-0.2 mg/dL); prothrombin time, 13 seconds (control of 13 s); and partial thromboplastin time, 32 seconds (control of 43 s). Fibrinogen level was 1.85 g/dL (normal range, 2-4 g/dL), triglyceride level was 392 mg/dL (normal range, 35-200 mg/dL), and ferritin level was 4660 ng/mL (normal range, 6-140 ng/mL). Immunological tests showed immunoglobulin (Ig) G of 914 mg/dL (normal range, 250-1190), IgM of 165 mg/dL (normal range, 24-167 mg/dL), and IgA of 155 mg/dL (normal range, 10-87 mg/dL). The results of serology testing and polymerase chain reaction for bacterial and viral infections were negative.

The chest x-ray was normal, although abdominal ultrasound revealed hepatosplenomegaly. A computed tomography scan of the brain with contrast showed mild atrophy. The analysis of cerebrospinal fluid was normal.

Bone marrow aspiration and bone marrow biopsy demonstrated hemophagocytosis without evidence of infiltrative or malignant processes (Figure 2). Microscopic examination of the hair showed irregular agglomerations of pigment in the hair shafts (Figure 3). The patient was diagnosed with Griscelli syndrome type 2 and molecular studies of the *RAB27A* gene were performed. Sequencing revealed a novel homozygous mutation in exon 5, namely, a single-base substitution (g.42996 A>G, EMBL: AF443871) leading to an amino acid change (S115G) from serine (AGC) to glycine (GGC).

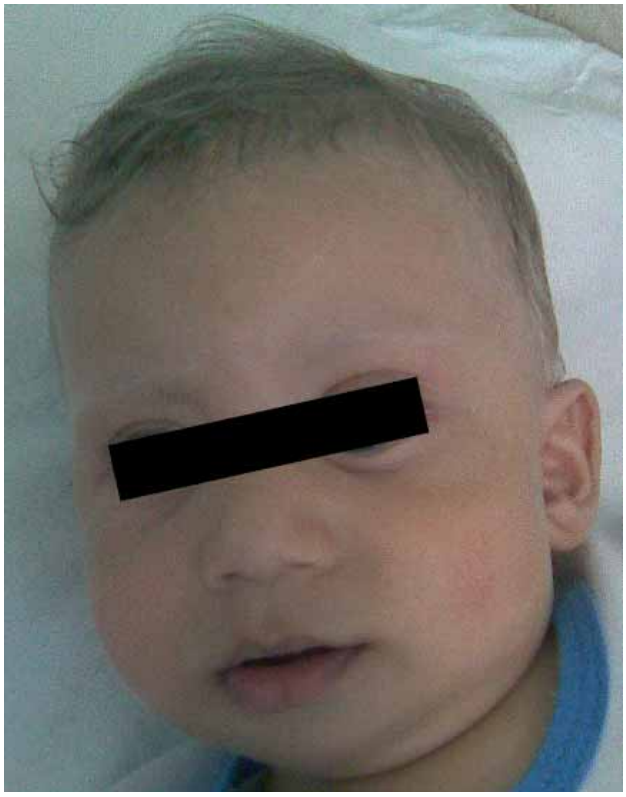

Figure 1. Oculocutaneous albinism and silvery hair.

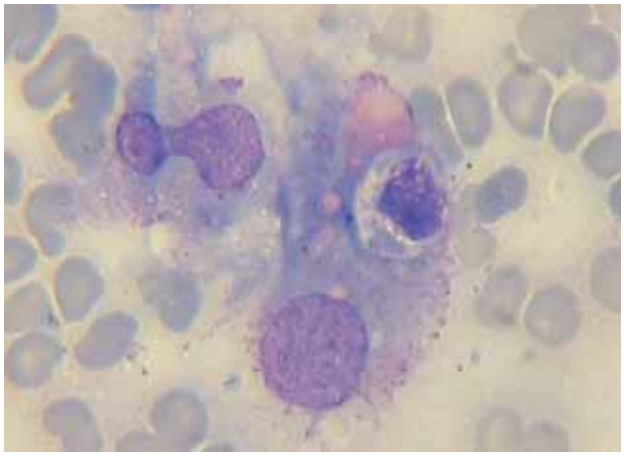

Figure 2. Hemophagocytosis in the bone marrow study.

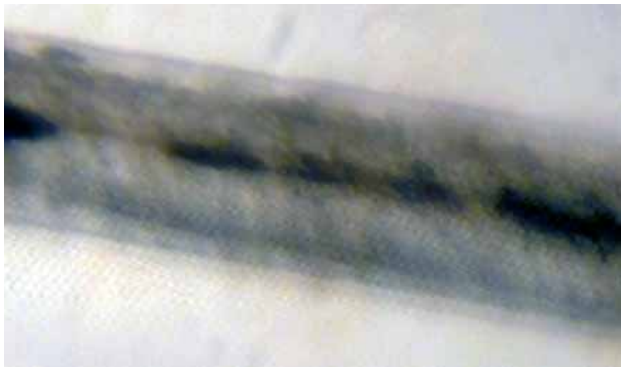

Figure 3. Microscopy of the hair shaft reveals irregular agglomeration of pigment.

The diagnosis of Griscelli syndrome type 2 was thus confirmed, and treatment was started with the HLH-2004 protocol. The patient underwent allogenic stem cell transplantation from his sister, who is an HLA-matched donor. The patient is now 1 year old and healthy.

Discussion

Three types of Griscelli syndrome have been identified. Silvery gray hair is common to all three, but immunological defects are only seen in the patients with Griscelli syndrome type 2 [2,3,7]. This syndrome is a rare inherited disorder that was originally described in 1978 [7]. Griscelli syndrome types 1 and 3 are caused by mutations in the *MYO5A* and *MLPH* genes, respectively, whereas type 2 is caused by mutations in *RAB27A* [5,6,8].

Oculocutaneous hypopigmentation may be associated with primary immunodeficiency diseases involving immune dysregulation. In addition to Griscelli syndrome type 2, Chediak-Higashi syndrome (caused by a mutation in the *LYST* gene), Hermansky-Pudlak syndrome type 2 (caused by a mutation in the *AP3B1* gene), and p14 deficiency (caused by a mutation in the *MAPBPIP* gene) are other autosomal recessive immunodeficiency diseases associated with oculocutaneous hypopigmentation [1,3]. Although patients with these mutations may have similar phenotypes, laboratory findings such as regular melanin granules (Chediak-Higashi syndrome), large irregular melanin granules (Griscelli syndrome type 2), and giant azurophilic granular inclusions in peripheral blood leukocytes (Chediak-Higashi syndrome) can help confirm the clinical diagnosis [1,3]. However, the definitive diagnosis can only be made after molecular analysis, once the mutation has been identified.

A number of mutations in the *RAB27A* gene have been identified in Griscelli syndrome type 2. Although most are truncating nonsense or frameshift changes, only a few missense mutations have been reported [9]. Our patient had a novel missense mutation in exon 5 leading to an amino acid change (serine to glycine). The severity of disease and the number of accelerated phases can vary, and different mutations have been reported in patients with this syndrome. Further studies are needed to assess the correlation between genotype and phenotype.

The prognosis of Griscelli syndrome type 2 is poor, and patients usually die in early childhood of complications such as hemophagocytic lymphohistiocytosis, unless they undergo hematopoietic stem cell transplantation [4]. Although this is the only curative treatment for patients with Griscelli syndrome type 2 [4], hemophagocytic lymphohistiocytosis should be treated first to induce remission before transplantation [10,11].

Our patient's parents were consanguineous. The rate of autosomal recessive diseases in consanguineous families is much higher than in the general population, and primary immunodeficiency diseases do not seem to be as rare as originally thought. The high rate of consanguinity in our region [12] could explain the higher rate of rare primary immunodeficiency. Genetic counseling and educational programs are essential in these regions.

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Bibi Shahin Shamsian, MD

Department of Pediatric Hematology-Oncology,
Mofid Children Hospital
Shahid Beheshti Medical University
Shariati Avenue, Tehran, Iran
E-mail: Shamsianb@yahoo.com
rezaei_nima@ tums.ac.ir