Keywords: Griscelli syndrome type 3; Gene mutation; Saudi Arabia

Abstract

Griscelli syndrome (GS) is a rare autosomal recessive disorder characterized by partial albinism. GS is a rare condition; its prevalence is unknown. Type 2 appears to be the most common of the three known types. The three different types of GS are caused by mutations in three different genes. Patients with GS type 1 have primary central nervous system dysfunction, resulting from mutations in the MYO5A gene. Type 2 patients commonly develop hemophagocytic lymphohistiocytosis, caused by mutations in the RAB27A gene, and type 3 have only partial albinism resulting from mutations in the MLPH. While hematopoietic stem cell transplantation is lifesaving in type 2, no specific therapy is required for types 1 and 3. Patients with GS types 1 and 3 are very rare. To date, 12 patients with similar presentation of GS-3 as our case have been reported. About 20 GS type 1 patients, including the patients described as Elejalde syndrome, have been reported. We report a 11 years old child with type 3 GS, referred to our clinic for partial albinism, healthy otherwise, having only pigmentary dilution; silvery gray hair, eye brows, and eyelashes. Though GS type 1 and 2 have been reported in the literature; however reports on GS type 3 from Saudi Arabia are very scanty. In communities with high incidence of consanguinity possibility of GS should be kept in mind.

Case Presentation

Eleven Years old Saudi boy, followed up at our clinic since the age of 2 months, for Partial Albinism since birth. The patient is a product of full term pregnancy, born by spontaneous vaginal delivery with good APGAR score and normal birth weight (3.1 kg), with no postnatal complications and discharged home with mother. He was born to consanguineous healthy parents (first degree cousins) with no history of similar condition in the family. The patient had no history of recurrent Sino pulmonary infection or skin infection. He is not dysmorphic, with silvery-gray hair including the eyebrows and eyelashes with normal skin (Figure 1). There was no lymphadenopathy or hepatosplenomegaly. Regularly performed neurologic assessments showed normal muscle tone and reflexes. Gross motor activities and cognitive functions, normal. His investigations revealed normal blood count, differential and peripheral blood smear. Immunoglobulin levels were normal. Nitro blue tetrazolium test (NBT) and lymphocyte subset analysis were normal with normal lymphocyte cytotoxic activities.

Figure 1: Patient with Griscelli Syndrome type 3 with the characteristic silver-gray hair and eyebrows. Informed consent of the photographs have been obtained from the child’s parents.
Light microscopy examination of his hair showed large clumps of pigment irregularly distributed along the hair shaft. Genomic DNA sequencing revealed a novel, homozygous mutation in MLHP gene at Exon 1. The patient genome contained a missense mutation (c.104 G>A) which resulted in an amino acid change from a conserved positively charged hydrophilic amino acid (Arginine; R) to a neutral amino acid (Glutamine; Q) at amino acid position of 35 (R35Q). Both parents were heterozygote for this mutation. This mutation has not been described previously (Figure 2c).

**Discussion**

Three types of GS have been identified, silvery gray hair is common to all three, but immunological defects are only seen in the patients
with GS type 2 [10,11]. GS types 1 and 3 are caused by mutations in the MYO5A and MLPH genes, respectively, whereas type 2 is caused by mutations in RAB27A (Figure 2) [12,13].

Oculo-cutaneous hypopigmentation may be associated with primary immunodeficiency diseases involving immune dys-regulation. The definitive diagnosis can only be made after molecular analysis.

Only 12 patients with confirm diagnoses of GS3 have been reported [14-17]. In this paper we are reporting the 13th case of GS3 in a normal 10 year old boy from Saudi Arabia. Only Two patients out of the reported 12 have congenital heart defect (one with hypoplastic left heart syndrome [14], the other one with an innocent cardiac murmur [15]. Fortunately our patient have no Cardiac involvement. Unlike all patients with GS3 in the literature, our patient was diagnosed during infancy. While the average age at GS3 diagnosed is 9.9 years which may highlight on that the GS3 may be under diagnosed. In addition our patient was born to a consanguineous parents similar to the 11 cases which have been reported with one case reported to be an Arab origin with no consanguinity.

Moreover our patient Genomic DNA sequencing revealed a novel, homozygous Mutation in MLHP gene (c.104G>A) whereas all reported cases have a homozygous for (c.102>T) [14-17]. GS is a fatal disorder leading to death in early life if not treated. However genotype-phenotype correlation suggests that the natural course of the disease and outcome is dictated by the site and type of the genetic mutation. Prognosis of GS type 2 is poor, and patients usually die in early childhood of complications such as hemophagocytic lymphohistiocytosis, unless they undergo hematopoietic stem cell transplantation. However the prognosis of GS3 is good where no special treatment needed [17,18] .

GS3 patients have no need for treatment and as seen in the present case the patient has attained 11 year of age and doing well with no deficit or medical illness.

GS is a fatal disorder leading to death in early life. However genotype-phenotype correlation suggests that the natural course of the disease and outcome is dictated by the site and type of the genetic mutation.

Survival of the patient beyond the second decade in the absence of specific treatment suggests some unusual or mild form of GS. Bone marrow transplant (BMT) or peripheral blood stem cell transplantation (PBSC/T) is advised as the curative therapy for GS as early as possible in the course of the disease, which suggests that the cells of hematopoietic origin are responsible for the fatal outcome in GS. However in present case the child is growing normal without any deficit.

Since prognosis, treatment options, and genetic counseling markedly differ among different types, molecular characterization has utmost importance in GS [19].

Conclusion

With high rate of consanguineous marriage in our country premarital Genetic counseling and educational programs for the families are essential in this regions. Moreover, we need to educate the physician about different phenotypes of GS. So any pediatric patient with striking presentation like grey hair color can be referred to pediatrician for evaluation of GS as to start early intervention to improve outcome.

References

1. Cadas D, Ozgur TT, Asal GT, Tezcan I, Metin A, et al. (2012) Griscelli syndrome type 1 and 3: analysis of four new cases and long-term evaluation of previously diagnosed patients. European 10: 1527-31.

2. http://ghr.nlm.nih.gov/condition/griscelli-syndrome. Accessed on 28/12/2015.

3. Ménasché G, Pastural E, Feldmann J, Certain S, Ensoy F, et al. (2000) Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. Nat Genet 25: 173-176.

4. Pastural E, Ensoy F, Yilmaz N, Wulfraat N, Grillo E, et al. (2000) Two genes are responsible for Griscelli syndrome at the same 15q21 locus. Genomics 63: 299-306.

5. Stinchcombe J, Bossi G, Griffiths GM (2004) Linking albinism and immunity: the secrets of secretory lysosomes. Science 305: 55-59.

6. Westbrook W, Klar A, Cullinane AR, Ziegler SG, Hurvitz H, et al. (2012) Cellular and clinical report of new Griscelli syndrome type III cases. Pigment Cell Melanoma Res 25: 47-56.

7. Ménasché G, Ho CH, Sanal O, Feldmann J, Tezcan I, et al. (2003) Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYOSA F-exon deletion (GS1). J Clin Invest 112: 450-456.

8. Klein C, Philippe N, Le Deist F, Fraye S, Frost C, et al. (1994) Partial albinism with immunodeficiency (Griscelli syndrome). J Pediatr 125: 886-895.

9. Pastural E, Barrat FJ, Dufourcq-Lagelouse R, Certain S, Sanal O, et al. (1997) Griscelli disease maps to chromosome 15q21 and is associated with mutations in the myosin-Va gene. Nat Genet 16: 289-292.

10. Baumeister FM, Stachel D, Schuster F, Schmid I, Schaller H, et al. (2000) Accelerated phase in partial albinism with immunodeficiency (Griscelli syndrome): genetics and stem cell transplantation in a 2-month-old girl. European Journal of Pediatrics 159: 74-78.

11. Al-Saud BK, Al-Sum Z, Alasiri H, Al-Ghonaium A, Al-Muhsen S, et al. (2013) Clinical, immunological, and molecular characterization of hyper-IgM syndrome due to CD40 deficiency in eleven patients. J Clin Immunol 33: 1325-1335.

12. Tomita Y, Suzuki T (2004) Genetics of pigmentary disorders. Am J Med Genet C Semin Med Genet 131C: 75-91.

13. Rezaei N, Moazzeni K, Aghamohammadi A, Klein C (2009) Neutropenia and primary immunodeficiency diseases. Int Rev Immunol 28: 335-366.

14. Wilson SM, Yip R, Swing DA, O’Sullivan TN, Zhang Y, et al. (2000) A mutation in Rab27a causes the vesicle transport defects observed in ashen mice. Proc Natl Acad Sci U S A 97: 7933-7938.

15. Marthess E, Calvagni V (2006) Case Report Griscelli syndrome: a rare neonatal syndrome. Malta Medical Journal 18: 21-24.

16. Nouriel A, Zisquil J, Helfand AM, Anikster Y, Greenberger S (2015) Griscelli Syndrome Type 3: Two New Cases and Review of the Literature. Pediatr Dermatol 32: e245-248.

17. Sanal O, Ensoy F, Tezcan I, Metin A, Yel L, et al. (2002) Griscelli disease: genotype-phenotype correlation in an array of clinical heterogeneity. J Clin Immunol 22: 237-243.

18. Meschede IP, Santos TO, Iizdoro-Toledo TC, Gurgel-Gianetti J, Espreafico EM (2008) Griscelli syndrome-type 2 in twin siblings: case report and update on RAB27A human mutations and gene structure. Braz J Med Biol Res 41: 839-848.

19. Khan I, Ahmed SA, Khan AB (2007) Case Report Griscelli syndrome in a young adult: A case report with the review of literature. Journal of Pakistan Association of Dermatologists 17: 122-124.