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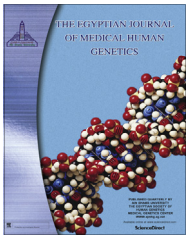

CASE REPORT

Griscelli syndrome type 2 – A case report and clinical approach to silver blonde hair

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KEYWORDS

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Abstract Griscelli syndrome type 2 is a rare autosomal recessive disease caused by mutations in the RAB27A gene. It is characterized by pigmentary dilution of the skin and hair causing silvery gray hair, hemophagocytic lymphohistiocytosis and characteristic light microscopy findings in scalp hair shaft seen as large irregular clumps of pigment as opposed to the evenly distributed pigment along the hair shaft without any clumps. We describe a boy with classic features of Griscelli syndrome type 2 from Pakistan in whom a homozygous mutation in the RAB27A gene was identified that showed a single base substitution (c.598C > T) predicted to cause premature protein termination (p.Arg200*). We also present a clinical approach to silver blonde hair differentiating between the Griscelli syndrome types 1, 2 and 3, Chediak Hegashi Syndrome and Elejalde Syndrome.

1. Introduction

Griscelli syndrome (GS) is a rare autosomal recessive disorder that was first described by Griscelli et al. in 1978 [1]. Silvery hair and hypopigmentation along with varying degrees of immunologic and neurologic dysfunction are the prominent clinical features of GS. Three subtypes, GS-1-3, share similar pigmentary dilution of the skin and hair causing silvery gray hair [2]. Mutations in the *MYO5A* gene causing GS-1 (OMIM # 214450) are clinically similar to Neuroectodermal melanolysosomal disease (Elejalde Syndrome OMIM # 256710) [3]. Both are characterized by neurological impairment without immunological impairment. GS-2 (OMIM # 607624) is caused by mutations in the *RAB27A* gene and is characterized by severe immunological impairment without primary neurological impairment [4]. The neurological deficit that occurs in GS-2 seems to be secondary to the infiltration and proliferation of leukocytes in the brain [5]. GS-3 (OMIM # 609227) is caused by a defect in the *MLPH* gene and presents with only partial albinism and silvery hair without the neurologic and immunologic involvement [2]. Prognosis of GS depends on the subtypes. There is no treatment for GS-1 and quality of life depends on the severity of neurological impairment. GS-3 does not require treatment. Patients with GS-2 succumb to illness due to the accelerated hemophagocytic syndrome phase secondary to immunological impairment unless an early bone marrow transplant (BMT) is performed [6]. Therefore, early recognition of GS-2 is critical.

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More than one hundred cases of GS have been reported worldwide [7] including one GS case from Pakistan, which was diagnosed clinically without molecular characterization of the subtype [8]. We present the first case of GS-2 from Pakistan in whom a homozygous non-sense mutation in the *RAB27A* gene was confirmed.

2. Case report

A 4 month old boy born to healthy first-cousin, once removed parents after an uneventful full term pregnancy was referred to a genetic clinic for the evaluation of hepatosplenomegaly noted from 3 months of age. At birth his weight was 3.3 kg, length was 52 cm and head circumference was 35.4 cm. As compared to the healthy family members, he was noted to have very fair skin, silvery blonde scalp hair, eyebrows and eye lashes. His early developmental miles stones were achieved at appropriate ages. Parents were concerned for his partial albinism in view of the two other children who died at 40 days of life with pneumonia and 6 years of age with sepsis and who also had hepatosplenomegaly. Both the deceased sibs had similar fair skin and silver blonde scalp hair as the proband. None of the other healthy sibs had similar skin hypopigmentation or silvery blonde hair. Parents reported a history of recurrent fever in the patient described in this paper, which were often treated with oral antibiotics. However, he was never admitted with a serious infection nor his blood cultures grew any pathogenic micro-organism. On further interviewing, parents described their deceased six-year old as an intelligent boy who had no neurological impairment. They further informed that with

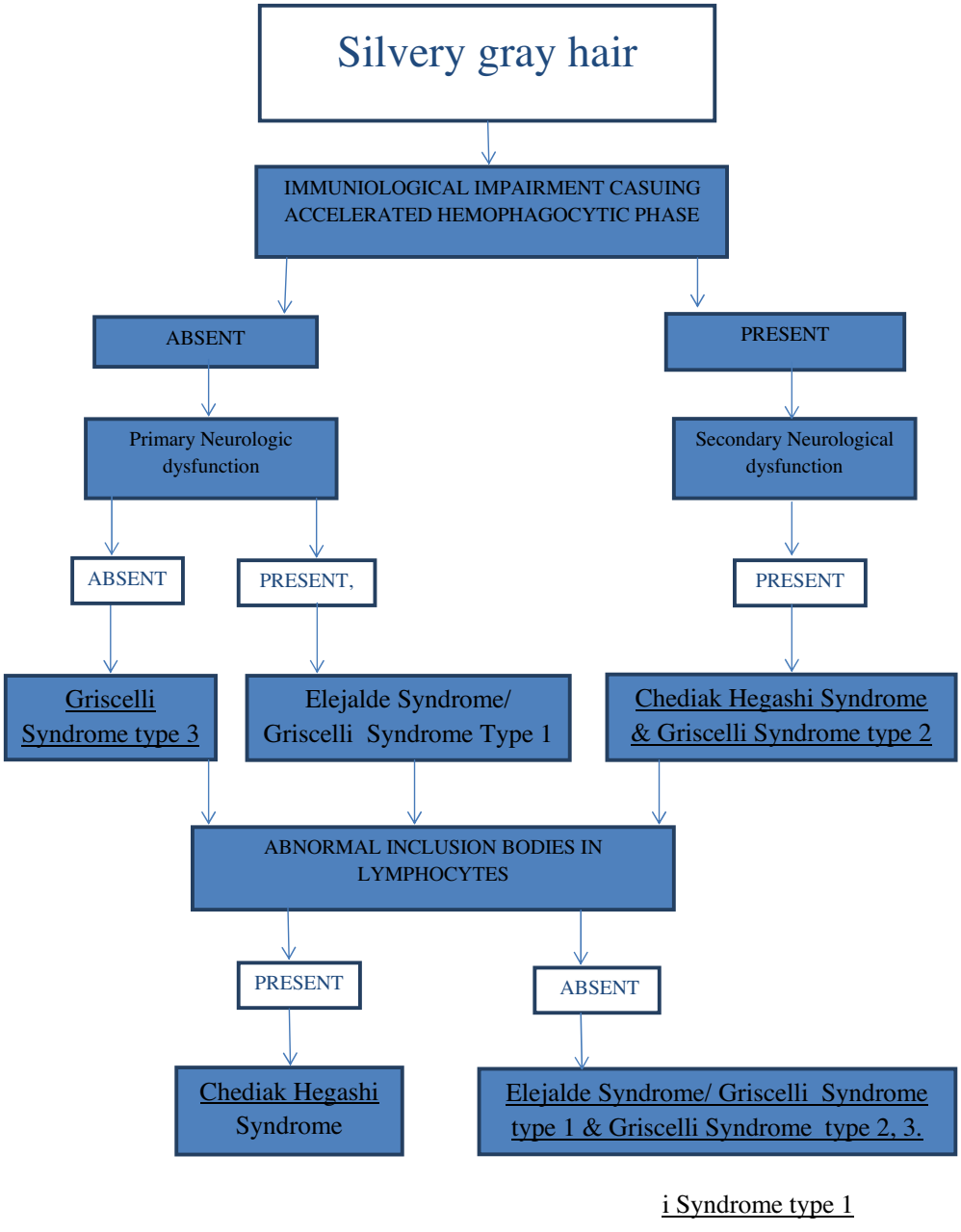

Figure 1 Approach to patients with silver blonde hair.

Figure 2 (a) Silver blonde scalp hair and eye brows and bronze tan skin. (b) Light microscopy of scalp hair shaft showing large irregular clumps of pigments.

age his fair complexion changed to bronze tanning especially in the sun exposed areas (see Fig. 1).

The physical examination of the proband revealed hepatosplenomegaly, however no lymphadenopathy was noted. The child had good eye contact, with good neck control and was socially interactive. His growth anthropometry including weight, height and occipital frontal head circumference were normal for age.

Investigations showed hemoglobin 7.4 g/dL, total leukocyte count: 2300/mm^3 with absolute neutrophil count of 800, platelet count of 85,000/mm^3. The peripheral blood smear showed normocytic and normochromic red blood cells. In view of the silver gray hair (Fig. 2a), hepatosplenomegaly and spared neurological manifestation differential diagnosis of Chediak Hegashi Syndrome and GS-2 was considered. Light microscopy of scalp hair shaft was performed, which showed large irregular clumps of pigment suggesting GS-2 (Fig. 2b). In the laboratory evidence of hemophagocytosis; hypertriglyceridemia of 352 mg/dL (normal < 150 mg/dL), hypofibrinogenmia of 104 mg/dL (normal: 150–450) and hyperferritinemia of 1534 ng/ml (normal: 50–200) were noted. Bone marrow aspirates for the hemophagocytosis were not done. For the assessment of humoral immunodeficiency serum IgG, IgA and IgM were done, which were noted to be low for his age. Flow cytometry for the assessment of the cellular immune deficiency was not done due to cost constraints. For the confirmation of the diagnosis of GS-2; *RAB27A2* gene sequencing was performed at Prevention Genetics in Marshfield, Wisconsin, U.S.A., which showed a homozygous single base pair substitution c.598C > T, which is predicted to causing premature protein termination (p.Arg200*).

At the time of writing this manuscript, preparation for allogenic BMT is in process and a HLA matched sibling has been identified.

3. Discussion

The hemophagocytic syndrome seen in GS-1 and GS-2 is also described as the accelerated phase. This is secondary to the uncontrollable T lymphocyte and macrophage hyperactivation. The main differentiation between GS-1 and GS-2 is the primary or secondary central nervous system (CNS) involvement. The secondary CNS involvement in GS-2 is caused by the infiltration of lymphocytes and histiocytes as a result of hemophagocytic syndrome. Temporary remission of the accelerated phase seen in GS-2 can be achieved with chemotherapy or immunotherapy [9]. However, recurrent relapses of increasing severity are frequently observed as infiltration of the CNS despite maintenance therapy. BMT is the only curative treatment of GS-2. Patients usually succumb to severe infection or CNS infiltration at an average age of 5 years without BMT [10]. Thus, prompt diagnosis is vital in the prognosis of GS-2.

We present the first report describing a case of molecularly confirmed GS-2 from Pakistan. In our patient, scalp hair microscopy was suggestive of GS. The hair microscopy finding together with the clinical and laboratory evidence of hemophagocytic syndrome without CNS involvement prompted us to the diagnosis of GS-2.

The homozygous c.598C > T mutation in *RAB27A* gene, predicted to cause premature protein termination (p.arg200*) confirmed the diagnosis of GS-2 in our patient. The same mutation in the *RAB27A* gene has been reported in a patient in whom hydrocephalus and multiple contrast enhancing lesions in the cerebellar, cerebral cortex, and spinal cord were described. However, these lesions showed lymphocyte and histiocyte infiltration with evidence of hemophagocytic lymphohistiocytosis [11].

Differentiation between GS-1 and GS-2 is essential because BMT is the definitive treatment for GS-2 but has no role in GS-1 caused by *MYO5A*. At the time of writing of this manuscript arrangements for an allogenic BMT from a HLA-matched sibling are underway.

Conflict of interest

Authors declare no conflict of interest.

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