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Case Report

Griscelli syndrome type 2: a tragic tale of two siblings

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ABSTRACT

Griscelli syndrome (GS) is a rare autosomal recessive disorder classified as an inborn error of immunity. Among its three variants, GS type 2, caused by mutations in the RAB27A gene, is marked by partial albinism and recurrent episodes of hemophagocytic lymphohistiocytosis (HLH). This case report chronicles the poignant journey of two siblings tragically lost to this condition. GS type 2 carries a high mortality rate, primarily due to HLH complications. Currently, hematopoietic stem cell transplantation (HSCT) remains the sole curative treatment for this devastating syndrome.

Keywords: Inborn error of immunity, RAB27A mutation, Hemophagocytic lymphohistiocytosis, Albinism

INTRODUCTION

Griscelli syndrome (GS) is a rare syndromic autosomal recessive inborn error of immunity. There are three types of GS: type 1, type 2, and type 3 are caused by pathogenic variants in the MYO5A (Myosin Va), RAB27A, and MLPH genes, respectively.[1] These genes are concerned with membrane transport and organelle trafficking inside the cell. GS type 2 is caused by mutations in the RAB27A gene, which is located on chromosome 15q and encodes a small 95 kDa GTPase widely expressed in melanocytes and granulocytes.[2] It plays a key role in the docking of cytotoxic T cell/NK cell granules containing perforin and granzyme B. As a result, emophagocytic lymphohistiocytosis (HLH) caused by granule exocytosis is seen only with the GS type 2 syndrome. GS type 2 is distinguished by partial albinism and recurrent HLH, often triggered by viral infections. The hair is sparse, and silvery grey in colour due to aberrant melanin deposition in the hair shaft.

Mortality of patients with GS type 2 is high, often due to predisposition to HLH.[3] HLH is a life-threatening immunological disorder characterised by fever, cytopenias, infiltration of the central nervous system (CNS) by lymphocytes and macrophages, hepatosplenomegaly and coagulopathy. Death usually occurs within 5 years due to recurring infections or CNS illness. Currently, hematopoietic stem cell transplantation (HSCT) is the only curative option for GS type 2. [4,5]

CASE REPORT

A five-year-old male child, second in birth order to a third-degree consanguineous parent was brought for evaluation. His past medical history was significant with history of seizures at 8 months of age, followed by recurrent upper and lower respiratory and gastrointestinal infections starting at 2 years of age. Notably, there was family history of silvery white hair observed in his sister (Figure 1) she also had pancytopenia and died at the age of 3.5 years.

He presented to the paediatric department in our hospital at the age of four years in view of recurrent generalized tonic-clonic seizures and was referred to the department of rheumatology in view of recurrent infections. On examination he exhibited silvery gray hair, including eyebrows and eyelashes, without any signs of organomegaly or focal neurological deficits (Figure 2).

Routine laboratory investigations, including complete blood count, liver function tests, creatinine levels, and erythrocyte sedimentation rate, yielded normal results. Imaging studies indicated bilateral cerebellitis (Figure 3 and 4), nodular leptomeningeal enhancement (Figure 5), diffuse cerebral edema (Figure 6) and obstructive hydrocephalus, necessitating a ventriculo-peritoneal shunt procedure at the age of four years. His T, B, and NK cell counts, as well as immunoglobulin subsets, were within normal ranges.

Due to the suspicion of an inborn error of immunity, particularly GS type 2, further investigations were done which revealed clumps of melanin pigment within the hair shafts upon microscopic examination (Figure 7). Genetic testing subsequently identified a homozygous missense variation c.340A>G (p.Ile114Val) in exon 4 of the RAB27A gene (NM_183235.3). The variant was classified as a 'variant of uncertain significance' (VUS; with the criteria PM2+PP2+PP4) as per the variant classification guidelines of the American college of medical genetics and genomics and the association for molecular pathology (ACMG/ AMP guidelines 2015). This variant is also listed in the ClinVar database as a VUS. However, in view of the strong phenotypic correlation, RAB27A gene-related GS type 2 was considered to be the most likely diagnosis in the child. Although planned for allogeneic hematopoietic stem cell transplantation (HSCT), he ultimately succumbed to refractory status epilepticus further complicated by pneumonia.

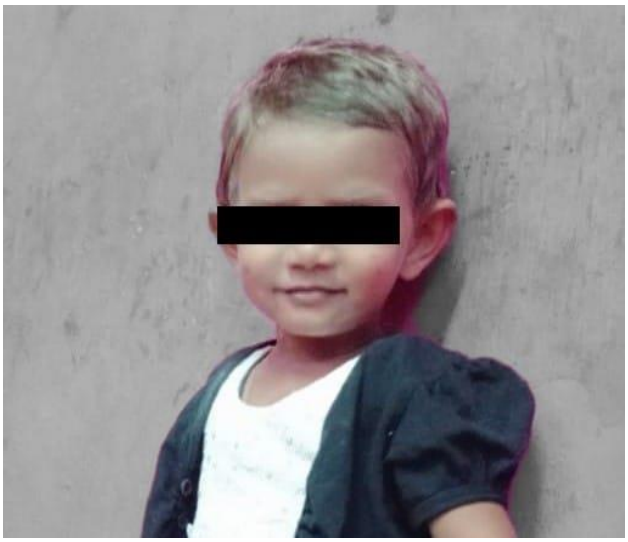

Figure 1: Clinical picture of the elder sister showing silvery grey hair over scalp and eyebrows.

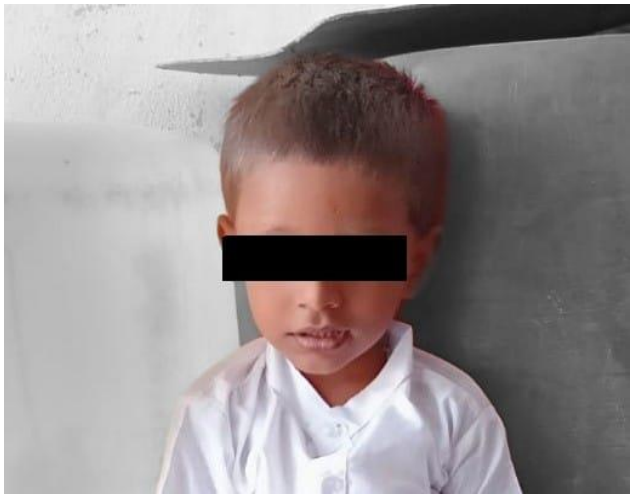

Figure 2: Clinical picture of the patient showing silvery grey hair over the scalp and eyebrows.

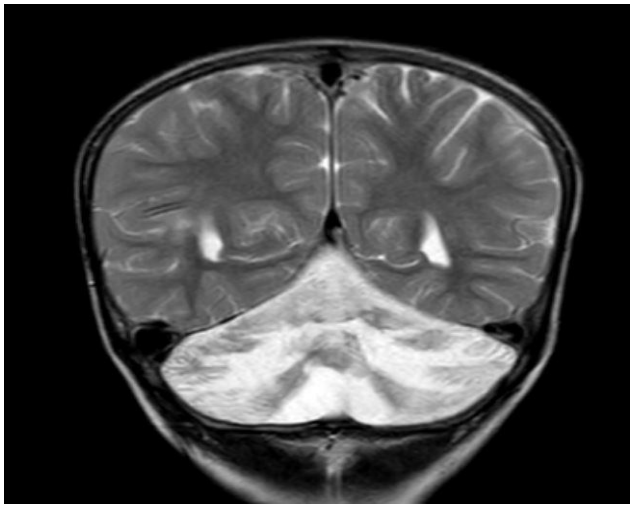

Figure 3: Coronal T2 weighted images showing diffuse hyperintensity in bilateral cerebellar hemispheres suggestive of cerebellitis.

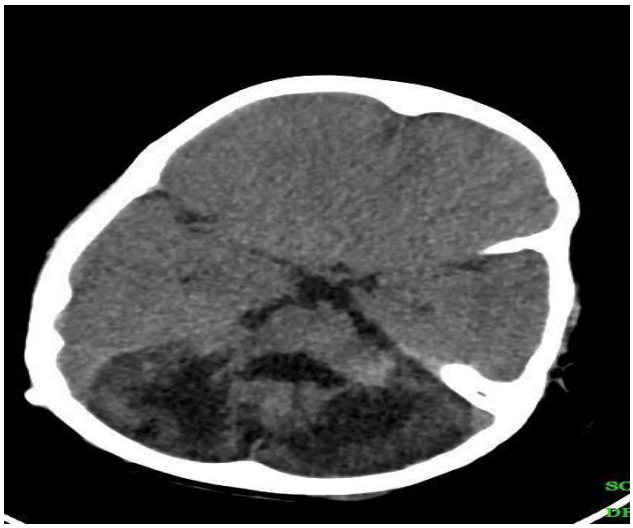

Figure 4: CT brain showing encephalomalacia changes in the bilateral cerebellar hemispheres.

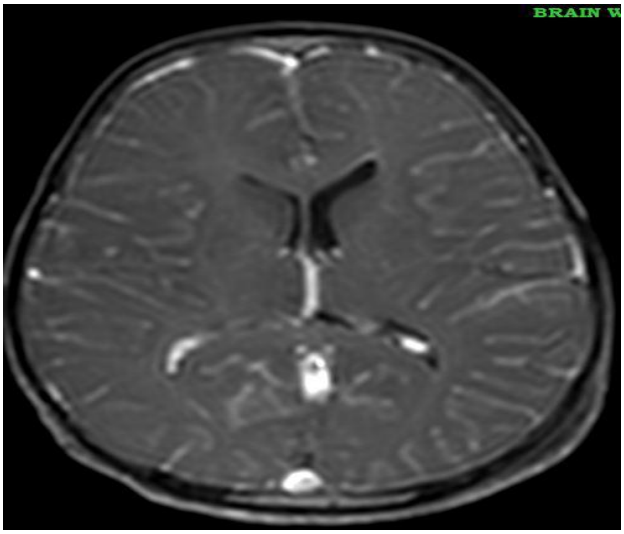

Figure 5: Contrast enhanced MRI axial T1 weighted images showing diffuse leptomeningeal enhancement.

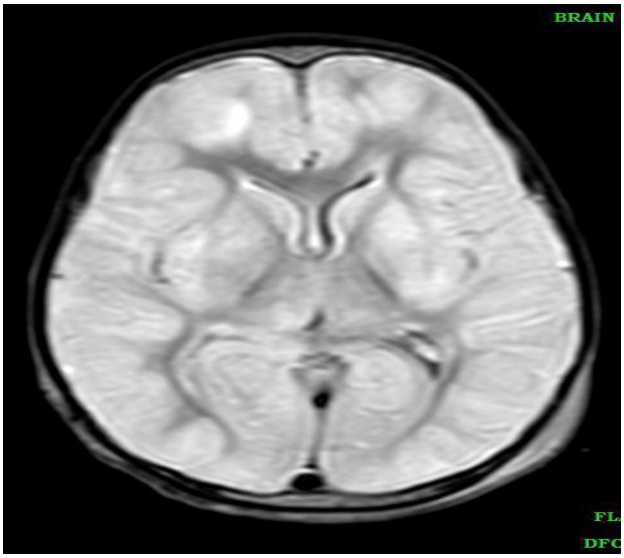

Figure 6: Flair axial images showing diffuse cerebral edema and gyral hyperintensities.

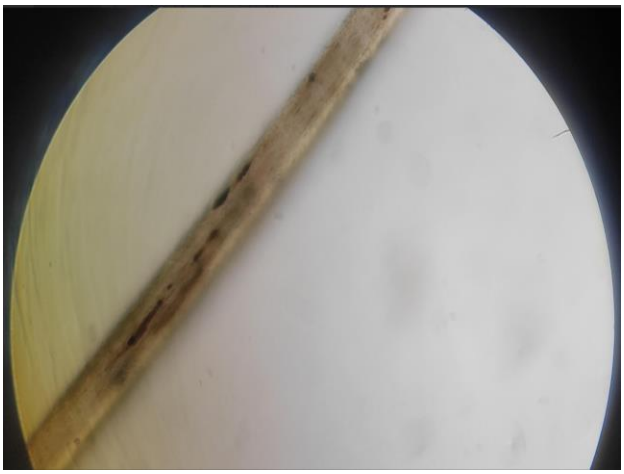

Figure 7: Hair microscopy showing clumps of melanin deposition in the hair shaft.

DISCUSSION

This is an example of GS type 2: two siblings in the same family having silvery grey hair. The elder one had pancytopenia and died before the age of five, and no genetic testing was done. The younger sibling exhibited substantial CNS symptoms, such as CNS HLH requiring a VP shunt and intractable seizures. He had a homozygous missense variant identified in the RAB27A gene and his clinical phenotype correlated with the expected clinical phenotype of RAB27A gene-related GS type 2. Despite being scheduled for HSCT, he died as a result of refractory seizures and pneumonia.

There have been approximately 56 different pathogenic variations of RAB27A reported, including intronic and structural variants.[6] Our patient has a homozygous missense mutation in exon 4 of the RAB27A gene (c.340A>G).

Maimaris et al conducted a literature review and comprehensive analysis of 149 GS type 2 patients, with HLH being the most common manifestation (80%), and CNS HLH accounting for 46%. Partial albinism was discovered in 70% of patients, characterized by silvery grey hair, hypopigmented skin, and irregular melanin pigmentation in the hair shaft under light microscopy. Other manifestations include fever (63%), splenomegaly (62%), hepatomegaly (59%), neurological features (41%), muscle weakness or myalgias (22%). Neurological dysfunction included ataxia, strabismus, and seizures. The mortality rate in this group is 34%; 44 patients had HSCT, 18 of them had an uncomplicated course, and the remainder had either a fatal infection (5 patients), chronic neurological impairments (4 patients), or death during HSCT (6 patients). Overall mortality was lower in HSCT patients than in non-transplanted patients (18% vs. 58%).[6] Similar to the cohort above, our patient had CNS HLH and partial albinism.

CONCLUSION

GS type 2 is a fatal immune disorder, characterized by silvery grey hair and CNS HLH. Hair microscopy and genetic testing aid in early detection of this disease. Treating these situations early with HSCT may improve the children's survival rates.

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Ethical approval: Not required

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