

# Griscelli syndrome: a rare neonatal syndrome

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## Introduction

Griscelli syndrome was first described by Griscelli and Siccardi in 1978 in a hospital in Paris.<sup>1</sup> It is a rare autosomal recessive disorder resulting in pigmentary dilution of the skin and hair, presence of large clumps of pigment in hair shafts and an accumulation of melanosomes in melanocytes.<sup>2</sup> It results in silver-grey hair along with variable cellular immunodeficiency or severe neurological impairment or both.<sup>2</sup> The condition is rare in all countries and up to January 2003 only 60 cases had been described in the world medical literature.<sup>2</sup> In most cases diagnosis occurs between the ages of 4 months to 7 years.<sup>2</sup>

The boy discussed here had silvery hair, eyebrows and eyelashes (Figure 1) and was admitted at the age of five months to hospital with fever, hepatosplenomegaly and pancytopenia.

## Case Report

A 5-month old Maltese boy, MS, was referred to our centre with a two-day history of fever and irritability. From birth he was noted to have silver grey (leaden) hair and silvery grey eyebrows and eyelashes. His parents were unrelated and MS was their only child. The physical examination revealed pallor, hepatomegaly and splenomegaly. The boy was thriving (wt: 7.9kg, P50) and his development was normal. The neurological examination was unremarkable.

The initial investigations showed pancytopenia, but there were no abnormal cells in the peripheral blood (Table 1). Biochemical tests of liver function showed moderately raised bilirubin and liver enzymes and the blood coagulation was abnormal with a raised INR and APTT (Table 1). Broad-spectrum antibiotics (piptazobactam and gentamicin) were started because of fever and neutropenia and MS was given a platelet and a blood transfusion.

Blood cultures and tests for EBV, CMV, visceral leishmaniasis and brucellosis were negative. The bone marrow showed abundant macrophages and ineffective erythropoiesis, whilst the CSF was normal. A raised serum triglyceride, LDH, serum ferritin and a low serum fibrinogen (Table 1) supported the diagnosis of haemophagocytic lymphohistiocytosis. Further evidence of HLH was given by lymphocyte subset studies that typically showed low Suppressor/Cytotoxic T lymphocytes, a raised Helper/Suppressor index and low Natural Killer T lymphocytes (Table 1).

Magnetic resonance imaging of the brain was completely normal and did not show any white matter infiltration or abnormality. Microscopic examination of MS's hair shafts showed large discrete clumps of melanin pigment along the length of the shaft and this was consistent with the Griscelli syndrome.

## Keywords

Griscelli syndrome, report

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**Figure 1:** MS with the typical pigmentary defect of the Griscelli syndrome. Note the silvery (leaden) hair and eyebrows. These changes are usually present at birth and should alert the physician of the possibility of the Griscelli syndrome.

**Table 1:** Initial blood investigations

Haemoglobin	7.8g/dl
White blood cell count	7.3 x 10 <sup>9</sup> /l
Neutrophil count	0.79 x 10 <sup>9</sup> /l
Platelets	32 x 10 <sup>9</sup> /l
Bilirubin	32 µmol/l
INR	1.4
APTT ratio	74s
Fibrinogen	0.83g/l (n.v. 2-4g/l)
Serum triglycerides	5.7mmol/l (n.v. 0.4-2.3)
Serum LDH	908U/l (n.v. <425)
Serum ferritin	1279 ng/ml (n.v. 28 – 365)
Total lymphocyte count	1501 Val/uL
Suppressor/Cytotoxic T cell count	143 Val/ul
Helper/Suppressor Index (CD4/CD8)	3.1 (n.v. 0.5 – 2.6)
Natural Killer T Cells	0.8% of the total lymphocyte count (n.v. 2- 25%)

Treatment according to the HLH-94 protocol, an international study co-ordinated by the Histiocyte Society for the treatment of Haemophagocytic Lymphohistiocytosis<sup>3</sup>, was commenced. The induction phase consisted of twice weekly etoposide for six weeks and oral dexamethasone for eight weeks. This resulted in resolution of the hepatosplenomegaly and the pancytopenia, with reversal of the LDH, fibrinogen and triglyceride levels to normal. Remission was maintained with daily cyclosporin A and etoposide/dexamethasone every fortnight.

Curative treatment for the Griscelli syndrome (accelerated phase) involves a stem cell transplant and since MS had no siblings an international search for an unrelated donor was commenced. The best available donor was that from the Italian cord blood panel and the donor was a 9/10 HLA match with our patient. A mismatched unrelated cord transplant was carried out at Great Ormond Street Hospital in London. Unfortunately the transplant was not successful and a second procedure was planned for October 2005.

## Discussion

This is the first time that a case of Griscelli syndrome is described in the Maltese medical literature and this case serves to highlight the salient features of the disease. Although Griscelli syndrome is a very rare condition the silvery grey (leaden) hair, eyebrows and eyelashes (Figure 1) are very characteristic and should alert the physician to the possibility of the syndrome.

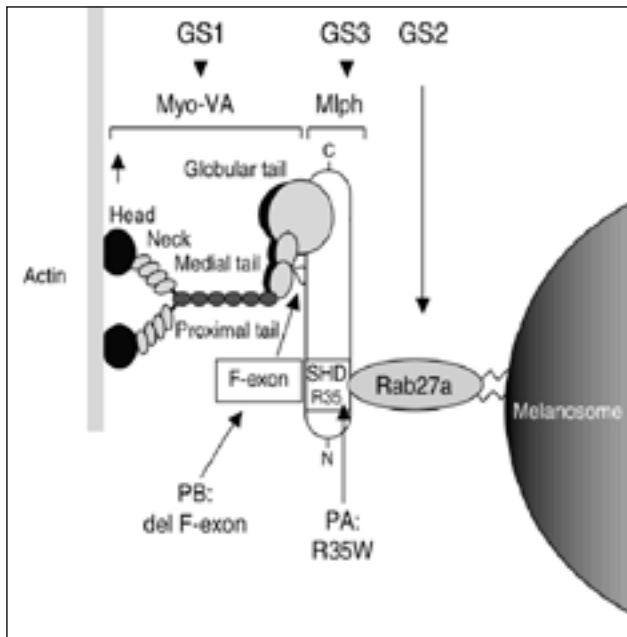
Griscelli and Siccardi first described the Griscelli syndrome in 1978.<sup>1</sup> It is an autosomal recessive disorder resulting in pigmentary dilution of the skin and hair with the presence of large clumps of pigment in hair shafts as a result of the accumulation of melanosomes in melanocytes.<sup>2</sup> More significantly the inherited metabolic defect can also be associated with haemophagocytic lymphohistiocytosis and/or

severe neurological impairment early in life.

Our patient presented with the pigment disorder and immune dysfunction resulting in partial albinism and haemophagocytic lymphohistiocytosis. In most cases diagnosis is made between the ages of 4 months to 7 years.<sup>2</sup>

Three main types of Griscelli syndrome are recognized and classified according to the mutation involved and the clinical presentation. The common pigmentary defect observed in the three types (GS1, GS2 and GS3) results from the absolute requirement and interaction of three encoded proteins for melanosome transport. GS1 associates characteristic albinism with a severe primary neurological impairment. Patients exhibit severe developmental delay and mental retardation occurring early in life. These patients carry mutations of the myosin 5A gene (MYO5A), which encodes an organelle motor protein, Myosin 5A (MyoVa), and has a determining role in neuron function.<sup>4,5</sup> The second type of Griscelli syndrome (GS2) is characterized by the same hypopigmentation associated with an immune defect, leading to episodes of life-threatening uncontrolled T lymphocyte and macrophage activation that are the hallmark of haemophagocytic lymphohistiocytosis (HLH).<sup>6</sup> During HLH activated T cells and macrophages infiltrate various organs (including the brain), leading to massive tissue damage, organ failure, and death in the absence of treatment.<sup>6</sup> The immune dysfunction can initially be controlled with immunosuppressive treatment but haematopoietic stem cell transplantation is the only definitive curative treatment for this condition.<sup>6</sup> Mutations in RAB27A, a gene that encodes a small GTPase protein (Rab27a) and is involved in the function of the intracellular-regulated secretory pathway, cause GS2.<sup>7</sup> The immune deregulation observed in GS2 patients is accounted for by the absolute requirement of the Rab27a protein function for lymphocyte cytotoxic granule release and underlines the determining role of this cytotoxic pathway in immune homeostasis.<sup>7</sup> Therefore in GS2 patients the ability of lymphocytes and natural killer cells to lyse target cells is impaired or absent due to a consistent inability to secrete cytotoxic granules. This inherited defect therefore accounts for the severe immunologic disorder characteristic of this syndrome, namely haemophagocytic lymphohistiocytosis. Both genes (MYO5A and RAB27A) map to the same chromosome 15q21.1 region and are distant from each other by less than 1.6 cM.<sup>8</sup> Homozygous missense mutation in human melanophilin (MLPH), leading to defective Rab27a – Mlph interaction, results in a third form of GS (GS3), the phenotype of which is restricted to hypopigmentation only.<sup>9</sup> Slac2/melanophilin is the link between myosin Va and GTP-Rab27a. In the absence of the tripartite protein complex (Rab27a-Mlph-MyoVa) formation in melanocytes, melanosomes cannot be connected to the actin network and thus transported toward the melanocytes tips (Figure 2).<sup>9,10</sup> Our patient, MS, probably has the GS2 form of Griscelli syndrome and the genetic studies done while the patient was in London are awaited.

The main differential diagnoses in our patient were the Chediak-Higashi syndrome (CHS) and Elejalde syndrome (ES). Both disorders can present with the characteristic silvery grey



**Figure 2:** Scheme of the heterotrimeric protein complex involved in human melanosome transport. A defect in any of the proteins, *MyoVa*, *Rab27a*, or *Mlph*, leads to identical pigmentary dilution, found in the three forms of GS. The F-exon on *MyoVa* is required for *MyoVa*-*Mlph* interaction and the SHD of *Mlph* for *Mlph*-*Rab27a* interaction.<sup>10</sup>

(lead) hair, eyebrows and eyelashes seen in our patient. In CHS the patients exhibit hypopigmentation of the skin, eyes and hair, prolonged bleeding times, easy bruisability, recurrent infections, abnormal killer cell function and peripheral neuropathy.<sup>11</sup> The hallmark of CHS is the presence of giant intracytoplasmic granules in virtually all granulated cells, which is never observed in GS.<sup>11</sup> In CHS, defective melanosome transfer is secondary to a primary defect in a protein called *LYST* (lysosome trafficking regulator).<sup>12</sup> This is a membrane-associated molecule that is important in protein docking and fusion and for membrane stability of certain organelles.<sup>12</sup> Therefore the basic defect in CHS results in the defective formation of giant melanosomes that are consequently difficult to transfer to keratinocytes. In GS, on the other hand, mature melanosomes are formed normally but it is the tripartite protein complex of *Rab27a*-*Mlph*-*MyoVa* (the transfer mechanism) that is defective. *Elejalde* syndrome<sup>15</sup> main features include silvery hair, intense tanning after sun exposure, severe neurological impairment and a wide spectrum of ophthalmological abnormalities.<sup>13</sup> The neurological impairment can be congenital or develops during childhood and includes seizures, severe hypotonia and mental retardation.<sup>13</sup> *ES* does not involve impairment of the immune system and appears related to or allelic to *GS1*, and thus associated with mutations in *MYOVA*. However its gene mutation has yet to be defined.<sup>14</sup> Like the *Griscelli* syndrome, both *CHS* and *ES* are inherited in an autosomal recessive way and therefore carry a recurrence risk of 1 in 4 for the index family.

Our patient, *MS*, presented with the characteristic phenotype of *GS2* including the silvery grey hair and evidence

of haemophagocytic lymphohistiocytosis (*HLH*). *HLH* is a Class II Histiocytosis or Non Langerhan Cell Histiocytosis and it can be secondary (e.g. infection associated) or primary (familial). Familial Haemophagocytic Lymphohistiocytosis (*FHL 1-3*) results from mutations of the perforin (*FHL2*)<sup>15</sup>, *Munc13-4* (*FHL3*)<sup>16</sup> and a yet unidentified gene mapped to human chromosome 9q21 (*FHL1*)<sup>17</sup>. A number of other conditions with an inherited metabolic defect that can lead to *HLH* have been described and *Griscelli* syndrome type 2 and *Chediak-Higashi* syndrome are good examples of these conditions. The most typical clinical findings of *HLH* are fever, hepatosplenomegaly, anaemia and bruising. Some patients present with neurological symptoms, lymphadenopathy, rash, jaundice and oedema. Common laboratory findings are pancytopenia, hypertriglyceridaemia, hypofibrinogenaemia, coagulopathy and liver dysfunction. Other abnormal laboratory findings are low natural killer cell activity, hypercytokinaemia and a high serum ferritin and lactate dehydrogenase. Most of these abnormalities, except for central nervous system involvement, were found in our patient *MS*.

An important clue to the diagnosis of the *Griscelli* syndrome is from the histological examination of the hair shaft of the patient. Examination of the hair shaft from our patient showed large discreet clumps of melanin pigment along the length of the shaft, instead of the homogeneous distribution of small pigment granules seen in normal hair.<sup>18</sup> In *Chediak-Higashi* syndrome, the hair shaft also contains a typical pattern of uneven accumulation of large pigment granules but in *GS* the clusters of melanin pigment on the hair shaft are six times larger than in *CHS*.<sup>18</sup>

Our patient, *MS*, is at present in the United Kingdom awaiting a second haematopoietic stem cell transplant (*HSCT*). A *HSCT* from a histocompatible donor offers the best chances of long-term survival for *Griscelli* syndrome patients with *HLH*.<sup>19</sup> Durable long-term remissions can be achieved with chemotherapy and cyclosporin A, and neuro-cerebral disease can also be controlled transiently with intrathecal methotrexate.<sup>20</sup> Patients will need aggressive support and monitoring during the course of their illness similar to patients having chemotherapy for oncological conditions. However, the prognosis for long term survival of patients with *Griscelli* Syndrome and *HLH* is poor for those patients who do not have a histocompatible donor or who relapse after a *HSCT*.

## Conclusion

We present the first documented case of the *Griscelli* syndrome in a Maltese patient. The characteristic phenotypic appearance, especially the pigment disorder of the patient's hair, is emphasized so that it is quite possible to suspect the diagnosis at the bedside. The underlying defects of the condition are also presented and these serve to shed important light on the importance of the secretory pathways required for normal lymphocyte cytotoxicity, melanosome transfer and neuro-synaptic transmission.

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