International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2013): 4.438

# Case Report: Griscelli Syndrome – A Unique Pigmentary Defect

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**Abstract:** ***Griscelli syndrome is a rare disorder with hypomelanosis of skin, silvery-gray hair due to abnormal melanosomal trafficking in melanocytes. It is caused by mutations in 3 genes: MYO5A, RAB-27A, MLPH (Melanophilin) and accordingly classified into 3 subtypes: GS1, GS2 and GS3 respectively. These 3 proteins interact and together form heterotrimeric complex responsible for intracellular vesicular transport and secretion. RAB27A is key effector of cytotoxic granule exocytosis. The feature common to all 3 variants is pigmentary dilution. GS1 patients have primary neurological disorder without immune defects, whereas GS2 group exhibit recurrent infections with hemophagocytosis. Agglomerates of mature melanosomes in hair shaft and skin microscopy, sparse pigmentation of adjacent keratinocytes, and absence of giant granules in neutrophils are diagnostic of GS. GS2 develop hemophagocytic syndrome characterized by uncontrolled activation of T lymphocytes, macrophages and generalized lymphohistiocytic infiltrates. Bone marrow transplantation remains only curative modality. We report a child with classical features of GS and pathognomonic histopathological features of skin and hair.***

**Key words:** Griscelli syndrome, silvery-gray hair, melanosomes, pigmentary dilution, immunodeficiency

## 1. Introduction

Griscelli syndrome (GS) is rare autosomal recessive disorder with pigmentary dilution, immunodeficiency and neurological involvement [1,2].

## 2. Case Report

11 months old boy presented with fever, convulsions and refractory circulatory shock to emergency. He was first conception born of non consanguineous union and had no family history of immunodeficiency. He had stormy course since birth requiring 4 admissions for recurrent infections. He developed neuroregression at 9 months age. There was striking hypopigmentation (silvery-gray sheen) of scalp hair and eyebrows (figure 1). Parents had normally pigmented hair. Examination revealed hepatosplenomegaly (liver 7 cm, spleen 4 cm below costal margin), mucocutaneous candidiasis, left supranuclear facial palsy, hypertonia, and hyperreflexia. Laboratory analysis revealed: Haemoglobin – 4.7gm/dl, White blood cells – 800 cells/mm3, Polymorphs – 10%, Platelet count – $49\times10^9$/L; Peripheral smear – toxic granules but no giant cytoplasmic granules in leukocytes; Blood culture – Klebsiella pneumonia; Cerebrospinal fluid analysis – Pyogenic meningitis (proteins – 282 mg/dl, 80 cells). Immunological abnormalities included: CD3 count – 540 cells/µl (690 – 2540), CD4 – 410 (438 – 1590), serum IgG – 391 mg/dl (700 – 1600), (IgM, IgA, IgE – normal). Bone marrow aspiration and biopsy demonstrated pancytopenia. MRI brain revealed patchy areas of altered signal intensity, increased T2 signal & focal abnormal enhancement in white matter suggestive of lymphohistiocytic infiltration. Examination of hair shaft showed irregular agglomerations of pigment (figure 2). In view of pigment dilution, immunodeficiency, typical skin and hair findings and absence of giant granules in neutrophils, diagnosis of GS was established. He was treated with repeated packed cells transfusions, higher antibiotics, antifungals, and high dose steroids. Despite initial remission, he developed multi-organ failure and succumbed to death. Unfortunately, molecular gene analysis wasn't possible.

## 3. Discussion

GS was first described in 1978 by Claude Griscelli and Michel Prunieras [1,3], and since then more than 100 cases have been reported. Clinical onset occurs between 4 months to 7 years age usually [3-6]. GS is classified into 3 types based on mutations in genes; MYO5A (GS1), RAB27A (GS2) or MLPH (GS3). Pigmentary defect is accompanied by neurologic impairment in GS1 and immune dysfunction in GS2. GS3 phenotype is restricted to pigmentation dysfunction [4, 6-7]. Genes MYO5A and RAB27A, colocalize on chromosome 15q21 to encode Myosin 5A and RAB27A respectively. MLPH lies on 2q37.3 [2-3,8]. MYO5A moves along actin cytoskeleton, tethers melanosome at plasma membrane ready for pigment delivery. Its mutation results in aberrant melanosome transportation. RAB27A is required at late stage of secretion to detach vesicle from microtubule cytoskeleton, dock at plasma membrane and fuse with

acceptor membrane [8]. Its precise function differs location wise. In melanocytes, RAB27A associates with melanosomal membrane, recruits MLPH (melanophilin), and together interact with MYO5A. RAB27A-MYO5A-MLPH form tripartite complex facilitating vesicular trafficking, intracellular melanosome transport and secretion [8]. Each member has specific role in peripheral distribution of melanosomes, a necessary step in skin pigmentation. Any mutation results in clustering of melanin pigment in hair shafts, accounting for pigmentary dilution, although melanin production is normal [7-8]. In cytotoxic T lymphocytes, RAB27A doesn't interact with either melanophilin or MYO5A. RAB27A-deficient cells have normal granule content in perforin and granzymes, but defective release, whereas MYO5A or melanophilin-deficient T cells are normal [2,9]. Only MYOVA is expressed in brain and plays role in secretion of neurotransmitters. This selective tissue expression is basis for phenotypic differences between subgroups [1-2,6-7].

Single most consistent dermatoskeletal expression of albinism is silvery-grayish sheen to hair. Light-microscopy shows typical pattern of uneven clusters of aggregated melanin and large pigment agglomerations accumulated in hair shaft medulla with adjacent keratinocytes containing only scanty pigment [5-6]. Skin histopathology and Electron microscopy reveals hyper-pigmented basal melanocytes with abundant, stage IV mature melanosomes, poorly pigmented keratinocytes with virtual absence of mature melanosomes [1,4]. This can be highlighted in Fontana-Masson stained sections. Appearance of hair has been described as silvery gray, silvery, grayish golden or dusty and patients generally have lighter hair than their unaffected family members [7]. Immunologically impaired Natural killer and cytotoxic T cells cause absent delayed hyper sensitivity, poor histocompatibility complex mediated cytotoxicity, and hypogammaglobulinemia culminating in immunodeficiency and Hemophagocytic syndrome (HS) [1-2,6,10]. Usually triggered by viruses, HS occurs commonly between 6-12 months age [1,7]. It involves unremitting polyclonal CD8+ T-cell expansion, lymphohistiocytic infiltration of visceral tissues (spleen, liver, lymph nodes, brain), macrophage activation and proliferation (hemophagocytosis), and deleterious release of cytokines, including interferon γ, interleukins, tumor necrosis factor-α [2,6-7]. HS is characterized by prolonged high fever, hepatosplenomegaly, jaundice, pallor, lymphadenopathy, pancytopenia, hypertriglyceridemia, hypofibrinogenemia, coagulopathy, intracranial hypertension, seizures, encephalopathy, and peripheral facial palsy [2]. Immunosuppressive regimens including chemotherapy, high dose corticosteroids, Anti thymocyte globulin, intrathecal Methotrexate, Cyclosporine have been tried to attenuate HS [2,9]. However, these are palliative and syndrome is inevitably fatal unless bone marrow transplantation (BMT) is undertaken [1,3,6,9]. GS1 develop early, severe and progressive primary neurological impairment and consist of hypotonia, loss of coordinated motor movements, retarded psychomotor development. Neurological involvement in GS2 is secondary to lymphohistiocytic infiltration [3,5]. Neuroradiology reveals cerebral hyperdense areas, ventricular dilation, white matter changes and periventricular calcifications in GS2 and isolated congenital cerebellar atrophy in GS1 [3]. Differential diagnosis of GS includes Chediak-Higashi syndrome (CHS), Elejalde syndrome (ES) [5,7,10]. Giant organelle inclusions in leukocytes are particular abnormality in CHS, differentiating it from GS. ES (Neuroectodermal melanolysosomal disease) is characterized by silvery hair, pigment defects, neurological dysfunction, ocular defects but without immunological abnormalities. Some authors believe ES is clinically and genetically equivalent to GS1 or its allelic variant [7,10].

No specific treatment can be proposed for GS1 and survival depends on severity of neurological impairment. GS3 does not need treatment. Gene therapy may prove to be an excellent tool but needs validation [6]. Prenatal diagnosis has been accomplished by examination of fetal scalp hair [4]. Mutation detection and sequencing candidate gene is paramount to understand spectrum of GS and formulate approach to adopt effective treatment. Knowledge about RAB27A-MLPH-MYO5A tripartite complex can be translated into possible therapeutic applications to reduce (hyper) pigmentation of skin and comprehend vesicular trafficking [8].

## 4. Conclusion

Concluding, all infants with silvery-gray hair should be evaluated early. GS should be promptly diagnosed to allow for early BMT, the only curative modality. Health program directed at perinatal diagnosis can be proposed for effective management [6].

## 5. Contributors

LD and AL diagnosed and managed this patient. AL reviewed literature and prepared manuscript draft. LD approved the draft. AL will act as guarantor.

**Funding:** None

**Conflict of interest:** None stated.

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