Griscelli syndrome: A unique pigmentary defect

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Introduction

Griscelli syndrome (GS) is rare autosomal recessive disorder with pigmentary dilution, immunodeficiency and neurological involvement¹-². We report a child with classical features of GS and pathognomonic histopathological features of skin and hair.

Case report

An 11 month old boy presented with fever, convulsions and refractory shock to emergency. He had a stormy course since birth requiring 4 admissions for recurrent infections. He developed neuroregression at 9 months of age. There was striking hypopigmentation (silvery-gray sheen) of scalp hair and eyebrows (Figure 1).

Examination revealed hepatosplenomegaly (liver 7 cm, spleen 4 cm), mucocutaneous candidiasis, and left supranuclear facial palsy. Laboratory analysis revealed: White blood cells – 800 cells/cu mm, Haemoglobin – 4.7g/dl, Platelet count – 49×10⁹/L, 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 depicted pancytopenia. MRI brain revealed patchy areas of altered signal intensity, focal abnormal enhancement in white matter suggestive of lymphohistiocytic infiltration. Hair examination showed irregular agglomerations of pigment (Figure 2).

Figure 2: Irregular agglomerations of melanin pigment on hair shaft microscopy

In view of pigment dilution, immunodeficiency, typical skin, hair findings and absence of giant granules in neutrophils, the diagnosis of GS was established. He was treated with repeated packed cell transfusions, antibiotics, antifungals, and high dose steroids. Despite initial remission, he developed multi-organ failure and succumbed. Unfortunately, molecular gene analysis was not possible.

Discussion

GS was first described in 1978 by Claude Griscelli and Michel Prunieras¹-³, and since then more than 100 cases have been reported. Clinical onset usually occurs from 4 months to 7 years of age³-⁶. 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\(^6,7\). Genes MYO5A and RAB27A, colocalize on chromosome 15q21 to encode Myosin 5A and RAB27A respectively. MLPH lies on 2q37.3 \(^3,8\). 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-MY05A-MLPH form tripartite complex facilitating vesicular trafficking, intracellular melanosome transport and secretion\(^9\). Each member has a 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 does not 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\(^4,9\). Only MYOVA is expressed in brain and plays a role in secretion of neurotransmitters. This selective tissue expression is the basis for phenotypic differences between subgroups\(^1,2,6,7\).

Single most consistent dermato-skeletal 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\(^6,5\). Skin histopathology and electron microscopy reveal hyper-pigmented basal melanocytes with abundant, stage IV mature melanosomes, poorly pigmented keratinocytes with virtual absence of mature melanosomes\(^1,3\). 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\(^5\). Immunologically impaired natural killer and cytotoxic T cells cause absent delayed hypersensitivity, poor histocompatibility complex mediated cytotoxicity, and hypogammaglobulinemia culminating in immunodeficiency and haemophagocytic syndrome (HS)\(^1,2,6,10\). Usually triggered by viruses, HS occurs commonly between 6-12 months of age\(^5,7\). It involves unremitting polyclonal CD8+ T-cell expansion, lymphohistiocytic infiltration of visceral tissues (spleen, liver, lymph nodes, brain), macrophage activation and proliferation (haemophagocytosis), and deleterious release of cytokines, including interferon γ, interleukins, tumour necrosis factor-α\(^3,6,7\). HS is characterized by prolonged high fever, hepatosplenomegaly, jaundice, pallor, lymphadenopathy, pancytopenia, hypertriglyceridaemia, hypofibrinogenaemia, coagulopathy, intracranial hypertension, seizures, encephalopathy and peripheral facial palsy\(^9\). Immunosuppressive regimens including chemotherapy, high dose corticosteroids, anti thymocyte globulin, intrathecal methotrexate, cyclosporine have been tried to attenuate HS\(^3,9\). However, these are palliative and the syndrome is inevitably fatal unless bone marrow transplantation (BMT) is undertaken\(^3,6,9\). 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\(^1,5\). Neuroradiology reveals cerebral hyperdense areas, ventricular dilation, white matter changes and periventricular calcifications in GS2 and isolated congenital cerebellar atrophy in GS1\(^1\). Differential diagnosis of GS includes Chediak-Higashi syndrome (CHS) and Elejalde syndrome (ES)\(^3,7,10\). 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\(^1,10\).

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\(^9\). Prenatal diagnosis has been accomplished by examination of fetal scalp hair\(^9\). 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 hyperpigmentation of skin and comprehend vesicular trafficking\(^8\). 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\(^4\).
References


