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 heterotrimetric 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 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 – 49x10^9/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...
Neuroradiology reveals cerebral hyperdense areas, secondary to lymphohistiocytic infiltration [3,5]. Development. Neurological involvement in GS2 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.

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References


