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Case Report on Griscelli Syndrome with Hemophagocytic Lymphohistiocytosis

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ABSTRACT

Objective: This case report was written with the intention of educating pediatric caregivers regarding the early detection and management of Griscelli Syndrome type 2 (GS2), thereby preventing fatal consequences, and to draw light on the necessity for premarital genetic counselling and education in public.

Case Report: A two months and 7 days old male baby presented with tachycardia, fever, abdominal distension, cough, loose stools, and vomiting. Head to toe examination showed hypo-pigmented hair with silvery grey eyebrows and eyelashes. Bone marrow aspiration showed increased histiocytes exhibiting haemophagocytosis. Suspecting Griscelli Syndrome, genetic test was done which indicated RAB27A gene mutations, thereby confirming the GS2 diagnosis. The child was treated with 2 litres of oxygen with nasal prong, meropenem, fluconazole, dexamethasone and packed red blood cell transfusion. In view of worsening sepsis baby was given with vancomycin, tigecycline and cyclosporine and later intubated.

Conclusion: Consanguineous marriages are common in India and are one of the major reasons for autosomal recessive disorders like GS2 in newborns. This highlights the need of both premarital genetic counseling and education among public.

Keywords: Hypopigmented hair, haemophagocytosis, abdominal distension, RAB27A mutation

INTRODUCTION

Griscelli syndrome (GS) is a rare autosomal recessive disorder characterized by pigmentary dilution of the skin and hair, large pigment clumps in hair shafts, aggregation of melanosomes within melanocytes and variable cellular immunodeficiency (1). It was first described by Griscelli in 1978(2). Three types of Griscelli syndrome have been identified: types 1,2 and3. GS- 2 is the most frequent and has the most severe symptoms if left untreated. GS type 2 is caused by a RAB27A gene mutation that affects a melanosome-anchoring complex in melanocytes, altering the release of cytolytic granules from T and natural killer cells. Children with GS-2 have uncontrolled T-lymphocyte and macrophage activation condition called as Hemophagocytic Syndrome (HS) or Hemophagocytic Lymphohistiocytosis (HLH) (1). History of consanguinity is quite prevalent since it has autosomal recessive patterns (each parent carries a defective gene). The disease is usually diagnosed between 4 months and 7 years of age (3).

CASE REPORT

A two months and 7 days old male baby was referred to our hospital in view of tachycardia and abdominal distension. Presenting complaints were fever (for past 15

days gradual in onset and progressive in nature), abdominal distension (2 days), cough (2 days), loose stools (2 days), and vomiting (2 days). Baby had no history of previous hospitalization. Child was not given one and half month immunization. Baby weighed 6 Kg body weight with length of 56 cm which was within normal limit. Head to toe examination indicated hypo-pigmented hair (Figure 1) with silvery grey eyebrows and eyelashes (Figure 2). Abdomen was distended with the 8cm liver span and the spleen was palpable 10 cm below left costal margin. Abdominal girth was found to be 47cm.

Investigations revealed a haemoglobin of 6.7 g/dl, a total leukocyte count of 4610 cells/cumm, thrombocytopenia 0.23 lakhs/cumm, a HCT of 20.1% and CRP of 71.6 mg/dl. Differential count indicated lymphocytes 85% and neutrophils 12%. Urea levels was 39mg/dl, direct bilirubin was 0.6 mg/dl, total protein was 3.2g/dl with albumin 2.3g/dl, globulins 0.9g/dl and GGT 664 U/L, triglycerides 224 mg/dl. HBsAg and antibodies for HIV and HCV, were negative. Blood culture showed no growth. Peripheral smear indicated pancytopenia with no megagranular leucocytes. Bone marrow aspiration was done which showed increased histiocytes exhibiting haemophagocytosis. USG abdomen and pelvis was suggestive of hepatosplenomegaly with no change in echo-texture, mild ascites, bilateral minimal pleural effusion, pancreas and pancreatic area obscured, urinary bladder was minimally distended. Microscopic examination of hair follicle showed small and large clumps of pigments irregularly distributed. Genetic analysis showed bidirectional sequencing and exon 2-6 coding version of RAB27A revealed homozygous mutation in exon 7. WES-Whole Exome Sequencing was performed and homozygous pathogenic variant consistent with phenotype was detected. These observations aligned with those findings seen in Griscelli syndrome.

The child was treated with 2 litres of oxygen with nasal prong, meropenem, fluconazole, dexamethasone and packed red blood cell transfusion initially. Patient's platelet was monitored. In view of worsening sepsis baby was given with vancomycin, tigecycline and cyclosporine. Patients' parents were explained about the disease progression and grave risk, counselled for taking the baby for further reference but they were not willing for the same. Patients abdominal girth was monitored, which was progressively increasing. He was transfused with 1 pint FFP and 2 pint PRBC. Oxygen was gradually tapered and stopped on day 10. On day 15 baby had one episode of bradycardia and desaturation for which he was given CPR with adrenaline. Despite best efforts baby's condition was deteriorating, could not be revived and was declared dead.

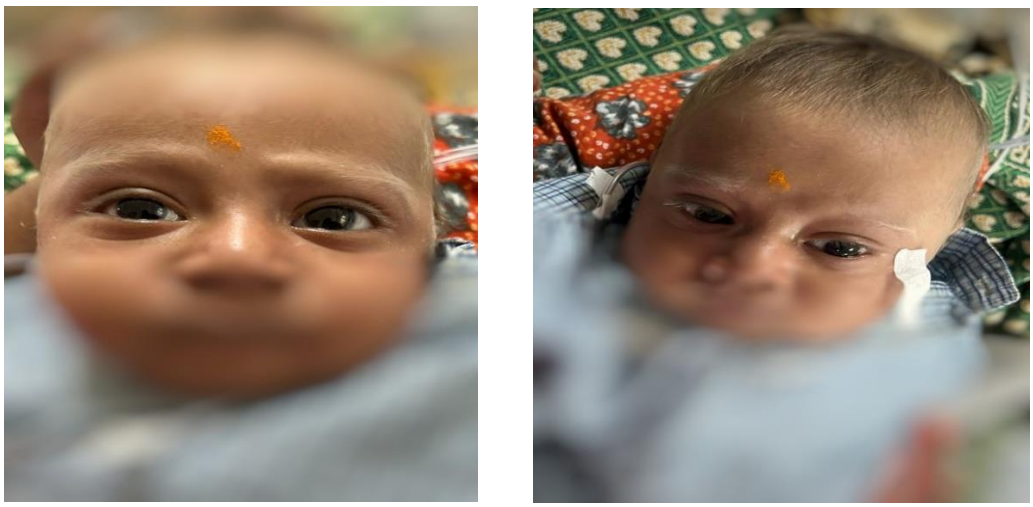

Fig.1and 2: Typical silvery grey hair, eyebrows and eyelashes with hypo-pigmented skin

DISCUSSION

In our case 3 differential diagnosis were considered: Lysosomal storage disorder (LSDs), Chediak Higashi Syndrome and GS-2

The lysosomal storage disorders are a collection of progressive, multisystem disorders that frequently present in childhood (4). They are rare but can lead to death if untreated. Excess substances built up in the cells and can cause a wide range of problems throughout the body, affecting organs including the brain, spleen, liver and muscles. Symptoms vary depending on the type of lysosomal storage disease. One or more of these symptoms may occur like delay in intellectual and physical development, seizures, facial and other bone deformities, joint stiffness and pain, difficulty in breathing, problems with vision and hearing, anemia, nosebleeds, swollen abdomen due to enlarged spleen or liver. Our patient was found to have abdominal distension.

GS or partial albinism can lead to pigmentary dilution of the skin and hair with the presentation of huge clumps of pigment granules in hair shafts that result in silver grey hair along with variable cellular immunodeficiency with or without severe neurological defects which makes it clinically similar to Chediak Higashi Syndrome(6,8)

An important clue to the diagnosis of the Griscelli syndrome is from the histological examination of the hair shaft of the patient(6). Peripheral blood smear of our patient was negative in view of megagranular leucocytes that are seen in Chediak Higashi syndrome. Hair shaft microscopic examination and clinical manifestations of the newborn led to speculation of GS2. In addition, genetic test was performed to confirm Griscelli syndrome type 2.

RAB27A gene mutations was seen, which confirmed GS2(5,8). Patients with this disorder are more likely to acquire infections frequently. Additionally, they develop hemophagocytic lymphohistiocytosis (HLH), an immunological disorder characterized by an excess of activated T-lymphocytes and macrophages (histiocytes) produced by the immune system. If the condition is left untreated, the over activity of these cells could damage organs and tissues throughout the body, leading to fatal consequences (3).

Most GS instances result in mortality during the first decade of life, with a dismal long-term prognosis. Few cases of survival for more than a decade have been reported. Bone marrow or stem cell transplantation provides curative hope, and even then, success rates are higher when the procedure is carried out early in the illness (9).

Palliative management includes treatment of associated infections, and immunomodulatory therapy during accelerated phases (high dose systemic methylprednisolone, etoposide, intrathecal methotrexate, cytosine arabino-side and prednisone, or antithymocyte globulin, cyclosporine and steroids) (9,10).

CONCLUSION

Griscelli syndrome (GS) is a rare autosomal recessive disorder. Consanguineous marriages are common in India and are one of the major reasons for autosomal recessive disorders in newborns. Due to dismal prognosis of GS2, it should be evaluated in pediatric patients presenting with splenomegaly, light colored hair, particularly if their parents are consanguineous couples. The patient was born to a third degree consanguineously married couple. Early detection and supporting treatment are the only measures that can aid in survival. This highlights the need of both premarital genetic counseling and education among public.

Declaration by Authors

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