GRISCELLI SYNDROME: CASE SERIES OF A RARE AND FATAL SYNDROME IN TELANGANA

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PRESENTATION OF CASES

Case 1

A 7-year-old male child was brought by his mother with chief complaints of fever, cough, increasing pallor since 10 days and shortness of breath since 2 days. History of (h/o or H/o) easy fatigue ability, h/o hypopigmentation of hair since birth. No h/o jaundice, abdominal distension, hematemesis, melena, pedal oedema, bleeding from any site. No h/o burning micturition, loss of appetite, significant loss of weight, No h/o contact with tuberculosis. History of similar complaints 6 months back was present. Child was admitted for fever & cough for 4 days and was given antibiotics, blood transfusion. Child was born out of 3rd degree consanguineous marriage. His perinatal & developmental history was normal. His brother aged 9 years was normal.

On general examination, child had hypopigmentation of hair, eyebrows, eye lashes & patchy hyperpigmentation over the face& significant pallor. (Figure 1)

Figure 1. Seven-Year-Old Boy with Griscelli Syndrome Type 2: Bronze Skin, Silvery Hair and Eyelashes

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No icterus, cyanosis, clubbing, lymphadenopathy, pedal oedema, no ocular albinism. All vital parameters were normal. Abdomen was distended, liver 5 cm palpable below right costal margin with a span of 13.5 cm, firm and non-tender. The spleen was palpable 10 cm below left costal margin and was firm inconsistency. His iris and retina had normal pigmentation. Rest of the physical examination was unremarkable.

CLINICAL DIAGNOSIS

Investigations

Revealed a haemoglobin of 6.9 g/dl, total leucocyte count 4500/cu mm, platelet count 2 lakhs and a reticulocyte count of 2%. There were no giant cytoplasm granules in leucocytes. Urine routine examination, CRP, ESR, chest X-ray were normal. Mantoux test was negative. Serum bilirubin was 1.4 mg/dl, total proteins and liver enzymes were normal. PT- 15 seconds (IN R of 1), A PTT-38 seconds, Vitamin B12 levels: 639 pg/ml (211-911 pg/ml), Folic acid levels: 23.3 ng/ml (>5.38 ng/ml) Serum iron: 23 microgm/dl (70-180 ug/dl),

Serum Ferritin- 549 ng/ml (22-322 ug/dl)
Total iron Binding Capacity: 173 microgm/dl (225-535 ug/dl), % transferrin saturation: 13% (13-45 ug/dl)
Total Cholesterol: 82 mg/dl (125-200 mg/dl)
HDL Cholesterol: <15 mg/dl (35-40 mg/dl)
Triglycerides: 499 mg/dl (25-200 mg/dl)
VLDL Cholesterol: 99.8 mg/dl (5-40 g/dl),
TC/HDL Cholesterol: 5.47(3-5),
Non-HDL Cholesterol: 67 mg/dl (<160 mg/dl)
Serum Immunoglobulin G: 16.3 gm/l (reference value: 7.0-16.0) IgM: 2.9 gm/l (0.40-2.30), IgA: 4.2 gm/l (0.7-4.0), Plasma fibrinogen level was normal &D-dimers were negative. HBsAg, &antibodies for HIV & HCV were negative. USG abdomen showed hepatosplenomegaly, distended Gall bladder &oedematous wall.

Dengue serology, malaria and Widal tests were negative blood and urine cultures were negative. Other routine biochemical, pathological and radiological tests were normal, and child was afebrile on 3rd day of IV ceftriaxone. Bone marrow aspiration and biopsy were done, which showed reactive marrow with erythroid hyperplasia,

No evidence of hemophagocytes or marrow aplasia /hypoplasia.

His silvery hair and bronze skin appearance made us suspect this as a case of silvery hair syndrome. Accordingly, we did a hair microscopy that showed large irregular clumps of pigment, irregular melanin granules, and monotonously white hair shaft suggestive of Griscelli syndrome type 2(Figure 2). We re-examined the peripheral blood smear thoroughly, but no inclusions were seen within leucocytes. Other investigations like genetic testing could not be done due to financial constraints.

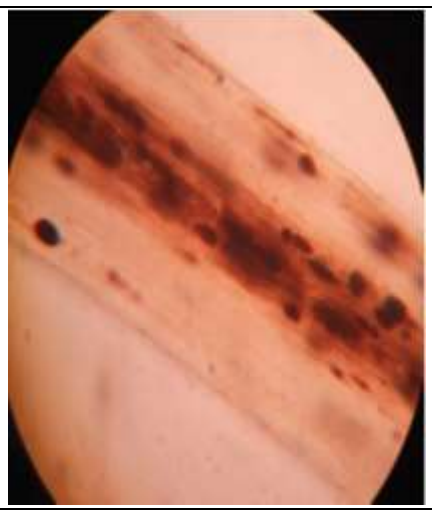


Figure 2. Light Microscopy of Hair Showing Large Melanin Clumps Mostly Near the Medulla of the Hair Shaft (×100)

Child had no developmental delay or neurological problems that rules out ED. Absence of recurrent infections & inclusions in leucocytes rules out CHS. Hence, a diagnosis of Griscelli Syndrome was made based on hair microscopy and presenting features. The child was treated with antibiotics and packed red cell transfusion & was discharged, as the child was thermodynamically stable. He got readmitted after a month with severe anaemia and was given packed red cell transfusions. Now the child is awaiting bone marrow transplantation.

Case 2

A 8 year old female child was brought by her mother with chief complaints of high grade fever, easy fatigue ability since 40 days. H/o melena was noted during hospital stay. No H/o jaundice, abdominal distension, pedal oedema, hematemesis, burning micturition. No H/o significant loss of appetite, loss of weight, No H/o contact with tuberculosis. No similar complaints in the past. Child had history of hypopigmentation of hair since birth. Perinatal history & mile stones were normal.

Child was born out of 2° consanguineous marriage. There was H/o sibling death at 3 years of age, who had silvery hair and seizures since birth.

On Examination

Pallor & hypopigmentation of skin, hair, eyebrows, eyelashes was present, No icterus, cyanosis, clubbing, lymphadenopathy, pedal oedema. Skin pigmentation was normal, no ocular albinism (Fig. 3) Abdomen was distended, liver 5 cm palpable below right costal margin with a span of 10.5 cms, firm and non-tender. The spleen was palpable 4 cm below left costal margin and was firm in consistency. Other systems examination was normal.

Investigations

Showed anaemia & leucopenia initially, haemoglobin improved after two transfusions, no granules were there in peripheral smear. Other fever work-up was normal. LFT showed bilirubin of 2.4 mg/dl, enzyme levels were normal. ANA Levels & dsDNA levels were normal. Serum ferritin & triglyceride levels were elevated with serum hypofibrinogenemia was noted for this case. Bone marrow aspiration showed reversal of myeloid to erythroid ratio &reactive marrow with erythroid hyperplasia. USG abdomen showed splenomegaly & oedematous gall bladder wall. Skin biopsy revealed irregular melanin clumps.

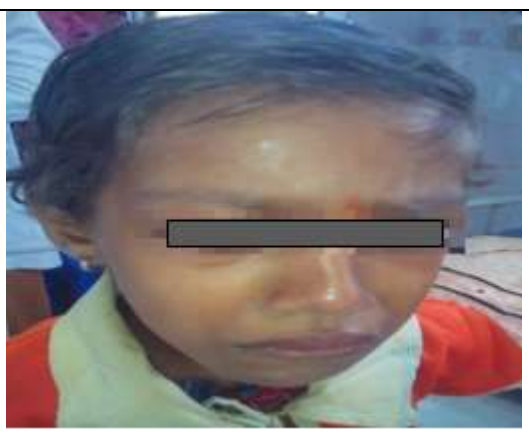


Figure 3. Eight Years Old Child with Griscelli Syndrome 2 with Silvery Hair & Eyebrows

Case 3

14-month-old male child born to 2nd degree consanguineous parents brought with chief complaints of fever since 2 weeks, cold and cough 2 weeks, pedal oedema 4 days. Fever gradual in onset, low grade, intermittent, subsided with medication, not associated with chills and rigor. No h/o noisy breathing, cyanosis, SOB, sweating over forehead. Pedal oedema since 4 days: gradual in onset, pitting in nature, started from lower limbs, progressed to generalised anasarca in a span of 8 to 10 days. Child developed ear discharge for 4 days. In the past, child had skin infection at 8 months of age, vesicular lesions all over the body, associated with (a/w) fever, cold, cough. Child was admitted and discharged after 2 days of hospital stay, no contact with tuberculosis, no past h/o seizures, no past h/o blood transfusions. Antenatal, perinatal history was normal, child was developmentally normal. There is history of elder sibling death at 2 yrs, due

to recurrent infections and ear discharge. The deceased also had hypo pigmented hair.

On general examination, hypopigmentation of hair & skin, lymphadenopathy, generalized oedema, hypo pigmented patches over the neck, left arm, left elbow, each measuring approximately 7×6 cm, no ocular albinism. (Figure 4)

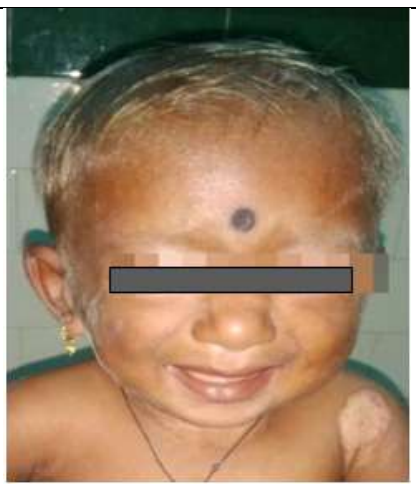


Figure 4. 14 Months Boy with Griscelli Syndrome 2 with Hypo Pigmented Hair, Eyebrows and Skin Over Left Arm. Vitals were Stable. On Examination: Child was Febrile, Hepatomegaly was Present, No Splenomegaly

Investigations

Hb 9.5 gm/dl, WBC: 18200/mm^3, Neutrophils: 35%, lymphocytes: 55%, monocytes: 5%, eosinophils: 2%, Platelets: 5 lakhs/mm3 with normocytic hypochromic RBC. CUE: normal. Pv/ pf & Widal test, dengue serology were negative. Serum electrolytes &renal parameters were normal, CRP-negative, Blood culture- no bacterial growth. Liver function test (LFT) showed TSB: 1.4 mg/Dl, direct bilirubin: 0.7 mg/dl, Indirect bilirubin 0.7 mg/dl, Total protein: 8 mg/dl, Albumin 5 mg/dl, globulin 3 mg/dl.

HIV: NR, Mantoux test: negative. Gastric aspirate for AFB negative, HBsAg was negative. Anti HAV-negative. PT: 15 secs, APTT: 32 secs, INR: 1, plasma fibrinogen levels: 260 mg/dl, vit B12: 639 pg/ml, folic acid levels: 23.3 ng/ml, serum iron: 23 ug/dl, serum ferritin: 19 ng/ml, total iron binding capacity: 173 ug/dl, % transferrin saturation: 13%, total cholesterol: 132 mg/dl, HDL cholesterol: 23 mg/dl, triglycerides: 482 mg/dl, VLDL cholesterol: 96 mg/dl, LDL cholesterol: 54 mg/dl, TC/HDL: 5.7, non HDL cholesterol 108 mg/dl, thyroid profile normal, immunoglobulin g: 110 mg/dl, IgM: <5mg/dl, IgA: <10 mg/dl, IgE: <1.5 IU/ml, CD3+: 89%, CD4+: 23%, CD8+: 61%, CD19: 0%, CD16 AND 56: 16%. USG abdomen showed mild hepatomegaly, no splenomegaly. On hair shaft microscopic examination there is pigment dilution, coarse irregular clumps of melanin.

Case 4

A 2.5-year-old male child born to 3rd degree consanguineous parents brought with chief complaints of fever since 20 days, cold and cough since 10 days. On examination: pallor, icterus, grey hair present, hypopigmentation of the skin present with hepatosplenomegaly. (Figure 5)

Figure 5. Showing Hypopigmentation of Skin & Hepatosplenomegaly in a 2.5 years Old Boy with Griscelli Syndrome 2

Investigations

CBP: Hb 6.4 gm/dl, TLC: 14000/mm3, platelets: 48000, retic count: 1%, serum ferritin: 1000 ng/dl, serum triglycerides: 584 mg/dl, serum fibrinogen levels: 120 mg/dl, bone marrow biopsy: reactive marrow with erythroid hyperplasia, hair microscopy: irregular melanin clumps.

Case 5

A 3 months old female baby was brought by parents with complaints of black coloured stools since 1 week, fever, cough & cold since 3 days. Child is 3rd born out of 3rd degree consanguineous marriage. Child had history of two sibling deaths at 5 months & 9 months of age respectively, both of them had light hair & recurrent infections.

On Examination

The child had pallor, light hair, very light pigmented eyebrows eyelashes (fig. 6) and hepatosplenomegaly.

Figure 6. 3 Months Girl with Hypopigmented Hair, Eyebrows & Eyelashes

Investigations

Hb: 6.5 g/dl, WBC count: 9430, platelets: 1.06 lakhs, serum ferritin: 212, serum triglycerides 287. Hair microscopy confirmed Griscelli syndrome with large clumps of pigments all over the hair shaft.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/sex	**7 y/male**	**8 y/female**	**14 months/male**	**2.5 y/male**	**3 months/male**
Clinical Presentation	Fever cough	Fever Easy fatigability H/o melena	Fever Cough Pedal oedema	Fever Cough cold	Malena Fever, Cough, cold
Findings	Silvery hair & eyelashes Pallor Hepatosplenomegaly	Hypopigmentation of skin/hair/ eye brows Pallor hepatosplenomegaly	Hypopigmentation of skin/hair/eye brows hepatosplenomegaly	Hypopigmentation of skin/hair Pallor icterus hepatosplenomegaly	Pallor Light grey hair hepatosplenomegaly
Family History	Non-consanguinity Sibling, 9 yrs. boy-Normal	H/o consanguinity+ H/o sibling death at 3 yrs. of age, who has silvery hair &seizures at birth	H/o consanguinity+ H/o sibling death at 2 yrs. of age due to recurrent seizures, who also has silvery hair.	H/o consanguinity+	H/o consanguinity+ H/o sibling death at 5 months/9 months of age respectively, both of them also has silvery hair.
Investigations	Anaemia, Hyperferritinemia Hypertriglyceridemia Reactive bone marrow with haemophagocytosis	Bicytopenia Hyperferritinemia Hypertriglyceridemia hypofibrinogenemia Reactive bone marrow with erythroid hyperplasia	Hypertriglyceridemia hyperfibrinogenaemia	Bicytopenia Hyperferritinemia Hypertriglyceridemia hypofibrinogenemia Reactive bone marrow with erythroid hyperplasia	Bicytopenia, Hyperferritinemia Hypertriglyceridemia
Skin/Hair Shaft Microscopy	Irregular clumps of melanin granules in hair shaft	Skin biopsy shows irregular clumps of melanin granules.	Hair shaft biopsy shows pigment dilution, coarse irregular clumps of melanin granules.	Irregular clumps of melanin granules in hair shaft	Irregular clumps of melanin granules in hair shaft

Table 1. Showing Summary of All the Five Cases of Griscelli Syndrome

DIFFERENTIAL DIAGNOSIS

Chediak Higashi Syndrome [1]

PATHOLOGICAL DISCUSSION

Syndrome	Gene	Chromosome	Partial Albinism	Neurological Manifestations	Immunodeficiency
GS1	Myosin-VaGene (MYO5A)	15q21	Present	YES	NO
GS2	RAB27A	15q21.1	Present	Usually No	YES
GS3	MLPH	2q37	Present	YES	NO

Table 2. Genetic Abnormality and Clinical Presentation in the Three Types of GS

The genetic abnormality and clinical presentation of the three types of GS are summarized in Table 1.

Three genetic forms of GS are known. Pigmentary dilution involving skin and hair is common to all three types. GS Type 1 is caused by mutations in the gene encoding the molecular motor protein Myosin Va (MyoVa) on chromosome 15q21.1.[2] It is associated with severe neurological impairment in the form of developmental delay, mental retardation, hypotonia, quadriplegia, seizures.

GS Type 2 is associated with immunodeficiency and is caused by mutations in GTPase Rab27a on 15q21.1. Like CHS, these children can also progress to an accelerated phase of hemophagocytosis.[3]

GS Type 3is caused by mutations in the gene that encodes melanophilin (MLPH), and its expression is restricted to hypopigmentation.[4-7] MYO5A F-exon deletion has also been reported to cause a similar expression as MLPH. Rab27a, Mlph, and MyoVa are proteins involved in the movement of melanosomes.[5-9] Prognosis and treatment vary among the different groups. Presence of neurological or immunological impairments carries a poor prognosis.

There is no treatment for GS Type 1 apart from palliative care. Bone marrow transplantation may be the only curative option in GS Type 2. GS3 has a good prognosis, and no treatment is required.[9,10]

The diagnosis of GS is based on the characteristic clinical features and the typical findings in skin and hair microscopy. However, light microscopy examination of the scalp hair is an easy way to differentiate GS & CHS (table 2).

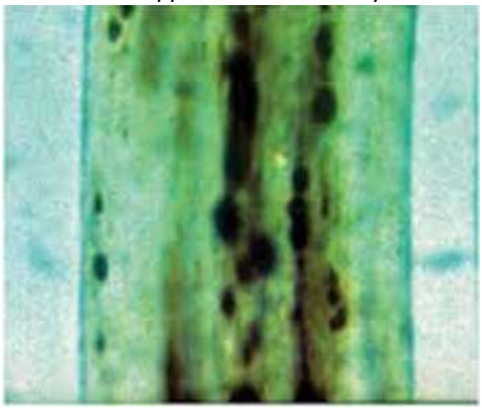
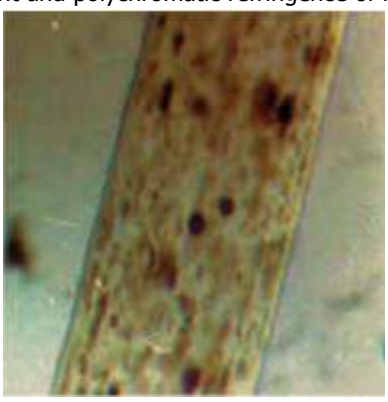
	Griscelli Syndrome	Chediak-Higashi Syndrome
Peripheral Blood Smear	No granules	Prominent intracellular granules
Light Microscopy of Hair	Small and large clumps of melanin in irregular pattern	Small clumps of regularly arranged melanin
Polarised Microscopy of Hair	Hair shaft appears monotonously white  ***Figure 7. GPS: Hair Light Microscopy (x100)***	Bright and polychromatic refringence of hair  ***Figure 8. CHS: Hair under Light Microscopy (x100)***
Histopathology of Skin	Excess pigmentation of melanocytes at basal layer	Large melanosomes in both melanocytes and keratinocytes
Electron Microscopy of Skin	Mature melanosomes in melanocytes and to some extent in keratinocytes	Large melanosomes in both melanocytes and keratinocytes

Table 3. Differentiating Features Between Griscelli Syndrome & Chediak-Higashi Syndrome

Several reports have described these children with CHS, ED and GS presenting with hyperpigmentation due to tanning after sun exposure[11-14] Light microscopy of skin and hair and peripheral blood smear examination is an easy method to differentiate among these silvery hair syndromes. Molecular methods help to characterize the genetic defect and correlate between phenotype and genotype.

In our series of 5 cases of GS type 2 with HLH, children presented with all the classical features of silvery hair, anaemia, hepatosplenomegaly& elevated levels of serum ferritin and triglycerides. We confirmed our diagnosis with the support of skin/hair shaft biopsy, which revealed irregular clumps of melanin granules unfortunately, genetic analysis could not be done for these cases, due to financial constraints.

The three main groups of "silvery hair syndromes" are GS, CHS and ED. CHS is due to mutation in the gene regulating lysosomal trafficking CHS1/LYST, on chromosome 1q42-43. Giant granules in all granule containing cells are the hallmark of CHS. It is characterized by the pigmentary dilution, silvery hair, bleeding tendency and progressive neurological defects. Immune dysregulation leads to recurrent infections and the fatal complication of hemophagocytic syndrome that is characterized by fever, pancytopenia, hepatosplenomegaly, and lymphohistiocytic infiltration of various organs.[14-20]

Declaration of Patient

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient parents have given their consent for his/her images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgment

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