Griscelli syndrome

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- 8 yr old female child ,born of NCM

  c/o

  fever

  abdominal distension for 45 days.

- h/o tanning on exposure to sunlight present

- h/o easy fatigability present

- Past history: uneventful.
- Antenatal, birth history: uneventful
- Development hihory(N)
- Family histotory: not contributory
- No h/o contact with TB

On examination

Conscious

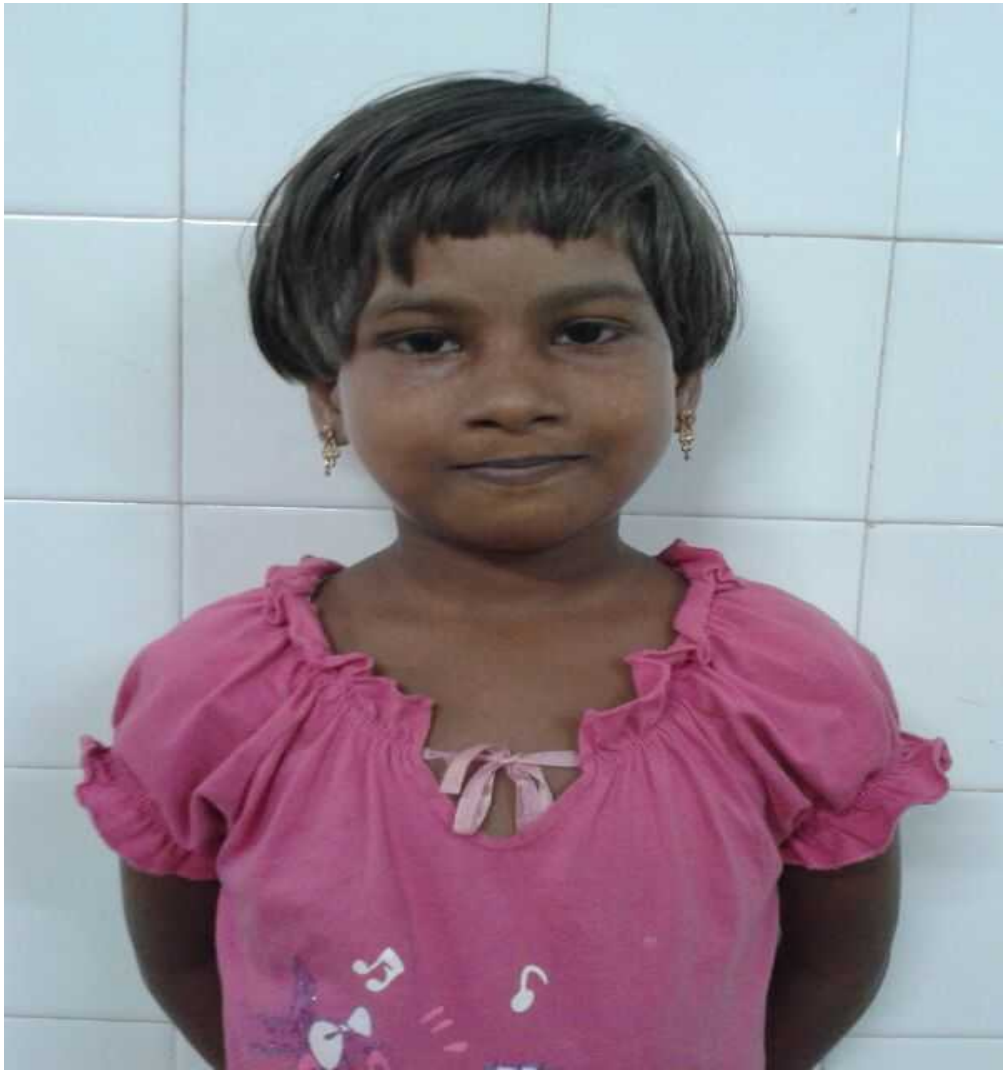
febrile

Pallor(+)

Silvery grey hair

diffuse hypopigmented macules seen throughout the body.

anthropometry-normal



Systemic examination

- CVS,RS,CNS: normal

- P/A: Liver 5 cm below RCM ,firm
  span 12 cm

  Spleen 6 cm below LCM.
  No free fluid

Lab investigation

- CBC : Pancyotopenie with normal DC

- RFT: (N)
- LFT:(N)

- Smear Mp-negative,Widal,MSAT-negative
- Urine c/s:No growth

- chest X-ray-Right paracardiac haziness
- Mantoux –negative, Sputum Afb-negative

Treatment

- Broad spectrum antibiotics(inj.ceftriaxone)
- chloroquine
- Culture sensitive antibiotics based on blood c/s report-cons growth
- Child responded symptomatically and was discharged after 20 days and was advised to follow up.

- The next week the child got admitted with fever
- Child was admitted repeatedly with fever episodes (3 episodes)
- CBC, PS study : pancytopenia
- relative lymphocytosis
- atypical lymphocytes

- In view of repeated fever episodes with persisting hepatospleenomegaly

Immunodeficiency suspected-

Ig asssay -IgA-179mg%(35-200),

IgM-128mg%(50-250),

IgG-1200mg%(700-1600)

Retroviral screening-negative

- As we suspected HLH with clinical features(fever, spleenomegaly,pancyopenia)
-

  lipid profile TGL-174mg/dl(<180)
  T.Cholesterol-128mg/dl(up to200)
  LDL-43mg/dl(100-190),
  HDL-35mg/dl (30-60)

- Ferritn 118(10-291)
- Fibrinogen-198(190-490)
- Bone marrow Examination: inconclusive(tiny fragments of marrow seen,blast<2%,M:E 2:1), no evidence of hemophagocytosis

- Based on grey hair and the clinical features suggestive of HLH, few syndromes were analysed

  Chediak Higashi syndrome(oculo cuteneos albunism, recurrent pyogenic infection)

  Hermansky Pudlak syndrome(oculo cutaneous albunism with bleeding disorder)

  tyrosinemia

  griscelli syndrome (partial albunism , immunodeficiency, HLH, neurological involvement)

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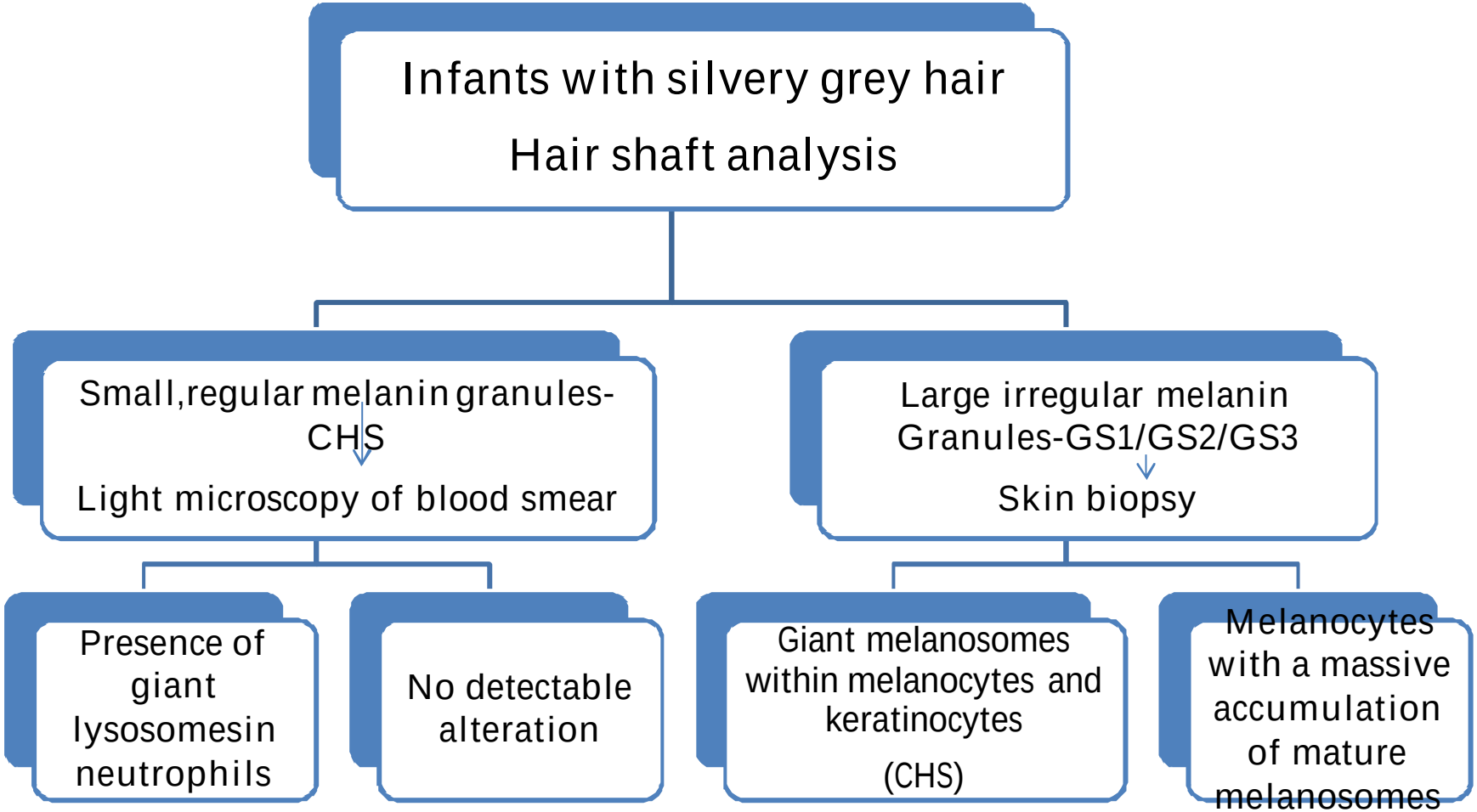
Infants with silvery grey hair
Hair shaft analysis
Small,regular melanin granules-CHS
Light microscopy of blood smear
Large irregular melanin Granules-GS1/GS2/GS3
Skin biopsy
Presence of giant lysosomesin neutrophils
No detectable alteration
Giant melanosomes within melanocytes and keratinocytes
(CHS)
Melanocytes with a massive accumulation of mature melanosomes

Hair shaft analysis: inconclusive(tygroid patter with hair shaft defect)

Skin biopsy normal

PS study: no giant cytoplasmic granules in leukocytes

Genetic analysis was sent

- Genetic analysis concluded it to be a case of Griscelli syndrome type 2.

Mutation analysis of the RAB27A gene

- Patient: homozygous for the mutation c.550C>T p.R184X
- Father: heterozygous for the mutation c.550C>T p.R184X
- Mother: heterozygous for the mutation c.550C>T p.R184X
- Asymptomatic sister: absence of familial mutation c.550C>T p.R184X

Aieop

ITT Istituto Toscano Tumori

Società Italiana di **Pediatria**

Familial Hemophagocytic Lymphohistiocytosis (FHL) Registry

Firenze 13.03.2014

Referring center	Apollo Specialty Hospital, Chennai, India
Referring physician	Dr. Revathi Raji, revaraj@yahoo.com
Patient	**LATHIKA S., female, born on 8.11.2006**, UPN 953
Clinical indication	Clinical diagnosis of HLH (criteria 4/7), suspected pigment deficiency syndrome; no parental consanguinity, no family history

Dear Colleague,

we have now completed the genetic study of the DNA of your patient **LATHIKA S, born on 8.11.2006,** who was clinically diagnosed with HLH and suspected pigment deficiency syndrome, based on grey hair and the clinical features of hemophagocytic lymphohistiocytosis (HLH), and thus referred to the "International Registry for HLH" (UPN 953) for the genetic study.

Mutation analysis of the RAB27A gene gave the following results:

- **LATHIKA S. (patient): homozygous for the mutation c.550C>T p.R184X**
- **LATHIKA Silambarasan (father): heterozygous for the mutation c.550C>T p.R184X**
- **LATHIKA Ammmu (mother): heterozygous for the mutation c.550C>T p.R184X**
- **LATHIKA Aishwarya (asymptomatic sister): absence of the familial mutation c.550C>T p.R184X**

In conclusion: the patients carries a damaging mutation of the RAB27A gene at the homozygous state. The same mutation was also identified in both parents at the heterozygous state. This finding could be compatible with potential consanguinity of the parents which yet was not reported.

Thus we can confirm the diagnosis of **Griscelli Syndrome type 2 (OMIM 607624)**.

The identification of the familial marker allows us to perform an enlarged familial study for identification of the carriers or prenatal diagnosis upon request.

Best regards,

- Steroids (inj.Dexamethasone 8mg iv od then tapered over next 2 weeks and stopped)
- Cyclosporin 25 mg 1 bd
- impovement in cell count and resolution of hepatospleenomegaly

Griscelli syndrome

Autosomal recessive disorder

Type-1

- mutation in MYO5A gene- severe primary neurological impairment such as developmental delay and MR,
- no cure

Type 2

- Mutation In RAB27A gene associated with primary immunodeficiency (HLH),
- BMT,immunosuppresssive therapy

Type 3

- Type-3 Mutation in MLPH gene Hypo pigmented defect alone-
- no need of treatment

Take Home message

- Common diagnoses are common but rare diagnoses are not always rare !!
- With emerging investigation modalities do not hesitate in sending for rare investigations !
- This was a treatable cause though not completely; child improved with dexamethasone and cyclosporine (resolution of organomegaly at present)

- Had this not been confirmed we would have hesitated to start with immunosuppresants which has improved the child now(bone marrow transplant curative- unfotunately child did not get a matching donor)
- All the features need not be present always!

  1. ferritin – normal

  2.triglycerides- no expected peak

  3.skin biopsy – normal

  4. bone marrow- inconclusive

  5. ps study – no histiocytosis! Only auto agglutination visible

  6.HLH criteria not met fully.

- This case is presented for its rarity as the child was born of ;

  - non consanguineous marriage with astonishing autosomal recessive pattern of the disease in both parents.

  - atypical biochemical parameters and inconclusive results of procedures done.

  -only one genetically confirmed case of griscelli repoted in india as far though quite a number of cases with similar clinical picture reported.

- Thanks to

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  Dr.Pushpa

  Dr. Ekambaranath

  Dr.Venkatesh

  Dr.Sivaganesh

Thank you!!!!