recurrent infections. Similarly, sensorineural hearing loss is described in just three cases till date and has not been shown to be syndromically associated [4]. In the index child it may be attributed to recurrent ear infections. A prominent superficial venous pattern described in around two-third of the patient may not be present in infancy and becomes prominent with age. Non-syndromic presentation of G6PC3 deficiency should thus always be thought of in a child with isolated congenital neutropenia [1].

The genetic diagnosis is important in SCN as phenotypic variability exists; wherein most severe cases may require early bone marrow transplant (BMT), while rest may require G-CSF and infection prophylaxis awaiting a definitive BMT. Chronic G-CSF therapy has been inconsistently reported to be associated with myelodysplastic syndrome/myeloid leukemia and may not correct functional deficiency of neutrophil despite reversing neutropenia to a safer limit [6]. The use of G-CSF without clinical benefit should be avoided.

To conclude, SCN-4 should be considered in differential diagnosis of early onset severe neutropenia and indiscriminate use of G-CSF should be curtailed unless clinically indicated.

Contributors: SK: concept, patient care and manuscript drafting; SuKP, SKP: Patient care and final manuscript drafting.
Funding: None; *Competing interest*: None stated.

SANJEEV KHERA[1]*, SK PRAMANIK[2] AND SK PATNAIK[1]
From [1]Department of Pediatrics and [2]Department of Hematology, Army Hospital Research and Referral, Delhi, India.
**kherakherakhera@gmail.com*

REFERENCES

1. Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: Diagnosis, molecular bases and patient management. Orphanet J Rare Dis. 2011;6:26.
2. Boztug K, Appaswamy G, Ashikov A, Schäffer AA, Salzer U, Diestelhorst J, *et al*. A syndrome with congenital neutropenia and mutations in G6PC3. N Engl J Med. 2009;360:32-43.
3. Xia J, Bolyard AA, Rodger E, Stein S, Aprikyan AA, Dale DC, *et al*. Prevalence of mutations in ELANE, GFI1, HAX1, SBDS, WAS and G6PC3 in patients with severe congenital neutropenia. Br J Haematol. 2009;147:535-42.
4. Banka S, Wynn R, Byers H, Arkwright PD, Newman WG. G6PC3 mutations cause non-syndromic severe congenital neutropenia. Mol Genet Metab. 2013;108:138-41.
5. Banka S, Chervinsky E, Newman WG, Crow YJ, Yeganeh S, Yacobovich J, *et al*. Further delineation of the phenotype of severe congenital neutropenia type 4 due to mutations in G6PC3. Eur J Hum Genet. 2011;19:18-22.
6. Rosenberg PS, Alter BP, Bolyard AA, Bonilla MA, Boxer LA, Cham B, *et al*. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. Blood. 2006; 107:4628-35.

An Untold Tale of Iron Deficiency Anemia

In India the prevalence of Iron deficiency anemia in children (6-59 months) is reported as 56% [1], most common by due to nutritional iron deficiency. Iron refractory iron deficiency anemia (IRIDA) is a rare genetic condition with autosomal recessive inheritance caused by mutation in *TMPRSS6* gene, located on chromosome 22 [2]. Suspicion of IRIDA usually occurs during pediatric age group when a child with iron deficiency anemia does not respond to standard therapy and has some suggestive markers of IRIDA.

The proband, a 9-year-old boy born of a consanguineous marriage, was diagnosed to have iron deficiency anemia at one year of age and treated with various iron preparation with inadequate response. Growth and development was adequate for the age. There was no icterus, bleeding manifestations, lymphadenopathy or hepatosplenomegaly. Blood examination revealed microcytic hypochromic anemia suggestive of iron deficiency anemia. His hemoglobin was 7g/dL; RBC count 5.4 × 10^9 L; mean corpuscular volume (MCV) 52 L, mean corpuscular hemoglobin (MCH), 15 pg/mL; mean corpuscular hemoglobin concentration (MCHC) 25.8%; red cell differential width (RDW) 19.6; serum iron, 1.2 µg/dL; Serum ferritin, 32 ng/mL; total iron binding capacity (TIBC) 352 µg/dL; and transfeerin saturation, 2.7%. Iron deficiency could not be explained from his diet, gastrointestinal losses or other symptoms. He was prescribed standard therapeutic doses of oral iron (6 mg/kg); however, response was not satisfactory (increase in hemoglobin Hb <0.5g in initial 4 weeks) despite adequate compliance. Further investigations revealed normal hemoglobin electro-phoresis and stool occult blood was tested negative. His younger brother was also detected to have anemia at 9 months of age and was on iron preparation with inadequate response.

Presently he is four years and clinical features and evaluation is suggestive of iron deficiency anemia. He was also started on oral iron preparation (6 mg/kg) but response was unsatisfactory despite adequate compliance (increase in hemoglobin <0.4g initial 4 weeks). In view of third degree consanguinity, similarly affected sibling, poor response to oral iron and no other causes of iron deficiency, we considered the possibility of IRIDA for both siblings.

Sequencing of the *TMPRSS6* gene in elder sibling showed a homozygous missense variation in exon 9 (chr22:g.37480810G>A) that resulted in the amino acid substitution of Leucine for Proline at codon 357 (p.Pro357Leu; ENST00000346753.3). However, hepcidin assay could not be done because of lack of availability of standard hepcidin assay.

IRIDA is characterized by microcytic hypochromic anemia with a very low mean corpuscular volume, low transferrin saturation (<5%), no or inadequate response to oral iron, and only a partial response to parenteral iron. In contrast to classic iron deficiency anemia, serum ferritin levels are usually low to normal, RBC count will be normal to high and serum or urinary hepcidin levels are inappropriately high for the degree of anemia [2]. In our case, the phenotype had all this features and laboratory evaluation was suggestive with. The family history of consanguinity and similar phenotype in other siblings were other features pointing to the diagnosis.

IRIDA should be differentiated from acquired iron deficiency anemia and other genetic microcytic anemias. Family history of consanguinity and affected sibling are pointers to hereditary condition. Acquired iron deficiency and IRIDA are rare in neonatal period and microcytosis at birth is suggestive of other genetic conditions like DNMT1 mutations or atransferrinemia. IRIDA can be differentiated from acquired iron deficiency anemia with increase RBC Count and normal/increased serum ferritin.Beta thalassemia carriers have similar picture, but can be differentiated by normal RDW, High RBC Count, slightly elevated iron parameters and elevated Hb A2 more than 3.5%. IRIDA will have a normal to increased hepcidin in contrast to acquired iron deficiency anemia where hepcidin is low. Sideroblastic anemia can also occur in childhood, but usually associated with markers of iron overload.

IRIDA results from germline mutations in *TMPRSS6*, encoding MT-2 [3]. Different mutations have been identified in *TMPRSS6* gene, with mutation analysis in the Indian population also showing mutational heterogeneity with both intronic and exonic mutations [4]. MT-2 is a type II transmembrane serine protease which plays an essential role in downregulating hepcidin expression in liver cells. In iron deficiency hepcidin levels are reduced, whereas in IRIDA, the levels are normal or high [5].

In Indian population,38% of children with refractory anaemia had a mutation in the TMPSS6 gene suggestive of IRIDA, which shows that this condition is grossly under-disgnosed [4]. Most patients of IRIDA will be refractory to oral iron therapy and intravenous iron will be needed for the correction. Initial trial of oral ferrous sulphate along with Vitamin C (30 mg/kg) for 6-8 weeks may l be beneficial in some patients, before intravenous iron treatment [6].

Contributors: LK: diagnosed the case; UCH: management of the case and prepared first draft of the manuscript; SVH: genetic testing, counselling and edited the manuscript.
Funding: None; *Competing interest*: None stated.

LALITHA KAILAS[1], CH UMAIR[1] AND VH SANKAR[2]*
Departments of Pediatrics, [1]Sree Gokulam Medical College and Research Foundation, Venjaramoodu; and [2]SAT Hospital, Government Medical College; Thiruvananthapuram, Kerala, India.
*sankarvh@gmail.com

REFERENCES

1. Bharati S, Pal M, Bharati P. Prevalence of anaemia among 6- to 59-month-old children in India: The latest picture through the NFHS-4. J Biosoc Sci. 2020;52:97-107.
2. Finberg KE. Iron-refractory iron deficiency anemia. Semin Hematol. 2009;46:378-86.
3. Finberg KE, Heeney MM, Campagna DR, Aydinok Y, Pearson HA, Hartman KR. *et al*. Mutations in *TMPRSS6* cause iron-refractory iron deficiency anemia (IRIDA) Nat Genet. 2008;40:569-71.
4. Bhatia P, Singh A, Hegde A, Jain R, Bansal D. Systematic evaluation of paediatric cohort with iron refractory iron deficiency anaemia (IRIDA) phenotype reveals multiple *TMPRSS6* gene variations. Br J Haematol. 2017;177: 311-8.
5. Melis MA, Cau M, Congiu R, Sole G, Barella S, Cao A, *et al*. A mutation in the *TMPRSS6* gene, encoding a transmembrane serine protease that suppresses hepcidin production, in familial iron deficiency anemia refractory to oral iron. Haematologica. 2008;93:1473-9.
6. Cau M, Galanello R, Giagu N, Melis MA. Responsiveness to oral iron and ascorbic acid in a patient with IRIDA. Blood Cells Mol Dis. 2012;48:121-3.