

## IMERSLUND GRASBECK SYNDROME



### Medical Science

**KEYWORDS :** dimorphic anemia, cubulin and amnionless genes, megaloblastic anemia

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### ABSTRACT

*Imerslund Grasbeck syndrome (IGS) is a rare disorder that is inherited autosomally recessive which is characterized by selective malabsorption of Vitamin B12 with asymptomatic proteinuria with no structural renal pathology(1). Usually the affected children are asymptomatic at birth but starts manifesting later in infancy to several years after birth. It is caused due to a defect in the receptor of the vitamin B12-intrinsic factor complex of the ileal enterocyte. Selective malabsorption of Vitamin B12 and proteinuria is due to the mutation in one of two genes, cubilin(CUBN) on chromosome 10 or amnionless (AMN) on chromosome 14.Both these proteins are components of vitamin B12-intrinsic factor complex receptors in ileum and the receptor that mediates tubular reabsorption of protein from the primary urine(2).IGS may also manifest with failure to thrive and grow, infections and neurological damage. We report here a case of a 2 year old female child referred to our hospital as a case of anemia for evaluation for past 6 months in nearby hospitals, finally diagnosed as IMERSLUND GRASBECK SYNDROME after workup. She was treated with vitamin B12 injection 1000 microgram intramuscularly for which the child showed good improvement. IGS should be suspected in any case of anemia with proteinuria not responding to oral vitB12. KEYWORDS - : Imerslund grasbeck syndrome, dimorphic anemia, cubulin and amnionless genes*

### CASE REPORT

A 2 year old female child was referred to our hospital as a case of anemia for evaluation. The child had fever for past 6 months which was low grade and intermittent. Child also had bleeding from gums for the past 2 days. Past history revealed similar episode 1 month back and child had poor appetite noticed by mother since 1 year of age. On examination child was alert, severe pallor present, B/L cervical lymphadenopathy 2\*2 cm, glossitis, angular stomatitis was present. Systemic examination were within normal limits. Investigations showed hemoglobin 3.2 g/dl, total count 9100 cells/cumm, platelet count 70,000 cells/cumm, hematocrit 9.9, mean corpuscular volume 109 fl, mean corpuscular hemoglobin 35 pg, mean corpuscular hemoglobin concentration 32%, red cell distribution width 45.8%, reticulocyte count 2.9%. peripheral smear showed dimorphic anemia with thrombocytopenia and lymphocytosis, total bilirubin 2.3 mg/dl, serum iron 81 ug/dl, serum ferritin 106.1 ng/ml, uric acid 3.8 mg/dl,

lactate dehydrogenase 1955 u/l. urine albumin 1+ was seen and as per hematologist opinion serum B12, folate levels and 24 hour urine protein was also looked which showed serum folic acid >28 ng/ml (normal) & Vit B 12 levels as very low (96.0 pg/ml). 24 hour urine protein was 410 mg suggestive of proteinuria. With these work up the diagnosis of Imerslund Grasbeck syndrome was arrived and child was started on injection vitamin B 12 1000 microgram intramuscular twice weekly for 6 doses then advised 1000 mg intramuscular once in a month for lifetime. Child showed good recovery after parenteral vit B12 on follow up visits.

### DISCUSSION

The Imerslund-Gräsbeck syndrome (IGS) is a rare autosomally recessive inherited disorder which results in vitamin B 12 (cobalamin) deficiency due to selective malabsorption of this vitamin causing megaloblastic anemia. Asymptomatic proteinuria is almost present in all cases. It is also termed as familial selective malabsorption of vit B12 associated with proteinuria. This condition was first described by Imerslund and Grasbeck et al(2). Megaloblastic anemia in children due to the abnormalities of the receptor for IF-Cbl in the ileum presents very rarely(3). Most of

the cases are caused due

to mutations in the cubilin CUBN and amnionless AMN genes, while a few cases are reported due to mutations in the gastric intrinsic factor gene GIF, which cause intrinsic factor deficiency (IFD). Approximately 300 IGS cases have been published worldwide. The estimated prevalence (calculated based on Scandinavian data) is less than 6:1,000,000(4). Misdiagnosis is still the commonest cause of anemia even in developed countries. Macrocytic anemia, decreased serum vit B12 level and proteinuria in absence structural renal pathology are the three typical features of IGS. The symptoms of IGS may not manifest at birth though the condition is congenitally inherited and starts manifesting from infancy. The inability to transport the vit B12 across the intestinal wall is the main pathology which causes IGS. In most cases, the defect in the absorption of vit B12 in intestine and protein in kidneys involves mutation in one or both of the two genes, cubilin on chromosome 10 or amnionless on chromosome 14. Both the proteins are components of the intestinal receptor in ileum for the vit B12-intrinsic factor complex and also in the receptor that mediates the tubular reabsorption of protein from the urine. The diagnosis of IGS can be arrived by detecting the presence of cobalamin deficiency by clinical symptoms, low levels of vitamin B12 by investigations, and exclude other causes of vit B12

malabsorption and to look for the response to parenteral vit B12 which should be good. In IGS there is no deficiency of intrinsic factor or the vitamin B12-intrinsic factor complex. The defect is in the uptake of the complex by the ileal receptors due to the mutations. This can be proved by the classic Schilling's test or the cobalamin absorption tests with radioactive vitamin B12. These tests demonstrate the defect in absorption even on supplementing intrinsic factor(5). Schilling test once considered as the gold standard method for detecting cobalamin absorption, is now outdated because of its reduced availability of test components, cost, radioactive waste disposal and concern about the animal derived tissues for human use (intrinsic factor)(6). The mechanism by which the clinical manifestations like aphthous stomatitis are caused due to vit B12 deficiency is not well estab-

lished. But a relation between neutrophil function & decreased vit B12 levels have been observed(7). This may be the reason for the cause for fever for more than 6 months along with stomatitis in our case. Patients with classical B12 deficiency shows megaloblastic anemia in peripheral smear but severe B12 deficiency cases may even present with pancytopenia and hence , we suspected B12 deficiency in this case even though peripheral smear reports suggested dimorphic anemia.

Regarding treatment issues, IGS is treated with parenteral vitamin B12. The vitamin B12 deficiency is first corrected by giving intramuscular injections of cobalamin and should be continued lifelong. There is enough evidence in literature that subclinical deficiency of cobalamin may contribute to the development of

atherosclerosis, dementia and osteoporosis and also cobalamin is considered as non-toxic. Hence it is suggested that patients should be treated with higher doses of cobalamin than necessary, rather than an insufficient dose. In our case the child showed good improvement after starting parenteral B 12 within few days. The condition is rare, the initial symptoms are vague and in theory, the deficiency may cause serious damage, especially to the brain. Early diagnosis is therefore important to start appropriate treatment. Since this disease is inherited as an autosomal recessive trait and also many Gynaecological studies shows that consanguinity and clustering of the origins of grandparents, genetic counseling is also important in management(8).

#### Acknowledgement

We would like to thank Dr. Kasiviswanath D.M (hematology), Head of the department of pediatric hemato-oncology, and Dr. Annapoorani M.D (paeds), dept of pediatric hemato-oncology, Meenakshi Mission Hospital & Research Centre for their valuable suggestions and guidance.

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