

# Imerslund-Grasbeck Syndrome: A Case Report

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## Introduction

Megaloblastic anemia is an uncommon problem in childhood most frequently associated with vitamin deficiency or gastrointestinal disease. The common causes of megaloblastic anemia are vitamin B12 (cobalamin) deficiency and folic acid deficiency.

Familial selective malabsorption of vitamin B12 associated with proteinuria firstly was described by Imerslund (1960) and Grasbeck et al (1960) (Imerslund-Grasbeck syndrome).<sup>1,2</sup> About 300 patients have been published worldwide, with new patients mostly appearing in eastern Mediterranean countries. However, lots of patients may be misdiagnosed.<sup>3</sup> Imerslund-Grasbeck syndrome (IGS), an autosomal recessive disease, is associated with megaloblastic anemia and proteinuria. The diagnosis should be considered when three typical features (macrocytic anemia, decreased serum B12 level, and proteinuria) are present. Symptoms may appear from the 4th month of age (not immediately after birth as in transcobalamin deficiency) up to several years later. The cause is a defect in the receptor of the vitamin B12-intrinsic factor complex on the ileal enterocytes. In most cases, the molecular basis of the selective malabsorption and proteinuria involves a mutation in one of two genes, cubilin (CUBN) on chromosome 10 or amnionless (AMN) on chromosome 14. Both proteins are components of the intestinal receptor for the vitamin B12- intrinsic factor complex and the receptor mediating the tubular reabsorption of protein from intraglomerular filtrate. Management includes life-long vitamin B12 injections, resulting in a long healthy life. Nevertheless, proteinuria persists. To diagnose the disease, it is important to be aware that cobalamin deficiency affects

enterocyte function; therefore, all tests suggesting general and cobalamin malabsorption should be repeated after resolving the deficiency.<sup>3</sup>

## Case Report

A 6-year-old girl presented with pallor, poor weight gain and constipation. She is the only child of healthy parents who were cousin .

Medical history of patient revealed paleness, weakness, loss of weight, abdominal pain and constipation since 5 month ago .

Physical examination showed mild glossitis and the neurological examination was normal. She revealed no sign of hypotonia or hyperreflexia and her mental status was also normal.

No organomegaly was detected. The patient weight was 14 Kg(<5% of percentile for age). Abdominal ultrasonography was normal. The peripheral blood smear showed hyper segmented neutrophils and macrocytic red blood cells with marked anisocytosis and poikilocytosis. In first CBC; WBC: 3900/ $\mu$ L, RBC: 1.86 $\times$ 10/ $\mu$ L , HB: 6.5g/dl, HCT: 20%; MCV: 106fl , MCH: 34pg , MCHC: 32g/dl, plt: 469 $\times$  , Retic count: 2.8% Coombs direct: negative .

Other patient,s hematological and biochemical Values was: ferritin: 100 ng/ml (normal:160-970 ng/ml) , Serum B12 : 31 pg/ml (normal range:160 -970 pg/ml), Serum folate: 15ng/ml(1.5-16.9), Serum bilirubin: Total; 1.1 Direct; 0.3, Hb electrophoresis: normal.

Result of bone marrow aspiration revealed sever megaloblastic change.No parasite was found on stool examination.

The laboratory values were consistent with vitamin B12 deficiency. the 24-hr urine collection showed an abnormal excretion of protein at 297 mg/

dl and the urinalysis showed 2+ protein .High daily dose of vitamin B12(1000 µgr IM ) administered for patient and the treatment continued with 1000µgr weekly/ IM. The anemia resolved after the vitamin B12 treatment but proteinuria (urine dipstick 1+ protein )was persistent.

## Discussion

Imerslund-Grasbeck syndrome should be considered when the three typical features are present: macrocytic anemia, decreased serum B12 level, and proteinuria.<sup>4</sup> This syndrome is an autosomal recessive disease. Proteinuria often, but not always, accompanies IGS. Proteinuria was neither typically glomerular nor tubular.<sup>5,6</sup> Even in properly treated patients, proteinuria persisted over the years with no deterioration in kidney function . Congenital abnormalities of the urinary tract (double ureters, horseshoe kidney) were found in some patients.<sup>1</sup> The pathogenesis of vitamin B12 malabsorption in this syndrome remains unknown. In one study, the uptake of vitamin B12-intrinsic factor (B12-IF) complex by homogenised ileal biopsy specimens of one patient was normal in vitro. It was therefore postulated that the defect is related to a later stage after the attachment of the B12-IF complex to the surface of ileal cells.<sup>7</sup> In another detailed study of two brothers affected by the syndrome, in vivo uptake of B12-IF complex in the ileum was examined by subcellular fractionation of ileal biopsy specimens.<sup>8</sup> No uptake of vitamin B12 was detected in the ileal tissue.<sup>9</sup> The presence of megaloblastic anemia in children should be followed by investigation for proteinuria, due to the existence of this rare disorder that has a simple diagnosis and an effective treatment.<sup>10</sup> The applied treatment resulted in improvement of the clinical and laboratory findings. Vitamin B12 deficiency as well as IGS is a well-known cause of recurrent aphthous stomatitis, although the mechanism by which this deficiency causes the stomatitis is not well understood.<sup>11</sup> Aphthous stomatitis was not detected in our patients.

## Conclusion

In conclusion, Imerslund-Grasbeck syndrome should be considered when a patient presents with general symptoms together with retarded growth and development, pallor, frequent infections,

anaemia, and proteinuria. This rare disorder has a simple diagnosis and can be treated effectively.

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