CASE REPORT OLGU SUNUMU

A Girl with Imerslund Grasbeck Syndrome: Presentıng with Hypocalcemia

Hipokalsemi ile Prezente Olan İmmeslund Grasbeck Sendromu Tanısı Alan Kız Hasta

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Abstract

Although Imerslund-Gräsbeck syndrome (IGS) is a rare disease, it can also cause rare comorbid clinical conditions. IGS or selective vitamin B12 (cobalamin) malabsorption with proteinuria is a rare autosomal recessive disorder characterized by vitamin B12 deficiency. IGS is caused by mutations in the gene CUBN encoding cubilin or AMN encoding amnionless. Homozygous or compound heterozygous mutations in either CUBN or AMN lead to IGS. Vitamin D deficiency is considered a major public health concern. Inadequate sun exposure, limited oral intake, and impaired intestinal absorption are common risk factors for vitamin D deficiency. Moreover, vitamin D binding receptor protein and 25-OHD urinary extraction are associated with profound vitamin D deficiency, in IGS. Constitutional symptoms, such as weakness and fatigue, are the conditions that may occur in the deficiency of both vitamin B12 and vitamin D. For this reason, we would like to emphasize the importance of monitoring vitamin D levels periodically in patients diagnosed with IGS, as clinical findings may be similar.

Keywords
Imerslund Grasbeck Syndrome, hypocalcemia, megaloblastic anemia

Öz

Imerslund-Gräsbeck sendromu (IGS) nadir görülen bir hastalık olmakla birlikte nadir görülen komorbid klinik durumlara da neden olabilir. IGS veya proteinüri ile birlikte selektif B12 vitamini (kobalamin) malabsorpsiyonu, B12 vitamini eksikliği ile karakterize nadir bir otozomal resesif hastalıktır. Cubulini kodlayan CUBN veya amnionlessi kodlayan AMN genlerinde homozigot ya da kompaund heterozigot mutasyonlar sonucunda oluşur. D vitamini eksikliği majör bir halk sağlığı sorunu olarak sıklıkla karşımıza çıkmaktaıdr. Yetersiz güneş ışığına maruziyet, yetersiz oral alım, intestinal emilimde bozukluk D vitamini eksikliğinin yaygın sebepleridir. Ayrıca IGS'de D vitamini bağlayıcı reseptör proteini ve 25-OHD idrar ekstraksiyonu derin D vitamini eksikliği ile ilişkilidir.Halsizlik, yorgunluk gibi yapısal belirtiler hem B12 vitamin eksikliğinde hem de D vitamini eksikliğinde ortaya çıkabilmektedir. Bu sebeple IGS tanısı alan hastalarda klinik olarak bulgular benzer olabileceğinden aralıklı olarak D vitamini düzeylerinin takibinin yapılması önemini vurgulamak isteriz.

Anahtar kelimeler
İmerslund Grasbeck Sendromu, hipokalsemi, megaloblastik anemi

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Introduction

Imerslund-Gräsbeck syndrome (IGS) or selective vitamin B12 (cobalamin) malabsorption with proteinuria is a rare autosomal recessive disorder characterized by vitamin B12 deficiency (1). IGS is caused by mutations in the gene CUBN encoding cubilin or AMN encoding amnionless. Homozygous or compound heterozygous mutations in either CUBN or AMN lead to IGS (2,3). Vitamin D deficiency is considered a major public health concern. Inadequate sun exposure, limited oral intake, and impaired intestinal absorption are common risk factors for vitamin D deficiency (4). Moreover, vitamin D binding receptor protein and 25-OHD urinary extraction are associated with profound vitamin D deficiency, in IGS. Constitutional symptoms, such as weakness and fatigue, are the conditions that may occur in the deficiency of both vitamin B12 and vitamin D. For this reason, we would like to emphasize the importance of monitoring vitamin D levels periodically in patients diagnosed with IGS, as clinical findings may be similar.

Case Report

An 11-year-old Syrian girl patient who complained of weakness, easy fatigue, numbness in hands and feet, loss of appetite, and hypocalcemia was detected in laboratory parameters. She was referred to the pediatric endocrinology clinic of our hospital. Height: 141cm (-0.5 SDS), weight: 41kg (0.4 SDS) BMI: 20.5 (0.8 SDS). There was consanguinity between the parents. Muscle weakness, cramps, limb paresthesia, Chovestek sign, and Trousseau sign were not detected. The neurologic examination evaluated according to age was normal. Abdominal examination was normal and the liver and spleen were nonpalpable. There was no jaundice, but she was pale.

Laboratory findings showed WBC: 6800/mm3, Hb: 9.8 g/dl, MCV: 116 fl, PLT: 280000/mm3, Calcium (Ca): 5.8mg/dl, Phosphorus (P): 3.1mg/dl, Alkaline Phosphatase (ALP): 360U/L, Magnesium:1.8mg/dl, 25-OH D3: 1.4ng/ml, Lactate Dehydrogenase (LDH): 589U/L, Parathormone (PTH): 406.2pg/ml, ionized Ca:1.1. In a spot urine sample, Calcium/Creatinine ratio was 0.02 and there was proteinuria (+2). In peripheral blood smear; poikilocytosis, anisocytosis, macroovalocytosis, and hypersegmented neutrophils were observed (Figure 1, 2). Iron levels and erythrocyte folate levels were normal. Folic Acid level was 8 ng/ml but Vitamin B12 level was found to be immeasurably low (Table 1).

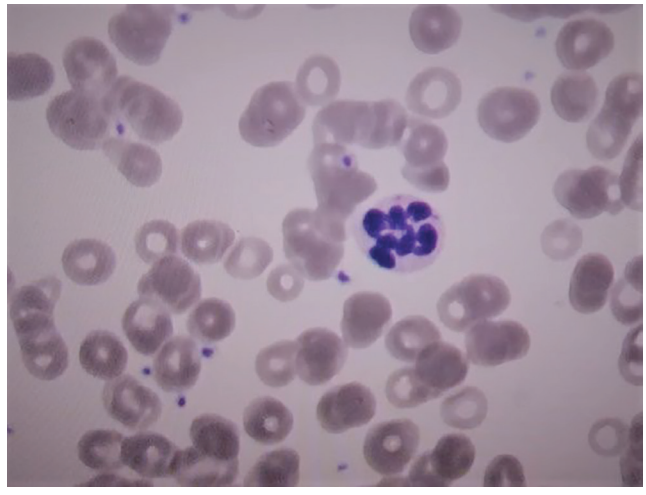

Figure 1. Peripheral Blood Smear - Hypersegmented neutrophil

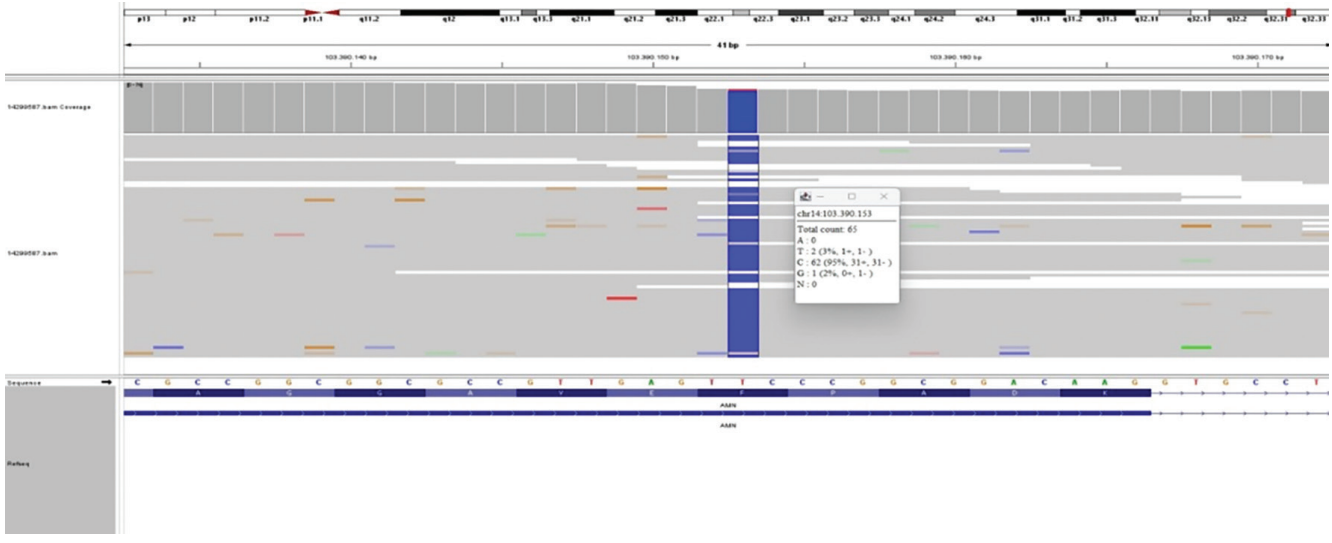

Figure 2. Genetic AMN variant

Tablo 1. The patient's laboratory findings before and after treatment (3 month later)			
Parametre	**Reference range**	**Before treatment**	**After treatment**
Hemoglobin (g/dL)	11.5 – 15.5	9.8	12.8
MCV (fL)	75 – 90	116	83
WBC (/mm³)	5,000 – 14,000	6800	7,200
Platelet (/mm³)	150,000 – 450,000	280,000	280,000
Vitamin B12 (pg/mL)	200 – 900	<83	640
Folat (ng/mL)	3 – 17	<3	9.2
25-OH D3 (ng/mL)	20 – 50	1.4	24
Ca (mg/dL)	8.5 – 10.5	5.8	9.4
Phosphorus (mg/dL)	2.5 – 5.5	3.1	4.3
Ürine protein	Negatif	++	Negatif
PTH (pg/ml)	15-65	406.2	90
ALP U/L	30-120	360	125

The initial differential diagnoses list included hypocalcemia, vitamin D deficiency, vitamin B12 deficiency, megaloblastic anemia and Imerslund-Gräsbeck syndrome (IGS). Megaloblastic anemia, proteinuria, and vitamin B12 deficiency were detected. She is the daughter of a family of Iraqi origin. Because the patient had a consanguineous marriage between the parents and described a diet rich in vitamin B12, IGS was primarily suspected and genetic testing was performed.

Intravenous Ca was given immediately as 1cc/kg and then oral Ca and vitamin D 6000 Ü/ day treatment was started. The first administration of cyanocobalamin (1000 mcg/day) IM for three consecutive days was given, and the maintenance dose consisted of 1000 mcg a week for one month (four doses overall), followed by 1000 mcg administered monthly.

Genomic DNA (gDNA) was extracted from peripheral venous blood samples taken from the patient following the manufacturer's protocol using High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany). Clinical Exome Sequencing Libraries were prepared according to the manufacturer's using Human Comprehensive Exome Panel (Twist Bioscience, South San Francisco). Following the target process, libraries were sequenced on the DNBSEQ-G400 (MGI Tech, China) at 80-100X on-target depth with 150 bp paired-end. Alignment to GRCh38 was done using BWA-MEM 0.7.17 (5). GenomizeSeq (Version 6.13.1) software was used for analysis with the reference human genome (GRCh38). Variants of interest were visually checked on Integrative Genomics Viewer (IGV) (6). The Human Genome Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php), VarSome (https://varsome.com/), and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), novel variants in the databases were checked. Genetic analysis showed a homozygous variant c.149T>C (p.Phe50Ser) in the AMN (NM_030943.4) gene. This change, defined as uncertain significance in the ClinVar database, was not recorded in the public population databases of the Leiden Open Variation Database (LOVD, https://www.lovd.nl) and Genome Aggregation Database (gnomAD, https://gnomad.broadinstitute.org/).

Our case presented with symptoms of vitamin D deficiency and was diagnosed with autosomal recessive hereditary imerslund-gräsbeck syndrome, which is a rare form of vitamin B12 deficiency. The patient 's nutritional history should be taken carefully, and his personal and family history should be questioned in detail. Although our patient had both vitamin D and vitamin B12 deficiencies, there were no specific physical examination findings for these deficiencies.

Discussion

Inherited causes of vitamin B12 malabsorption in children include lack of intrinsic factor, abnormal intrinsic factor, and a deficiency of transcobalamin II (7). IGS is a relatively rare cause of megaloblastic anemia due to the malabsorption of vitamin B12. The clinical and laboratory abnormalities show a significant overlap in IGS and intrinsic factor deficiency (IFD) and are characterized by megaloblastic anemia and low vitamin B12. The presence of asymptomatic proteinuria is specific to IGS. In the past, the Schilling test was used to differentiate between conditions. Currently, genetic testing is

used as the first line of investigation (8). Proteinuria has been described in many IGS cases, although its absence does not exclude the diagnosis (9).

In our patient, the detection of asymptomatic proteinuria in repeated urine analyses was an important clue that led us to the diagnosis. As a result of the genetic test, AMN c.149T>C homozygous pathogenic variant was detected. The CUBN and AMN genes encode two subunits (cubilin and amnionless) of the cobalamin intrinsic factor of the ileal mucosa (10). The cubilin-amnionless complex is called cubam, and is considered to be essential for intestinal cobalamin uptake, renal protein reabsorption and early rodent embryogenesis (11). The Cubam receptor is expressed in the small intestine and proximal renal tubules of the kidney. Low-molecular-weight proteinüria had been previously reported in some IGS patients due to CUBN and AMN gene mutations previously (12). The common feature of these patients is the lack of cubilin cell surface expression, which is caused by both mutation. Also, our patient had vitamin D deficiency and hypocalcemia. But, we could not associate vitamin D deficiency at a level that would cause hypocalcemia with low intake alone. Fyfe et al. (11) demonstrated that the functional cobalamin–intrinsic factor receptor consists of a complex of cubilin and amnionless.

Several IGS cases have been reported from Türkiye, mostly in consanguineous families (3-13,14). Karagüzel et al. (13) described two Turkish children with homozygous CUBN mutations, both presenting with proteinuria and megaloblastic anemia. Similarly, Karagüzel et al. (13) and Aksu et al. (14) emphasized that unexplained megaloblastic anemia accompanied by mild proteinuria should raise suspicion for IGS in the Turkish pediatric population (13,14). Including these regional data underscores the need for awareness in areas where consanguineous marriage is prevalent.

In 2013, Storm reported four Imerslund gräsbeck patients with AMN gene mutation and showed ürinary extraction of albumin, transferrin, VDBP, apoa1, α1M, and RPB proteins. Our observation of vitamin D deficiency in our affected patient is thus consistent with the proposed hypothesis.

From a clinical perspective, hypocalcemia and vitamin D deficiency in our patient highlight the importance of a multidisciplinary approach, involving hematology, endocrinology, and genetics. Patients with IGS should be monitored for metabolic abnormalities beyond cobalamin deficiency. Periodic follow-up of calcium, phosphorus, and vitamin D status is recommended to ensure optimal long-term management.

Conclusion

Our patient demonstrates that Imerslund–Gräsbeck syndrome may coexist with profound vitamin D deficiency, leading to an unusual presentation with hypocalcemia. Clinicians should consider evaluating vitamin D status in patients with IGS to ensure comprehensive management. Reporting such cases is crucial to improve understanding of the phenotypic variability and optimize long-term follow-up strategies.

Footnotes

Conflict of Interest: The authors reported no potential conflict of interest.

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