DOI: https://doi.org/10.22516/25007440.933

Case report

# Imerslund-Gräsbeck Syndrome: Clinical Case

Ledmar Jovanny Vargas-Rodríguez,[1*] Edwar J. Rozo-Ortiz,[2] Camila Andrea Acosta-P.,[3] Javier O. Barón,[4] Mariana Siachoque-Morantes.[5]

OPEN ACCESS

**Citation:**
Vargas-Rodríguez LJ, Rozo-Ortiz EJ, Acosta-P. CA, Barón JO, Siachoque-Morantes M. Imerslund-Gräsbeck Syndrome: Clinical Case. Revista. colomb. Gastroenterol. 2023;38(3):352-354. https://doi.org/10.22516/25007440.933

[1] General practitioner, lecturer, Universidad de Boyacá. Tunja, Colombia.
[2] Internal medicine specialist, internist, Hospital Regional de Chiquinquirá. Chiquinquirá, Colombia.
[3] General practitioner, researcher, Hospital Universitario San Rafael de Tunja. Tunja, Colombia.
[4] Physician, internal medicine specialist, Hospital Universitario San Rafael de Tunja. Tunja, Colombia.
[5] Physician, Universidad de Boyacá. Tunja, Colombia.

***Correspondence:** Ledmar Jovanny Vargas-Rodríguez.
lejovaro@gmail.com

Received: 29/06/2022
Accepted: 07/09/2022

## Abstract

**Introduction:** Imerslund-Gräsbeck syndrome (IGS) is a rare congenital disorder characterized by decreased vitamin $B_{12}$, megaloblastic anemia, and proteinuria. **Clinical case:** A 58-year-old woman with four episodes of generalized tonic movements whose paraclinical findings showed cyanocobalamin deficiency. The presence of gait disturbances and constitutional syndrome was reported upon questioning, which required further investigation. The extension tests confirmed type 1 IGS, so it was decided to continue the cyanocobalamin management and nutrition evaluation, with which an adequate evolution was achieved. The patient was eventually discharged. **Conclusion:** This pathology is low prevalence and mainly affects the first decade of life. It prefers the female sex and is characterized by a decrease in vitamin $B_{12}$, which can predispose to other disorders such as ataxia and growth retardation.

## Keywords

Imerslund-Gräsbeck syndrome, recessive megaloblastic anemia, proteinuria, vitamin $B_{12}$, cobalamin.

## INTRODUCTION

Imerslund-Gräsbeck syndrome is an autosomal recessive inherited disease[1-3] characterized by poor absorption of vitamin $B_{12}$[4]. It manifests with megaloblastic anemia[5] and proteinuria without affecting kidney function since the receptor is identical to cubilin, which also binds to albumin and other proteins; therefore, it participates in the tubular reabsorption of urine proteins[3-6]. This diagnosis should be considered when the three typical characteristics are present: macrocytic anemia, low serum vitamin $B_{12}$ levels, and proteinuria without kidney disease[7-9].

This pathology is caused by a mutation of the cubilin gene (*CUBN*) on chromosome 10 or the amnionless gene (*AMN*) on chromosome 14, provoking a defect in the receptor for the vitamin B12-intrinsic factor complex of the ileal enterocyte[5,10,11]. This manuscript presents the case of a patient with Imerslund-Gräsbeck syndrome.

## CLINICAL CASE

A 58-year-old woman was taken by ambulance to the emergency room due to four episodes of generalized tonic movements of unknown duration accompanied by sphincter relaxation and supraversion without recovery of consciousness in the interictal periods. The crisis was controlled with midazolam 2 mg. Her companion said it was the first time she had exhibited such symptoms; however, he

deemed it relevant to report that the patient had lost 10 kg in the last month. Within the history, he commented that she had a diagnosis of depression and atypical Parkinson's disease (MSA type) under management with quetiapine, escitalopram, levodopa, carbidopa, and clonazepam (completed one week before the picture).

On physical examination, she had normal vital signs. She was alert, oriented, and cooperative, with euthymia, bradypsychia, and bradylalia without death or delusional ideas, no alteration of cranial nerves, independent gait with a severe alteration of balance, and ataxic gait with limitation in the range of movements of large joints in the limbs associated with counting coins at rest. Paraclinical tests were performed, which turned out normal. So, given these findings, it was suspected that the patient was having a first seizure episode secondary to benzodiazepine withdrawal. However, cyanocobalamin deficiency, gait alterations, and constitutional syndrome drew our attention, requiring further studies.

Extension tests included a gastroduodenoscopy that reported chronic atrophic pangastritis without *Helicobacter pylori*, a colonoscopy within normal limits, and a negative fecal occult blood test. The genetic study of individual exome sequencing reported an alteration of the *CUBN* gene, compatible with Imerslund-Gräsbeck syndrome type 1; thus, it was decided to continue management with cyanocobalamin and assessment by nutrition, achieving an adequate evolution. The patient was eventually discharged.

## DISCUSSION

Imerslund-Gräsbeck syndrome, also known as *juvenile megaloblastic anemia* or *hereditary megaloblastic anemia*, is a syndrome whose representative characteristic is a vitamin $B_{12}$ deficiency, along with megaloblastic anemia and proteinuria[12]. This disease occurs more frequently in Europe, with an incidence of five per million people in Scandinavian countries[13].

The clinical picture is characterized by vitamin B12 deficiency, megaloblastic anemia, and proteinuria without renal involvement secondary to this deficiency. Signs such as palpitations, sweating, dizziness, and slow-onset heart failure may also be found[13], and some may present with anatomical anomalies of the urinary tract, neurological manifestations, and growth retardation[14]. Digestive disorders include anorexia, diarrhea, angular stomatitis, and a smooth, intense red depapillated tongue painful to the touch called *Hunter's glossitis*[9].

For diagnosis, tests such as serum vitamin $B_{12}$[1] levels, which will be decreased and are associated with macrocytic anemia, are performed initially and as a guide. Meanwhile, the level of anti-intrinsic factor antibodies, anti-parietal cell antibodies, and gastrin levels could be evaluated[1]. However, the genetic study confirms the diagnosis of this pathological entity[13,14].

Treatment involves supplementation therapy with vitamin $B_{12}$. Its doses are adjusted, according to the patient: In children, it starts with 1 mg/day for 3 days and then once a month, while in adults, a daily dose of 1 mg is administered intramuscularly for a week, followed by injections administered weekly for 4 weeks, and then for a month. If administered orally, the recommended dose is 1 to 2 mg daily[15-17].

## CONCLUSION

This pathology is of low prevalence and is most frequently identified early (under 10); however, some patients can reach advanced ages. The characteristic triad of these patients is vitamin $B_{12}$ deficiency with macrocytic anemia, neurological symptoms in older patients, and proteinuria without renal involvement, which requires prior suspicion and confirmation through a genetic study. Management is based on supplementation with cyanocobalamin.

## REFERENCES


1. Huemer M, Baumgartner MR. The clinical presentation of cobalamin-related disorders: From acquired deficiencies to inborn errors of absorption and intracellular pathways. J Inherit Metab Dis. 2019;42(4):686-705. https://doi.org/10.1002/jimd.12012
2. Udagawa T, Harita Y, Miura K, Mitsui J, Ode KL, Morishita S, et al. Amnionless-mediated glycosylation is crucial for cell surface targeting of cubilin in renal and intestinal cells. Sci Rep. 2018;8(1):2351. https://doi.org/10.1038/s41598-018-20731-4
3. Kozyraki R, Cases O. Vitamin B12 absorption: mammalian physiology and acquired and inherited disorders. Biochimie. 2013;95(5):1002-7. https://doi.org/10.1016/j.biochi.2012.11.004
4. Storm T, Zeitz C, Cases O, Amsellem S, Verroust PJ, Madsen M, et al. Detailed investigations of proximal tubular function in Imerslund-Gräsbeck syndrome. BMC Med Genet. 2013;14(1):111. https://doi.org/10.1186/1471-2350-14-111
5. Tanner SM, Sturm AC, Baack EC, Liyanarachchi S, de la Chapelle A. Inherited cobalamin malabsorption. Mutations in three genes reveal functional and ethnic patterns. Orphanet J Rare Dis. 2012;7:56. https://doi.org/10.1186/1750-1172-7-56

6. Watkins D, Rosenblatt DS. Inborn errors of cobalamin absorption and metabolism. Am J Med Genet C Semin Med Genet. 2011;157C(1):33-44. https://doi.org/10.1002/ajmg.c.30288
7. Gräsbeck R. Hooked to vitamin B12 since 1955: a historical perspective. Biochimie. 2013;95(5):970-5. https://doi.org/10.1016/j.biochi.2012.12.007
8. Beech CM, Liyanarachchi S, Shah NP, Sturm AC, Sadiq MF, de la Chapelle A, et al. Ancient founder mutation is responsible for Imerslund-Gräsbeck Syndrome among diverse ethnicities. Orphanet J Rare Dis. 2011;6:74. https://doi.org/10.1186/1750-1172-6-74
9. Scully C, Langdon J, Evans J. Marathon of eponyms: 9 Imerslund-Grasbeck syndrome (Juvenile pernicious anaemia). Oral Dis. 2010;16(2):219-20. https://doi.org/10.1111/j.1601-0825.2009.01541.x
10. Fyfe JC, Madsen M, Højrup P, Christensen EI, Tanner SM, de la Chapelle A, et al. The functional cobalamin (vitamin B12)-intrinsic factor receptor is a novel complex of cubilin and amnionless. Blood. 2004;103(5):1573-9. https://doi.org/10.1182/blood-2003-08-2852
11. Namour F, Dobrovoljski G, Chery C, Audonnet S, Feillet F, Sperl W, et al. Luminal expression of cubilin is impaired in Imerslund-Grasbeck syndrome with compound AMN mutations in intron 3 and exon 7. Haematologica. 2011;96(11):1715-9. https://doi.org/10.3324/haematol.2011.043984
12. Means RT, Fairfield KM. Causes and pathophysiology of vitamin B12 and folate deficiencies [Internet]. Uptodate.com. [consultado el 19 de junio de 2022]. Disponible en: https://www.uptodate.com/contents/causes-and-pathophysiology-of-vitamin-b12-and-folate-deficiencies?search=Imerslund&source=search_result&selectedTitle=1~1&usage_type=default&display_rank=1#H618258678
13. Elshinawy M, Gao HH, Al-Nabhani DM, Al-Thihli KA. Clinical and molecular characteristics of imerslund-gräsbeck syndrome: First report of a novel Frameshift variant in Exon 11 of AMN gene. Int J Lab Hematol. 2021;43(5):1009-15. https://doi.org/10.1111/ijlh.13473
14. Eslamiyeh H. Acute cerebellar ataxia as the first manifestation of Imerslund-Gräsbeck syndrome. Iran J Child Neurol. 2021;15(4):105-8. http://doi.org/10.22037/ijcn.v15i4.27482
15. Choquet P, Levrat V, Pondarre C, Vianney C, Guffon N. Maladie d'Imerslund-Gräsbeck. Arch Pediatr. 2009;16(12):1559-61. https://doi.org/10.1016/j.arcped.2009.09.010
16. Ganiele M. Suplementación de vitamina b12 en pacientes con déficit crónico. Evid Act Pract Ambul. 2011;14(4):158-9. https://doi.org/10.51987/evidencia.v14i4.6057
17. Vargas Rodríguez LJ, Espitia Lozano N, De la Peña Triana HM, Vargas Vargas JL, Barón Barón JO, Rozo Ortiz EJ, et al. Síndrome de Imerslund-Gränsbeck: revisión sistemática de casos clínicos. CES Med [Internet]. 2022;36(3):26-37. https://dx.doi.org/10.21615/cesmedicina.6781