CASE REPORT

Imerslund-Gräsbeck Syndrome in a Paediatric Patient with Renal Failure and Multisystem Complications: A Case Report

Alia Abdul Rashid[1], Chan Mei Yan[2], Mohamad Ikram Ilias[3], Nor Azni Yahaya[1], Nik Nasiruddin Nik Leh[1]

[1] Department of Paediatrics, Hospital Raja Perempuan Zainab II, 15586 Kota Bharu, Malaysia.
[2] Department of Genetics, Hospital Kuala Lumpur, 50586 Kuala Lumpur, Malaysia.
[3] Department of Paediatrics, Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kota Bharu, Malaysia.

ABSTRACT

Imerslund-Gräsbeck syndrome (IGS) is a rare autosomal recessive disorder that impairs vitamin B12 absorption, often leading to chronic megaloblastic anaemia, proteinuria, and multisystem complications. This report describes a 16-year-old male diagnosed with IGS via whole exome sequencing after a prolonged course complicated by end-stage renal failure requiring dialysis. He also had hypertension, recurrent anaemia, renal bone disorder, hypertensive crises causing posterior reversible encephalopathy syndrome (PRES), cardiopulmonary arrest, epilepsy, intellectual disability, persistent thrombocytopenia, and recurrent infections. Family history revealed early mortality in two siblings due to renal failure. The patient also developed Burkholderia pseudomallei septicaemia and splenic abscesses requiring long-term antibiotics and ultimately succumbed to the infection. While proteinuria is typical in IGS, progressive renal deterioration and end-stage renal failure have not been previously reported, suggesting a potential new comorbidity. This case underscores the complexity of managing IGS with multiple complications and highlights the importance of early genetic diagnosis and multidisciplinary care to improve outcomes.
Malaysian Journal of Medicine and Health Sciences (2026) 22(SUPP2):185-187. doi:10.47836/mjmhs.22.s2.31

Keywords: Imerslund-Gräsbeck Syndrome, Vitamin B12 Deficiency, Proteinuria, Megaloblastic Anemia, Renal Failure

Corresponding Author:
Alia Abdul Rashid, MD
Email: aliarashid1010@yahoo.com
Tel: +6011-26017146

INTRODUCTION

Imerslund-Gräsbeck syndrome (IGS) is a rare autosomal recessive disorder characterised by megaloblastic anaemia due to selective vitamin B12 (cobalamin) malabsorption with asymptomatic proteinuria. Vitamin B12 absorption is low and is not corrected with the administration of intrinsic factor (1).

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 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 (1,5).

The syndrome was first described in Finland and Norway in 1960 (3), where the prevalence is about 1:200,000. Among the patients reported, ethnicity was documented; 22% were Turkish, 15% Finnish, 7% Norwegian, 6% Tunisian, 5% Bedouin and 6% were from the United States of America. All other origins occurred in less than 3%. The parents were also reported to be consanguineous (2). The median age of onset of the symptoms was 2,3 years, while the median age at diagnosis was 7,2 years (2). In 52% of cases, the diagnosis of Imerslund-Gräsbeck syndrome (IGS) was confirmed by genetic analysis, 22% was confirmed by Schilling test, and in 2%, the diagnosis of the patient was suspected due to negative IF antibodies (2).

Proteinuria is commonly reported in Imerslund-Gräsbeck syndrome (IGS), however renal deterioration has not been reported before. Based on a comprehensive review of reported cases, 92% of IGS patients had proteinuria (2). This syndrome also has multisystem manifestations. Management includes lifelong intramuscular injection of vitamin B12.

CASE REPORT

A 16-year-old boy with a disability certificate presented with pallor, poor weight gain, fever and abdominal pain. He is the 10th of 11 siblings from non-consanguineous parents. This case is reported in Kelantan, east coast of Malaysia.

Medical history revealed that he was on serial follow-ups since the age of 7 years old for speech delay with intellectual disability. He presented at the age of 10 years old with pallor, acute pulmonary oedema and renal failure evidenced by Urea of 32 mmol/L, Creatinine of 1169 umol/L and bilateral small kidneys on ultrasound. He was on renal replacement therapy which was continuous ambulatory peritoneal dialysis from 12 years old for 3 years before converting to haemodialysis for one year. He suffered from hypertensive crises that led to posterior reversible encephalopathy syndrome (PRES) and had a history of cardiopulmonary arrest. He also experienced recurrent infections with multiple positive cultures, persistent thrombocytopenia, anaemia that required multiple packed cell transfusions despite subcutaneous erythropoietin, mineral bone disease, mild pericardial effusion and neurological sequelae such as epilepsy, and learning disability.

Physical examination showed pallor and tenderness on palpation over the abdomen. There was a huge hepatosplenomegaly (liver measures 19.2cm, spleen measures 12.1cm). Otherwise, other systemic examinations were unremarkable. His weight was 22kg (< 5th percentile for age). Abdominal ultrasonography reported multiple small splenic lesions, with the differential diagnosis of splenic micro abscess, hepatosplenomegaly with simple cystic lesion at segment VIII of the liver, bilateral renal parenchymal disease with bilateral renal cysts and intra-abdominal complex ascites.

The peripheral blood smear showed a few hypo-lobulated neutrophils, no blast cells, normochromic normocytic anaemia, acanthocytes, thrombocytopenia with no clumps, and no leucoerythroblastic picture. In the complete blood count (CBC), total white cell (TWC) 4.780 x 10^9/L, red blood cell (RBC) 1.52 x 10^9/L, mean corpuscular volume (MCV) 88fL, 28pg, mean corpuscular haemoglobin concentration (MCHC) 31 g/dL, haemoglobin 4.3 g/dL, Platelet 117 x 10^9/L, Retic counts 0.4%, haematocrit 13.5%.

Other biochemical and haematological results: Ferritin 7921 ug/L (normal range 23.9 - 336), Iron 25.5 umol/L (9 - 21.5), Vitamin B12 882 pmol/L (normal range 133 – 675), C-reactive protein 142 mg/L, and Procalcitonin 48. Blood culture grew Burkholderia Pseudomallei.

The result of the bone marrow aspiration revealed normal marrow. No parasite was found in the stool sample. No urine sample was sent because he was anuric.

He had a significant family history where his two older siblings, both with disability certificates, experienced early mortality with a background history of developmental delay, intellectual disability and chronic kidney disease. His late brother, aged 9 years old, required no renal replacement therapy, he was noted to have established chronic kidney disease when he fell ill and passed away at emergency department, while his late sister, aged 14 years old, was on continuous ambulatory peritoneal dialysis (CAPD) since 6 years old.

Whole exome sequencing identified compound heterozygous pathogenic variants in *CUBN* (NM_001081.4):c.6088C>T (p.Arg2030Ter), and c.5428C>T (p.Arg1810Ter). In addition, a heterozygous likely pathogenic variant was identified in *SLC*4A1:c.1199_1225del(p.Ala400_Ala408del). Compound heterozygous variants were identified in *NUP*160. *NUP*160:c. 3032C>A(p.Ser1011Ter) which is classified as likely pathogenic, and *NUP*160:c. c.1112A>T(p.Asp371Val), which is classified as a variant of uncertain significance (VUS).

The child passed away due to complications of melioidosis septicaemia leading to multiorgan failure. Blood culture confirmed Burkholderia pseudomallei infection and imaging demonstrated splenic micro abscesses. Despite escalation of antibiotic therapy and addition of antifungal treatment, his clinical condition continued to deteriorate due to ongoing sepsis, compounded by his immunocompromised state and multiple chronic complications including anaemia, recurrent infections and pericardial effusion. He also developed breakthrough seizures which were likely multifactorial (epilepsy, metabolic instability and possible neuromelioidosis). Despite maximal measures, he eventually developed refractory septic shock, respiratory failure and cardiovascular collapse.

DISCUSSION

Both the c.6088C>T (p.Arg2030Ter), and c.5428C>T (p.Arg1810Ter) variants in the *CUBN* gene are nonsense variants which result in loss of protein function through protein truncation and have been reported at least twice as pathogenic. Both variants are observed at extremely low frequencies in population databases.

Biallelic pathogenic variants in the *CUBN* gene are associated with Imerslund-Gräsbeck syndrome which has an autosomal recessive mode of inheritance. We were unable to perform parental testing to phase the variants. However as both variants are pathogenic, and there is good clinical correlation, these variants are likely the cause of his clinical phenotype. Genetic tests were not performed for his two deceased siblings.

*SLC*4A1 pathogenic variants cause distal renal tubular acidosis and South East Asian Ovalostomatocytosis which can have an autosomal dominant or recessive inheritance. There are no documented case reports of renal failure caused by this disorder. As there is poor genotype-phenotype correlation, this is not likely to be the cause for his renal failure.

Biallelic pathogenic variants in *NUP*160 cause steroid

resistant nephrotic syndrome, which may be complicated by end-stage renal failure. However, one of the variants identified, *NUP*160:c. c.1112A>T(p.Asp371Val) is classified as a variant of uncertain significance (VUS). This is a missense variant that is not observed in the gnomAD dataset. In silico tools predict a non-deleterious effect.

In the light of whole exome sequencing confirmed diagnosis, it can be concluded that the symptoms experienced by the child which are mainly haematological manifestations (severe chronic anaemia, thrombocytopenia, leukopenia), intellectual disability, seizures, hepatosplenomegaly and recurrent infections are attributable to Imerslund-Gräsbeck syndrome (IGS). In a comprehensive review of reported cases where clinical manifestations before diagnosis was provided in 325 of 456 patients, 31% experienced gastrointestinal manifestations (diarrhoea, vomiting, failure to thrive = 51%, hepatosplenomegaly 37%, jaundice 6%), respiratory symptoms were present in 3% of patients, including recurrent respiratory infection, bronchopneumonia, and exertional dyspnoea, neurological manifestations were observed in 16% of the patients where 6% experienced seizures. (2) Of 325 patients, 48 (15%) were reported to have associated comorbidities where urogenital tract abnormalities were most often observed followed by haematological manifestations. (2)

This patient's vitamin B12 level was measured once after the whole exome sequencing result was known and was 882 pmol/L (high). Falsely elevated vitamin B12 levels have been reported before due to assay errors in the presence of pernicious anaemia. He received intradialytic parenteral nutrition multiple times during his recent admission, but there was no vitamin B12 content. Even though he received multiple packed cell transfusions, based on a prospective multicentre study, changes in mean values of cobalamin are statistically insignificant. (4) Serial MCV taken ranges between 77-89 and is not suggestive of megaloblastic anaemia.

While proteinuria is commonly reported in Imerslund-Gräsbeck syndrome (IGS), progressive renal deterioration has not been reported before. No genetic cause was identified that could explain this patient's end-stage renal failure. In IGS, multiple renal comorbidities have been reported, including Alport syndrome, focal segmental glomerulosclerosis, Ig A nephropathy, membranous glomerulonephritis, vesicoureteric reflux, and structural genitourinary tract abnormalities. (2)

Prognosis is generally favourable with early detection and treatment commencement in a timely manner. (2) Vitamin B12 deficiency in IGS patients are treated by lifelong monthly intramuscular cobalamin injections. Effective oral treatment with sufficiently high doses of vitamin B12 has also been described. IGS patients treated early with vitamin B12 are clinically and haematologically normal. Proteinuria persists but does not increase in severity, and does not progress to end-stage renal failure. (2)

CONCLUSION

This report highlights the complexities of diagnosing and managing IGS, particularly in the presence of extensive comorbidities. Early genetic diagnosis and coordinated, multidisciplinary management may improve the patient's quality of life. Increased awareness and understanding of IGS with multisystem involvement could facilitate earlier diagnosis and more effective intervention strategies for this rare disorder.

ACKNOWLEDGEMENT

We would like to thank the Director General of Health, Ministry of Higher Education, Malaysia for the permission to publish the article.

REFERENCES

1. Gräsbeck R. Imerslund-Gräsbeck syndrome (selective vitamin B 12 malabsorption with proteinuria). Orphanet journal of rare diseases. 2006;1:1-6.doi: 10.1186/1750-1172-1-17.
2. Kingma SD, Neven J, Bael A, Meuwissen ME, van den Akker M. Imerslund-Gräsbeck syndrome: a comprehensive review of reported cases. Orphanet Journal of Rare Diseases. 2023;18(1):291. doi:10.1186/s13023-023-02889-x
3. Gräsbeck R, Gordin R, Kantero I, Kuhlbäck B. Selective vitamin B12 malabsorption and proteinuria in young people a syndrome. Acta medica Scandinavica. 1960;167(4):289-96. doi:10.1111/j.0954-6820.1960.tb03549.x
4. Froissart A, Rossi B, Ranque B, Jarrin I, Bergmann JF, Beaune S, Dautheville S, Breau N, Dauvergne A, Deluche L, Robert T. Effect of a red blood cell transfusion on biological markers used to determine the cause of anemia: a prospective study. The American journal of medicine. 2018;131(3):319-22. doi: 10.1016/j.amjmed.2017.10.005
5. Fyfe JC, Madsen M, Hшjrup P, Christensen EI, Tanner SM, De La Chapelle A, He Q, Moestrup SK. The functional cobalamin (vitamin B12)–intrinsic factor receptor is a novel complex of cubilin and amnionless. Blood. 2004;103(5):1573-9.. doi: 10.1182/blood-2003-08-2852.