Research Square

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Inherited vitamin B12 malabsorption in South Indian children: A Case series

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Abstract

Background

Inherited deficiency of vitamin B12 absorption is caused by recessive mutations in AMN, CUBN, or GIF genes and leads to severe haematological and potentially irreversible neurological sequelae. Imerslund-Gräsbeck syndrome (IGS), caused by AMN or CUBN mutations, is characterised by selective cobalamin malabsorption and proteinuria. Hereditary intrinsic factor deficiency (HIFD), caused by GIF mutations, presents similarly but without proteinuria. Clinical diagnosis remains challenging owing to phenotypic heterogeneity. Published data from South India are limited.

Results

We present a retrospective case series of seven paediatric cases (ages 2–12 years; six males, one female) from consanguineous South Indian families who presented with heterogeneous clinical features of inherited vitamin B12 deficiency. All had serum vitamin B12 below 100 pg/mL and failed oral supplementation. AMN gene mutations were confirmed in five cases establishing IGS (Cases 1,2,3,4 and 6); one case (Case 5, female) was not tested genetically but had clinical and biochemical features consistent with inherited cobalamin malabsorption; Case 7 was the index case with suspected hereditary intrinsic factor deficiency (HIFD) after IGS was ruled out by mutation analysis. A notable presentation was Case 4 who presented with congestive cardiac failure and demonstrated a dramatic haematological response to parenteral vitamin B12. All seven cases responded to monthly parenteral vitamin B12 supplementation.

Conclusions

Inherited vitamin B12 malabsorption in South Indian children presents with phenotypic heterogeneity but consistent biochemical markers. Pallor, hyperpigmentation of knuckles, and proteinuria failure to respond to oral cobalamin should prompt genetic investigation for AMN, CUBN, and GIF mutations. These findings provide the first evidence of AMN-associated IGS and suspected HIFD in the South Indian paediatric population and highlight the need for epidemiological studies to define the regional mutation spectrum.

Background

Inherited cobalamin defects are categorized as rare orphan diseases. The overall global prevalence of these combined genetic errors is estimated at roughly 1 in 100,000 live births [1]. The prevalence of cblC deficiency is notably higher in East Asia (China) than the global average with incidence of 1 in 3,920 live births in Shandong Province [2]. South and West Asia (India, Pakistan, and Middle East): The exact overall prevalence remains understudied and not documented [3]. Vitamin B12 (cobalamin) is an essential micronutrient required for DNA synthesis, erythropoiesis, and maintenance of normal neurological function, including myelin integrity. Vitamin B12 deficiency may result from inadequate dietary intake, gastrointestinal disease, medications, or inherited defects affecting cobalamin transport and absorption [4,5]. Unlike nutritional deficiency, inherited disorders of cobalamin absorption impair the physiological uptake of cobalamin and generally require lifelong parenteral replacement therapy.

Physiological cobalamin absorption is a multistep process culminating in receptor-mediated uptake of the gastric intrinsic factor (GIF)–cobalamin complex in the terminal ileum. This process is mediated by the cubilin–amnionless (CUBAM) receptor complex, comprising cubilin (CUBN) and amnionless (AMN) [6,7]. Biallelic pathogenic variants in *CUBN* or *AMN* disrupt this pathway and cause Imerslund–Gräsbeck syndrome (IGS; OMIM 261100), a rare autosomal recessive disorder characterized by selective intestinal cobalamin malabsorption, typically accompanied by low-molecular-weight proteinuria [8,9]. Approximately 300 cases of IGS have been reported worldwide, with recurrent or founder variants described in several populations, including Finnish, Scandinavian, and Middle Eastern populations [9]. In contrast, biallelic pathogenic variants in the GIF gene (OMIM

261000) cause hereditary intrinsic factor deficiency (IFD), which produces a similar phenotype of severe cobalamin deficiency but typically lacks the proteinuria characteristic of IGS [10–12].

Recognition of inherited cobalamin malabsorption can be challenging because of considerable clinical and genetic heterogeneity, together with nonspecific presenting features. Delayed diagnosis and treatment may result in serious and potentially irreversible neurological complications [13,14]. Early recognition of clinical clues such as unexplained megaloblastic anemia, mucocutaneous changes, growth or developmental abnormalities, and persistent proteinuria may therefore facilitate timely diagnosis and treatment.

Data on inherited disorders of cobalamin absorption in children from South India remain limited. We report a retrospective case series of seven paediatric patients with inherited cobalamin malabsorption, with their clinical and biochemical features, molecular findings, diagnostic challenges, and response to parenteral vitamin B12 therapy. This series aims to highlight clinical features that may facilitate earlier recognition of these rare but treatable disorders.

Methods

Study design and setting

Retrospective case series at the Department of Paediatric Haematology Oncology, Institute of Child Health and Hospital for Children (ICH&HC), Egmore, Chennai, Tamil Nadu, South India. Clinical trial number is not applicable.

Participants

Seven paediatric patients with confirmed vitamin B12 deficiency and an inadequate response to oral supplementation were evaluated for inherited disorders of cobalamin deficiency. This is a retrospective Case series through review of clinical records from December 2020 to April 2022.

Investigations

Laboratory investigations included complete blood count with peripheral blood smear, serum vitamin B12, serum bilirubin, serum lactate dehydrogenase (LDH), urine albumin by dipstick, and spot urine protein-to-creatinine ratio (UPCR). Genetic testing was performed using next-generation sequencing (NGS; Neuberg Jeenomics Laboratory, Chennai) on an Illumina platform with paired-end 2 × 150-bp sequencing and alignment to the GRCh37/hg19 reference genome. AMN gene sequencing was performed in five of seven patients (Cases 1–4 and 6). Case 7 underwent targeted AMN variant analysis, which was negative. GIF gene sequencing was not performed in Case 7, in whom hereditary intrinsic factor deficiency (HIFD) was clinically suspected.

Supplementation

All patients received parenteral hydroxocobalamin (300–500 µg) at monthly intervals. This retrospective case series was conducted in accordance with applicable institutional policies governing the use and reporting of clinical data. Individual informed consent for publication was not required, as only anonymized retrospective clinical data is presented.

Generative AI Statement: Artificial intelligence (AI)-assisted tools were used to support manuscript language editing during the preparation of this manuscript. All AI-assisted content was reviewed and verified by the authors for factual accuracy, consistency with the primary clinical and laboratory data presented, and overall integrity of the work. The authors retain full accountability for the originality, accuracy, and completeness of the manuscript.

Results

Seven cases are presented (six males, one female), aged 2–12 years, all from consanguineous families. All had mixed diets. All failed oral vitamin B12 supplementation and responded to parenteral hydroxocobalamin administration. Haematological and clinical data are summarized in Table 1. Diagnostic delay timelines for all cases are illustrated in Fig. 1.

Case 1

A 10-year-old boy, the second child of a second-degree consanguineous marriage and receiving a mixed diet, presented with easy fatigability and hyperpigmentation of the knuckles and palms for two weeks. Similar episodes were experienced at 3 and 9 years of age, both requiring blood transfusion. On examination, he was nutritionally compromised with pallor, glossitis, hyperpigmentation of the knuckles and palms, and mild splenomegaly. Complete blood count revealed pancytopenia, and peripheral blood smear showed macro-ovalocytes. Serum vitamin B12 was < 100 pg/mL, with moderate hyperbilirubinemia, markedly elevated lactate dehydrogenase (LDH; 3,016 U/L), and 2 + urine albumin. Molecular analysis of AMN showed a homozygous intronic splice-site variant, c.513 + 2T > C, confirming the diagnosis of Imerslund–Gräsbeck syndrome (IGS). The patient demonstrated clinical and hematological improvement following parenteral vitamin B12 supplementation.

Case 2

A 2-year-old boy, the third child of a third-degree consanguineous marriage, presented with fever, vomiting, diarrhoea, and failure to thrive. On examination he had severe pallor and hypotonia. Laboratory Investigations of CBC showed pancytopenia, and peripheral blood smear demonstrated macro-ovalocytes, moderate hyperbilirubinemia, markedly elevated lactate dehydrogenase (LDH; 4,611 U/L), a serum vitamin B12 concentration of 32 pg/mL, and a spot urine spot PCR of 1.7. Molecular analysis of AMN showed a homozygous 5' splice-site variant in intron 7 (c.760 + 1G > A), affecting the invariant GT donor splice site, confirming the diagnosis of Imerslund–Gräsbeck syndrome (IGS). although proteinuria persisted. Representative clinical and haematological findings are shown in Fig. 3.

Case 3

An 11-year-old boy, the second child of a second-degree consanguineous marriage, presented with a 5-month history of glossitis, easy fatigability, and hyperpigmentation of the knuckles. According to the available medical history, he had been well until 2 years of age, when he was hospitalized with fever and severe anemia requiring blood transfusion. He subsequently experienced recurrent episodes managed with intermittent intramuscular vitamin B12 supplementation, with symptomatic improvement. On examination, he had a moderate nutritional status, hyperpigmentation of the knuckles, and glossitis. Laboratory investigations revealed a serum vitamin B12 concentration of < 50 pg/mL, a spot urine PCR of 1.42, and normal iron and folate levels. Molecular analysis of AMN identified a homozygous pathogenic 5' splice-site variant (c.513 + 2T > C), confirming the diagnosis of Imerslund–Gräsbeck syndrome (IGS). The patient demonstrated clinical and hematological improvement following parenteral vitamin B12 supplementation.

Case 4

A 10-year-old boy, the second child of a third-degree consanguineous marriage and receiving a mixed diet, presented with a 3-month history of dysphagia, lethargy, easy fatigability, and hyperpigmentation of the knuckles and soles. Notably, he presented with features of congestive cardiac failure (CCF) in the setting of severe anemia. He had previously been hospitalized at 7 months and 3 years of age for similar symptoms, on both occasions requiring packed red blood cell transfusion. On examination, he had severe pallor and hyperpigmentation of the knuckles and soles. Complete blood count revealed severe macrocytic anemia (hemoglobin, 5.9 g/dL), with macro-ovalocytes on peripheral blood smear. Serum vitamin B12 was < 100 pg/mL, with moderate indirect hyperbilirubinemia, markedly elevated lactate dehydrogenase (LDH; 2,968 U/L), and a spot urine PCR of 1.17(UPCR).Next-generation sequencing (Neuberg Jeenomics Laboratory, Chennai) identified a homozygous AMN c.208-1G > C variant (NM_030943.4), affecting the intron 3 splice-site acceptor. The variant was classified as likely pathogenic in ClinVar and was not reported in gnomAD Exomes or the 1000 Genomes database, confirming the diagnosis of Imerslund–Gräsbeck syndrome (IGS). Following parenteral vitamin B12 supplementation, the patient showed a marked and rapid hematological response, accompanied by complete resolution of the clinical features of congestive cardiac failure.

Case 5

A 7-year-old female, third born of a third-degree consanguineous marriage, presented with hyperpigmentation of knuckles and palms for 6 months. She had been hospitalized at 8 months of age for diarrhoea and failure to thrive. Examination revealed pallor, glossitis, and hyperpigmentation. CBC showed anaemia (hemoglobin, 9.9 g/dL) with peripheral smear of macrocytic picture, Serum vitamin B12 was < 100 pg/mL, elevated LDH (2,100 U/L) and urine spot PCR of 1.76 were present. Genetic testing for AMN mutations was not performed at the time of evaluation; the diagnosis was therefore based on the clinical and biochemical findings. The patient received parenteral vitamin B12 supplementation, with subsequent improvement in clinical and hematological symptoms.

Case 6

A 15-month-old boy, the second child of a second-degree consanguineous marriage, with normal developmental milestones, presented with a 1-week history of lethargy and hyperpigmentation. On examination, he was thin-built and had pallor, icterus, and hyperpigmentation of the knuckles. Complete blood count revealed severe macrocytic anemia (hemoglobin, 4.8 g/dL), with macro-ovalocytes on peripheral blood smear. Serum vitamin B12 concentration was < 100 pg/mL, with markedly elevated lactate dehydrogenase (LDH; 2,560 U/L) and a spot urine protein of 2.96 (UPCR). Following parenteral vitamin B12 supplementation, the patient showed clinical and hematological improvement. Molecular analysis of the AMN gene confirmed Imerslund–Gräsbeck syndrome (IGS).

Case 7

A 12-year-old boy, the second child of a second-degree consanguineous marriage, with normal developmental milestones and receiving a mixed diet, served as the index case that prompted this series. He presented with glossitis, easy fatigability, and hyperpigmentation of the knuckles and palms. His medical history revealed hospitalization at 6 months of age for diarrhoea and failure to thrive, when his serum vitamin B12 concentration was 4 pg/mL. He subsequently had an episode of acrodermatitis enteropathica at 2 years of age, treated with zinc supplementation, and pneumonia at 3 years of age. He had been exclusively breastfed until 6 months of age, with no history of goat-milk consumption, making dietary cobalamin deficiency less likely. Parenteral vitamin B12 supplementation was continued until 9 years of age, after which he was switched to oral supplementation for 2 years; recurrence of symptoms following this transition suggested inadequate absorption of oral cobalamin.

Anthropometric assessment showed a weight of 26 kg and height of 135 cm, both below − 2 SD for age, consistent with growth impairment. On examination, pallor and hyperpigmentation of the knuckles were noted. Neurological examination revealed normal tone and posture, brisk deep tendon reflexes (++), and no focal neurological deficits. Complete blood count showed hemoglobin 12.4 g/dL, MCV 106.7 fL, RDW 15.3%, WBC count 9,100/µL, and platelet count 440,000/µL. Peripheral blood smear demonstrated macro-ovalocytes and hypersegmented neutrophils. LDH was 329 U/L, total bilirubin 0.6 mg/dL (direct bilirubin, 0.4 mg/dL), and SGOT and SGPT were 37 and 76 U/L, respectively. Urine albumin was 1+, with a spot urine PCR < 1, and serum vitamin B12 remained < 100 pg/mL.

Clinical exome sequencing did not identify pathogenic or likely pathogenic variants in AMN, thereby providing no molecular evidence for Imerslund–Gräsbeck syndrome (IGS). Given the persistent severe cobalamin deficiency, recurrence of symptoms following transition to oral supplementation, and intermittent proteinuria, hereditary intrinsic factor deficiency (HIFD) was considered the probable diagnosis. However, GIF was not included in the genetic analysis; therefore, molecular confirmation of HIFD was not available and would require targeted GIF sequencing.

Discussion

This case series highlights the clinical heterogeneity and diagnostic challenges of inherited vitamin B12 malabsorption in South Indian children. Seven paediatric patients from consanguineous families presented with diverse manifestations ranging from mucocutaneous abnormalities and growth impairment to severe anemia, neurological involvement, and congestive cardiac

failure. Despite this phenotypic variability, several common features emerged, including profound vitamin B12 deficiency, inadequate response to oral supplementation, and proteinuria in most patients. The occurrence of these features in the setting of consanguinity should raise suspicion for an inherited disorder of cobalamin absorption and prompt appropriate molecular evaluation.

A particularly notable presentation was the child who developed congestive cardiac failure in association with severe anemia. Severe megaloblastic anemia can rarely result in high-output cardiac failure through increased cardiac workload and reduced oxygen-carrying capacity. The rapid clinical and hematological improvement following parenteral vitamin B12 replacement, including resolution of the cardiac manifestations, emphasizes the potentially reversible nature of this complication when the underlying cobalamin deficiency is recognized and treated promptly. In children, unexplained cardiac failure accompanied by severe anemia should therefore prompt consideration of potentially reversible nutritional and metabolic causes, including vitamin B12 deficiency.

The index case illustrates another important diagnostic challenge. Despite profound and persistent cobalamin deficiency and recurrence of symptoms following transition from parenteral to oral supplementation, AMN analysis was negative. In the context of a compatible phenotype, hereditary intrinsic factor deficiency (HIFD) was considered. However, because GIF sequencing was not performed, HIFD could not be genetically confirmed. This case demonstrates the limitations of testing a single gene in patients with suspected inherited cobalamin malabsorption. When AMN and/or CUBN testing is negative despite a strong clinical suspicion, evaluation of GIF and other genes involved in cobalamin absorption and intracellular processing should be considered. The diagnostic delay observed in our series is consistent with published experience. In the largest systematic review of IGS to date, encompassing 456 cases, Kingma et al. reported a median age of symptom onset of 2.3 years but a median age at diagnosis of 7.2 years, underscoring the protracted diagnostic journey typical of this condition [14]. Our series, drawn from a consanguineous South Indian population with limited access to metabolic diagnostics, reflects a similar pattern. Comparative data from published case reports support the heterogeneous presentation observed in our series. Di Sario et al. described a 23-month-old Italian boy with severe pancytopenia as the presenting feature of IGS caused by compound heterozygous AMN variants, without prominent neurological involvement, emphasising that severe cytopenias alone can herald the diagnosis [15]. Similarly, Makrooni et al. reported a 15-year-old Iranian adolescent with a 12-year history of intermittent proteinuria and recurrent anaemia before IGS was recognised, highlighting the particular risk of under-diagnosis in the Middle East and South Asian region [16]. In our series, the c.513 + 2T > C splice-site variant in AMN was identified in three of five genotyped cases, suggesting a potential founder effect in South Indian AMN-related IGS, analogous to the c.208-2A > G founder variant reported in Turkish populations [14]. Prior Indian reports of inherited cobalamin malabsorption remain sparse; Glader et al. described a single child of Indian descent with IGS [17], and Gupta et al. reported AMN-related megaloblastic anaemia in Indian children [18], underscoring the scarcity of published series from this population and the value of the present case series.

Biochemical and haematological markers at presentation are shown in Fig. 2. Proteinuria was documented in six of the seven patients and provided an important clinical clue to IGS. Biallelic pathogenic variants in AMN or CUBN impair the function of the cubilin–amnionless receptor complex, which is involved not only in intestinal cobalamin absorption but also in renal tubular reabsorption of filtered low-molecular-weight proteins. Consequently, the combination of profound cobalamin deficiency and persistent low-molecular-weight proteinuria can help distinguish IGS from other causes of inherited cobalamin deficiency. In the patient without molecular confirmation, the coexistence of severe cobalamin deficiency, proteinuria, consanguinity, and inadequate response to oral supplementation was clinically suggestive of an inherited absorptive disorder, although a specific molecular diagnosis could not be established.

Molecular analysis confirmed AMN variants in five patients. Three splice-site variants were identified, including c.513 + 2T > C in two patients, c.760 + 1G > A, and c.208-1G > C. The recurrence of c.513 + 2T > C in two unrelated patients is noteworthy; however, the small sample size and absence of haplotype or population-level analysis do not permit inference of a founder effect. Larger studies incorporating comprehensive molecular characterization and segregation analysis will be required to determine whether recurrent variants represent regional enrichment or shared ancestral variation.

An important observation in this series was the prolonged interval between initial clinical presentation and recognition of the underlying disorder. Several patients had experienced recurrent episodes of anemia or gastrointestinal symptoms during early childhood, with some requiring blood transfusions before the underlying cause was established. Such recurrent, otherwise unexplained anemia particularly when accompanied by macrocytosis, mucocutaneous changes, severe biochemical cobalamin deficiency, or proteinuria should prompt consideration of inherited cobalamin malabsorption. Hyperpigmentation of the knuckles and palms was also observed in several patients and may provide an additional clinical clue, particularly in settings where access to specialized diagnostic testing is limited.

The findings also reinforce the importance of distinguishing inherited cobalamin malabsorption from dietary deficiency. Although dietary insufficiency remains an important cause of vitamin B12 deficiency, profound deficiency that persists or recurs despite adequate oral supplementation should prompt evaluation for an absorptive defect. Early recognition is particularly important in children because prolonged cobalamin deficiency can result in irreversible neurological injury and impaired growth and development. Parenteral cobalamin replacement can produce substantial hematological and clinical improvement, as demonstrated across all seven patients in this series, although the extent and speed of recovery may depend on the severity and duration of deficiency and the presence of established complications.

This study has several limitations. Its retrospective design and small sample size limit generalizability, and complete molecular characterization was not available for all patients. GIF testing was not performed in the index case, while one patient with a clinically suggestive phenotype did not undergo AMN testing. In addition, CUBN and other genes associated with inherited cobalamin disorders were not systematically evaluated across the cohort. The absence of standardized longitudinal neurological, hematological, and biochemical assessments also limits assessment of long-term outcomes. Nevertheless, the series provides clinically relevant insight into the recognition and molecular evaluation of inherited cobalamin malabsorption in children from South India.

In summary, this series demonstrates that inherited cobalamin malabsorption may present with a broad spectrum of clinical manifestations, while profound vitamin B12 deficiency, inadequate response to oral supplementation, and proteinuria provide important diagnostic clues. A combination of careful clinical assessment and comprehensive molecular testing including AMN, CUBN, and GIF where appropriate may facilitate earlier diagnosis and targeted lifelong parenteral replacement. Larger multicentre studies incorporating systematic genetic testing are warranted to establish the regional prevalence, mutation spectrum, and clinical characteristics of these rare but treatable disorders.

Conclusions

This case series represents an important contribution to the limited literature on inherited vitamin B12 malabsorption from South India, bringing together a clinically diverse group of paediatric patients with molecularly confirmed AMN-associated Imerslund–Gräsbeck syndrome (IGS) and clinically suspected hereditary intrinsic factor deficiency. The consistent presence of profound cobalamin deficiency, inadequate response to oral supplementation, and proteinuria provides practical diagnostic clues for early recognition. Severe anaemia complicated by congestive cardiac failure further illustrates the potentially serious yet reversible consequences of delayed diagnosis. Recognition of this characteristic phenotype should prompt early molecular evaluation of AMN, CUBN, and GIF and timely parenteral cobalamin replacement. This series provides a valuable regional clinical and molecular perspective and supports the need for larger multicentre studies to define the spectrum and genetic epidemiology of inherited cobalamin malabsorption in South India.

Abbreviations

AMN: Amnionless; CCF: Congestive cardiac failure; CUBN: Cubilin; GIF: Gastric intrinsic factor; Hb: Haemoglobin; HIFD: Hereditary intrinsic factor deficiency; IGS: Imerslund-Gräsbeck syndrome; LDH: Lactate dehydrogenase; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; PCR: Protein/creatinine ratio; PRBC: Packed red blood cells; RDW: Red cell distribution width.

Declarations

Ethics approval and consent to participate

This retrospective case series was conducted in accordance with the ethical principles of the Declaration of Helsinki. Formal ethics committee approval was not required, as this study involved only retrospective review of anonymised clinical data collected during routine medical care, with no prospective interventions or experimental procedures. This is consistent with applicable institutional and national guidelines governing retrospective clinical data reporting in India (ICMR guidelines)

Consent for publication

Individual written informed consent for publication was not required for this retrospective case series, as all patient data are fully anonymised and no individually identifiable information, images, or details are presented

Availability of data and materials

All data generated are included in this article and its tables. Individual case data are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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No external funding was received for this study.

Authors' contributions

DP: clinical identification and management of cases, data collection, and manuscript drafting. AR: clinical management, data collection, and manuscript review. JR: data analysis, literature review, and manuscript preparation. JK: data interpretation and manuscript review. RC: clinical supervision, study conception, and critical revision of the manuscript. All authors read and approved the final manuscript.

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A subset of the data (four cases) was presented in abstract and poster form at 46th Annual PEDICON 2022 (National Conference of the Indian Academy of Pediatrics).

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Table

Table 1. Clinical and genetic characteristics of 7 cases of inherited vitamin B12 malabsorption.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Demographics							
Age (years)	10	2.5	11	10	7	1.25	12
Sex	M	M	M	M	F	M	M
Consanguinity	2°	3°	3°	3°	3°	3°	2°
Diet	Mixed	Mixed	Veg (Includes Dairy)	Mixed	Mixed	Veg (Includes Dairy)	Mixed
Diagnosis	IGS	IGS	IGS	IGS + CCF	Clinical IGS	IGS	HIFD
Presentation							
Symptom onset	2–6 yr	<6 mo	2–6 yr	2–6 yr	<6 mo	<6 mo	<6 mo
Chief complaint	Fatigue, glossitis	FTT, pallor	Fatigue, hyperpig.	Dysphagia, fatigue	Fatigue, glossitis	FTT, pallor	Dysphagia
Past hospitalizations	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Transfusion history	Yes	Yes	Yes	Yes	No	Yes	No
Haematology							
Hb (g/dL)	4.9	3.3	7	5.9	9.9	4.8	12.4
MCV (fL)	102	92	104.4	105	106.7	106	106.7
Platelet (×10³/µL)	103	117	117	102	256	71	440
Smear	Macro-oval, pancytopenia	Macro-oval, pancytopenia	Macro-oval, pancytopenia	Macrocytic	Macrocytic	Macrocytic	Macro-oval, hyperseg. neutrophil
Serum B12	<50 pg/mL	31 pg/mL	<100 pg/mL	<100 pg/mL	88 pg/mL	<83 pg/mL	4 pg/mL
LDH (U/L)	3,016	4,611	2450	2,968	2,100	2,560	329
Urine							
Spot PCR	1	1.7	1.42	1.17	1.76	2.96	<1
Genetics							
Gene	AMN	AMN	AMN	AMN	—	AMN	AMN neg.
Variant (HGVS)	c.513+2T>C	c.760+1G>A	c.513+2T>C	c.208-1G>C	Not tested	Confirmed IGS	No LP/P variant
Location	Intron 5	Intron 7	Intron 5	Intron 3	—	—	—
Zygosity	Hom.	Hom.	Hom.	Hom.	—	—	—
Treatment & outcome							
Parenteral B12	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oral B12 failure	—	—	—	—	—	—	Yes

Haem. response	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Hom. = homozygous; FTT = failure to thrive; Hyperpig. = hyperpigmentation; Macro-oval = macroovalocytes; Hyperseg. = hypersegmented; IGS = Imerslund-Gräsbeck syndrome; HIFD = hereditary intrinsic factor deficiency; CCF = congestive cardiac failure; PCR = protein/creatinine ratio; LP/P = likely pathogenic/pathogenic. Spot PCR normal threshold ≤0.2.

Figures

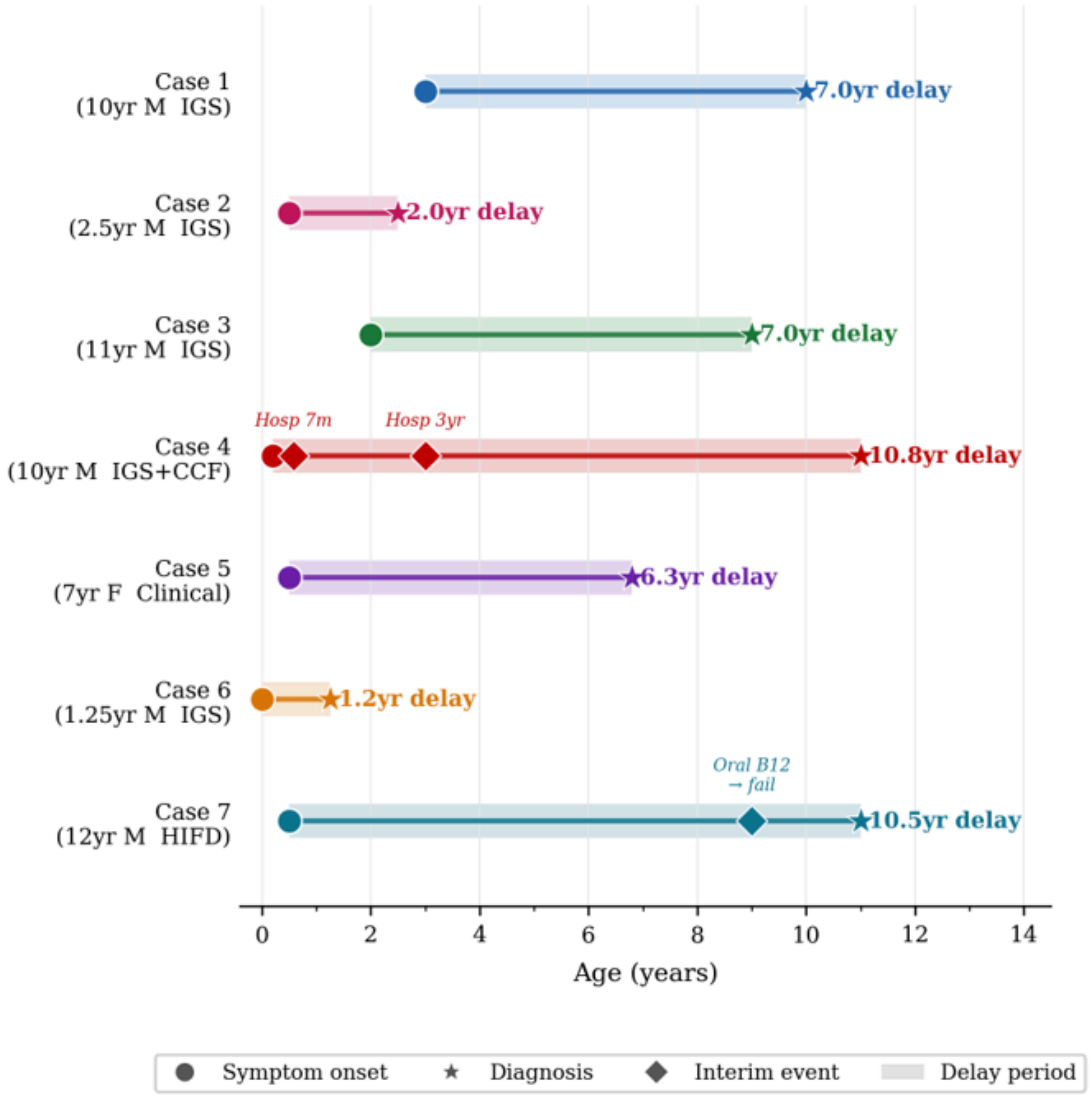


Figure 1

Diagnostic delay timeline from symptom onset (filled circle) to confirmed diagnosis (star). Delays ranged from 0 to 10.8 years (Case 4). IGS = Imerslund-Gräsbeck syndrome; HIFD = hereditary intrinsic factor deficiency.

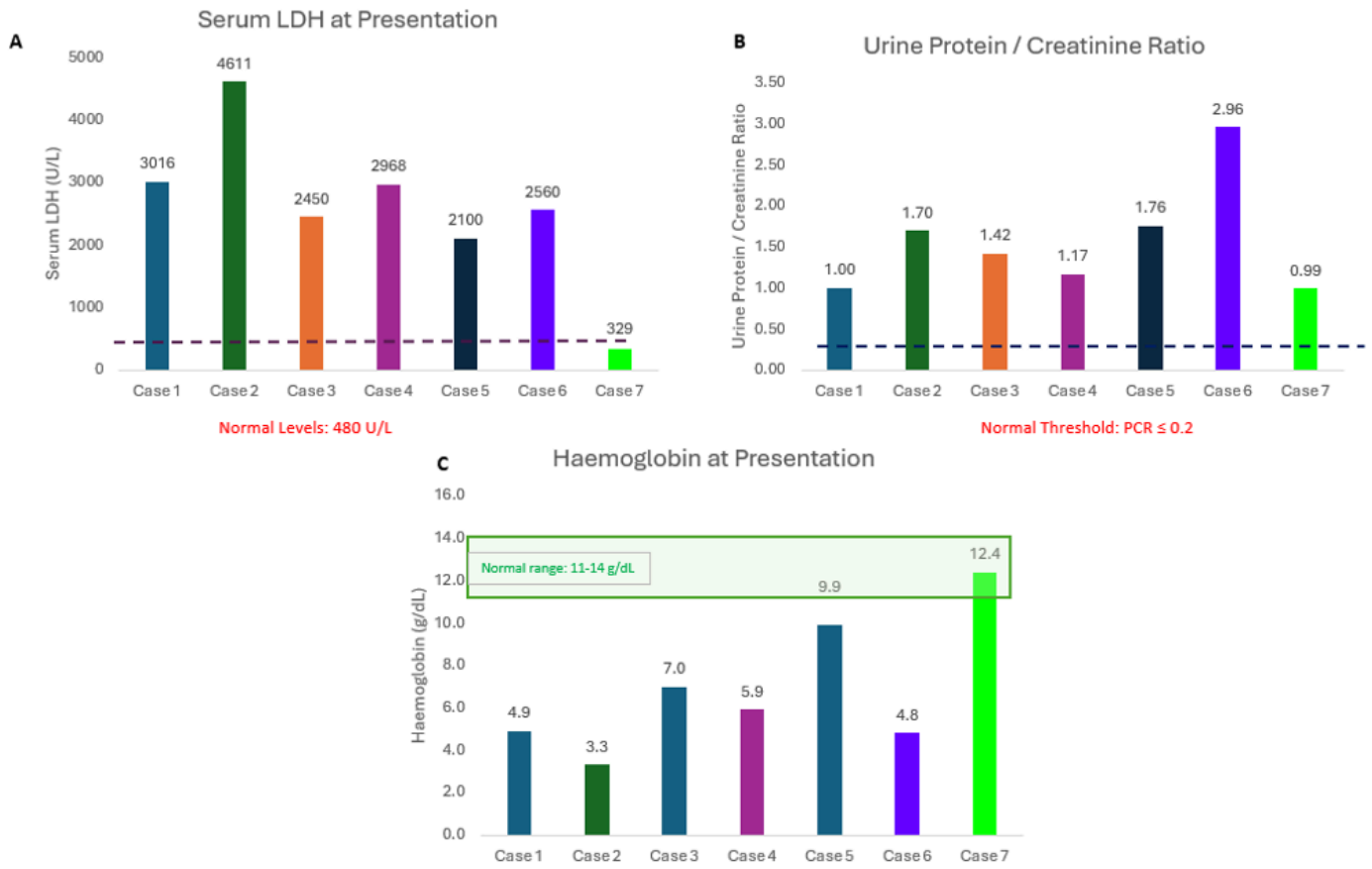


Figure 2

Biochemical and haematological markers at presentation. Panel A: Serum LDH; markedly elevated in all IGS cases; Case 7 (HIFD) within normal range (329 U/L), consistent with haemolysis-predominant IGS versus non-haemolytic HIFD. Panel B: Urine protein/creatinine ratio; all recorded values exceed the normal threshold (≤0.2). Panel C: Haemoglobin at presentation; severe anaemia in most IGS cases; Case 7 presented with near-normal haemoglobin. Red dashed lines = normal upper limits; green shading = normal reference range.



Figure 3

Representative clinical and haematological findings. Panel A: Hyperpigmentation of the knuckles, nail beds, and dorsum of the feet — present in 6 of 7 cases. Panel B: Atrophic glossitis with smooth depapillated mucosa — present in 4 of 7 cases. Panel C: Peripheral blood smear (low power) showing macroovalocytes, anisocytosis, and thrombocytopenia. Panel D: High-power view of a hypersegmented neutrophil (≥6 lobes), pathognomonic for megaloblastic anaemia.