Are all Vitamin B12 deficiencies nutritional? – Case of ACQUIRED INTRINSIC FACTOR DEFICIENCY

Dr Bijjam Lakshmi Sri Harika Reddy, Dr Abhilasha Sampagar
[1] *Department of Pediatrics- Division of Haematology Oncology, Jawaharlal Nehru Medical College, Belagavi, Karnataka, India*

INTRODUCTION

Megaloblastic anaemia with its prevalence at 47% is the second most common cause of nutritional anaemia in our country thereby making it's way as a common clinical scenario witnessed in Pediatric age group, in our day to day OPD practices.

But little do we know that it is not always due to simple nutritional deficiency. Owing to the complex nature of it's bio- kinetic pathway right from Ingestion, to Absorption (intrinsic factor deficiency, Imerslund-Gräsbeck syndrome), to Transport (transcobalamin deficiency), identifying and targeting the defect at the exact level has been a challenge when it comes to making a diagnosis.

Pernicious anaemia is an important condition which presents with Megaloblastic anaemia. However, there are certain Acquired causes which are often missed like Autoimmune Pernicious Anaemia and Gastrointestinal diseases like Crohn's disease, gastric bypass. These are often missed because of paucity of literature about their clinical presentation or due to lack of awareness about the clinical presentation and the diagnostic tests for Pernicious anaemia.

In Pernicious Anaemia, some cases may develop gastric malignancies. Its deficiency leads to Megaloblastic anaemia and some patients may have neurological complications and even gastric malignancies.

Understanding these causes is crucial for early diagnosis and effective management of B12 deficiency, as it has multiple clinical implications of not only anaemia but other complications like neurocognitive disorders.

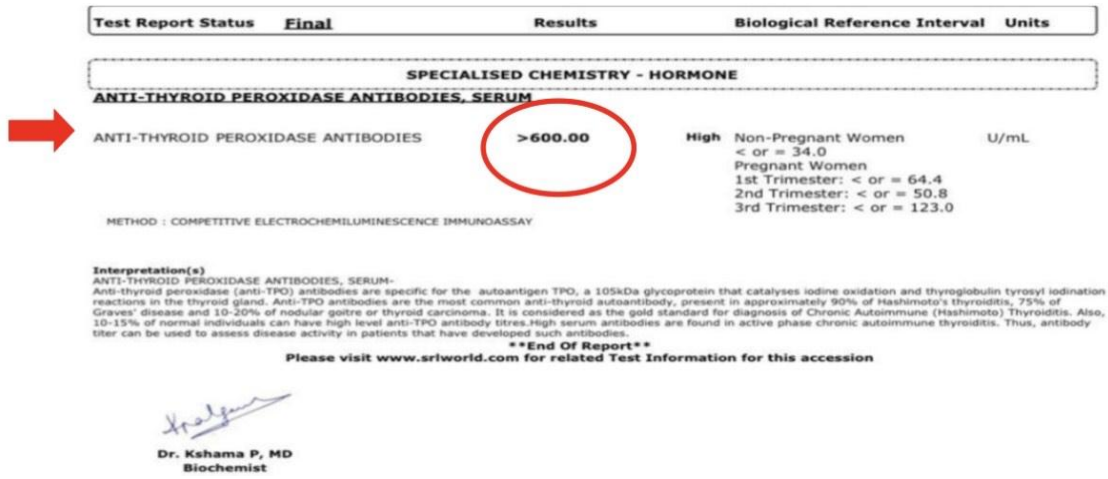
CASE REPORT

A 13-year-old girl, born to non-consanguineous parents, presented with constant history of constipation, complaints of progressive pallor, dry skin and easy fatiguability for the past two months. There was no history of bleeding tendencies, jaundice or recent infections. Her nutritional status was adequate, with a weight of 45 kg, height of 147 cm and a BMI of 20.8. She reported a history of a mixed diet, suggesting no dietary restrictions that could lead to vitamin deficiencies.

On clinical examination, the patient appeared pale and there was evidence of generalized hyperpigmentation, particularly on the knuckles suggesting features of Megaloblastic anaemia.

Laboratory investigations included a complete hemogram, which revealed macrocytic hypochromic anemia with associated thrombocytopenia. Liver function tests (LFT) and renal function tests (RFT) were within normal limits. However, lactate dehydrogenase (LDH) levels were markedly elevated at 3200 U/L, raising suspicion of megaloblastic anaemia, but B12 level was completely Normal and she also had features of Hypothyroidism.

Following which owing to the age predilection, thyroid profile along with anti-thyroid antibodies of the girl was done which was strongly suggestive of HYPOTHYROIDISM with antithyroid antibodies being POSITIVE. Which showed Hypothyroidism and her anti-thyroid antibodies was strongly POSITIVE.



Test Report Status **Final**	Results	Biological Reference Interval	Units

SPECIALISED CHEMISTRY - HORMONE

ANTI-THYROID PEROXIDASE ANTIBODIES, SERUM

ANTI-THYROID PEROXIDASE ANTIBODIES	>600.00	High	Non-Pregnant Women < or = 34.0 Pregnant Women 1st Trimester: < or = 64.4 2nd Trimester: < or = 50.8 3rd Trimester: < or = 123.0	U/mL

METHOD : COMPETITIVE ELECTROCHEMILUMINESCENCE IMMUNOASSAY

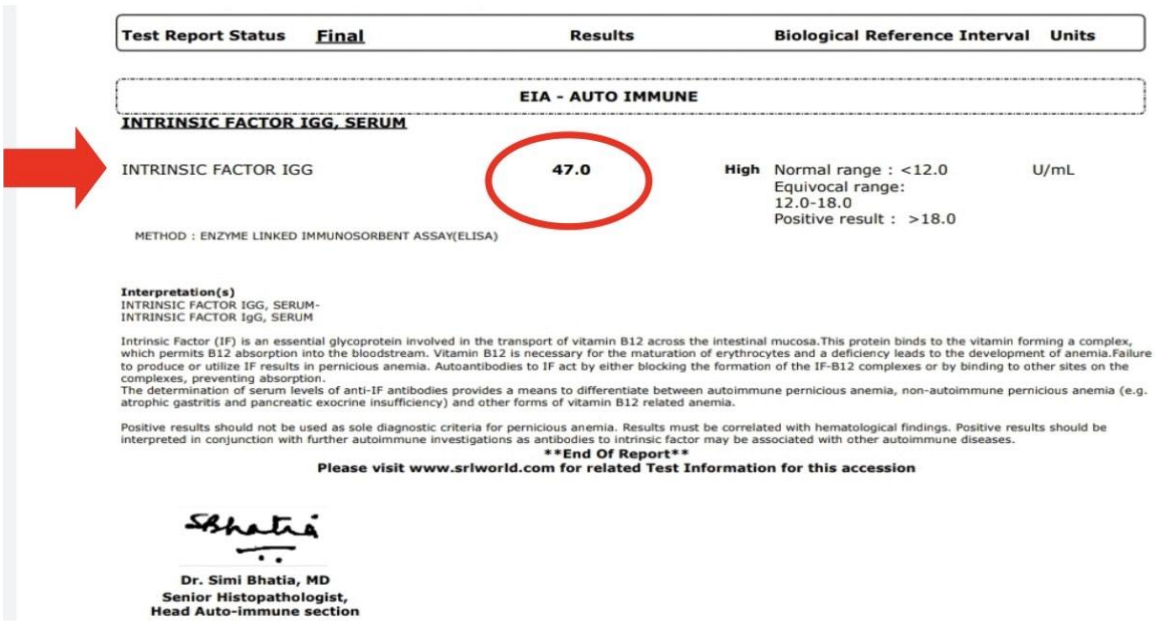
Interpretation(s)
ANTI-THYROID PEROXIDASE ANTIBODIES, SERUM-
Anti-thyroid peroxidase (anti-TPO) antibodies are specific for the autoantigen TPO, a 105kDa glycoprotein that catalyses iodine oxidation and thyroglobulin tyrosyl iodination reactions in the thyroid gland. Anti-TPO antibodies are the most common anti-thyroid autoantibody, present in approximately 90% of Hashimoto's thyroiditis, 75% of Graves' disease and 10-20% of nodular goitre or thyroid carcinoma. It is considered as the gold standard for diagnosis of Chronic Autoimmune (Hashimoto) Thyroiditis. Also, 10-15% of normal individuals can have high level anti-TPO antibody titres.High serum antibodies are found in active phase chronic autoimmune thyroiditis. Thus, antibody titer can be used to assess disease activity in patients that have developed such antibodies.

****End Of Report****

Please visit www.srlworld.com for related Test Information for this accession

Dr. Kshama P, MD
Biochemist

So, we entertained a differential diagnosis of Pernicious Anaemia, as the patient already had one antibody, which suggests that child is having Autoimmune disease. Just to further our diagnosis, the following day Serum Homocysteine levels and Serum Methylmalonic acid levels were sent along with Anti- Intrinsic Factor antibodies and Anti – parietal cell antibodies – and much to our expectation- both titres were raised along the both antibodies showing POSITIVE STATUS. Hence, we have made a final diagnosis of Acquired Intrinsic Factor Deficiency.



Test Report Status **Final**	Results	Biological Reference Interval	Units

EIA - AUTO IMMUNE

INTRINSIC FACTOR IGG, SERUM

INTRINSIC FACTOR IGG	47.0	High	Normal range : <12.0 Equivocal range: 12.0-18.0 Positive result : >18.0	U/mL

METHOD : ENZYME LINKED IMMUNOSORBENT ASSAY(ELISA)

Interpretation(s)
INTRINSIC FACTOR IGG, SERUM-
INTRINSIC FACTOR IgG, SERUM

Intrinsic Factor (IF) is an essential glycoprotein involved in the transport of vitamin B12 across the intestinal mucosa.This protein binds to the vitamin forming a complex, which permits B12 absorption into the bloodstream. Vitamin B12 is necessary for the maturation of erythrocytes and a deficiency leads to the development of anemia.Failure to produce or utilize IF results in pernicious anemia. Autoantibodies to IF act by either blocking the formation of the IF-B12 complexes or by binding to other sites on the complexes, preventing absorption.
The determination of serum levels of anti-IF antibodies provides a means to differentiate between autoimmune pernicious anemia, non-autoimmune pernicious anemia (e.g. atrophic gastritis and pancreatic exocrine insufficiency) and other forms of vitamin B12 related anemia.

Positive results should not be used as sole diagnostic criteria for pernicious anemia. Results must be correlated with hematological findings. Positive results should be interpreted in conjunction with further autoimmune investigations as antibodies to intrinsic factor may be associated with other autoimmune diseases.

****End Of Report****

Please visit www.srlworld.com for related Test Information for this accession

Dr. Simi Bhatia, MD
Senior Histopathologist,
Head Auto-immune section

DISCUSSION

Autoimmune causes especially HASHIMOTO'S THYROIDITS can be a common non- nutritional cause of Vitamin B12 deficiency owing to the auto-antibodies produced which cross react with the Intrinsic Factor- greatly responsible for Vitamin B12 transport and absorption thus causing ACQUIRED INTRINSIC FACTOR DEFICIENCY.

BUT THEN WHY VITB12 LEVELS ARE RAISED? - In Pernicious Anaemia anti -intrinsic factor antibody interferes with B12 assay, causing falsely high value. Folate level is very sensitive to recent folate intake. Thereby any child presenting with features of Vitamin B12 deficiency with Normal to high Vitamin B12 levels, like in our case, rule out, ACQUIRED INTRINSIC FACTOR DEFICIENCY.

Only Homocysteine is high in Folate deficiency whereas both Homocysteine and MMA is high in cobalamin deficiency.

CONCLUSION

Child had received Vitamin B12 Injections with initial dose of 1000mcg IM daily for 2 weeks (to replenish stores) and then maintenance dose of 1000mcg IM once weekly for a month and then 1000mcg IM once monthly for life. Child's serum Vitamin B12 levels were periodically monitored.

AFTER TREATMENT

Effective management of Pernicious Anaemia requires ongoing collaboration between medical specialists to ensure a comprehensive approach and the best possible patient care.

REFERENCES

[1] Annibale, B.; Lahner, E.; Fave, G.D. Diagnosis and management of pernicious anemia. Curr. Gastroenterol. Rep. 2011, 13, 518–524. [CrossRef] [PubMed]

[2] Carabotti, M.; Annibale, B.; Lahner, E. Common Pitfalls in the Management of Patients with Micronutrient Deficiency: Keep in Mind the Stomach. Nutrients 2021, 13, 208. [CrossRef] [PubMed]

[3] Lenti, M.V.; Rugge, M.; Lahner, E.; Miceli, E.; Toh, B.H.; Genta, R.M.; De Block, C.; Hershko, C.; Di Sabatino, A. Autoimmune gastritis. Nat. Rev. Dis. Primers 2020, 6, 56. [CrossRef] [PubMed]

[4] Lenti, M.V.; Miceli, E.; Cococcia, S.; Klersy, C.; Staiani, M.; Guglielmi, F.; Giuffrida, P.; Vanoli, A.; Luinetti, O.; De Grazia, F.; et al. Determinants of diagnostic delay in autoimmune atrophic gastritis. Aliment. Pharmacol. Ther. 2019, 50, 167–175. [CrossRef]

[5] Friedlander, R. D. : The racial factor in pernicious anemia. Amer. J. Med. Sci. 187: 634, 1934.

[6] Schwartz, S. 0., and Rappolt, L. A.: Pernicious anemia in Chinese. Arch. Intern. Med. (Chicago) 75 :404, 1945.

[7] Taylor, G. F., and Chitkara, R. N.: Report of two postmortems and five cases of addisonian pernicious anemia. Indian Med. Gaz. 75 :16, 1940.

[8] Chuttani, P. N. : A report of 46 cases in the Punjab with special reference to nutritional macrocytic and pernicious anemia. Indian Med. Gaz. 83 :508, 1948.