Letters to the editor

OVERVIEW

Please submit letters for the editor's consideration within three weeks of receipt of *Clinical Medicine*. Letters should ideally be limited to 350 words, and sent by email to: clinicalmedicine@rcplondon.ac.uk

Vitamin B₁₂ deficiency – A 21st century perspective

Editor – I read with interest 'Vitamin B₁₂ deficiency – A 21st century perspective' (Clin Med 2015;15:145–50). I would like to make some comments.

First, the authors never mentioned the possibility of spuriously normal or elevated cobalamin level in pernicious anaemia (PA), a recognised phenomenon, attributable to the circulating intrinsic factor antibodies (IFA) interfering with the competitive-binding luminescence cobalamin assays.^{1–3} This can lead to serious consequences such as delayed PA diagnosis or even misdiagnosis such as myelodysplasia.⁴ In this scenario, serum methylmalonic acid (MMA) and fasting plasma homocysteine levels can be helpful in the context of right clinical setting.

Second, the sensitivity of IFA in PA is 50–70% and therefore 30–50% of PA cases can be missed if IFA serology is solely used. In this situation, the fasting serum gastrin level and gastric biopsy could be helpful in establishing PA diagnosis (gastrin level will be high and biopsy could reveal atrophic gastritis in the body and fundus).^{5–6}

Third, false-positive IFA can be seen if IFA sampling is performed after cobalamin injections and therefore it is extremely important to perform IFA sampling before starting cobalamin injections.⁷

Fourth, some patients may have high MMA levels due to concomitant renal failure or bacterial overgrowth.⁵ They may just present with macrocytic anaemia, hypersegmented neutrophils and macroovalocytes, but with normal vitamin B₁₂ levels. Those patients might benefit from a therapeutic trial of cobalamin.

Fifth, despite exhaustive arrays of investigations, some patients with macrocytic anaemia eventually require bone marrow biopsies (BMBs). If the BMB reveals unexplained megaloblastic changes, a therapeutic trial of cobalamin is warranted, because cobalamin, MMA and homocysteine testing may be unreliable in some cases.⁸

Sixth, iron deficiency can coexist with cobalamin deficiency in patients with PA or other malabsorption states.⁹ Therefore, it is recommended that serum cobalamin, folate and iron profile be assessed in tandem. If iron deficiency exists, it further supports the need for gastroscopy with or without biopsy.

Finally, careful blood smear examination for hypersegmented neutrophils and macroovalocytes may lead to the diagnosis of cobalamin deficiency in many cases (in the right context)

and even if patients present with no anaemia but with neuropsychiatric manifestations only.^{5,10} ■

DR THEIN H OO

Associate professor of medicine,
University of Texas MD Anderson Cancer Center
Houston, TX, USA

References

- 1 Yang DT, Cook RJ. Spurious elevations of vitamin B12 with pernicious anemia. *N Engl J Med* 2012;366:1742–3.
- 2 Hamilton MS, Blackmore S, Lee A. Possible cause of false normal B-12 assays. *BMJ* 2006;333:654–55.
- 3 Carmel R, Agrawal YP. Failures of cobalamin assays in pernicious anemia. *N Engl J Med* 2012;367:385–6.
- 4 Shah DR, Daver N, Borthakur G *et al*. Pernicious anemia with spuriously normal vitamin B12 level might be misdiagnosed as myelodysplastic syndrome. *Clin Lymphoma Myeloma Leuk* 2014;14:e141–3.
- 5 Rojas Hernandez CM, Oo TH. Advances in mechanisms, diagnosis, and treatment of pernicious anemia. *Discov Med* 2015;19:159–68.
- 6 Varbanova M, Frauenschläger K, Malfertheiner P. Chronic gastritis – an update. *Best Pract Res Clin Gastroenterol* 2014;28:1031–42.
- 7 Muckerheide M. Therapeutic doses of vitamin B12 give false-positive values for intrinsic-factor-blocking antibodies. *Clin Chem* 1984;30:1579.
- 8 Solomon LR. Cobalamin-responsive disorders in the ambulatory care setting: unreliability of cobalamin, methylmalonic acid, and homocysteine testing. *Blood* 2005;105:978–85.
- 9 Carmel R, Weiner JM, Johnson CS. Iron deficiency occurs frequently in patients with pernicious anemia. *JAMA* 1987; 257:1081–3.
- 10 Heaton EB, Savage DG, Brust JC *et al*. Neurologic aspects of cobalamin deficiency. *Medicine (Baltimore)* 1991;70:229–45.

Response

Editor – Many thanks for the authors interest in our review. We fully agree with the several diagnostic pitfalls which need to be kept in mind while considering the diagnosis of vitamin B₁₂ deficiency and pernicious anaemia.

However, there are certain issues which we need to consider in this scenario. Firstly, performing serum methyl malonic acid and plasma homocysteine levels as routine work-up for vitamin B₁₂ deficiency is not common practice and also not available in many laboratories in the UK. The other issue which is becoming more common is considering serum B₁₂ testing as part of 'routine blood tests' without adequate thought into the clinical situation. This can lead to problems like the ordering physician overlooking vitamin deficiency as still a possibility for the patient's symptoms when normal serum B₁₂ levels are reported. Ideally in such cases, specialised tests like methyl malonic acid and serum homocysteine need to be performed.