PE1408/Z

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Ms Sigrid Robinson
Assistant Clerk to the Public Petitions Committee
T3.40
The Scottish Parliament
Edinburgh
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26 November 2015

Dear Ms Robinson

I refer to Petition PE1408, lodged by Mrs Andrea MacArthur, which called on the Scottish Parliament to urge the Scottish Government (SG) to review and overhaul the current out-dated and ineffective method of diagnosing and treating Pernicious Anaemia / Vitamin B12 Deficiency.

My letter to the Public Petitions Committee (PPC) of 8 December 2014 confirmed that existing British Committee for Standards in Haematology (BCSH) guidelines had been considered by the Diagnostic Steering Group (DSG). This group had determined that the BCSH guidelines were not presented in a suitable form for use in the GP practice setting. DSG therefore asked the Scottish Haematology Society (SHS) to prepare a summary document (based on BCSH guidelines) to provide GPs in Scotland with appropriate advice on B12 deficiency investigations.

My last letter to you of 3 November 2015 confirmed that the draft document was still under development. It also stated that we hoped to be able to share a draft with the DSG at its meeting on 17 November and that, only once the group were satisfied with the draft, would the SG be in a position to share it with the PPC.

The DSG has now seen the draft advice. This is attached for the Committee. Please note that the draft document aims to provide GPs in Scotland with appropriate advice to help in the diagnosis process and supplements recommendations in the BCSH guidelines, published in 2014.

I hope that the PPC and the Petitioner find the draft advice helpful.

Yours sincerely

Elizabeth Porterfield
Head, Strategic Planning/Clinical Priorities

November 2015

Advice to GPs regarding vitamin B_{12} investigation

Dear Doctor,

Introduction

Trying to Diagnose B12 deficiency is a common event in primary care but can be difficult. Clinical features can be non-specific and interpretation of B12 levels is also often difficult, particularly in patients who are otherwise well. There remains no "gold standard" test to define deficiency. Tests to examine B12 absorption (Schilling test) are no longer available. Ancillary tests (tHcy, MMA, HoloTC *) are not universally available and can come with their own difficulties. These difficulties can be challenging and frustrating to both clinicians and patients (ref: Public Petitions Committee of Scottish Parliament, March 2012).

Recent guidelines published by the British Committee for Standards in Haematology are geared towards secondary care: doi: 10.1111/bjh.12959. These are relatively complex but provide very useful background information to the challenges of diagnosis.

To help in this diagnostic process we have tried to devise a management plan for these patients for use in primary care, and a flow chart for guiding investigations. These are designed to be pragmatic. We hope these prove helpful. However, no guideline can cover all eventualities, particularly in a condition with no definitive test (see above).

Background

The B_{12} assay is a frequently requested test generating many results out with the reference range and thus reported as abnormal. It must be remembered, that as with most biological assays, many results out with the reference range will be found in normal individuals (**and *vice versa***).

Vitamin B_{12} deficiency - as defined by serum vitamin B_{12} levels below the reference range on two separate occasions a month apart - is a common finding; however, the identification of significant pathology either underlying or secondary to this deficiency is not.

This guidance aims to provide a simple means of assessing and replacing vitamin B_{12}, which will ensure adequate treatment of those with severe deficiency or underlying disease whilst minimising the treatment and investigative burden of the many minor deficiencies.

Testing

- As there is little evidence that population screening for vitamin B_{12} deficiency is of benefit, the assay should be reserved for those with signs or symptoms that suggest B_{12} deficiency is likely – a list of indications is attached.

- B_{12} and folate assays should be assessed concurrently due to their close relationship in metabolism (false low B_{12} levels may be seen in folate deficiency).

- If the serum vitamin B_{12} level is reduced on initial haematinic assay, a repeat serum vitamin B_{12} assay should be requested approximately one month after this initial test (note: computerised laboratory systems may block repeat request undertaken $\leq$ 30 days). Patients with clear and relevant symptoms, or blood count abnormalities, should be treated immediately (see below) and then re-assessed.

- Testing for the presence of Intrinsic Factor (IF) antibodies should be requested in addition at this stage. The laboratory location for IF antibody testing will vary with Health Board.

- Samples for IF testing should be taken before starting any B_{12} therapy as this can lead to false positive IF results. Equally, some assays may give false normal B_{12} results in sera with high IF titres.

- Gastric Parietal Cell antibodies are sensitive but not specific and not recommended for diagnosing pernicious anaemia (PA). On the other hand, IF antibody positivity is strongly predictive for pernicious anaemia (95% positive predictive value, 1-2% false positive rate i.e. high specificity) and should be considered diagnostic unless clinical features suggest otherwise. However, IF antibody is only present in 50% of cases of PA.

- The **Schilling Test of B12 absorption with/without intrinsic factor is no longer available** due to discontinuation of reagent manufacture. Historically, this investigation was a common reason for hospital referral.

- No specific level of B_{12} is considered a threshold for major deficiency, though the lower the serum vitamin B_{12} level the more likely clinical symptoms or macrocytosis will be present. The level at which clinically significant deficiency occurs is particularly variable in the elderly. Thus clinically significant B12 deficiency may be present despite B12 levels well within the reference range.

- B_{12} deficiency due to PA and malabsorption should be treated as per the BNF.

- Standard initial therapy for patients without neurological involvement is hydroxocobalamin 1000µg, intramuscularly (i.m.), three times a week for 2 weeks and with maintenance hydroxocobalamin 1000µg, i.m, every 3 months.

- Standard initial therapy for patients presenting with neurological involvement is hydroxocobalamin 1000µg, i.m, on alternate days until there is no further improvement – the BCSH guideline (see refs) suggests review at 3 weeks. Maintenance hydroxocobalamin 1000µg, i.m, is then given every 2 months (discussed further in BCSH guideline).

- Hydroxocobalamin is generally well tolerated (for side-effects see BNF and BCSH guideline).

- But most causes of vitamin B_{12} deficiency (apart from PA and malabsorption) will respond to oral vitamin B_{12} replacement (see below)

and this can be used as a screening test. A patient responding to oral therapy could then either continue oral replacement or use an IM preparation but would **not** need further investigation.

- Hospital referral should be reserved for those with **severe symptoms** or in whom standard investigations fail to clarify the cause of a **clinically significant** deficiency.

- A flow diagram is attached to guide investigation and vitamin B_{12} replacement.

Food-Cobalamin Malabsorption

Many patients with vitamin B_{12} deficiency have a negative IF screen, would historically have had a normal Schilling test and have no clinical malabsorption syndrome. Recently the syndrome of "Food-Cobalamin Malabsorption" has been described. In this syndrome the absorption of vitamin B_{12} bound to food is impaired but the absorption of free vitamin $B_{12,}$ such as in oral vitamin B_{12} supplements, is normal. This appears to be related to altered acid levels in the stomach impairing absorption. It is common in the elderly and in those taking antacid therapies. A full list of causes is appended.

The advent of food cobalamin syndrome as a diagnosis suggests a greater role for oral vitamin B_{12} in diagnosis and replacement therapy.

- It is suggested that between 125 and 250µg of oral cobalamin daily should be sufficient in dietary deficiency or food-cobalamin malabsorption.

- The only licensed formulation available at present is Cytacon containing 50µg cyanocobalamin. A trial of oral vitamin B_{12} should consist of Cytacon 150µg daily for 2 months.

It is hoped that this approach will allow a diagnosis to be made in Primary Care in the majority of patients and that unnecessary investigation can be avoided

Yours sincerely,

Dr

On behalf of:

Comments and suggestions in this guidance are welcome and should be directed to:

tHcy: Plasma total Homocysteine

MMA: Plasma methylmalonic acid

HoloTC: Holotranscobolamin (formerly transcobalamin II – the “active” form)

References

Vitamin B12 (cobalamin) deficiency in elderly patients. Andrès,E. CMAJ 2004; 171 (3) 251-9

Current concepts in cobalamin deficiency. Carmel, R. Annu. Rev. Med. 2000; 51:357–375

Serum folate and Vitamin B12 levels in women using modern oral contraceptives (OC) containing 20 µg ethinyl estradiol. Sütterlin M. Eur J O&G and RB. 2003; 107: 57-61

Oral Contraceptives Can Cause Falsely Low Vitamin B12 Levels. Gardyn, J. Acta Haematol 2000;104:22–24

Guidelines for the diagnosis and treatment of cobalamin and folate disorders. BCSH. Devalia V, Hamilton M, Molloy A. B J Haem 2014; 166: 496-513.

Indications for requesting serum vitamin B_{12} assay.

Macrocytosis (MCV ≥ 100fl)
Note: Liver disease, alcohol, hypothyroidism and chronic hypoxia should also be considered as possible causes of a macrocytosis. Patients on Hydroxycarbamide long term are all macrocytic due to the effects of the drug and further investigation is not warranted routinely.

Unexplained neurological signs and symptoms.
e.g. Peripheral neuropathy, visual loss and dementia.

Severe depression (especially in the elderly)

GI symptoms.
e.g. Glossitis, abnormal taste, surgery or radiotherapy to stomach/small bowel, malabsorption or unexplained diarrhoea.

Vegan Diet (long term)

Notes

1 Tiredness is **not** an indication for serum vitamin B_{12} assay.

2 Serum vitamin B_{12} assays should **not** be performed as first line in any routine haematological screen,

3 Oestrogen containing **OCP** and **HRT** use and pregnancy lower serum vitamin B_{12} levels without causing tissue deficiency or macrocytosis. Therefore it is generally **not helpful to check serum vitamin B_{12} in females taking the Combined OCP or HRT** unless there is a clinical indication such as described above.

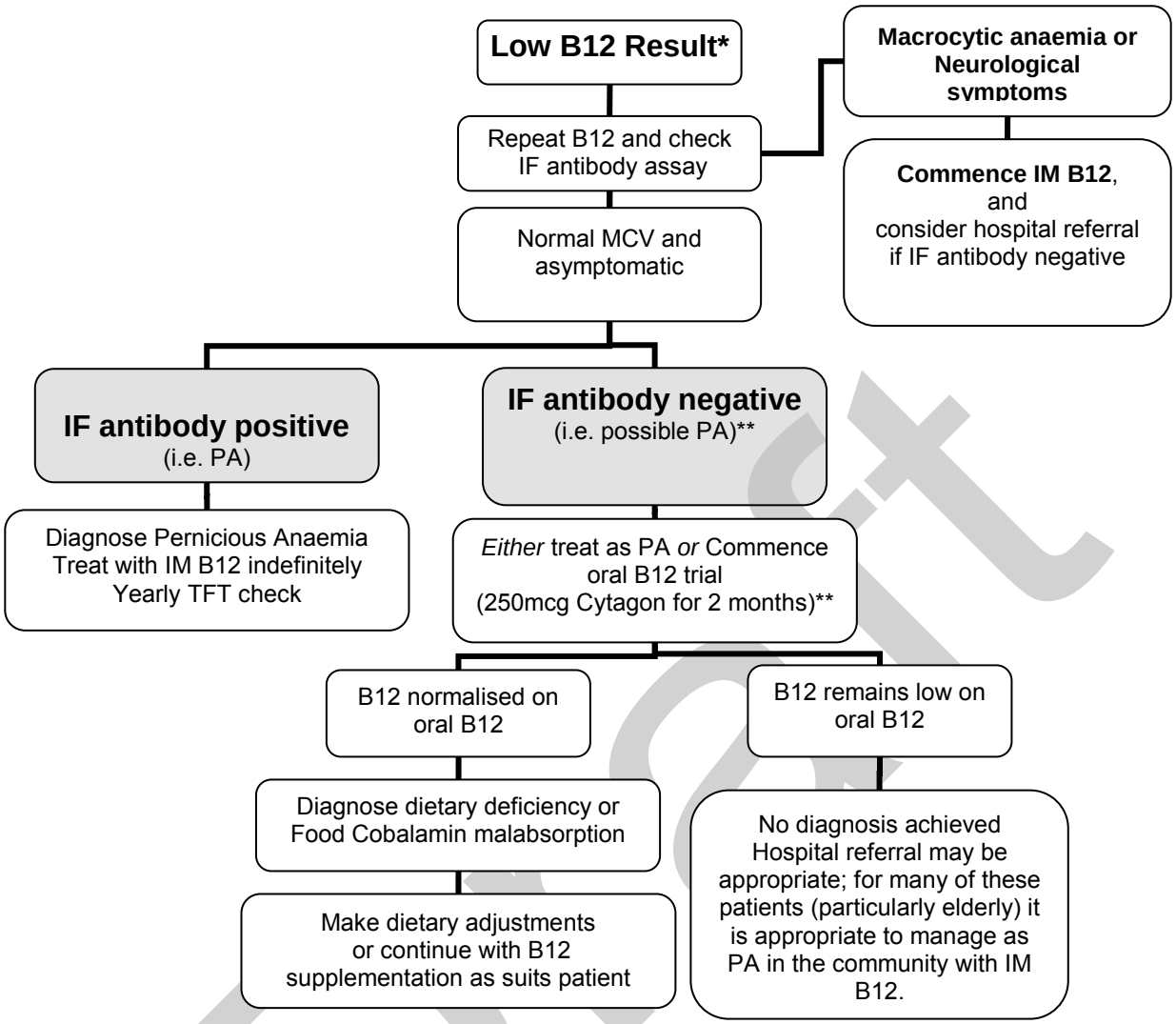
4 Local laboratory serum vitamin B_{12} assay reference intervals:

Please refer to your local laboratory

5 Predisposing Factors for Food Cobalamin Malabsorption

- Atrophic gastritis, chronic H. pylori infection
- Microbial proliferation, AIDS
- Long-term ingestion of antacids or biguanides (commonly seen with metformin).
- Chronic alcoholism
- Gastrectomy, gastric bypass surgery
- Pancreatic exocrine failure
- Idiopathic (age related)

Recommended action on obtaining abnormal B12 result.



Note: Patients in whom B12 deficiency is part of a wider malabsorptive disorder or who have associated bowel symptoms should be referred to Gastroenterology in the first instance and should not follow this schematic.

** If patients are on an oestrogen containing OCP or HRT preparation this should be ignored in the absence of relevant clinical or haematological abnormalities.*

*** In patients who have a low repeat B12, but negative IF antibodies (i.e. possible PA), it is appropriate to give a trial of oral B12. If unsuccessful, elderly patients should be treated in the community as PA (i.e. IM B12) thereby avoiding hospital referral. For younger patients it may be preferable to either have the diagnosis confirmed via hospital investigation or accept long-term IM B12 as a pragmatic measure.*