A case of chronic fatigue

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History

A woman in her 30s with a 10 year history of fatigue

- Worsening symptoms over the previous 2 years
- Past history of iron deficiency (due to menorrhagia) and

  Vitamin D deficiency. All other bloods normal except parietal cell antibodies positive

  Prone to constipation

- Little improvement with iron and vitamin D supplementation in the past.
- No other significant medical history or symptoms
- No regular medication
- Family history of Coeliac disease

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- What are your thoughts?
- What else would you ask about/explore?
- What would you do next?
- What tests would you consider? If any?

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Tests for causes of fatigue

- Fbc
- Electrolytes
- Liver function tests
- Ferritin
- B12 and folate
- TFTs
- Hba1c
- Coeliac screen
- Vitamin D
- Glandular fever screen if suspected from history
- HIV tests if patient at risk
- Hepatitis screen if patient at risk
- CXR if suspecting TB or concerns regarding possible malignancy
- Consider autoantibody screen

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This patient's test results

- Fbc normal
- Electrolytes normal
- LFTs normal
- TFT normal
- Hba1c normal
- Coeliac screen (TTG antibody) negative
- Vitamin D > 50 nmol/l (normal)
- Ferritin 46 µg/l (normal range 15-200)
- B12 292 ng/l (normal range 211-911)
- Folate 12.2 µg/l (normal)
- Parietal cell antibodies positive
- Intrinsic Factor antibody negative

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What next?

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- 7% of people with Coeliac disease can have a negative TTG antibody screen… [5]

- **However,** in this patient a previous 3 month trial of a gluten-free diet made little difference to her symptoms

- **What next??**

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Next step ...

- Trial of treatment with B12 injections
- IM Hydroxocobalamin 1mg 3 times a week for 2 weeks and then every 3 months

- Plan to review at 3 months

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What was the outcome?

- The patient's symptoms resolved!
- Why treat with B12 when the levels were normal?

  Low "normal" B12 levels
  Parietal cell antibodies positive
  Family history of autoimmune disease

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A review of the diagnosis and management of Vitamin B12 deficiency

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Vitamin B12

- Is an essential cofactor that is integral to methylation processes important in reactions related to DNA and cell metabolism
- A deficiency may lead to disruption of DNA and cell metabolism and thus have serious clinical consequences [6]

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Sources of dietary vitamin B12

- Foods of animal origin including meat, fish, milk, cheese, yoghurt and eggs are sources of vitamin B12
- Dietary deficiency, therefore, is mainly seen in strict vegans
- Daily requirement is small, 1-2 µg per day compared with total body stores of 2000-5000µg, which are mostly stored in the liver [3]

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Absorption of vitamin B12

- Dietary B12 is freed from food protein by pepsin in the acid gastric environment and binds to haptocorrin, a protein secreted in saliva
- Haptocorrin is degraded in the small intestine by pancreatic enzymes and vitamin B12 is released where it binds with intrinsic factor (IF secreted by gastric parietal cells)
- The IF-B12 complex binds to receptors in the terminal ileum where it is actively absorbed
- 1-2% of daily intake is passively absorbed across the entire absorptive surface of the intestinal tract [3]

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Causes of vitamin B12 deficiency

- **All ages**

• Infections	H.pylori, Giardiasis , Fish tapeworm
• Malabsorption	Pernicious anaemia
• Medical conditions	Gastric resection for obesity or cancer, Coeliac disease, Tropical sprue, Crohns disease
• Inadequate diet	Low intake B12 rich foods
• Drugs	Proton pump inhibitors, metformin, oral contraceptive pill, H2 receptor antagonists, alcohol, nitrous oxide, colchicine, cholestyramine, slow K (potassium chloride) preparations [6]

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- **Infants and children**
  - Genetic disorders
  - Inadequate intake — vegan diet
- **Women of childbearing age**
  - Pregnancy and lactation — Low B12 diet may lead to signs of deficiency by 3rd trimester
- **Older people**
  - Malabsorption — Achlorydia due to atrophic gastritis and PPIs result in malabsorption of food-bound B12. Slow development of B12 deficiency because secretion of intrinsic factor continues

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Clinical features to guide clinicians in suspected vitamin B12 deficiency

- **Anaemia**

  Exclude other causes of anaemia

- **Evaluation of diet**

  Is the patient vegan or vegetarian? Is the patient anorexic? Are there any food fads or indication of poor diet?

- **Personal and family history of autoimmune disease**

  A positive family history or personal autoimmune conditions increases the pre-test probability of Pernicious Anaemia

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- **History of glossitis or mouth ulcers**

  Glossitis is common in B12 deficiency

- **History of paraesthesia, unsteadiness, peripheral neuropathy**

- **Features of malabsorption**

  Ask about pale stool, abdominal pain, mouth or perianal ulceration. Steatorrhoea may be due to pancreatitis or small bowel disease. Crohns disease may present with ulceration. Consider history of pancreatitis due to alcohol excess

  Ask about stomach surgery including partial gastrectomy, bariatric surgery and small bowel resection. Gastrectomy will deplete B12 stores within 1-2 years

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- **Drug history**

  Prolonged use of PPIs, e.g. Omeprazole, cause a gastric pH of 3.0 or above which may affect release of vitamin B12 from food and cause deficiency. Normal gastric pH is usually between 1-3.

  Metformin may cause malabsorption

  Combined oral contraceptive pill may be associated with mildly reduced B12 levels although this may not be clinically significant

- **Pregnancy**

  Low B12 levels in third trimester may be physiological

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Tests to confirm/diagnose B12 deficiency: **MCV and Blood film**

- Oval macrocytes, hypersegmented neutrophils and circulating megaloblasts in the blood film and megaloblastic change in bone marrow are typical features of clinical B12 deficiency

- They are NOT SPECIFIC and there is a need to exclude other causes of elevated MCV including alcohol, drugs and myelodysplasia

- **Absence of a raised MCV cannot be used to exclude the need for B12 testing because neurological impairment occurs with a normal MCV in 25% of cases**

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Serum B12 (cobalamin)

- Currently the standard initial routine diagnostic test. Widely available and low cost
- Quantitates both the “inactive” and “active” forms of B12 in serum
- Lacks the specificity and sensitivity required of a robust diagnostic test

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- Serum B12 results should be interpreted taking into account clinical symptoms and the following limitations [4]

  1. The test measures total, NOT metabolically active, vitamin B12

  2. Levels are not easily correlated with clinical symptoms

  3. There is a large "grey zone" between normal and abnormal levels and reference values (and units) may vary between labs

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- 4. In Japan, the lower limit of normal is set at 500ng/l compared to around 200ng/l in UK labs [7]

- 5. **Clinically significant Vitamin B12 deficiency may be present even with B12 levels in the normal range – especially in elderly people**

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Plasma total homocysteine (tHcy)

- B12 (cobalamin) deficiency results in elevation of plasma total homocysteine
- A sensitive biomarker of B12 deficiency. It rises early in the course of deficiency, sometimes preceding symptoms and progresses as the disease worsens
- It is **not specific** to B12 deficiency and is elevated in folate deficiency, renal failure, hypothyroidism and some genetic polymorphisms too
- Not routinely available and the sample needs to be at the lab within a short period of time after collection (30mins in Calderdale)

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Plasma methylmalonic acid (MMA)

- Raised in B12 deficiency but may also be elevated in renal disease, small bowel bacterial overgrowth and haemoconcentration
- Despite the above limitations, exceptionally high levels of MMA (0.75µmol/l) almost invariably indicate B12 deficiency
- High cost test and not routinely available!

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Holotranscobalamin (HoloTC)

- This is the “active” fraction of cobalamin (B12) and may be more specific than serum cobalamin levels
- Holotranscobalamin accounts for 6-20% of bound serum vitamin B12. Only vitamin B12 bound as holotranscobalamin is presented for cellular uptake [6]
- The assay is NOT routinely available

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- In clinical research, the assay performs better than serum cobalamin in assessing deficiency based on MMA levels and red cell cobalamin levels. But arguments have been raised against accepting this, as MMA and red cell cobalamin cannot even be regarded as gold standard tests for deficiency

- Despite the above, the assay has a smaller “grey zone” (uncertainty range) than serum cobalamin assays with better sensitivity and specificity characteristics

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Tests to determine aetiology of B12 deficiency: Intrinsic Factor antibodies

- Pernicious anaemia (PA) is characteristically diagnosed by the presence of Intrinsic Factor antibodies. A low serum B12 level can be further evaluated with this test

- It is **highly specific** with a high positive predictive value of 95% for the presence of pernicious anaemia. It identifies those who will need lifelong B12 replacement

- However, it is only positive in 40-60% of cases (**low sensitivity**). **A negative Intrinsic factor antibody test, therefore, does not rule out pernicious anaemia**

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- Positivity of the test increases with age and in certain racial groups (Latino-Americans and African-Americans)

- **High titre IF antibody may interfere with serum B12 assays leading to false normal serum B12 levels**

- **Testing for IF antibodies is therefore advised in patients with strong clinical features of deficiency DESPITE normal serum B12 level. In these cases, pre-treatment serum should be stored for investigation with an alternate test such as MMA**

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Gastric parietal cell antibodies

- Positive in 80% of people with Pernicious Anaemia, so **high sensitivity ..** That means if it is negative it is likely the patient does not have Pernicious Anaemia, although not impossible. **Most patients with Pernicious Anaemia have positive parietal cell antibodies but not all patients with positive parietal cell antibodies have Pernicious anaemia**

- The test is also positive in 10% of normal individuals and in other conditions such as hypothyroidism

- The British Society of Haematology 2014 guidelines do not recommend it as a diagnostic test due to its **low specificity**

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Schilling test

- No longer performed. Expensive and difficult to source radioactively-labelled B12
- In the past patients with negative IF antibodies and low serum B12 levels would have had this test
- It provided objective evidence of vitamin B12 malabsorption using radioactively labelled B12 (Part 1) and evidence of whether this was corrected with the addition of intrinsic factor (Part 2)

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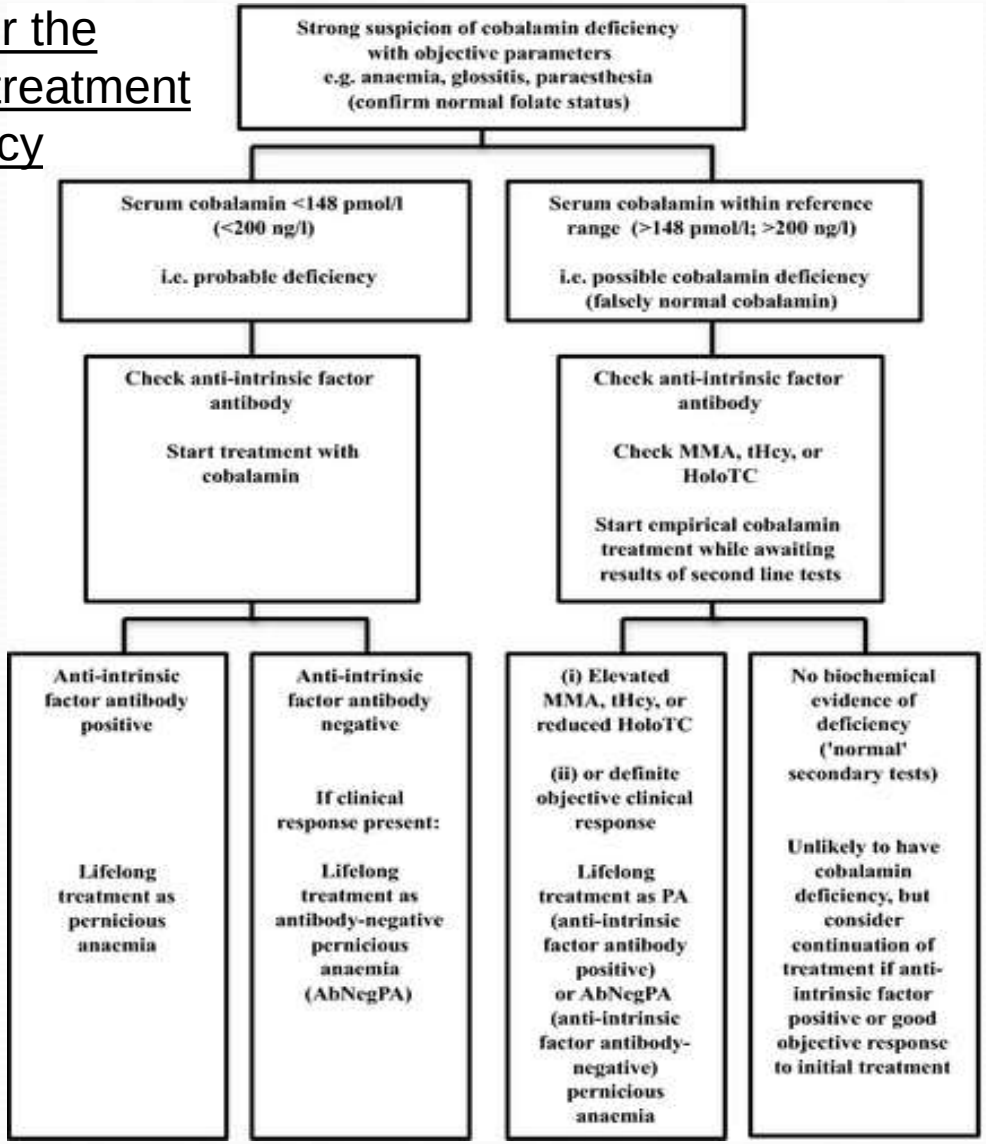
An algorithm for the diagnosis and treatment of B12 deficiency



British Journal of Haematology
Volume 166, Issue 4, pages 496-513,
18 JUN 2014 DOI: 10.1111/bjh.12959

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Treatment

- Standard treatment is 1mg hydroxocobalamin IM 3 x week for 2 weeks then every 3 months as per the BNF advice
- If neurological symptoms are present then the regime is alternate days till no further improvement and then every 2 months
- Hydroxocobalamin is generally well tolerated

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- High dose oral cyanocobalamin 1000-2000µg daily is licensed for use in several countries outside the UK and available on the internet. Passive, intrinsic factor independent absorption of a small fraction of such large doses should suffice to meet daily requirements

- Low dose oral cyanocobalamin (50- 150µg) is licensed in the UK and may improve levels in borderline cases

- A pragmatic protocol for treatment at The Newcastle upon Tyne Hospitals Trust

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Take home messages

- Interpret serum B12 levels in the light of the clinical context and awareness of its limitations. There is no ideal test to define deficiency and therefore the clinical condition of patients is of utmost importance
- Be aware that clinically significant B12 deficiency may be present with normal serum B12 levels, especially in the elderly
- Absence of a raised MCV does not exclude the need for B12 testing as neurological impairment occurs with a normal MCV in 25 % of cases
- A negative IF antibody test does not rule out Pernicious Anaemia

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- High IF antibodies can cause a false normal serum B12. Therefore, patients in whom there is a high clinical suspicion for Pernicious Anaemia should be tested for them even if they have normal serum B12 levels

- If the clinical features suggest deficiency then it is important to treat patients to avoid neurological impairment, even if there may be discordance between the results and clinical features [6]

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References

- 1.British Journal of Haematalogy 2014 Guideline for the diagnosis and treatment of cobalamin and folate disorders
- 2.Newcastle upon Tyne Foundation Trust Notes on use and interpretation of Vitamin B12 and allied measurements
- 3.Royal United Hospital Bath Trust Guidelines for investigation and management of B12 deficiency
- 4.CKS 2015 Anaemia - B12 and folate deficiency guideline summary

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- 5.BMJ 2014: Clinical Review: Coeliac Disease
- 6.BMJ Sep 2014 Clinical Review: Vitamin B12 deficiency
- 7.Japan Journal of Psychiatry and Neurology 1988 Serum and cerebrospinal fluid vitamin B12 levels in demented patients with CH3-B12 treatment--preliminary study

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