Patient journeys: diagnosis and treatment of pernicious anaemia

Martyn Hooper, Peter Hudson, Fiona Porter and Andrew McCaddon

Abstract

Background: **Instigating a patient support group for patients with pernicious anaemia (PA) revealed dissatisfaction with its current diagnosis and treatment. The authors investigated the clinical features, patient experience of diagnosis and treatment of PA in the UK.** ***Methods:*** **A total of 889 patients registered with the PA Society support group completed an online survey or postal questionnaire. Outcome measures included clinical features, length of time to diagnosis and patient satisfaction with current treatment** ***Results*****: One-third of patients experienced symptoms for up to 1 year before diagnosis; 14% waited more than 10 years for a diagnosis. Neurological features were highly prevalent, the most common being memory loss and poor concentration. Nearly two-thirds of respondents were dissatisfied with current treatment; 10% used a non-licensed form of B12 to supplement their prescribed injections.** ***Conclusion:*** **The diagnosis and treatment of PA should be subject to a thorough review. This article discusses the patient survey and results and makes recommendations for how the diagnosis and treatment of PA may be evaluated.**

Key words: Vitamin B12 deficiency ■ Anaemia ■ Pernicious ■ Diagnosis ■ Therapy ■ General Practice

A fatal form of anaemia associated with stomach degeneration was first described in 1824 by JS Combe in Edinburgh and later by Thomas Addison, a physician at Guy's Hospital in 1849 (Combe, 1824; Pearce, 2004). Biermer (1872) coined the term pernicious anaemia (PA) based on the inevitably fatal outcome of the disorder. PA prevents the body from absorbing vitamin B12, which is of course essential for life.

This disease remained incurable until 1926 when two American physicians, Minot and Murphy, described a raw liver diet that cured PA (Minot and Murphy, 1926). Liver extracts were made which reversed PA in dogs and humans. For the next two decades, liver was the main source of this unknown curing factor called 'extrinsic factor'. Castle (1929) observed that gastric juice contained a protein he called 'intrinsic factor', which further enhanced the curative effects of the extrinsic factor.

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In 1948, two independent teams in the USA (Rickes et al, 1948) and England (Smith and Parker, 1948) isolated the mysterious extrinsic factor as a pure crystal. Folkers called it 'vitamin B12.' Dorothy Hodgkin, a British chemist, elucidated the unique and complex chemical structure of this large molecule using X-Ray crystallography (Hodgkin et al, 1955) (*Figure 1*). She was awarded the Nobel Prize for chemistry in 1964 for this monumental achievement. The production of vitamin B12 on an industrial scale in the early fifties enabled its worldwide medical application to treat PA.

Total human body content of vitamin B12 is 2–5 mg. Daily losses are estimated to be about 0.1–0.2% of the total content and correspond equally to urinary and digestive excretion. A normal diet provides 5–15 µg of vitamin B12 per day but 60–80% of ingested vitamin is eliminated in stools or metabolised by intestinal flora. Requirements vary depending on age. The recommended daily dietary amounts for adults, pregnant women, and infants are set at 3.0, 4.0, and 0.5 µg respectively (Green and Miller, 2007).

Vitamin B12 occurs solely in food of animal or bacterial origin. Examples of foods high in B12 include shellfish (cooked clams 98.9 µg/100 g); liver (83.1 µg/100 g); fish (mackerel 19 µg/100 g); red meat (beef 6 µg/100 g); cheese (swiss 3.3 µg/100 g); eggs (yolks 2 µg/100 g; typical whole egg 0.36 µg); and skimmed milk (0.5 µg/100 g). Some foods are fortified with vitamin B12, and can be used as alternative sources, e.g. cereal ('All Bran' 20 µg/100 g); soy products ('Silken Tofu' 2.4 µg/100 g) and yeast extracts ('Marmite' 0.5 µg/100 g). The vitamin B12 in these foods is mainly in the form of methyl-B12 and adenosyl-B12. Food B12 is always protein-bound and released by the sequential processes of cooking and acid-dependent peptic digestion.

Absorbtion of vitamin B12

To understand why vitamin B12 deficiency occurs, it is necessary to know how it is normally absorbed from food. From the point of entry at the mouth, food is acted upon by a series of enzymes before the vitamin is finally released into the blood stream.

Saliva is a major source of cobalophilin (CP)—the first protein to bind B12 in its assimilation. In the stomach, gastric chyme and pepsin release B12 from dietary protein enabling it to bind to CP. Gastric parietal cells are the source of a second B12-binding protein, intrinsic factor (IF) mentioned above. In the alkaline conditions of the duodenum, this binds

strongly to the small amounts of B12 released from food and degraded CP-B12. The subsequent IF-B12 complex is resistant to further digestion; it binds to a specific receptor in the terminal ileum. Bile is also important for the body's regulation of B12. There is an entero-hepatic circulation of the vitamin that perhaps helps eliminate its potentially harmful analogues (el Kholty et al, 1991). Corrinoids (active B12 and its inactive analogues) are excreted in bile bound to CP. Partial degradation of CP by pancreatic enzymes releases active B12 that binds to IF and is re-absorbed, whereas inactive analogues are excreted.

There are two mechanisms for B12 absorption in the ileum: passive diffusion and uptake via a specific IF-B12 complex receptor. B12 is rapidly internalised in enterocytes where it is transformed into methyl-B12 in the cytosol and adenosyl-B12 in the mitochondria. These then attach to a third binding protein, transcobalamin (TC), and 3 hours after absorption, the vitamin is transported into the blood as holo-TC.

Following binding of holo-TC to the TC receptor on cells, B12 is retained and converted to its coenzyme forms (Quadros et al, 2009). There are two B12-dependent enzymes in mammalian cells, methylmalonyl-CoA mutase (MCM) and methionine synthase. MCM catalyses the conversion of L-methylmalonyl-CoA to succinyl-CoA. This requires adenosyl-B12 as a cofactor. Methionine synthase catalyses the conversion of homocysteine to methionine and requires methyl-B12 as a cofactor.

PA and other causes of vitamin B12 deficiency

Reduced dietary intake is an uncommon cause of B12 deficiency, occurring only in vegans, children of vegans, and in cases of severe prolonged malnutrition. Vegans make up 2% of the UK population (Department for Environment, Food and Rural Affairs, 2007). The prevalence of vitamin B12 deficiency ranges from 47.8% to as high as 86.5% in strict vegans (Pawlak et al, 2014). More commonly, the vitamin may be malabsorbed as a result of disorders affecting any part of the gastrointestinal tract from the stomach to the ileum.

Intra-gastric factors

Acid and pepsin are necessary for the release of B12 from food and its transfer to CP in the stomach. Potential causes of deficiency therefore include non-specific gastritis (associated with helicobacter pylori) and other gastric diseases and surgery, acid-suppressing drugs and alcohol abuse.

Intrinsic factor deficiency

Intrinsic factor (IF) deficiency may result from an autoimmune disorder (e.g. PA), atrophic gastritis or surgical resection, all of which result in defective secretion.

Autoimmune PA is prevalent in Europeans, especially Scandinavians. It is frequently associated with other autoimmune diseases such as Hashimoto's thyroiditis and adrenocortical insufficiency. In addition to anaemia, patients may have pathognomonic anti-IF antibodies and antiparietal cell antibodies in serum.

Some forms of atrophic gastritis are accompanied by B12 deficiency, and can be difficult to distinguish from PA although they are far more frequent. Total and partial gastrectomy and/or vagotomy can also result in deficiency (Roos, 1978).

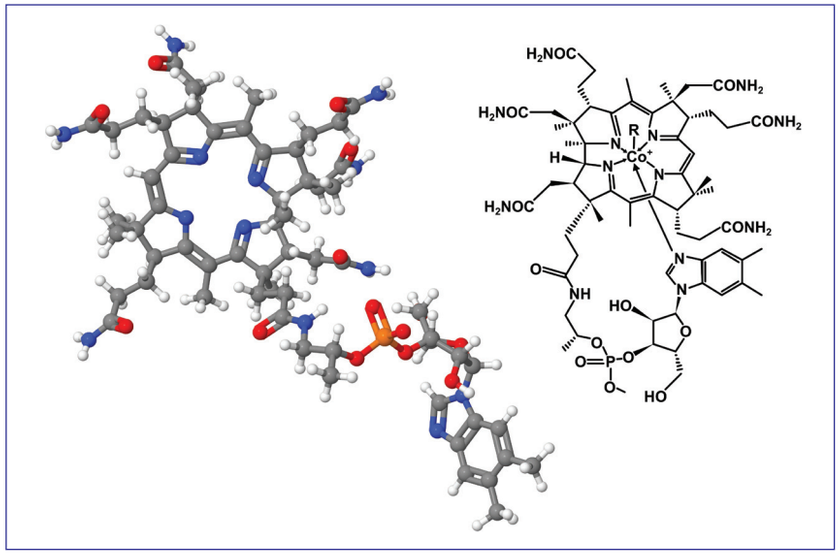

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Figure 1. Chemical structure of Vitamin B12 using X-ray crystallography

Pancreatic insufficiency

B12 deficiency can also occur as a result of chronic pancreatitis, other exocrine pancreatic insufficiencies and cystic fibrosis.

Intestinal factors

There are many potential causes of B12 malabsorption relating to the intestine including ileal resection, radiation injury, ileal disease such as Crohn's disease, parasitic infestation, obstructive jaundice and coeliac disease.

Rare causes

Rare causes of deficiency include non-functional transport through the ileum (Imerslund Gräsbeck syndrome) and deficiency of binders (holo-TC deficiency) (Linnell and Bhatt, 1995). There is also the possibility that deficiency can result from excess requirements or increased catabolism of the vitamin (McCaddon, 2013).

Treatment of vitamin B12 deficiency

In the UK, replacement therapy is usually given by regular intramuscular injections of hydroxocobalamin (1000 µg), bypassing the need for IF and allowing the vitamin to absorb by diffusion. About 10% of the injected dose is retained. For patients without neurological involvement, this is usually given three times a week for 2 weeks, then at 3-monthly intervals. For patients with neurological involvement, it should be given on alternate days until there is no further improvement and then at 3-monthly intervals (Royal Pharmaceutical Society, 2013). There is some evidence that daily oral high doses of vitamin B12 (1000–2000 µg) are as effective as intramuscular injection in achieving haematological and neurological responses (Butler et al, 2006). Oral replacement is used in some countries, including Sweden and Canada. Some patients with PA subsequently develop iron deficiency

resulting from an associated chronic atrophic gastritis. Such patients should be further investigated with endoscopy owing to a slight increased risk of gastric carcinoma (Hvas and Nexo, 2006). Some experts also suggest surveillance endoscopy for gastric malignancy and carcinoid every 5 years in young patients with PA (Borch, 1986; Armbrecht et al, 1990).

The Pernicious Anaemia (PA) Society was established as a patient support group in 2006. Its remit was to provide patients with a plain English explanation of their diagnosis. It soon became clear from posts in the society's online forum, and later from telephone enquiries, that there were issues and concerns surrounding the time taken for patients to be diagnosed with PA.

It also became apparent that many patients were unhappy with the treatment they were receiving. In particular, they felt doctors failed to appreciate that more frequent injections often helped their symptoms; these were usually denied on the basis of vitamin B12 levels returning to normal. More worryingly, several patients reported that replacement, which should be lifelong, was discontinued following restoration of blood vitamin B12 levels.

The society realised that in order to raise awareness of these problems, it would need more than anecdotal evidence no matter how plentiful this was. This article describes the results of a survey of PA Society members in the UK collected over an 18-month period.

Methodology

An online survey was designed by a GP using SurveyMonkey software and placed on the charity's website (http://www.surveymonkey.com/s/XMNY6R5).

Existing online members (approximately 3500) logging onto the website were given the opportunity to complete the survey but once completed, members would not be prompted to complete the survey again on subsequent logins.

The society's 'paper members' (approximately 200) were also sent a hard copy to complete and return. All responses were collated in a single electronic dataset. Every new online member was offered the same opportunity as full members to complete the survey when they first logged on during the study period.

A total of 38 questions were asked. These included:

- General information (sex, age at diagnosis, ethnicity, eye and hair colour)
- Symptoms (divided into systems, e.g. gastrointestinal, cardiovascular, neurological)
- Past medical history
- Tests done (e.g. B12 level, folic acid, anti-IF antibodies, parietal cell antibodies)
- Medication (type, frequency and mode of delivery)
- Patient satisfaction with diagnosis and treatment
- Two opportunities to make comments (one about their current treatment and one about their diagnosis).

These questions fell into one of three formats:

- A yes/no type (e.g. 'Do you have PA?')
- A single selection (e.g. 'Which of the following hair colours do you have?')
- A multi-tick question (e.g. 'Which of the following symptoms have you experienced? Tick all that apply.')

When asked to think about the way in which their condition was investigated and diagnosed, and then rate their medical treatment, they were asked to select one answer on a scale ranging from 'Excellent' to 'Very Poor.'

NHS Research Ethics Committee (NRES) approval was not required; the project was designed solely to evaluate current care. It did not involve randomisation or allocation to any intervention and was thus classified as an audit rather than clinical research (NRES, 2009).

Results

Between August 2010 and November 2012, 1184 individuals completed the questionnaire. After eliminating those who filled in the questionnaire on behalf of a friend or family member, and non-UK respondents, 889 completed questionnaires remained. All reported percentages are based on this total number.

There were 721 female and 168 male respondents. There is no direct data regarding the incidence of PA between sexes but the much higher incidence of females in the family history of PA suggests it may be more prevalent in females. We have to note however that this survey was taken from members of the PA society, and that females are perhaps more likely to join forums and societies than men. The ages of respondents at the time of diagnosis of PA varied from less than 10 years (4 individuals) to greater than 80 years (12 individuals). The most frequent age at diagnosis was 41–50 years (228 individuals). The majority of respondents (850) regarded their ethnicity as 'White European'. Again, the PA Society, though world-wide, is based in the UK, and UK residents, most of whom are White European, make up a very high percentage of its membership.

Of the respondents, 135 had a parent with PA. Other reported family members with the disorder included a grandparent (130), a sibling (54), a child (20), an uncle or aunt (83) and a cousin (33).

There were 304 individuals who experienced symptoms of the disorder for up to a year before the diagnosis of PA was made. Some had to wait up 2 years (193), 5 years (173), 10 years (40) or more; 127 individuals experienced symptoms for more than 10 years prior to receiving their diagnosis.

Most of the individuals (99%) reported a range of general symptoms, predominantly tiredness (96%) but also (in decreasing order of frequency) 'waking up tired' (87%), dry skin (58%), brittle nails with (47%) or without (37%) ridging, flushes or fever (43%), glossitis (34%), hair loss or greying (30%), weight loss (21%) and jaundice (6%). The remaining 1% reported no symptoms and their B12 deficiency will have been an incidental finding.

Most individuals (98%) also reported a range of neurological symptoms including memory loss (78%), poor concentration (75%), clumsiness (66%), pins and needles (66%), poor sleep (64%), confusion (62%), dizziness (59%), headaches (52%), nominal aphasia (word-finding difficulties) (50%), 'shoulder bumps' (frequently bumping into things as a result of balance problems) (48%), unable to stand with eyes closed (34%), Grierson syndrome (33%) and vertigo (33%). Cardio-respiratory symptoms were reported by 86% of individuals, comprising shortness of breath (73%) and palpitations (56%).

Gastrointestinal problems were commonly reported (82%). These included diarrhoea (58%), indigestion (42%), diarrhoea following constipation (40%), stomach cramps (39%), loss of appetite (27%) and loss of taste (26%).

Emotional symptoms were also commonly reported (86%), including irritability (75%), impatience (64%), mood swings (58%) and suicidal thoughts (22%). Finally, 21% reported urinary tract infection.

Many patients reported a co-existing diagnosis. These included depression (45%), tinnitus (34%), psoriasis, eczema or acne (28%), folic acid deficiency (23%), arrhythmia (21%), hypothyroidism (19%), vitiligo (patchy skin depigmentation) (13%), rheumatoid arthritis (8%), diabetes mellitus (6%), coeliac disease (6%), previous Helicobacter pylori infection (5%), psoriatic arthritis (4%), hyperthyroidism (3%), hyperparathyroidism (1%), gastrectomy (1%), multiple sclerosis (0.2%) and gastric cancer (0.1%).

At diagnosis, the following investigations were undertaken: serum B12 (67% of individuals), serum folate (34%), serum intrinsic factor antibodies (IFA) (32%), endoscopy (15%) and serum parietal cell antibodies (PCA) (14%).

The results showed low serum B12 (51% of individuals), low serum folate (17%), positive IFA (10%), normal serum folate (9%), negative IFA (9%), positive PCA (6%), normal endoscopy result (6%), negative PCA (4%), abnormal endoscopy result (3%) and normal serum B12 (2%).

Individuals were asked to report which form of B12 they were taking. A total of 56% were taking hydroxocobalamin, 10% were taking methylcobalamin and 8% were taking cyanocobalamin. These were delivered mainly via intramuscular injection (88%). Sublingual tablets (4%), tablets (3%), subcutaneous injection (3%) and sublingual spray, sublingual drops, behind the ear patch and nasal spray (all 1% or less) were also lesser used modes of delivery. Therapy was usually administered at a health clinic (83%), and by a smaller group of people via self-injection (6%), by a friend or family member (2%) or at a private clinic (1%).

Of those individuals receiving B12 by injection, <1% were being treated more than once a day; 1% were being treated daily; 2% weekly; 9% monthly; 15% twice-monthly, 50% once every 3 months and 10% were being treated at some 'other' frequency.

When asked if they were satisfied with their treatment, 64% said 'No', 28% said 'Yes' and the remaining 8% did not provide an answer. Respondents were asked which word best described how they rated their medical care. The results were: Very Poor (20%), Inadequate (18%), Good (10%), Poor (10%), Undecided (9%), Reasonable (8%), Adequate (8%), Very Good (7%), Excellent (3%) and Unreasonable (2%). The remaining respondents did not answer the question.

Before the final diagnosis of PA was made, respondents were asked if they were incorrectly given another explanation for their symptoms. 50% said 'No', 44% said 'Yes' and the remaining 6% did not answer. The respondents were invited to describe these. The most frequent was anxiety or depression (143). The next most common were chronic fatigue syndrome/myalgic encephalopathy (46), anaemia/iron deficiency (42), irritable bowel syndrome (39), hypothyroidism (35), multiple sclerosis (24), hypochondria (22), fibromyalgia (21), coeliac disease (18), fatigue (14), menopause (14), diabetes (11) and post-viral (11). There were numerous other explanations with less than 10 respondents identifying each.

Discussion

Recent appraisals of the clinical features and diagnostic course of PA are sparse (Hvas and Nexo, 2006; Song et al, 2013; Stabler, 2013). The survey described in this article was prompted because PA Society members expressed dissatisfaction with their treatment and the time taken to reach a diagnosis. This was confirmed by finding that nearly two-thirds of respondents were dissatisfied with current treatment and that one-third had experienced symptoms for up to a year before diagnosis. Nearly 22% had to wait 2 years, 19% for 5 years and 4% for 10 years. Regrettably, 14% of individuals experienced symptoms for more than 10 years before arriving at their diagnosis.

Many symptoms described are non-specific but nevertheless recognised by health professionals as possible features of PA. However, the survey also revealed a high prevalence of less typical features that should alert health professionals to the possibility of B12 deficiency. It also provided additional insight into otherwise 'textbook' features. For example, tiredness was an almost universal symptom, but described as 'waking up tired,' and a 'strange tiredness' despite an adequate period of sleep. Other features not typically associated with PA include frequent reports of brittle nails, flushing, fever, hair loss and greying.

Patients had a markedly high prevalence of neurological features, the most common being memory loss and poor concentration. This is consistent with the increasingly recognised importance of the vitamin in relation to cognitive decline and incident dementia (Grober et al, 2013; McCaddon, 2013). In a recent study of metabolic B-vitamin deficiency in patients with mild cognitive impairment, the beneficial effects of three B vitamins in slowing brain shrinkage were predominantly mediated by vitamin B12 (Douaud et al, 2013). It is important for health professionals to be aware that the neurological and haematological features of vitamin B12 deficiency are frequently dissociated (Lindenbaum et al, 1988). In addition to typical neurological features such as paraesthesia (pins and needles), half of patients also reported word-finding difficulties. Nominal aphasia is not a recognised feature of PA but has been reported in association with metabolic B12 deficiency (McCracken et al, 2006).

Gastrointestinal features including diarrhoea were also extremely common, as were emotional symptoms such as irritability and mood swings. Interestingly, there is increased awareness of an association between vitamin B12 deficiency and depressive symptomatology, particularly in the elderly (Tiemeier et al, 2002; Lachner et al, 2012).

Surprisingly, one third of individuals reported not having had a B12 assay at the time of diagnosis. Similarly, only one-third reported having had anti-IF antibodies measured. However, patients were instructed to leave these questions unanswered if they were unsure. Most patients received intramuscular injections at a health clinic. Of these, half reported an injection at a frequency of every 3 months.

The majority of patients were dissatisfied with their

KEY POINTS

- Pernicious anaemia prevents the body from absorbing vitamin B12
- Vitamin B12 was first identified 65 years ago
- Treatment regimes for its deficiency are based on metabolic studies in the 1960s
- A patient support group highlighted dissatisfaction with the current treatment and diagnosis of PA
- The survey described in this article confirms this, suggesting that a review of the clinical management of B12 deficiency should be undertaken

treatment; half reported it as being poor, very poor, inadequate or unreasonable. According to personal observations by the lead author, patients who are unhappy with current NHS treatment increasingly seek alternative sources of vitamin B12. As well as intravenous infusions, which make up the most common delivery method, other modes of delivery include sublingual sprays and drops as well as skin patches and nasal sprays. Patients who are unable to convince their doctor that they need more frequent injections than the one usually prescribed every 12 weeks in the UK increasingly resort to such alternatives. This has been driven by the many social media sites found on the internet and by manufacturers reacting to a demand for self-administered treatments. No thorough investigation into their efficacy has been carried out. Most new products use methyl-B12, although it is not licensed for use in the UK. Of the survey respondents, 10% reported using methyl-B12 to either replace or supplement their prescribed injections. It is difficult to comment on the initial 'misdiagnosis' of 44% of respondents. Physicians may have either attributed symptoms to a spurious diagnosis or a pre-existing condition.

One potential source of bias is that dissatisfied PA patients are perhaps more likely to register with a patient support group. Another difficulty of interpretation is whether patients completing the questionnaire 'genuinely' had PA; they may incorrectly believe that the condition is synonymous with B12 deficiency which, in addition to the causes listed previously, can also arise from recreational use of nitrous oxide (whippits) and several prescription medicines including metformin, colchicine and proton pump inhibitors.

Nevertheless, whatever the underlying cause, it is clear that the recognition of vitamin B12 deficiency and its treatment are considered sub-optimal by most patients. Treatment dissatisfaction presumably arises from individual variability in clinical response to vitamin-B12 replacement. The reasons for this are unknown. It might reflect an overly prescriptive approach to treatment coupled with genetic determinants of B12-tissue delivery such as polymorphisms of the B12-transport protein (TC), and/or its receptor (McCaddon, 2013). The authors are not aware of any other surveys showing the considerable length of time taken to reach a diagnosis of PA, and health professionals are likely to be unaware of this. This study is important in highlighting the current situation.

The role of the nurse

The survey revealed considerable patient dissatisfaction with treatment. The role of the nurse is vital in the management of B12-deficient patients. As the health professional likely to have the most ongoing contact with the patient, nurses are best suited to re-evaluate patient symptoms and discuss optimal dosing with both the patient and physician.

Recommendations

This large UK-based survey revealed considerable dissatisfaction among patients, suggesting that a review of the current diagnosis and treatment of PA in particular, and vitamin B12 deficiency in general, should perhaps be undertaken.

As well as validating some of the novel symptomatology presented here, such a review could further evaluate the use of newly developed tests for B12 status including breath tests (Wagner et al, 2011) and the 'active B12 test' (holo-TC) (Sobczynska-Malefora et al, 2014). The clinical role of ancillary tests of absorption (the 'CobaSorb' test) also needs clarification. In CobaSorb, the absorption of an oral dose of B12 is reflected by an increase in holo-TC in healthy individuals (Hvas et al, 2011). So far, this has only been evaluated in a few patients with acquired vitamin B12 deficiency, including PA.

It would also be helpful to formally evaluate the alternative delivery methods for replacement B12 therapy that have become available in recent years; these include nasal sprays, sub-lingual drops and sprays, transdermal patches, suppositories and self-administered sub-cutaneous injections of methyl-B12.

The survey described in this article suggests that patients are currently diagnosed late, their symptoms are poorly controlled and their satisfaction with their condition's management is poor.

Health professionals have a responsibility for providing good care. Tests currently used by the NHS for the diagnosis of PA are relatively insensitive. The only guidelines for treatment are given in the BNF, and these are both outdated in their approach and restrictive. With modern advancement in this field, there is likely to be an increase in the number of patients diagnosed with B12 deficiency. In addition, if patients are treated according to their symptoms, injections will also become more frequent.

Nurses are ideally placed to act as the patient's advocate in achieving a better standard of care in B12 deficiency. The symptoms experienced by these patients are often lifestyle-limiting and sometimes life-limiting. The impact of better care to patients would be immeasurable. BJN

Conflict of Interest: PH and AM are scientific advisors and shareholders of COBALZ Limited—a private limited company developing novel B-vitamin and antioxidant supplements.

Author's Contributions: MH conceived the survey and assisted FP with the design and implementation of data collection. PH analysed the data. AM drafted the initial version of the paper. All authors contributed to subsequent drafts and revisions of the paper.

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