# Chapter 6 Neurological disorders – SACD/MS-like presentation

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*Though the mountains may fall, and the hills turn to dust,*
*yet the love of the Lord will stand as a shelter*
*for all who will call on his name.*
*Sing the praise and glory of God.*

*Could the Lord ever leave you?*
*Could the Lord forget his love?*
*Though the Mother forsake her child,*
*he will not abandon you.*

*Should you turn and forsake him,*
*he will gently call your name.*
*Should you wander away from him,*
*he will always take you back.*

*Go to him when you're weary;*
*he will give you eagle's wings.*
*You will run, never tire,*
*for your God will be your strength.*

*As he swore to your Fathers,*
*when the flood destroyed the land.*
*He will never forsake you;*
*he will swear you again.*

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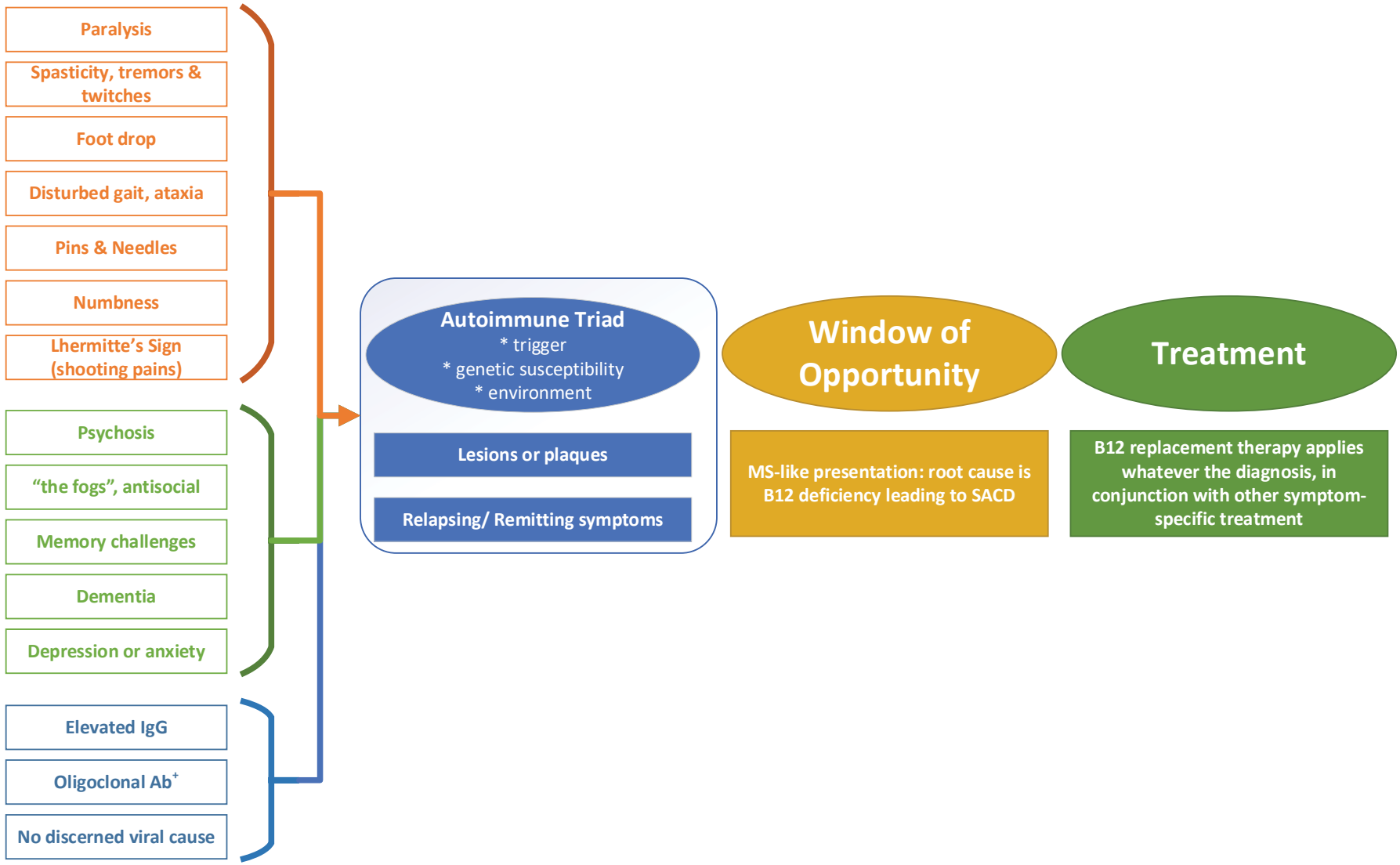
Daniel L. Schutte, Society of Jesus

*Figure 6-1 Key points regarding B12 deficiency and neurological disorders*



## 6.1 Vitamin B12 deficiency and neurological disorders

Vitamin B12 is essential for the proper functioning of the nervous system through several routes. Through the action of the B12-dependent enzyme methylmalonyl CoA mutase, it contributes to synthesis of fatty acids which are required for the integrity of the myelin[27] sheath (Scalabrino, 2001). Vitamin B12 affects every single cell, including the Schwann cell,[28] which is vital for neurological function (Nishimoto et al., 2015). Another B12-dependent enzyme, methionine synthase, is crucial for the proper functioning of the methionine cycle which leads to supply of S-adenosylmethionine (SAMe). B12 deficiency affects levels of SAMe, leading to impaired methylation reactions needed for the synthesis of proteins and neurotransmitters[29] in the Central Nervous System (CNS) (Varela-Rey et al., 2014). It has also been suggested that vitamin B12 may have other effects on the nervous system, for instance as a regulator of cytokines[30] (Scalabrino, 2001).

In our experience, neurological and neuropsychiatric signs and symptoms are the most frequently encountered presentations of vitamin B12 deficiency today. Research has shown that neurological symptoms manifest in up to 75% of B12-deficient patients (Carrazana, 2002). If untreated these symptoms may lead rapidly to the severe vitamin B12-deficiency condition known as Sub Acute Combined Degeneration of the spinal cord (SACD). This can be a devastating condition causing irreversible nerve damage and eventually death. Symptoms include debility, abnormal sensations such as tingling and numbness, mobility difficulties, mental disorders, and problems with vision, all of which gradually worsen if undiagnosed and untreated. The term "combined" is used because the condition affects the brain and the peripheral (body) nerves as well as the spinal cord.

## 6.2 SACD: a "forgotten" illness

SACD has been known for more than a century (see below) but today it is scarcely mentioned in medical textbooks and clinical guidelines. To our knowledge there are no guidelines – other than our own – which deal specifically with its clinical symptoms. For instance, SACD did not feature in the 16th edition of the medical textbook *Harrison's Principles of Internal Medicine* and is mentioned only in a short paragraph in the 20th edition (Hauser, 2018). Similarly, at the time of writing, there is no mention of SACD in the National Institute for Care and Excellence (NICE) Clinical Knowledge Summaries [online], one of the foremost reference authorities for clinicians. It is for this reason that we have termed vitamin B12 deficiency a "forgotten illness".

A few decades ago, SACD was a more generally recognised diagnosis than it is today. The condition is also known as Putnam-Dana Syndrome or Lichtheim's disease after early interpreters of the condition. James Jackson Putnam (1846–1918), Charles Loomis Dana (1852-1935) and Ludwig Lichtheim linked anaemia with spinal cord degeneration in the late 1880s and early 1890s (Pearce, 2008).The first complete clinical description of the condition, however, was given by the eminent neurologist James Samuel Risien Russell (1863-1939) in a paper published in *Brain* (Russell et al., 1900). At that time, much of the diagnosis had to be made from post-mortem dissection. He described plaques in the diseased brain and spinal cord, which have now become diagnostic

[27] Myelin is an insulating sheath around nerves which is made of protein and fatty acids. It allows electrical impulses to transmit effectively along nerve cells.
[28] Schwann cells play a crucial role in maintaining the peripheral nervous system (PNS).
[29] Neurotransmitters are chemicals used by the nervous system to transmit messages between neurons or from neurons to muscles.
[30] Cytokines are proteins released by cells that aid cell communication in immune responses.

characteristics of Multiple Sclerosis (MS) (viewed on MRI scans today). Many other early clinical studies also identified a link between vitamin B12 deficiency and severe neuropathy (Scott & Molloy, 2012). For example, in a chapter on "Vitamin B12 Neuropathy" published in 1969, Chanarin gave a detailed description of the condition (Chanarin, 1969).

## 6.3 SACD: difficulty of diagnosis by traditional means

Carrazana (2002) describes the effects of SACD thus: "[It…] is the classic nervous system manifestation of vitamin B12 deficiency. It affects the dorsal columns with resulting deficits of position and vibration sense, broad-based ataxic gait and, occasionally, Lhermitte's sign. Involvement of the corticospinal tracts leads to weakness, spasticity, hyperreflexia, clonus, Babinski sign and urinary/faecal incontinence".

From our own experience, and as tabulated in Table 6-2, we have encountered the following neurological symptoms in vitamin B12-deficient patients (note that this list is not exhaustive): weakness of limbs; fatigue; disturbance of gait; loss of tendon reflex; spasticity; paresthesia (unusual sensations); hypoesthesia (reduced sensation); painful spasms; sensory impairment; eyesight disorders; depression; memory loss; impaired attention; paroxysmal symptoms; slow information processing; facial weakness. In other words, neurological symptoms predominate in these patients and may, or may not, be accompanied by haematological evidence in the form of macrocytosis, anti-IF antibodies and low serum B12 levels.

Partly because of the lack of prominent guidelines, SACD is often missed as a diagnosis and its symptoms attributed mistakenly to other illnesses or even viewed as being "all in the patient's mind". In our experience it has been misdiagnosed as a variety of other conditions, such as Chronic Fatigue Syndrome (CFS), Myalgic Encephalomyelitis (ME) and particularly MS. Neurologists often fail to consider SACD as a differential diagnosis for MS whose symptoms it mimics. The similarities between the two conditions (mapped in Table 6-2) are very close but the diagnosis of SACD is frequently overlooked, we believe, because of lack of knowledge of the condition and/or over-reliance on serum B12 levels and whether macrocytosis and anti-IF antibodies are present – the classic signs of vitamin B12 deficiency (whose drawbacks as diagnostic criteria are discussed in Chapter 2). For example, in the brief mention of SACD in *Harrison's Principles of Internal Medicine*, we read: "The diagnosis is confirmed by the finding of macrocytic red blood cells, a low serum B12 concentration, and elevated serum levels of homocysteine and methylmalonic acid" (Hauser, 2018, p. 3181).

As emphasised throughout this book, we advocate a holistic approach to patient care which has proved indispensable in vitamin B12-deficiency diagnosis. It is through applying such an approach (via our Patient-Safe Protocol) that we have been able to diagnose and treat many missed cases of SACD – some of long standing – with successful results. The five cases presented here are evidence of this success.

## 6.4 Examples of misdiagnosis of SACD

In their case report on rapid healing of a patient with dramatic SACD, researchers Roessler and Wolff (Roessler & Wolff, 2017), noting the lack of consensus or guidelines for the diagnosis of vitamin B12 deficiency, state: "Frequently, the diagnosis of cobalamin deficiency is difficult, because anaemia or macrocytosis are frequently absent, cobalamin concentrations are mostly borderline (Lindenbaum et

al., 1988), and solely psychiatric syndromes are present which are sometimes variable, unspecific, subtle, and uneven in rate (Reynolds, 2006; Wong, 2015)". Roessler and Wolff's study is of a 57-year-old man suffering from myelosis of the cervical posterior columns whose symptoms were initially thought to stem from a traumatic injury. He demonstrated neurological symptoms but no others, particularly no provable gastrointestinal, haematological or psychiatric disorders. His cobalamin (vitamin B12) serum level was normal. The diagnosis of SACD was confirmed by an elevated methylmalonic acid, and hyperhomocysteinaemia, together with the neurological evidence. The authors conclude, as we and others have also found, that "normal cobalamin serum levels do not rule out a cobalamin deficiency".

Another example of how misleading blood serum levels of vitamin B12 can be in diagnosing this condition is provided by a case report from the Department of Neurology, University Hospital Zürich (Ulrich et al., 2015). The patient was suspected to be suffering from SACD but initial tests showed nearly normal holotranscobalamin, suggesting no vitamin B12 deficiency. Further testing showed high methylmalonic acid (MMA) and plasma total homocysteine levels, indicating impaired vitamin B12-dependent metabolism. The cause of the mismatch between the blood serum vitamin B12 level and the underlying condition of vitamin B12 deficiency was found to be oral supplementation of vitamin B12 that the patient had taken for three days prior to hospital admission. His blood serum B12 level was by then almost "normal" but this would not have been enough to reverse the neurological damage.

The number of misdiagnosed or undiagnosed cases of SACD that we have encountered in our Practice leaves us in no doubt that a broader approach to diagnosis is needed as well as clear and prominent guidelines. As described in the case notes below, if a holistic approach is followed that takes into account family and dietary history, signs and symptoms, as well as blood test results, SACD can be effectively diagnosed and treated before it becomes an irreversible condition.

In saying this, we realise that we are challenging accepted medical wisdom, but as Dr Jonathan Wallis (Consultant Haematologist, the Freeman Hospital, Newcastle-upon-Tyne) said in the BBC programme *Inside Out* in answer to a question from the interviewer:

> *"I think we should all question the perceived wisdom and the norm, and a lot of medical progress has been made by people who have taken on the medical profession. So I think it is credible what Dr Chandy is doing, but you have to be careful to get it right" (Jackson, 2006).*

## 6.5 Misdiagnosis as MS (Multiple Sclerosis)

One of the most frequent misdiagnoses of SACD that we have encountered is its diagnosis as MS because SACD gives an MS-like presentation. As shown in Table 6-2 the parallels are so close that the two conditions are almost indistinguishable. MS, however, is given much greater publicity in medical textbooks and guidelines (a whole chapter, for example, is dedicated to it in various editions of *Harrison's Principles of Internal Medicine* (Cree & Hauser, 2018; Hauser & Goodin, 2005, 2008, 2012)) whereas SACD appears to have almost disappeared from view.

As stated above, some of our patients had been diagnosed by neurologists as suffering from MS. After we had treated one of these patients with vitamin B12 and their condition had improved, one neurologist wrote to us: "This is to confirm that the above patient was investigated several years ago

in the neurology clinic for episodes of possible recurrent optic neuritis. A diagnosis of possible MS was considered but her investigations including several MR brain scans and spinal fluid analysis failed to confirm the diagnosis. Her clinical course has remained uneventful and the previous possible diagnosis of MS now seems unlikely."

In other cases the diagnosis was inconclusive, but all responded well to vitamin B12 therapy, demonstrating that SACD was the true diagnosis. Ours is not an isolated finding; Polish researchers reported two cases where SACD had been misdiagnosed as MS, explaining that: "Because of heterogeneous manifestations of MS, an incorrect diagnosis is not uncommon" (Kurkowska-Jastrzębska et al., 2006).

Others have commented on the similarities between the two conditions and a possible "significant" or "causal" relationship between them: "Multiple Sclerosis (MS) and vitamin B12 deficiency share common inflammatory and neurodegenerative pathophysiological characteristics. Due to similarities in the clinical presentations and MRI findings, the differential diagnosis between vitamin B12 deficiency and MS may be difficult. Additionally, low or decreased levels of vitamin B12 have been demonstrated in MS patients. Moreover, recent studies suggest that vitamin B12, in addition to its known role as a co-factor in myelin formation, has important immunomodulatory and neurotrophic effects. These observations raise the questions of possible causal relationship between the two disorders, and suggest further studies of the need to close monitoring of vitamin B12 levels as well as the potential requirement for supplementation of vitamin B12 alone or in combination with the immunotherapies for MS patients" (Kocer et al., 2009; Miller et al., 2005). The possibility of a causal link between B12 deficiency and MS is also discussed by Pacholok and Stuart (2011, pp. 53-80).

One researcher has suggested that the two conditions are indeed both caused by vitamin B12 deficiency but by different routes. After being diagnosed with MS, he researched the illness and experimented on himself over 10 years by injection of 4 mg (or more) of B12 in the form of adenosylcobalamin (AdoCbl). Following this research, he put forward the 'MS-AdoCbl hypothesis', which is that MS results from autoimmune attack induced by bacteria from particular agricultural crops (legumes with rhizobia class bacteria) which could enter the bloodstream through, for example, a cut. The attack targets an enzyme called adeno-syltransferase (ATR) that is needed to convert cobalamins to the bioactive form adenosylcobalamin AdoCbl. "When the concentration of ATR is reduced, production of AdoCbl is limited resulting in metabolic changes" that damage the nervous system. He found that almost all his CNS symptoms were eliminated and the improvement continued for about two days, but the MS symptoms returned if the injections were stopped. He recommends that further research be conducted on treatment of MS with AdoCbl (Boucher, 2017).

It is well known that MS is particularly difficult to diagnose. In their chapter on MS in *Harrison's Principles of Internal Medicine 20th edition*, 2018, pp. 3191-3192, Cree and Hauser write:

> **Diagnosis:** "There is no single diagnostic test for MS."
>
> **Differential Diagnosis:** "The possibility of an alternative diagnosis should always be considered…"

Similarly, the UK's *NHS* web site states (February 2016) in relation to MS: "Diagnosing MS is complicated because no single test can positively diagnose it. Other possible causes of your symptoms may need to be ruled out first" (NHS, 2016b).

The advice given by NICE UK is that a patient showing signs and symptoms suggestive of MS should be referred promptly to a consultant neurologist, and that "Only a consultant neurologist should make the diagnosis of MS" (NICE CKS, 2018b). NICE does recommend arranging blood tests, which includes screening for vitamin B12 deficiency but, as reported above, serum B12 levels are often misleading.

In classic treatments, there is "no cure" for MS. Symptom-relieving treatments only are given.[31] In the long term, patients are admitted to nursing homes and eventually require PEG feeding (costly nutritional drinks). If treatment is offered, it mainly consists of symptom-modifying drugs such as beta interferons (typical cost £7,000 per year) and Fincolimod (typical cost £17,640 per year) which treat the symptoms and not the cause, in combination with other drugs to treat the side-effects. The above drugs are contra-indicated in patients with immunodeficiency because of the risk of opportunistic infection, and in those with severe liver impairment.

Since there is a real possibility that the condition may in fact be SACD, at the very least doctors might try a therapeutic trial of three months of vitamin B12 injections. There is no known toxicity of vitamin B12 whereas the consequences of SACD being left untreated are devastating. Researchers into this condition in 1998 concluded that the clinical, electrophysiological, and MRI findings associated with SACD in vitamin B12 deficiency are so diverse that "vitamin B12 deficiency should be considered in the differential diagnosis of all spinal cord, peripheral nerve, and neuropsychiatric disorders" (Hemmer et al., 1998). Japanese researchers have also concluded that use of massive dose vitamin B12 as an additional therapy is warranted in MS because of the potential toxicity of the immunosuppressant drugs currently used. They treated patients with 60 mg a day of methylcobalamin for six months (Kira et al., 1994).

## 6.6 Comparison of symptoms: SACD and MS

By definition, MS involves scleroses in the spinal column. It takes at least two forms: relapsing/remitting or coming and going; and progressive or steadily deteriorating.

Typical presenting signs are:

- Unilateral optic neuritis, cerebellar signs, Lhermitte's sign (shooting electric shock-like pain) in arms/legs/back on flexing neck (e.g. turning head), facial palsy, epilepsy, aphasia, euphoria, dementia, depression, often accompanied by fatigue (Hauser & Goodin, 2005);
- Remissions and relapses with later progressive accumulation of disability.

A diagnosis of vitamin B12 deficiency accounts for all of the symptoms of MS just as it does for SACD. Whereas there is no treatment that improves MS (although some treatments may modify the

[31] New stem cell treatment has brought hope that disability can be slowed or even reversed. The treatment, called "Autologous Haematopoietic Stem Cell Transplantation (AHSTC)", is being developed at Sheffield Teaching Hospitals. Sufferers are given high-dose chemotherapy to destroy the faulty immune system. However, the MS Society warned that the treatment may not help every sufferer and it does come with chemotherapy side effects (Radowitz, 2016). Perhaps B12-replacement therapy is a better solution? Further information is available from http://www.sth.nhs.uk/news/news?action=view&newsID=787

symptoms), treatment with vitamin B12-replacement therapy appears to remit many of its symptoms (symptoms are no longer present or minimal so the patient has a normal life).

We are confident in saying this because all the patients diagnosed by us as suffering from SACD responded to vitamin B12-replacement therapy, which confirmed our original diagnosis.

In diagnosing MS, the tests required are cerebrospinal fluid (CSF) and an MRI scan. What is not considered as part of the differential diagnosis is the patient's family history in relation to vitamin B12 deficiency, their dietary history and haematinic screening e.g. FBC, vitamin B12 or folic acid level. The Protocol we have developed for diagnosing vitamin B12 deficiency (see Appendix 1) takes all these factors into account. It is on the basis of this holistic Protocol that we have been able to diagnose the patients described in the case notes here as vitamin B12 deficient and treat them accordingly.

### *Table 6-1 Some possible inadvertent misdiagnoses of SACD*

Acute Disseminated Encephalomyelitis (ADEM)
Balo's Concentric Sclerosis
Behçet's disease
Chronic Fatigue Syndrome (CFS)
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Fibromyalgia
Leukodystrophies
Lyme Disease
Myasthenia Gravis
Myalgic Encephalopathy (ME)
Neuromyelitis optica spectrum disorder (NMOSD)
Sarcoidosis
Sjögren's Syndrome
Systemic Lupus Erythematosus (SLE)

Compiled from (Godman, 2017), (Jewells et al., 2015) and (Singhal & Berger, 2012).

More than 100 disorders can mimic MS (Singhal & Berger, 2012). Given the frequency with which SACD is mistaken for MS, this implies that SACD could equally be confused with many other disorders. Above (Table 6-1) is a list of other illnesses which we believe could be caused by vitamin B12 deficiency and cured or relieved by vitamin B12 therapy. In this regard, Swedish researchers have reported favourable response to vitamin B12 injections with oral folic acid in ME and Fibromyalgia (Regland et al., 2015). *Harrison's Principles of Internal Medicine* notes that "vitamin B12 injections are used in a wide variety of diseases, often neurologic, despite normal serum B12 and folate levels and a normal blood count and in the absence of randomized, double-blind, controlled trials. These conditions include multiple sclerosis and chronic fatigue syndrome/myalgic encephomyelitis (ME)…" Unfortunately for patients, *Harrison's* attributes any benefit from these injections to "the placebo effect of a usually painless, pink injection" and states that oral vitamin B12 administration in ME has "not been beneficial, supporting the view of the effect of the injections being placebo only" (Hoffbrand, 2018, p. 707).

## 6.7 "Window of opportunity" for treatment

We understand a great deal about the risks of withdrawing vitamin B12-replacement therapy in relation to neuropathic symptoms because of the enforced cessation of our treatment of our patients on two separate occasions. This cessation of treatment by a Primary Care Trust (PCT), and later its successor, affected hundreds of our patients and resulted in re-emergence of the patients' previous symptoms. This was particularly noticeable for major disabilities such as those implicated in SACD. For some, their disabilities became irreversible in spite of later recommencing the former vitamin B12-replacement regime, leading us to think there may be a "window of opportunity" during which a patient's health can be restored (see cases in this chapter which demonstrate this), and after which the symptoms become irreversible. However, the timeframe for this window appears to be unique to each person and unpredictable. We cannot stress enough the importance of quick action on first diagnosis. For example, when Brenda Berry (Case 6-3) presented in June 2006 we offered vitamin B12 therapy but she asked for a referral. She was treated by a neurologist for MS for four years. Her condition nevertheless deteriorated and her blood serum B12 level dropped to 157 ng/L in July 2010. It was only then that, at her mother's recommendation, she came to us for vitamin B12 therapy. Her serum B12 rose to 544 ng/L in May 2011 after injections and she has steadily improved.

## 6.8 Patterns emerging from our cases

The following patterns are seen in the cases in this chapter:

- A clear sign of the likelihood of vitamin B12 deficiency is where patients have a family history of the condition. For example, in the family of Brenda Berry (Case 6-3) vitamin B12 deficiency had been diagnosed in other family members. We were able to detect deficiency in seven generations (Figure 6-2), five of which we diagnosed ourselves over several decades. We also suspected B12 deficiency in the two earlier generations because Brenda's mother recalled that her grandfather had been diagnosed with pernicious anaemia and been treated with liver extract (not something that a grandchild would likely forget!).
- Patients may have "normal" blood serum B12 levels but nevertheless be severely deficient. For example, Linda Skilton (Case 6-6) had a vitamin B12 blood level of 707 ng/L on presentation in November 2006, considered well into the normal range, but which we read as "false normal" because of her other symptoms. Questioning revealed that oral supplementation she was taking had falsified the results.
- Patients presented with multiple symptoms, which would not be consistent with a single diagnosis such as MS. These could include tiredness and sickness. Patients from the same family (Case 6-4) had different symptoms.
- Characteristic neurological symptoms include a non-symmetrical weakness, Lhermitte's Sign (shooting pain in weaker side limbs and back, often triggered by stretching the neck), sometimes symptoms manifesting on the head (outside the skull), such as nystagmus, blurred vision, depression. Two of the patients were misdiagnosed with MS (Cases 6-1, 6-5).
- The hospital will often run CT and MRI scans, and on failure to find plaques, may suggest a hysterical or mental cause of the condition and recommend no treatment.
- All patients recovered well, and some experienced dramatic improvement, on receiving vitamin B12 therapy.

## 6.9 Genetic link in MS

In this chapter we have shown that vitamin B12 deficiency is often mistaken for MS; and in Chapter 5 we showed that there is often family inheritance of vitamin B12 deficiency – that is, in some people it may have a genetic cause. It is therefore interesting to note that in the 1990s researchers Rothwell and Charlton interpreted the unusually high incidence of MS in Scotland (12.2 per 100,000 in the Lothian Region and 10.1 per 100,000 in the Border Region) as being of genetic origin, rather than resulting from an environmental risk factor (Rothwell & Charlton, 1998). Could it be that at least some of these cases are of inherited vitamin B12 deficiency?

### *Case 6-1 SACD - not stroke or MS (Chelsea Chicken)*

Chelsea presented aged 17 (in 2014) having attended an Urgent Care Centre (three times), a GP surgery, and Acute Hospital A&E due to falls and shooting pains, constipation and aches and pains all over her body.

The initial diagnosis by a neurologist had been stroke because the patient was wheelchair/crutches' dependent, and the scans and tests did not give the signs of MS. In consequence, the neurologist advised that the patient must have been attention-seeking, and the condition must have been all in her mind.

I knew the family well. I was shocked to see this young lady walking along the corridor with the aid of two crutches, accompanied by a relative. It was evident that she was struggling to walk, even with the crutches, and in considerable pain. We had previously diagnosed and treated her mother and other members of the family for vitamin B12 deficiency with successful outcomes.

Following detailed history-taking and thorough neurological examination, I explained our findings and the provisional clinical diagnosis I had arrived at:

1) The patient must have been suffering from undiagnosed B12 deficiency for a few years (most females in her family, including her mother, were suffering from vitamin B12 deficiency).

2) The shooting pain travelling down her left side and left leg was Lhermitte's Sign.

3) The weakness, pain, absence of reflexes etc. was more pronounced in the left side than the right (non-symmetrical). This is commonly called **single limb paralysis.**

4) If left untreated, the patient could be expected to develop Subacute Combined Degeneration (MS-like presentation).

Further blood tests were ordered to exclude other conditions and confirm this diagnosis. Loading doses of vitamin B12 were commenced immediately.

One month later, the patient had already gained weight and was able to walk without crutches part of the time. The pain was diminishing.

## *Case 6-2 Left oculomotor nerve paralysis*

Julia Johnson presented with double vision, ptosis in the left eye, and an orbital headache (symptoms of nerve damage, either optic nerve or oculomotor nerve) in May 2009, and when tested, her plasma B12 level was 252 ng/L. We referred her to a specialist eye hospital where she spent 9 days, but was subsequently discharged with no diagnosis and no treatment (she was given an eye patch and sent home – the photo right shows the blanked-off glasses lens).

Because of her low B12 level and obvious neuropathy, we started her on injections of vitamin B12 every 2 months. This did not prove adequate, but when we increased the frequency of the injections to monthly, her sight was fully restored. She now works in SpecSavers.

## *Case 6-3 "Incurable with various symptoms" – Brenda Berry*

This patient, Brenda Berry, aged 34 (when she presented in 2014), had a long history of anaemia and fainting, collapse and tiredness, and more recently of spastic contractions. Her family medical history (sisters, grandparents and cousins) included diagnoses of vitamin B12 deficiency and under-active thyroid.

| **Brenda Berry: vitamin B12 blood serum levels** | | | | |
|---|---|---|---|---|
| **Date of Test** | June 2006 | July 2010 | May 2011 | May 2013 |
| **Blood serum B12 (ng/L)** | 268 | 157 | 544 | 375 |

The local acute hospital had attempted a number of diagnostic and treatment interventions, including lumbar puncture attempts (1997), and had recorded progressive loss of sensation/loss of tone and muscle weakness, although these symptoms were accompanied by non-specific pains and weakness which could have indicated an alternative diagnosis.

Although her serum B12 level, 268 ng/L in June 2006, had fallen to 210 ng/L and then 157 ng/L four years later, the neurologist did not diagnose vitamin B12 deficiency, but rather treated her with immunosuppressants because he considered her condition to be MS. Her general condition, and weakness of the left side, worsened.

We diagnosed vitamin B12 deficiency as the most likely underlying cause and commenced treatment. However, this safe replacement therapy had to be stopped on two occasions because of the PCT restrictions on administration of treatment (see the Introduction).

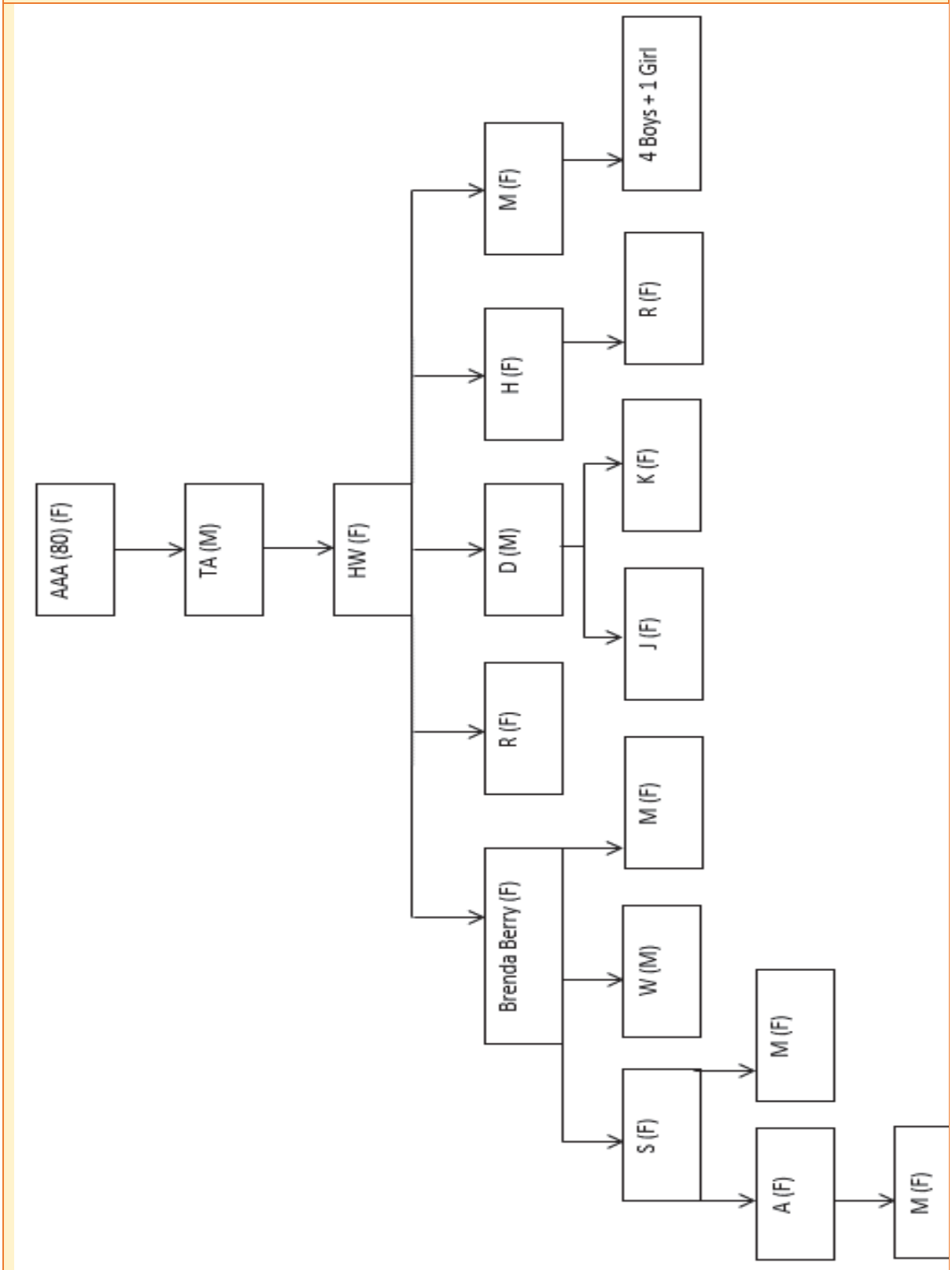
To us, the diagnosis had been clear as her blood serum B12 levels had dropped and symptoms not normally used to diagnose MS were reported in hospital letters making this diagnosis. However, we had a restriction on our ability to make a diagnosis of vitamin B12 deficiency.

Due to the intervention of her mother, who was aware of the family history of vitamin B12 deficiency, the diagnosis of MS was overturned. We confirmed the true diagnosis of Subacute Combined Degeneration (SACD) due to demyelination of the spinal column. Now she is on regular vitamin B12 injections and is steadily improving, and less dependent on crutches and a wheelchair.

Her mother, Mrs Hilda Wiffen, had been diagnosed as B12 deficient in December 2005 (her vitamin B12 level was 211 ng/L) and she received OC (oral) B12-replacement therapy.

See also Figure 6-2 Family history of vitamin B12 deficiency identified in seven generations, where Brenda Berry is identified in the fourth generation.

***Figure 6-2 Family history of vitamin B12 deficiency identified in seven generations***



## *Case 6-4 MS/SACD - three different presentations in same family*

This case group concerns three members of the same family (maternal uncle, mother and daughter) who all presented with MS/SACD but with different symptoms.

**Male born 1940**

This patient's vitamin B12 level in May 2006 was 120 ng/L. He opted for OC ("Over the Counter") vitamin B12 tablets, which maintained the patient with minimal signs and symptoms.

In January 2011 he presented with worsening symptoms, classified as "moderate". They did not include SACD or severe neurological symptoms although his serum B12 level at that time was very low at 90 ng/L. At the patient's request, vitamin B12 injections commenced. This reduced the symptoms.

**Female born 1952**

This patient was diagnosed with myxoedema in 1995. In July 2004, she presented with moderate-to-severe neuropsychiatric symptoms. Her vitamin B12 level was 363 ng/L.

*Because of the Easington PCT embargo on diagnosis and treatment, I refrained from treating her on this occasion.*

During the five-year period (2004-9) her lower limbs became weak and she had to rely on a wheelchair. In September 2009, a diagnosis of SACD was made. She was referred to hospital. The neurologist report stated: "I note her family history of B12 deficiency although her levels have been 'normal'. On 1 May 2009 she developed sudden onset neuropathy and paralysis of her entire left leg [single limb paralysis], suspecting worsening B12 deficiency". Her vitamin B12 level was checked. **The level had dropped to 258 ng/L.** At this level, treatment was not allowed by County Durham PCT which had taken over from Easington PCT. However, I felt clinically obliged to treat her (as per GMC guidelines on Good Medical Practice).

Following the commencement of treatment, she began to improve steadily. She recovered fully from her left upper limb paralysis and was able to discard the wheelchair. At the time of writing she uses two crutches when required and most of the time does not use aids.

**Female born 1987**

In January 2004 at the age of 16, this patient presented with fainting attacks three to four times a month, passing out without warning for one to two minutes at a time (no fits), and shaking of head when reaching out with her hand. She had a pale yellow complexion, dizziness, pins and needles in her fingers, hair loss, depression, paralysis of her left leg below the knee and loss of sensation. She was walking with two crutches (her vitamin B12 level was 247 ng/L).

During February 2004, I clinically diagnosed her with severe vitamin B12 deficiency with neuropsychiatric signs and symptoms. Unfortunately, at that time the embargo by Easington PCT (from February 2004 to March 2005) prevented me from diagnosing or treating any new patient for vitamin B12 deficiency. However, I knew that if I missed this "window of opportunity" she would develop SACD/lower limb paralysis and would be wheelchair-bound for the rest of her life. Therefore, in contravention of the embargo, I gave a loading dose of six injections over two weeks, followed by weekly injections. (This was recorded clearly on the patient record, along with the decision for the diagnosis and a record that we were aware of the embargo. This was supported by reference to the BNF (BNF, 2009), which gives clear instructions for loading doses followed by regular frequent injections "until no further improvement".)

The patient was able to report symptom improvement, starting with her dizziness abating and no further fainting, by 30 March 2004. In July 2004 the patient reported that power had returned to her left leg. In September 2004 she reported regaining sensation below the knee. From December 2004 to January 2005 she was able to discard first one crutch then the other.

The patient was assessed week by week. On a few occasions her regular treatment was interrupted (for example, she decided that she was well and needed no further injections; holidays; etc.) and the weakness in her left leg as well as other signs and symptoms reappeared. She again had to rely on crutches until she made the connection between vitamin B12 injections and symptoms returning, and returned to the surgery for injections.

It is widely known that if we miss the "window of opportunity" to provide treatment the first time we suspect a neurological condition, and fail to treat decisively and rigorously, the patient will end up with irreversible conditions (this is also emphasised in BMJ Best Practice (2018d)). In the case of failure to treat vitamin B12 deficiency, the condition may result in paralysis (SACD-like presentation), depression, psychosis etc. The decision to treat despite the embargo was commended by a letter from the neurologist on 25 August 2004 which read, "Coming to our mutual patient, I hope that the Vitamin B12 replacement helps her. On several discussions with her I could never detect any pressures or other reasons why this functional behaviour should have come about, but in my experience this is the case in the majority of patients. I think it is great that you have the enthusiasm to look at this in your patients."

## *Case 6-5 MS-like presentation - Wendy Imms*

Wendy Imms, born 1972, had a family history of vitamin B12 deficiency. Her mother was diagnosed with B12 deficiency and her maternal aunt was diagnosed with both vitamin B12 deficiency and MS.

In 1995, Wendy suffered from depression and was under the care of a Community Psychiatric Nurse (CPN). In 1996 she developed menorrhagia and dysmenorrhoea.

In 1997 (aged 25) she presented with pins and needles in her hands and feet, unsteadiness, dizziness, depression, fatigue and sleepiness, heavy periods and pain. She was referred to a neurologist who reported: - "mildly disarthria, angle clonus, bilateral finger nose and heel shin ataxia, impaired sensation to pain below Rt knee … ?demyelinating. MRI – brain plaques of demyelination. Cervical cord signal abnormality is consistent with demyelination. CSF - oligoclonal bands in CSF and not in serum."

Her vitamin B12 level was 189 ng/L. In April 1997, I commenced treatment. Five months later, in September, the neurologist reported: "She has improved considerably since I last saw her in May. There is mild limb ataxia".

In early 2002 the **PCT embargo required me to discontinue the vitamin B12 treatment.**

In late 2002 she again presented with depression and anxiety, using a wheelchair more, registered blind with optic atrophy and incontinence. Her blood serum B12 level was 340 ng/L, dropping to 158 ng/L in August 2003.

Treatment was restarted in that month. By 2006, both patient and husband were delighted with the improvement in both her mental and physical states. She was managing to get through most household chores and no longer wheelchair dependent. Her blood serum B12 had risen to 819 ng/L.

## *Case 6-6 When it's hard to go on - Linda Skilton*

On 16 November 2006, having worked in the south of England all week, Mr Skilton returned home to spend the weekend with his wife; to his shock he found Linda in a terrible state (in the same pose as pictured in the photograph, taken at Christmas 2006). She was sitting with a cat in her lap and a note for her husband stating that she did not wish to live in this dreadful state any longer. Mr Skilton was aware that his wife had seen a number of specialists in south England. Since moving north to Easington she had seen numerous local practitioners and specialists. Until then she had not been my patient.

That evening I received a call from Mr Skilton. Although it was nearing surgery closing I agreed to see Linda straightaway. Within 30 minutes Mr Skilton brought Linda to the surgery in a wheelchair. I could sense that Linda had almost given up on ever getting out of the wheelchair. I listened to them both intently until they finished conveying the whole story to me. I spent some time going through Linda's background history. I made the decision not to trouble her getting in and out of her wheelchair to do a physical or neurological examination. After a short pause, I said to Linda and her husband: "I know what is the matter with Linda, the true diagnosis, and I will treat her; I will get her out of that wheelchair and enable her to drive the car by herself in three months". There was a total silence for five minutes then Linda declared: "I will call you the Jesus of Peterlee".

| Linda Skilton: Blood test results | | | | | | |
|---|---|---|---|---|---|---|
| | **23/11/05** | **27/03/06** | **31/08/06** | **16/11/06** | **18/01/07** | **25/05/07** |
| B12 blood serum (ng/L) | 524 | 418 | | 707 | 520 | 2000 |
| Folate blood serum (µg/L) | 7.4 | 7.2 | | 14.3 | 10.9 | 15.6 |
| Thyroid Stimulating Hormone | 4.4 | 6.78 | 2.32 | | 4.13 | 1.77 |
| Haemoglobin | 13.9 | 13.7 | 13 | 13.9 | 13.7 | 13.6 |
| Mean Corpuscular Volume (fL) | 90.9 | 89.5 | 89.2 | 87.1 | 88.7 | 90.5 |

**History of illness:**

**15/07/1975** Hospital A: Polymyositis/adenopathy and sarcoid myopathy affecting lungs with enlarged liver and abnormal liver function tests (LFTs). Has a poor prognosis of ultimate functional recovery.

**21/11/1986** Hospital B: Total abdominal hysterectomy.

**Oct 1992** Hospital C: Past history of nephrectomy.

**16/09/1994** Road traffic accident: limited neck movement.

**02/11/1999** Hepatitis. Raised LFTs. No cause found.

**13/01/2001** Hospital B: Phlebitis right calf.

**22/10/2001** Patient of another practice: excessive twitching getting worse at night and depressed.

**04/02/2002** Complaining of excessive twitching all over the body and now affecting the left eye. Referred to consultant neurologist.

**04/02/2002** Private referral to neurologist. Shaking getting worse: could not even hold a cup of tea; "can't live on this way". Medication prescribed by neurologist: Clonazepam 0.5 mg two tablets at night and Temazepam 10 mg one tablet at night.

**13/05/2002** Previous history of sarcoidosis.

**13/05/2002** Consultant neurologist private appointment: "EMG arranged. She has a neurological syndrome with invisible ocular twitching and restlessness as well as more overt myoclonic movements. Please note that three years ago she had hepatitis."

**25/09/2002** History of myoclonic seizure so is taking Clonazepam.

**31/02/2003** Complaining of headache, blurred vision, heartburn and pins and needles in right arm for seven weeks.

**11/04/2003** Deep Vein Thrombosis. Warfarin commenced.

**12/06/2003** "Please find enclosed the report on this lady's EMG which would be in keeping with sensory neuropathy."

**31/12/2003** Headache, blurred vision, heart murmur and pins and needles in right arm for seven weeks. Blood pressure (BP): 180/100.

**02/01/2004** TSH 4.17 (0.2 – 4.0), Free T4 13 Pmol/L (11-30).

**13/02/2004** Well. All bloods normal.

**26/11/2004** Shinwell Medical Practice: Letter from neurologist dated 24/11/2004: "Periodic movements during sleep and myoclonic jerks. Controlled 90% of the time on Clonazepam. She does have some slurred speech which I suspect is a side-effect of the medications. I do not think any of these symptoms represent any significant recurrence of Polymyositis".

**27/03/2006-16/11/2006** Due to general deterioration in condition, patient taking vitamin B12 supplements (OC - "over the counter" or purchased by self).

**16/11/2006** When requested appointment at Shinwell Medical Practice by husband: extreme fatigue, sleepy all day, experiencing dizziness, falls, blurred vision, low mood, suicidal feelings, depression, weepy, agitation, tingling in hands and feet, unexplained hair loss, headache, loss of libido, neuropathic pain (painful hips), spasm of lower limb.

Though her serum B12 level was recorded as 520 ng/L clinically I came to the conclusion from signs and symptoms that this was a false normal B12 level. (This has since been shown to be common (Carmel & Agrawal, 2012).) I diagnosed that she was suffering from subtle vitamin B12 deficiency (Babior & Bunn, 2005), and to confirm this I treated her with daily vitamin B12 injections.

Medical orthodoxy would have maintained that because of her serum B12 level she was not B12 deficient, but a holistic approach, including 45 minutes of history-taking, convinced me that she was severely B12 deficient.

On each of her visits to the surgery I noticed massive improvement in all systems of the body, especially the neuropsychiatric area. As I had promised Linda and her family, she was out of the wheelchair and able to drive to the surgery herself within 3 months of commencing treatment and her B12 level rose to 2000 ng/L without any adverse reactions. Unfortunately, this was the time (March 2007 to February 2011) when the local PCT enforced a further embargo on vitamin B12 injections to all the Practice patients. This caused untold mental and physical damage to all my patients, including Linda, who began to suffer when her B12 level dropped to 380 ng/L within 2 months of the embargo being imposed and her previous symptoms (for instance, Restless Leg Syndrome) began to re-emerge. Fortunately, the Practice has since managed to have the embargo reversed once and for all.

The photo above is from June 2007: Linda at her niece's wedding.

**Clinical record for her recovery period shows:**

**16/11/2006** Injections commenced/three-month therapeutic trial.

**16/01/2007** Feeling much better.

**14/06/2007** Dramatic improvement in all areas. Says she feels like a new person; walking stick discarded; no longer uses commode.

### *Case 6-7 Lhermitte's Sign - shooting pain*

Gemma Bates, born 1982, presented with MS-like symptoms and muscle spasm due to Lhermitte's Sign which caused her to lean to the right. She was also unable to sleep because of the pain. In July 2013 her vitamin B12 level was 194 ng/L.

Injections of vitamin B12 were commenced and within two months there was significant improvement. She was so delighted with the improvement that she asked to be photographed posing in her previous twisted posture to show the change.

### *Case 6-8 Glossopharyngeal nerve pathology causing persistent cough*

Mr Billyards had been a delivery driver but was unable to sleep because of a cough, so he could not stay awake at the wheel. He also had difficulty swallowing. His vitamin B12 level in March 2010 was 164 ng/L. He is now receiving 1 mg vitamin B12 each month by injection which has restored his nerve function. He no longer has either the cough or swallowing difficulty. By March 2011 he was back to his previous job.

The next chapter will explore the possibility that vitamin B12 deficiency is also responsible for autoimmune conditions. In this regard we note the comment by John Snowden of Sheffield Royal Hallamshire Hospital:

> *"It is unclear what causes MS but some doctors believe it is the immune system itself that attacks the brain and spinal cord"* (Priestley & Cummings, 2016).

| ***Table 6-2 Comparison of Multiple Sclerosis and vitamin B12 deficiency symptoms*** | | | |
|---|---|---|---|
| This detailed comparison illustrates that Multiple Sclerosis (MS) is an indefinite diagnosis, whereas vitamin B12 deficiency accounts for all of the symptoms and offers a specific treatment with a strong possibility of recovery. | | | |
| **Clinical features** | **Multiple Sclerosis** | **Vitamin B12 deficiency causing SACD** | **Observations and comments** |
| | Vitamin B12 deficiency-like signs and symptoms in MS | Subacute Combined Degeneration of the posterior and lateral spinal column: vitamin B12 deficiency paralysis | |
| **General** | | | |
| Demyelinating disorder. | Yes. | Yes. | These disorders may be caused by impaired DNA synthesis in rapidly dividing cells (red blood cells, gastrointestinal (GI), genito-urinary (GU), RS, CNS, skin) which all require vitamin B12 for maturation and are in a constant state of breakdown/repair. Vitamin B12 deficiency leads to incomplete maturation of these cells, which in red blood cells results in megaloblastosis. |
| Characterised by inflammation. | Yes. | Yes. | |
| Selective destruction of Central Nervous System (CNS). | Yes. | CNS is involved (but not necessarily). | True disease process in MS has not been proved clinically or scientifically.<br>Many, if not all, cases of MS record that the patient also suffers other systemic illnesses, particularly autoimmune conditions. |
| Peripheral Nervous System (PNS). | Is spared in some cases. | PNS is involved. | |
| Evidence of associated systemic illness. | No. Textbook claims this is not found in clinical practice (but see Observations and comments column). | Yes – multi-system polyglandular/endocrine disease. | |
| **Pathogenesis Physiology** | | | |
| Characterised by triads of inflammation, demyelination, Gliosis (scarring). | Yes. | Yes. | |

| *Table 6-2 Comparison of Multiple Sclerosis and vitamin B12 deficiency symptoms* | | | |
|---|---|---|---|
| Course of illness relapsing-remitting or progressive | Yes. | Yes. | Insidious onset and progressing steadily. Irreversible end stage if no vitamin B12 replacement given. |
| Lesions or plaques visible on MRI scan of brain or spinal column: Size from 1-2 mm. | Yes. | Yes. | |
| Myelin specific autoimmune antibodies cause demyelination and stimulate macrophages and microglia cells. | Yes. | Vitamin B12 deficiency disrupts lipid metabolism which is essential for the formation of myelin sheath. | In vitamin B12 deficiency the cause of demyelination is clearly identified. |
| Fundamentally different pathologies in different patients. | Cause/pathology unknown so far. | Vitamin B12 deficiency the main cause. | In MS is possibly due to different pathologies. However, no definite causative factor identified so far. |
| Total or partial axonal destruction. | Yes. | Yes. | Vitamin B12 deficiency is the cause of axonal destruction. |
| Axonal loss is a major cause of irreversible neurologic disability. | Yes. | Yes, but this is preventable by vitamin B12 therapy to ensure correct myelination of the adult and correct expression of DNA in offspring. | Reversed and restored by vitamin B12 replacement. |
| Conduction block occurs in the demyelination. | Yes. | Yes. | Also early diagnosis/treatment of vitamin B12/folic acid deficiency prevents demyelination/conduction block. |

| *Table 6-2 Comparison of Multiple Sclerosis and vitamin B12 deficiency symptoms* | | | |
|---|---|---|---|
| **Epidemiology** | | | |
| Incidence<br>Male : Female | M : F<br>35% : 65% | M : F<br>20% : 80% | See prevalence below. |
| Age of onset. | 20 to 40 years.<br>Rarely under 2 years of age. | Usual onset is in adults. However, the condition can occur in children. | This is a genetic condition and we have come across children as young as five who are diagnosed with vitamin B12 deficiency. |
| Highest prevalence. | 205 per 100,000 in the Orkney Islands, north Scotland (Rothwell & Charlton, 1998). | 200 per 100,000 (0.2%) suffering from pernicious anaemia (PA) in Scotland. | Prevalence in Shinwell Medical Practice, in 2015, out of a Practice population of 5,760, approximately 1,060 patients observed to have vitamin B12 deficiency with neuropsychiatric symptoms. This equals 18% of the Shinwell Medical Practice population. |
| Higher prevalence. | North European Caucasian population, northern US and Canada. | High prevalence in these same areas amongst similar population.<br>Some prevalence in India due to vegetarian diet. | |
| Low prevalence. | Japan, Asia, Equatorial Africa and Middle East. Japan: 2 per 100,000; fish diet may be preventative. | Similar low prevalence within these same areas. | |
| **Immunology** | | | |
| Autoimmune cause. | Yes. | Yes. | Oligoclonal immunoglobulins (IgG) are also detected in other inflammatory conditions, including infections, and thus not specific to MS or vitamin B12 deficiency. Oligoclonal bands seen on spectrometry. |
| Cerebrospinal fluid (CSF). | Elevated CSF immunoglobulins (IgG), oligoclonal antibody present. | Raised protein (IgG) immunoglobulins. | |
| **Subclinical disease** | | | |
| MRI has demonstrated bursts of disease activity 7 to 10 times more frequently than is clinically apparent. | There is a large reservoir of subclinical disease activity in MS, especially during the early stages of the disease. | There is clear evidence of a large number of patients in subclinical state of vitamin B12 deficiency (due to insidious onset).<br>Also, a group of patients whose serum B12 level is 300-500 ng/L but whose tissue level of B12 is low. | The triggers causing these bursts are unknown in MS. Vitamin B12 deficiency also causes myelin destruction of CNS. |

| *Table 6-2 Comparison of Multiple Sclerosis and vitamin B12 deficiency symptoms* | | | |
|---|---|---|---|
| | | Both these groups respond to empirical treatment with vitamin B12 supplementation. | |
| **Microbiology** | | | |
| Viral-induced demyelinating disease. | No clear proof to implicate viral infection. | Demyelination solely due to vitamin B12 deficiency. | Demyelination of both CNS and PNS. |
| **Clinical manifestations** | | | |
| Onset. | Abrupt or insidious. | Abrupt or insidious. | Similar onset and progression of the disease. |
| Severity of symptoms. | May be severe, or seem so trivial that the patient may not seek medical attention for months or years. | Similar. | |
| Asymptomatic cases. | Yes. | Yes. | |
| Symptoms extremely varied. | Yes. | Yes. | |
| **Signs and symptoms** | | | |
| Weakness of limbs. | Weakness of limbs, fatigue, disturbance of gait. | Yes. | As a result of posterior and lateral column involvement of the spinal cord due to Subacute Combined Degeneration of the spinal cord (SACD), which develops as a result of vitamin B12 deficiency. |
| | Upper motor neurone type, weakness of limbs, spasticity, hyper-reflexa, Babinski reflex positive. | Yes. | |
| | Tendon reflex lost (simulating lower motor neuron lesion – spinal cord involvement). | Yes. | |
| Spasticity. | 30% of MS patients have moderate to severe spasticity, especially in the legs.<br>Painful spasms. | Yes. | Eventually progresses to Subacute Combined Degeneration presentation (SACD). |

| *Table 6-2 Comparison of Multiple Sclerosis and vitamin B12 deficiency symptoms* | | | |
|---|---|---|---|
| Optic neuritis and monocular pallor of the optic disc. | Diminished visual acuity. Decreased colour perception. Progress towards severe visual loss, usually mono-ocular. | Yes. | |
| Peri-orbital pain. | Peri-orbital pain often precedes or accompanies the visual loss. | Yes. | |
| Visual Blurring.<br>Diploplia.<br>Nystagmus. | This may result from internuclear opthalmoplegia (INO) or palsy, via the oculomotor cranial nerve (CNIII) or optic nerve (CNII). | Yes. | |
| **Sensory symptoms** | | | |
| Paresthesias. | Tingling, prickling, pins and needles, painful, burning. | Yes. | Strong similarity. |
| Hypoesthesia. | Reduced sensation, numbness or a dead feeling. | Yes. | |
| Unpleasant sensation. | Feeling that body parts are swollen, wet, raw or tightly wrapped. | Yes. | Similar onset and progression of the disease. |
| Sensory impairment of the trunk and legs below horizontal line. | Indicator - spinal cord is the origin of the sensory disturbance. Often accompanied by a band-like sensation of tightness around torso. | Yes. | |
| Pain. | Pain is a common symptom of MS experienced by >50% of patients. Pain can occur anywhere in the body. | Yes. | |

| *Table 6-2 Comparison of Multiple Sclerosis and vitamin B12 deficiency symptoms* | | | |
|---|---|---|---|
| Ataxia. | Manifests as ataxia. May involve head, trunk and cerebellar dysarthria (scanning speech). | Yes. | Eventually progresses to Subacute Combined Degeneration (SACD) presentation due to B12 deficiency. |
| Bladder and bowel dysfunction. | 90% of MS patients suffer from bladder dysfunction. | Yes. | |
| Constipation. | Occurs in >30% of patients. Bowel continence 15%. | Yes. | |
| Cognitive dysfunction. | Memory loss; impaired attention; difficulties in problem solving. Slowed information processing; euphoria (elevated mood). | Yes. | |
| Depression. | Experienced by 50-60% of patients. Can be reactive or endogenous. Can contribute to fatigue. | Yes. | SACD/MS-like presentation due to vitamin B12 deficiency. |
| Fatigue. | Experienced by 90% of patients. Moderate to severe. Generalised motor weakness; limited ability to concentrate; extreme loss of energy; an overwhelming sense of exhaustion that requires patient to rest or fall asleep. Fatigue maximum during mid-afternoon. Exacerbated by elevated temperatures, by depression and by effort to accomplish basic tasks. | Yes. | |

| Table 6-2 Comparison of Multiple Sclerosis and vitamin B12 deficiency symptoms | | | |
|---|---|---|---|
| Sexual dysfunction/loss of libido. | Is common in MS. | Yes. | |
| Facial weakness. | Due to a lesion in the intraparenchymal pathway of the seventh cranial nerve, may resemble idiopathic Bell's Palsy. | Yes. | |
| Vertigo. | Appears suddenly and resembles acute labyrinthitis. | Yes. | |
| Heat sensitivity symptom. | Hot shower may cause transient blurring. | Yes. | |
| Paroxysmal symptoms. | Electric shock-like sensation includes: Lhermitte's Sign; tonic contractions of a limb, face or trunk (tonic seizures); paroxysmal dysarthria; ataxia; paroxysmal sensory disturbance. | Yes. | |
| Trigeminal neuralgia (hemifacial spasm; glossopharyngeal neuralgia). | Occurs when demyelinating lesions involve root entry or exit zone of $5^{th}$, $7^{th}$ and $9^{th}$ cranial nerves (CN V, VII and IX). | Yes. | |
| Facial myokymia. | Persistent rapid flickering contractions of the facial musculature (orbicularis oculi). | Yes. | |

| *Table 6-2 Comparison of Multiple Sclerosis and vitamin B12 deficiency symptoms* | | | |
|---|---|---|---|
| **Diagnosis** | | | |
| **Five diagnostic criteria to be fulfilled for definite MS (see *Harrison's Principles of Internal Medicine*, 16th, 17th and 18th edns):**<br>**1.Relapsing/remitting MS**<br>**2. Secondary progressive**<br>**3.Primary progressive**<br>**4. Progressive/ relapsing**<br>**5. The patient's neurological condition could not be better attributed to another disease.** | There are no definitive tests, symptoms or signs. MRI, spectrometry. | A definite diagnosis of vitamin B12 deficiency can be reached using our Protocol – see Appendix 1 | Signs and symptoms severe; low/subnormal B12 level; strong family history of vitamin B12 deficiency or symptoms associated with vitamin B12 deficiency. |
| | No single clinical sign or test is diagnostic of MS. Possibility of an alternative diagnosis should always be considered, especially when clinical course is progressive from the outset. | Vitamin B12 deficiency with neuropsychiatric symptoms is diagnosed and where patient shows positive response to empirical treatment with vitamin B12, the diagnosis of vitamin B12 deficiency is confirmed. Improvement following three-month therapeutic trial reconfirms original diagnosis of SACD/vitamin B12 deficiency. | SACD diagnosis due to vitamin B12 deficiency. MS-like presentation, not MS. |
| | Uncommon or rare symptoms in MS (aphasia, Parkinsonism, chorea, isolated dementia, severe muscular atrophy, peripheral neuropathy, episodic loss of consciousness, fever, headache, seizures, coma) should increase concern about alternative diagnosis. | Vitamin B12 deficiency (most common demyelinating condition in which we see these uncommon signs and symptoms). | *Harrison's Principles of Internal Medicine* (18th edition (Hauser & Goodin, 2012)) states that another condition must be considered first before a diagnosis of MS can be made. Page 3402 lists 'Disorders that can mimic MS' which include vitamin B12 deficiency. |
| **Prognosis** | | | |
| Prognosis | Most patients with MS experience progressive neurologic disability. | Neurological disability can be totally reversed if vitamin B12 deficiency is diagnosed early and treated promptly and the correct diagnosis of SACD not missed. | **Withholding or delaying treatment can result in irreversible neurological symptoms.** |

| *Table 6-2 Comparison of Multiple Sclerosis and vitamin B12 deficiency symptoms* | | | |
|---|---|---|---|
| **Disease Process** | | | |
| | MS disease process may have two separate phases:<br>Inflammatory (demyelination resulting in attacks);<br>Neurodegeneration (gradual loss of axons underlines progressive MS). | Similar process in vitamin B12 deficiency: demyelination followed by axonal deaths. | Totally preventable by early diagnosis and vitamin B12-replacement therapy.<br>SACD presentation due to vitamin B12 deficiency. |
| **Treatment** | | | |
| Treatment | No satisfactory treatment available for MS.<br>Treatment that promotes remyelination or neural repair does not currently exist.<br>Symptom-modifying treatments include:<br>Fingolimod 0.5mg daily: cost = £1,470 for 28 days = £17,640 a year.<br>B-interferon injection: cost = £7,000 for a year.<br>Copaxone injection: cost = £18.36 per injection. | Satisfactory vitamin B12-replacement therapy with no side-effects is available which provides full and total recovery.<br>Prompt initiation of vitamin B12-replacement therapy leads to remyelination and neural repair and prevents irreversible damage. Plaque formation (characteristic of MS) is also reversed.<br>Vitamin B12-replacement therapy costs £1.10 per injection, loading dose 6 injections alternate days, followed by one injection every 28 days = £20.90 a year. | Vitamin B12 deficiency may occur with autoimmune polyendocrine syndrome (APS) Type II or III. Therefore, exclude all other possible co-existing conditions:<br>primary/secondary adrenal insufficiency;<br>underactive thyroid;<br>vitamin D deficiency;<br>low ferritin.<br>also exclude gout.<br><br>WHAT ARE WE WAITING FOR? |
| **Source: Multiple Sclerosis symptoms from Hauser and Goodin (2012). SACD symptoms as observed in our patients at the Shinwell Medical Practice.** | | | |