Vitamin B12 and D deficiency as cofactors of COVID-19 vaccine-induced chronic neurological adverse reactions: Two cases and a hypothesis

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Case Report

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Vitamin B12 and D deficiency as cofactors of COVID-19 vaccine-induced chronic neurological adverse reactions: Two cases and a hypothesis

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Key words: cobalamin; COVID-19 vaccine; deficiency; demyelination; dysautonomia; long COVID; neuropathy; post-acute sequelae of COVID-19; serious adverse events; vaccine injuries; vitamin B12; vitamin D

Conflicts of interest: KAD has received speaking honoraria from Amgen, NAPP and AstraZeneca in the past ten years. HAC and ECM declare no conflicts of interest.

Abbreviations: CT, computerised tomography; IL, interleukin; MRI, magnetic resonance imaging; PASC, post-acute sequelae of COVID-19; PCR, polymerase chain reaction; POTS, postural orthostatic tachycardia syndrome

PLEASE NOTE: This is a live manuscript (version 1) that will be updated following any further progress and tests conducted. We welcome constructive peer-review.

Abstract

Background: The COVID-19 vaccines have been an essential measure to help reduce COVID-19-related injury and death. However, in some cases, vaccination has caused severe and chronic reactions, akin to post-acute sequelae of COVID-19 (long COVID).
Cases: Here we present two cases (Case 1: male, age 43 years, Pfizer BNT162b2 vaccination; Case 2: female, age 30 years, Oxford-AstraZeneca ChAdOx1nCoV-19 vaccination) with severe neurological adverse reaction post-vaccine and concomitant vitamin B12 deficiency. Both cases presented with non-textbook symptomatology of vitamin B12 deficiency. Case 1 had full symptom resolution with vitamin B12 replacement therapy. In Case 2, frank vitamin D deficiency and chronically elevated D-dimer were also found. Case 2 is still undergoing replacement therapy and this manuscript will be updated as appropriate.
Discussion: Vaccines, including the COVID-19 vaccines, are known to cause severe and/or chronic neurological reactions in rare cases. We support screening for vitamin B12 deficiency prior to vaccination in high-risk groups (e.g. those following an animal produce free diet), those suffering atypical/chronic vaccine reactions, and those with similar conditions, such as post-acute sequelae of COVID-19 (long COVID). A hypothesis is also presented demonstrating the links between vitamin B12 and vitamin D deficiency and other pathologies (e.g. mast cell activation disorders) that, if validated, could help explain some vaccine hyperreactions.

This is a live manuscript that will be updated following any further progress and tests conducted

Introduction

The net benefits of vaccination against COVID-19 have been well established in clinical trials (e.g. Polack *et al*., 2020) and real-world effectiveness studies (e.g. Hall *et al.,* 2021). The COVID-19 vaccination has been rolled out at an unprecedented speed. Whilst the initial studies were carried out in tens of thousands of people, these are not large enough to detect rarer side effects. Recent research has shown vaccination against COVID-19 can increase the risk of severe and acute cardiovascular and neurological events, such as Guillain-Barré syndrome (Patone *et al.*, 2021), though these risks were lower than with SARS-CoV-2 infection. However, it is increasingly becoming apparent that some patients have a severe and chronic reaction to COVID-19 vaccination. We have recently outlined the key pathophysiology that mostly patient (led) groups have found to explain their symptoms (Carroll & Deans, 2022, *in press*). Here we present two cases of vitamin B12 deficiency (and one with concomitant vitamin D deficiency) found post-vaccination with corresponding neurological symptoms. We also offer a working hypothesis to help explain vitamin B12- (and vitamin D-)mediated vaccine reactions, which requires testing to assess its validity.

Please note: due to the urgent nature of the vaccine rollout we are publishing this prematurely and will update with new data and hypothesis refinement as appropriate.

Case reports

Both cases have given full consent to be written up as case studies. Characteristics of both cases are presented in **Table 1**. Both cases were relatively healthy prior to vaccination, including keeping up with their work commitments without problems.

Table 1. Case characteristics (at time of first vaccination)

	Case 1	Case 2 (HAC)
Sex	Male	Female
Age (y)	43	30
Body mass index (kg/m^2)	30.0 (estimated)	20.6
Regular medication use	N/A	Naproxen, lansoprazole, dihydrocodeine (5-7 days/month) 8-10 mg melatonin (3 days/week)
Dietary comments	Vegetarian, high coffee intake	Vegan; irregular supplementation with 1.25 mcg/d cyanocobalamin and 626 mg iron
Vaccine brand	BNT162b2 (Pfizer)	ChAdOx1nCoV-19 (Astra Zeneca)
Date of vaccination 1	21 December 2020	**20 March 2021***
Date of vaccination 2	**16 January 2021***	N/A
Date of vaccination 3	25 October 2021	N/A

* Asterisk and bolded denotes the offending vaccination dose

Case 1 received the flu vaccination at the same time as their third COVID-19 BNT162b2 (Pfizer) vaccination. Case 2 has not received any further vaccinations for any disease since their first COVID-19 ChAdOx1nCoV-19 (Astra Zeneca) vaccination

Case 1

Case 1 is a physician, and reports having suspected COVID-19 (unconfirmed by polymerase chain reaction; PCR) in April 2020, with no indication of post-acute sequelae of COVID-19 (PASC) (long COVID). Approximately three months post-(suspected) COVID-19, Case 1 had their nucleocapsid antibodies measured (serum IgG immunoassay, Alinity I platform, Abbott Laboratories, UK), with a negative result. As such it is unclear whether Case 1 had a SARS-CoV-2 infection or not. Case 1 received their first vaccination against COVID-19 (BNT162b2) on 21 December 2020, reporting no adverse reactions except a sore arm at the injection site and a mild transient temperature. The acute phase of their second BNT162b2 vaccination was similar to their first dose.

Approximately one to two weeks post-vaccination dose 2, Case 1 reported sudden onset dizziness, ascending weakness in the flexor compartments of his forearms, increased tone in his upper limbs, leg weakness, light-headedness, unsteadiness on his feet, brain fog, and word-finding difficulties. Knee-jerk and brachioradialis reflexes were retained, as was power upon self-assessment (5/5 on finger spreading, finger flexion, bilateral finger extension), though he reported feeling weak (especially index, middle, and small finger on both sides). Initial assessment by a general practitioner queried multiple sclerosis, albeit with atypical symptomatology.

Subsequently, Case 1 reported stiffness, and sore muscles in upper and lower limbs (like he had been exercising). Self-examination showed: no cogwheel rigidity, plantars downgoing, no fasciculation, and Hoffmann sign negative. For several weeks, Case 1 reported facial paraesthesia and tingling in the lips. His face “felt like stone”, like “weights were pulling it down”. Case 1 struggled to relax his fingers, describing the sensation as if his fingers were “made of lead or weighted”, and that the “command to relax my muscles was not coming through quick enough”. Case 1 also noticed reduced muscle mass between the thumb and index finger. These symptoms started to resolve along with the light-headedness. There was no indication of weight loss, night sweats, focal neurology, eye pain or colour vision loss, gastrointestinal problems, or breathing difficulties. Guillain-Barré syndrome was considered unlikely on clinical grounds.

Case 1 did not require time off work for these symptoms, though reported struggling day-to-day. His symptoms were fluctuant throughout this time, though they were noticeable all the time. **Table S1** (appendix) outlines blood test results in this time, with nothing remarkable, except serum vitamin B12 status showing deficiency (< 148 pg/mL). Intramuscular hydroxocobalamin (1 mg) was administered (12 doses over four weeks). Intrinsic factor antibodies were negative. Case 1 unilaterally decided to continue vitamin B12 therapy via 1 mg oral cyanocobalamin supplementation until symptom resolution, which occurred approximately two weeks after completing the intramuscular course (i.e. six weeks total treatment). During treatment, symptoms remained undulating.

In October 2021, Case 1 opted to have a third dose of BNT162b2 alongside his flu vaccination. Acutely, he reported feeling “wiped out” for 2-3 days with fatigue and exhaustion. This was accompanied by a return of his light-headedness, increased tone in his upper limbs, and his fingers locking as if he had “trigger finger” whilst handling notes. Once again he commenced 1-2 mg daily oral cyanocobalamin replacement until resolution of symptoms.

Case 2 (HAC)

Case 2 is the primary author of this paper (HAC), and works as a part-time (three days per week) clinical researcher, alongside other research commitments, which she usually worked on for another two to three days per week prior to vaccination. She has never had COVID-19 (confirmed by regular PCR tests and nucleocapsid antibody tests as above). Prior to vaccination, HAC reported some fatigue and sleep problems since at least puberty, and is awaiting a diagnostic laparoscopy for suspected endometriosis. She quite often felt "ill" with common cold-like symptoms, but these were mild and did not interfere significantly with her life. HAC received the ChAdOx1nCoV-19 vaccination on 20 March 2021. Flu-like symptom onset occurred within approximately 6 hours and lasted approximately 30 hours. During the flu-like symptoms, HAC experienced dysautonomia including dizziness, nausea, weakness, bradykinesia, brain fog, early waking, fatigue, "jelly-legs", changes to walking gait, increased appetite and changes to appetite desires, some transient changes to taste, mild polydipsia, numbness in hands ("like they are swollen"), tinnitus and pulsatile tinnitus, micrographia and headaches, among other symptoms. The dysautonomia did not resolve after the flu-like symptoms had ended. Symptoms were severe enough to leave HAC near-bedbound for approximately two to three weeks.

Symptoms remained fluctuant but overall improving until a head computerised tomography (CT) scan on 20 July 2021 with contrast dye which caused a severe relapse within minutes, lasting 3-4 weeks. It is unclear whether this was a reaction to the contrast dye or the sensory stimulation of the scanner (noise, vibrations, and bright lights in the scanning room). However, a subsequent MRI scan without contrast (4 February 2022, discussed below) induced significant symptoms without a proper relapse, suggesting the contrast dye with the CT scan was the major trigger (common with mast cell activation syndrome, see **Discussion** section). After another ~3 weeks of being near-bedbound, symptoms improved again, whilst remaining fluctuant. A peculiar symptom was "incapacity episodes" whereby HAC feels an overwhelming general feeling of "unwell" and "not right" often accompanied by nauseous and/or fatigued. These result in HAC having to lay down near motionless for anywhere between 10 minutes and six hours.

Subsequently, symptoms continued to fluctuate; often the three days at work required the full four days off to recover, significantly impacting other research commitments. Some key triggers were identified, usually from sensory stimulation (e.g. watching cartoons, listening to music, video/phone calls) and from tiredness. Additionally, symptoms are generally worse with menses onset and during the follicular phase. It is unclear whether medication use (**Table 1**) during menstruation exacerbated these symptoms (also common with mast cell activation syndrome), as prior to vaccination, menstruation caused (mild) dysautonomia and feelings of unwell (alongside pain and other more typical menstruation symptoms), albeit to a lesser extent than post-vaccination.

New symptoms occurred around November 2021, including pins and needles in the legs, "waves of electricity" in the legs, proprioceptive problems (e.g. unable to distinguish which leg is which, or feeling like her hand was on her head when it was on her belly), internal vibrations (particularly on the top of the right thigh), an intermittent tremor primarily in the right hand, random bouts of uncontrollable whole-body shivering, breathlessness, muscle aches in quadriceps, hypersensitive skin (including burning and skin flushing from alcohol

hand gel or soap that was previously unproblematic), micrographia returning, myoclonic jerks which were usually more prominent when sitting (sometimes preceded by a “feeling” that they are about to happen), and thermodysregulation (frequently having a body temperature of 35 °C). Increasing general malaise resulted in a significantly lower quality of life during this time even when other symptoms were calmer. Towards the end of 2021 and the beginning of 2022, symptom fluctuations were more rapid, for example, being near bedbound one day, and being nearly back to “normal” the next. HAC has not had a completely symptom free day, however. Some added events and symptom details are discussed in the appendix which may be relevant or may be coincidental.

CT venogram showed no signs of cerebral venous thrombosis. Blood tests overall showed nothing remarkable (**Table S2**, appendix) with the exception of seemingly chronically elevated D-dimer (1040 ng/mL on 13 May 2021, and 886 ng/mL on 29 December 2021). Spike antibody levels were measured frequently and are reported in Table S3 (appendix). In January 2022, a profound deficiency of circulating vitamins B12, D2, D3, and total D were found (all below detectable range). Intrinsic factor antibody was negative. Upon basic neurological examination (12 January 2022), HAC was noted to have a resting tremor in her right hand; she scored 4/5 on finger flexion bilaterally and had a positive Romberg’s test. Other tests were unremarkable, with no evidence of past-pointing or dysdiadochokinesia and normal heel-toe walking. A neurologist (17 January 2022) reported Hoover’s test to be positive. Of interest, we analysed a historical research serum sample from March 2020, which showed undetectable concentrations of vitamin B12 (< 148 ng/L), indicating chronic severe deficiency even prior to the COVID-19 vaccination.

Treatment with 1 mg intramuscular hydroxocobalamin three times a week commenced on 13 January 2022 (with a hiatus after six doses against medical advice between 26 January and 3 February 2022, inclusive, as HAC did not want to skew the MRI). 50,000 IU per week Stexerol-D3 commenced 19 January 2022. It is planned that intramuscular hydroxocobalamin replacement will continue until symptom improvement has plateaued, then daily oral supplementation will continue. Vitamin D3 supplementation has reduced to 1000 IU per day after completing the six week loading dose. HAC also started supplementation with omega 3 (207 mg DHA, 132 mg EPA; capsules included an unspecified amount of tocopherol) and essential amino acids (~3 g mixed essential amino acids with 1.38 mg vitamin B6) daily from 12 February 2022, and continues with daily iron supplements (626 mg) that she was already (infrequently) taking.

A MRI head and cervical spine scan was done on 4 February 2022. As mentioned above, this did result in a worsening of symptoms. Immediately after, dizziness, bradykinesia, slight tremoring, nausea, fatigue, numb hands, and weakness were most prominent. The subsequent day symptoms were much improved, with dizziness and bradykinesia the most notable symptoms. That evening, a general feeling of unwell occurred, like the beginning of a common cold. A lateral flow test for SARS-CoV-2 was negative. There were several times since vaccination that such an “ill” feeling has occurred. The MRI radiographer’s report stated that there was a prominent frontal subdural space with no evidence of acute or chronic haemorrhage; some very small high T2 and FLAIR signal abnormalities in the deep white matter, of “questionable significance” and no definitive changes of demyelination. No other relevant abnormalities were noted. A neurologist (22 February) looked briefly at the

imaging and felt there were no clear abnormalities, particularly in relation to signs of demyelination.

Since vitamin replacement therapy, HAC reports feeling less fatigued day-to-day, with better thermoregulation. The tremor has virtually gone. Symptoms such as bradykinesia, dizziness, nausea, paraesthesia, and numb hands have not particularly changed (outwith the usual fluctuations HAC was already experiencing prior to vitamin replacement). However, shortly prior to publishing this paper, she did experience a short relapse with menstruation (discussed further in the **Discussion**).

HAC's case is still under medical investigation. We will update this paper after further test results have been received and to update on HACs symptom progress, as appropriate.

Discussion

Here we present two cases of severe and prolonged neurological problems from COVID-19 vaccination, with concomitant severe vitamin B12 (and in one case vitamin D) deficiency. These two cases were symptomatically and diagnostically concordant with similar cases of post-COVID-19 vaccination dysautonomia/similar we are aware of. Anecdotally, several other vaccine-injured patients have reported similar symptoms; some have confirmed vitamin B12 deficiency, others have commenced vitamin B12 replacement therapy without confirmatory tests and/or medical support. In some, but not all, cases vitamin B12 replacement has been helpful in resolving at least some symptoms. Based on vaccine injured patients we have encountered as well as speaking to physicians who have dealt with post-vaccine syndrome in the past, fluctuant symptoms seem typical of chronic vaccine reactions. Such presentation may throw clinicians off in terms of identifying contributory or causal nutritional factors such as vitamin B12 deficiency, as occurred in HAC's case.

Vaccines for other diseases (e.g. influenza) have been associated with neurological (including demyelinating) episodes (Karussis & Petrou, 2014). A recent systematic review showed COVID-19 vaccinations may result in demyelination in (seemingly) rare cases (Ismail & Salama, 2022). We would like to raise awareness that the typical (case) studies in the literature are of recognised diseases, like transverse myelitis. However, based on our experience, many patients' symptoms are atypical and clear diagnoses are difficult or unable to be made. Thus we speculate that post-(COVID-19) vaccination neurological problems (and other atypical clinical presentations) may be undercounted due to lack of awareness and clear diagnostics.

Previous research has suggested a range of neuro-immune mediated COVID-19 vaccine responses, although the link to neuro-autoimmunity is not clear (Csefalvay, 2021). To our knowledge, the role of vitamin B12 deficiency has not been properly investigated as part of these responses. This seems particularly true for chronic adverse reactions. We are aware of one case study of post-COVID-19 vaccination transverse myelitis with comorbid vitamin B12 deficiency (131 pg/mL) (Gao *et al.*, 2021). Another case, presenting similarly to HAC described above, had vitamin B12 deficiency (< 50 pg/mL), and positive intrinsic factor; lactate dehydrogenase was elevated (4332 U/L) and schistocytes were present suggestive of vitamin B12 deficiency-mediated haemolysis (Jaydev *et al.*, 2022). Thus the diagnosis was vaccine-induced autoimmune haemolytic anaemia, in line with two other case studies we are aware of (Brito *et al.*, 2021; Pérez-Lamas *et al.*, 2021).

The underlying pathophysiology of COVID-19 vaccination induced neurological problems is currently unclear, though some hypotheses have been offered (Ismail & Salama, 2022). One key idea is autoimmunity. It is currently not established with confidence how vaccines can induce autoimmunity. Molecular mimicry has been posited as a possible explanation (Rojas *et al.*, 2018), including potential theoretical links to COVID-19 vaccination (Chen *et al.*, 2022), though these have been disputed (Keddie *et al.*, 2021). Another idea is that of anti-idiotype antibody production resulting in autoimmunity (Murphy & Longo, 2021).

However, considering the time trend and onset, it seems more likely that vaccine-induced inflammation (Talotta, 2021) was the primary trigger initiating the reactions (notwithstanding that inflammation may in itself trigger autoimmunity) in the cases we present. Indeed, there

have been reports of inflammation-mediated adverse neurological and other events post-COVID-19 vaccination, such as: reactive arthritis (An *et al*., 2021); Vogt-Koyanagi-Hara disease (Koong *et al*., 2021); peripheral and central nervous system inflammation and demyelination (AlKolfat *et al*., 2022; Camera *et al*., 2021; Khayat-Khoei *et al*, 2021); acute disseminated encephalomyelitis (Cao & Ren, 2021; Kania *et al*., 2021; Lazaro *et al*., 2021; Permezel *et al*., 2021; Rinaldi *et al*., 2021; Vogrig *et al*., 2021); chronic inflammatory demyelinating polyneuropathy (post-SARS-CoV-2 infection and vaccination) (Suri *et al*., 2021); and adult multisystem inflammatory syndrome (Stappers *et al*., 2021). Further, 27 cases of post-COVID-19 vaccination immune-mediated disease flares have been reported by Watad *et al.* (2021), including one case of demyelination. Similarly, another case series found 21 cases of new-onset, or flares of, inflammatory/autoimmune neurological conditions following COVID-19 vaccination, including eight cases of central nervous system demyelination, four cases of inflammatory peripheral neuropathies, and three cases of myositis (Kaulen *et al*., 2021). Finally, neuroinflammation and demyelination following COVID-19 vaccination have been imaged using MRI (Camera *et al*., 2021; Kania *et al*., 2021; Rinaldi *et al*, 2021; Sriwastava *et al*., 2021).

Based on our cases above and others we are aware of, we consider that post-COVID-19 vaccination neurological dysfunction may be a relatively common occurrence, perhaps explaining some of the acute post-vaccination symptoms. However, as most people have adequate vitamin B12 stores and intake, any damage remains minimal and acute. Both of our cases had diets that were low in vitamin B12, thus we think making any necessary repairs difficult.

We want to highlight that in both Case 1 and Case 2 (HAC), all other haematological markers were unremarkable, including haemoglobin and mean corpuscular volume. These markers are often out of range with vitamin B12 deficiency, and in HAC's case, a clinician dismissed the need to measure vitamin B12 based on these normal results. Accordingly, we support guidelines that state the importance of measuring vitamin B12 status when patients present with neurological symptoms, regardless of other haematological parameters (Devalia *et al*., 2014).

It is unclear whether those who experience vaccine-induced neurological (and other) problems have a peculiar inflammatory response or whether such issues can occur with general inflammation. Vitamin B12 is involved with immunomodulation, and therefore if patients have low vitamin B12 stores, this may in itself contribute to a hyperinflammatory or otherwise dysregulated response. Specifically, vitamin B12 has roles in immune regulatory pathways that when dysregulated can stimulate demyelination (Mikkelsen & Apostolopoulos, 2019). Additionally, vitamin B12 deficiency may decrease $CD8^+$ cells and natural killer cell activity (Tamura *et al*., 1999) which has been associated with autoimmunity and inflammation as well as demyelinating diseases such as multiple sclerosis (Chanvillard *et al*, 2013; McBride & Striker, 2017; Pender, 2011).

In terms of Case 2 (HAC), a hyperinflammatory response may in part due to profound vitamin D deficiency. Her acute post-vaccination symptoms would support a hyperinflammatory response, including chills, fever, aches, severe fatigue, plus the aforementioned dysautonomia. She described this acute phase as "at least as bad as flu, if not worse". Vitamin D is involved in both innate and adaptive immunomodulation via many

pathways. Vitamin D has roles in reducing the production of inflammatory cytokines such as interleukin (IL)-17, and increasing production of anti-inflammatory cytokines such as IL-10, as well as gamma interferon, B and T cell production (Aranow, 2011). Further, vitamin D aids in inhibiting dendritic cell differentiation and maturation, which links to autoimmunity. As such, it has been reasoned that vitamin D has a role in neuro-inflammatory and neuro-autoimmune diseases, for example multiple sclerosis (Aranow, 2011). This is in fitting with the roles vitamin D likely has in maintaining neurological health and repairing the myelin sheath (Faye *et al.*, 2019; Gomez-Pinedo *et al.*, 2020). Vitamin D may also have roles in mast cell stabilisation (Liu *et al.*, 2017). Mast cells seem to be contributors of (inflammatory) demyelination and degeneration, including in conditions typically associated with vaccination reactions, such as Guillain-Barré syndrome (Dines & Powell, 1997). Both autoimmunity and mast cell activation can cause the symptoms HAC described.

Further, HAC reports symptoms flares during menses. She is awaiting a diagnostic laparoscopy for suspected endometriosis. She often reports feeling unwell during menstruation, including mild flu-like symptoms (even prior to vaccination). Such symptoms have been exaggerated since vaccination; it is noteworthy that HAC had a slightly early onset menses post-COVID-19 vaccination, which was one of the worst in terms of pain. Menstruation is an inflammatory event with mast cell activation, and particularly in the context of endometriosis, is associated with autoimmunity and immune dysfunction (Berbic & Fraser, 2013; Kempuraj *et al*, 2004; Matarase *et al.*, 2003). It is noted that HAC takes naproxen to help with dysmenorrhea, which inhibits mast cell products; whilst this seems to reduce pain, HAC reports greater dysautonomia symptoms during menses which seem to get worse after taking naproxen.

Several markers of autoimmunity were checked in HAC: antinuclear antibody, anti-myeloperoxidase, anti-proteinase 3, anti-tissue transglutaminase, anti-intrinsic factor, and rheumatoid factor. Whilst these tests came back negative, that does not necessarily rule out autoimmunity against specific proteins. Thus it may be that HAC is predisposed to hyperimmune reactions, which may trigger mast cell activation and/or autoimmunity. With likely gradually depleting vitamin D over at least several months prior to vaccination, we offer speculation that HAC's immune response may have become exaggerated, resulting in the immune hyper-response to the COVID-19 vaccination. HAC is still under investigation, with autoimmunity and mast cell activation syndrome being potential further pathologies to explore, depending on symptom resolution. *We will update this paper with any further tests*.

Based on the above, we propose a hypothesis explaining the above two case presentations, with potential broader applicability to the wider vaccine injured community who may share some, if not all, of these mechanistic pathways (**Figure 1**). Our hypothesis, which requires testing and likely refinement, is that low baseline vitamin B12, contributes to a hyperinflammatory response which is triggered by an immune stimulus (in this case the COVID-19 vaccination). In an attempt to repair any neurological damage, vitamin B12 gets further depleted due to insufficient dietary intake. Alongside this, in some people (such as HAC), low baseline vitamin D adds to a hyperinflammatory response, perhaps contributing to autoimmunity and/or mast cell activation. This results in a physiological milieu that might exaggerate neurological problems and/or inhibit neurological repair.

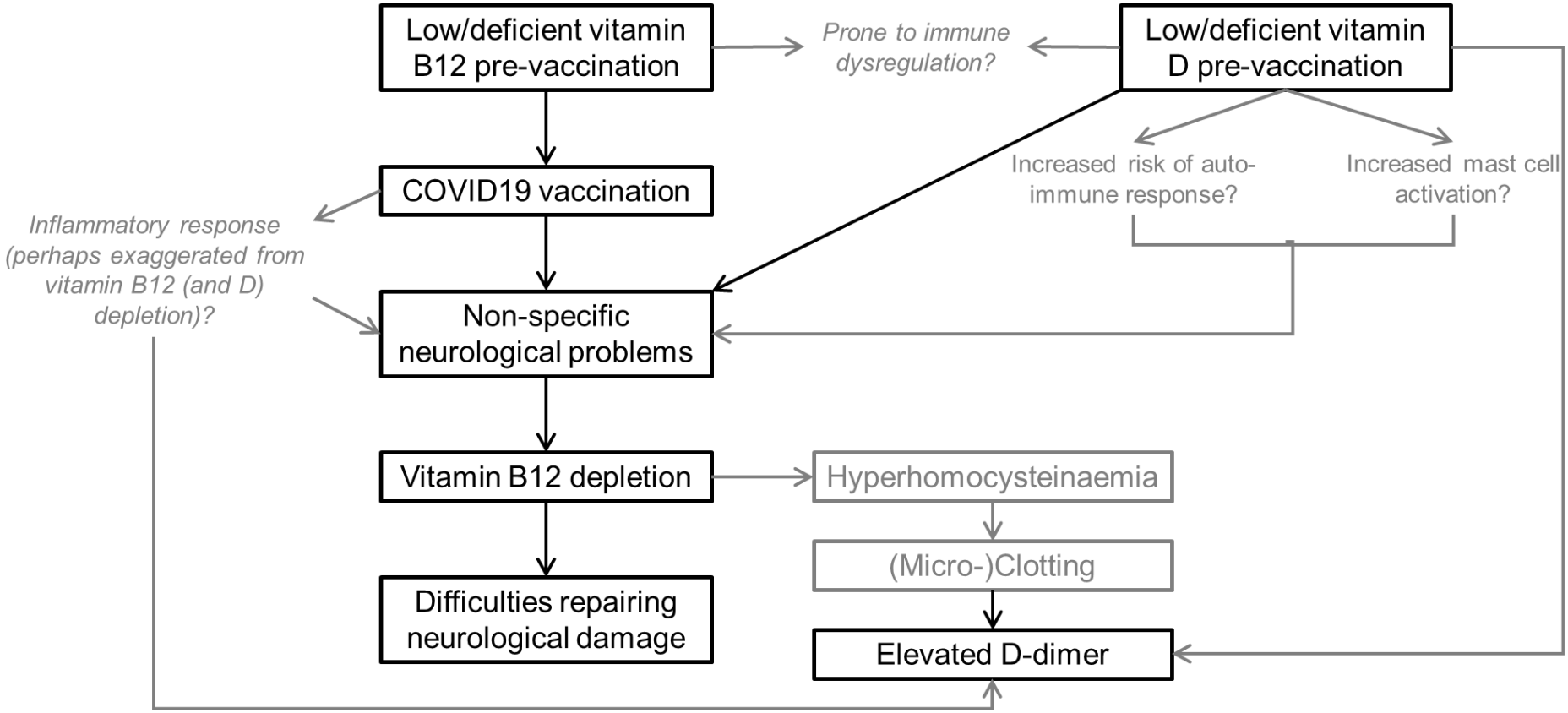

Figure 1. Proposed mechanism from low/deficient vitamin B12 and D to a severe and chronic vaccine reaction. In black are the pathways we have evidence for; in grey are the pathways we propose *could* be involved

Within this hypothesis, we have attempted to explain HAC's elevated D-dimer. D-dimer is a non-specific marker of inflammation and/or coagulation and can reflect hyperinflammatory states such as cytokine storms (Baktash *et al*., 2021). D-dimer has been shown to have a relatively high false positive rate in relation to pulmonary embolism (Crawford *et al*., 2016) which also did not symptomatically fit HAC's presentation. A head CT scan with contrast dye was done to check for cerebral venous thrombosis, showing nothing remarkable. Vascular endothelial growth factor was also measured (January 2022) to identify whether there was signs of cardiovascular injury, also coming back within the reference interval. We attempted to identify whether there were signs of "microclots" (Pretorius *et al*., 2021) via light microscopy of platelet-poor plasma (an unvalidated method). We found what could be evidence of microclots. However, without fluorescence and with suboptimal equipment these tests were difficult to interpret and thus inconclusive. We want to raise awareness that some (Kell *et al*., 2022) have hypothesised that microclots could skew blood results to incorrectly come back "normal", for example by entrapment of inflammatory proteins. The slight abnormalities shown as white matter hyperintensities in HAC's MRI scan may be indicative of vascular damage and/or neurodegeneration (i.e. in line with elevated D-dimer) and are typically associated with ageing (Wardlaw *et al*, 2015). Such changes have also been associated with symptoms HAC experienced, such as cognitive impairment, abnormal gait, and disturbed balance (Wardlaw *et al*., 2015). However, these MRI findings were queried by a neurologist, and could be non-clinically significant.

Considering our fairly extensive investigation of obvious inflammatory and cardiovascular causes of elevated D-dimer, we propose that D-dimer may be (at least in part) a clinical indication of severe vitamin B12 deficiency, particularly in the face of other unremarkable blood results. Such a hypothesis should be further investigated, and in the meantime, clinicians should be aware that D-dimer may have a relation to nutrient status. The biochemical pathway we propose is that vitamin B12 deficiency causes hyperhomocysteinaemia, thus activating clotting cascades (Jahangiri *et al*., 2021). Thus, as D-dimer is indicative of clot breakdown, B12 deficiency may result in elevated D-dimer levels. As seen in **Table S2**, HAC's pre-B12 replacement therapy D-dimer was lower in December 2021 (886 ng/mL) than in May 2021 (1040 ng/mL), though we expect to see a significant and more meaningful trend downwards as B12 replacement therapy progresses (we note D-dimer concentration of 755 ng/mL in February 2022). The reduction in D-dimer prior to B12 replacement may also indicate fluctuations in inflammation. The aforementioned neurologist (from February 2022) stated that in their clinical experience, most post-vaccine syndrome patients have symptom resolution within 1-2 years. Thus, the lower D-dimer measured in December 2021 could equally (or partially) be indicative of natural resolution of the vaccine reaction. As such, the causal role of B12 deficiency in elevating D-dimer should be investigated, especially as any further reduction in HAC's case will have an unclear pathophysiological cause.

Moreover, increased D-dimer has been associated with low vitamin D levels in several patient populations, such as immune reconstitution inflammatory syndrome (Musselwhite *et al*., 2016), primary ovarian insufficiency (Kebapcilar *et al*., 2013), and indeed PASC (long COVID) (Baktash *et al*., 2021; Ricci *et al*., 2021). Biochemically, vitamin D may act by upregulating anticoagulant glycoprotein expression and downregulating coagulation factors (Koyama & Hirosawa, 1998). Thus this link makes sense, and it seems likely that HAC's elevated D-dimer could be a result of vitamin B12 and/or vitamin D deficiency, perhaps

initiated/exacerbated by (chronic and fluctuant) inflammation initially caused by the COVID-19 vaccine. Previous research has shown COVID-19 vaccinations to elevate D-dimer, particularly with viral vector vaccines like ChAdOx1nCoV-19, at least acutely (Favaloro, 2021); with HAC's presentation, such a response remained chronic, possibly due to vitamin deficiency. However, we do not have pre-vaccination data on HAC's D-dimer to confirm our inference; as with B12, we propose further testing of this hypothesis.

As the prevalence of chronic vaccine injuries becomes more apparent, it seems increasingly likely that the acute post-vaccination reaction may be akin to the acute reaction in some patients to SARS-CoV-2 infection; thus similarly, the chronic impacts between vaccination and infection have overlap. Accordingly, the above hypothesis may be useful for COVID-19 and PASC (long COVID) patients, and perhaps other post-infectious conditions (e.g. Myalgic Encephalomyelitis, chronic Lyme disease). Indeed, SARS-CoV-2 infection has been reported to cause neurological problems including demyelination (Zanin *et al.*, 2020) via multiple mechanisms including host inflammatory response and autoimmunity (Shabani, 2021).

Further, PASC (long COVID) often presents with similar neurological symptomatology to our two cases (Proal & VanElzakker, 2021; Shabani, 2021). Indeed, one small study of older adults hospitalised with COVID-19 found favourable outcomes when patients were administered combined vitamin D (1000 IU), magnesium (150 mg), and vitamin B12 (500 µg) (Tan *et al.,* 2020). Further, both autoimmunity (Su *et al.*, 2022) and mast cell activation (Weinstock *et al.*, 2021) may underly both acute SARS-CoV-2 infection and PASC (long COVID), similar to cases in chronic COVID-19 vaccine reactions. Whilst we do not rule out unique effects of SARS-CoV-2 infection, the commonality between PASC (long COVID) and chronic COVID-19 vaccine adverse reactions is the spike protein. Thus, such concordant reactions may suggest the introduction of the novel spike protein to a susceptible host has a key role in invoking immune hyperreactions, which may cause severe acute COVID-19, PASC (long COVID), and/or severe/chronic COVID-19 vaccine reactions.

Linking back to our hypothesis (**Figure 1**), it is of interest that both vitamin B12 and D have been recommended to optimise vaccine efficacy (Rayman & Calder, 2021); though safety was not the aim of this recommendation, we believe ensuring adequate vitamin B12 and D status has the potential to reduce hyperreactions and the chronic consequences of them, particularly in patients who are at risk of having low or deficient stores. Accordingly, we would support pre-vaccination vitamin B12 screening in those at high risk of deficiency (e.g. older adults, those on vegan diets, those with pernicious anaemia). We also emphasise current population recommendations for vitamin D supplementation. Such an approach may also have utility for reducing COVID-19 severity, and perhaps mitigating PASC (long COVID). These ideas should be tested in order to understand their utility and validity.

Importantly, we would like to emphasise that this hypothesis, if correct, is only relevant for a subgroup of vaccine injured patients. Many patients we have encountered have no evidence of vitamins B12 and/or D deficiency. Severe and chronic reactions seem to occur with any of the (current) COVID-19 vaccines, implicating the spike protein specifically as the key insult (rather than something specific to a type of vaccination). We encourage researchers to examine this hypothesis in more detail, and would support a precautionary approach of B12 preloading in high risk groups in the meantime, and post-vaccination nutritional status testing

if prolonged or unusual reactions occur. We also encourage researchers to examine other causes of vaccine injuries, such as autoimmunity to non-standard proteins (such as FGFR3, ACE2, AT1, etc), mast cell activation, and microclots.

Both of our cases were diagnosed with subacute combined degeneration of the spinal cord. Only HAC received a diagnostic MRI scan. Of the two cases, based on dietary factors and time-to-diagnosis, we believe HAC had a longer period of time being vitamin B12 deficient along with positive Romberg's test (which became negative on 13 February 2022 after several rounds of intramuscular hydroxocobalamin), and therefore may have been more likely to have visible demyelination. This supported by a stored serum sample from March 2020, which showed vitamin B12 to be below the detectable range (< 148 ng/L). As such, we expected clear demyelination to be present on the MRI, which was not found. Some research has shown that MRI may have low sensitivity in diagnosing subacute combined degeneration of the cord (Jain *et al.*, 2014). We initially hypothesised that in our two cases COVID-19 vaccination resulted in demyelination and B12 deficiency meant remyelination was difficult. We revised this hypothesis in light of no *clear* evidence of demyelination.

Beyond myelin, vitamin B12 and its cofactors have many functions in neurological health and disease (Calderón-Ospina & Nava-Mesa, 2020). Thus our revised hypothesis is more precautionary in relation to the two cases presented, though demyelination cannot be completely ruled out (especially in Case 1 who did not receive a diagnostic MRI). Other patients may also have clear demyelination. Whilst both reactions can be classed as post-vaccine syndrome, a key question that remains is whether these reactions would have occurred if there were no nutritional deficiencies. In Case 1, we think vitamin B12 deficiency was indeed the key pathology considering his quick recovery after initiating B12 replacement when symptoms recurred after his next vaccine. However, whether the primary mediator is demyelination or another neurological pathway remains unclear and is an important area for future research.

In contrast, in HAC's case, we think B12 deficiency is a contributory factor, but perhaps not the primary pathology. Our reasoning is that shortly prior to publishing this paper HAC had a relapse in line with menses onset. Symptoms included extreme dizziness, nausea, fatigue, increased numbness in hands, paraesthesia in legs, and a general overwhelming feeling of unwell, lasting ~6 days. She was significantly incapacitated during the first 3-4 days. However, in contrast to previous relapses, thermodysregulation, tremoring, and other symptoms remained minimal or non-existent, perhaps due to improved B12 and vitamin D status. On days 3-6, HAC took 10 mg loratadine. This relieved symptoms within ~1 hour. However, on day 6, loratadine had minimal effect and she had to leave work early, ending in an incapacity episode once she was home. By day 7, symptoms had markedly improved, and HAC was able to work a full day again. We will likely test for mast cell activation at the next relapse.

Finally, we wish to emphasise that all medical procedures come with risks. Based on current data, it is clear that the risks of vaccination are significantly outweighed by the benefits at a population level. However, it is important to acknowledge the (seemingly) rare cases of severe reactions. This serves several purposes. Firstly, identifying vaccination injuries *versus* coincidental findings aids in understanding causality. This may help make safer vaccines in the future. Secondly, understanding the pathophysiology means new patients

presenting with similar post-vaccination symptomatology can have targeted tests that rapidly identify or rule out other pathologies. This aids in targeted treatments with minimal delays. Thirdly, such investigation offers potential for identifying patients who might be higher risk of severe and/or chronic vaccine reactions. This offers opportunity for pre-vaccination screening, allowing patients to make an informed risk-benefit calculation regarding vaccination *versus* infection risk. In the case of B12 deficiency, there is a potential and relatively easy preventative measure which could prevent patient suffering, i.e. pre-vaccination screening/preloading and post-vaccination intake of vitamin B12.

Conclusion

We report two cases, presenting with a range of fluctuant neurological symptoms, of vitamin B12 (and in one case, also vitamin D) deficiency-mediated neurological problems post-COVID-19 vaccination. Case 1 has had complete resolution with vitamin B12 replacement therapy; Case 2 is currently undergoing vitamins B12 and D replacement therapy and we will update this paper accordingly. Based on these two cases, plus the wider literature, we propose that COVID-19 vaccination causes an acute hyperinflammatory milieu in some people (possibly mediated by vitamin deficiency in our cases). Inflammation-mediated non-specific neurological damage occurs, and without sufficient vitamin B12 (and possibly vitamin D), neurological repair is limited. Within these pathways, we propose a potential role for autoimmunity and/or mast cell activation. Additionally, vitamin B12 and D deficiency, perhaps in combination with inflammation, appears to have presented with an elevated D-dimer in one of our cases and we propose that there may be a causal link. These ideas should be further investigated to establish their validity; in the meantime, clinicians should be aware that D-dimer *could* represent nutrient deficiency if triggered by an immunological stimulus. Based on these cases (and others we are aware of), we would support vitamin B12 screening prior to vaccination in high risk groups, and for population vitamin D supplementation (as per dietary guidelines), pending further testing.

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Appendix

Table S1. Blood test results for Case 1

	24/02/2021	08/03/2021
Full Blood Count		
Haemoglobin (g/L)	149	
Red blood cell ($x10^{12}$/L)	5.0	
Haematocrit (L/L)	0.46	
Mean corpuscular volume (fl)	92	
Mean corpuscular haemoglobin (pg)	30	
Platelet ($x10^9$/L)	188	
White blood cell ($x10^9$/L)	5.3	
Neutrophils ($x10^9$/L)	3.1	
Eosinophils ($x10^9$/L)	0.20	
Basophils ($x10^9$/L)	0.07	
Lymphocytes ($x10^9$/L)	1.4	
Monocytes ($x10^9$/L)	0.5	
Haematinics		
Ferritin (μg/L)		32.5
Folate (μg/L)		5.3
Vitamin B12 (ng/L)		< 148
Urea and electrolytes		
Sodium (mmol/L)	140	
Potassium (mmol/L)	4.1	
Chloride (mmol/L)	105	
Bicarbonate (mmol/L)	26	
Urea (mmol/L)	4.3	
Creatinine (μmol/L)	70	
eGFR (mL/min/1.73m^2)	> 60	
Liver Function Tests		
Alkaline phosphatase (U/L)	62	
Albumin (g/L)	44	
Total protein (g/L)	68	
Alanine aminotransferase (U/L)	18	
Aspartate aminotransferase (U/L)	14	
Gamma-glutamyl transferase (U/L)	24	
Total bilirubin (μmol/L)	7	
Inflammatory Markers		
C-reactive protein (mg/L)	< 1	
Endocrine Markers		
Thyroid stimulating hormone (mU/L)	0.72	
Free thyroxine (T4) (pmol/L)	11.0	
Other biochemistry		
Adjusted calcium (mmol/L)	2.15	
Phosphate (mmol/L)	0.99	
Creatine kinase (U/L)	81	

Glucose (mmol/L)	5.0

Autoantibodies

Intrinsic factor antibody	Negative

Results with grey background indicate out of reference range, and the reference ranges for these data are shown below. Abbreviations: eGFR, estimated glomerular filtration rate
Vitamin B12 reference range: 200-700 ng/L
Calcium (adjusted) reference range: 2.20-2.60 mmol/L

Additional events from Case 2 (HAC)

Event 1: Nerve damage from wisdom tooth removal

On 18 September 2021, HAC had her lower right wisdom tooth removed due to ongoing problems with it. The tooth was difficult to remove. The surgery lasted approximately 40 minutes, using Lidocaine anaesthetic which had to be topped up midway through due to pain. Post-surgery, the liquid diet severely increased nausea, such that HAC had to move onto solid foods within 48 hours. Recovery was very slow, with swelling subsiding in about two weeks, despite taking naproxen, ibuprofen, and paracetamol at various points throughout the recovery. The lingual nerve appeared to be damaged; as such HACs tongue remained numb, had burning mouth syndrome, and experienced ageusia, on the right side. Little recovery has been made, except that as of December 2021, some patches could detect hot and cold quite sensitively. This has been mentioned as Lidocaine sensitivity has been reported by those with mast cell activation disorders, so may be implicated in both the initial nerve damage, and the poor recovery. Furthermore, the lack of improvement is in fitting with an inability to properly repair nerve damage due to vitamin B12 deficiency. Additionally, the vitamin D deficiency may have contributed to a hyperinflammatory response.

Event 2: Unexplained rash

At the beginning of November 2021, HAC started getting a rash consisting of raised red spots. These were not in themselves itchy, but she reports feeling generally itchier. The first spots noticed were on the neck and face, and they spread over a matter of days to the torso, back, arms and legs. As they disappeared, sometimes they would get (minimally) flaky. The event lasted a few weeks, from noticing the first spots to the final spots disappearing. The rash had some similarities to rosacea pityriasis, though no diagnosis was given. A pharmacist said it could be Varicella zoster with atypical presentation, or meningitis, though both of these seemed unlikely. Subsequently a general practitioner gave HAC some anti-fungal cream based on an online consultation form with pictures. HAC did not use any of the creams provided. Unexplained rashes can be caused by mast cell activation disorders as well as autoimmune conditions, hence why this event has been mentioned. Rashes can also be a sign of vitamin D deficiency.

Further symptom details

HAC is diagnosed with depression and obsessive compulsive disorder. Both of these are associated with autoimmunity and inflammatory profiles. Further, depression is associated with vitamin D deficiency. However, both conditions remained largely minimal and well-controlled since the vaccine. During incapacity episodes, HAC reported depressive symptoms, but these alleviated with the episode ending.

Further testing

In March 2022, we used the NASA Lean Test to investigate postural orthostatic tachycardia syndrome (POTS) as this has anecdotally been reported in other post-vaccine syndrome patients. POTS has also been associated with neuro-immunological dysfunction symptomatically similar to HAC (e.g. ME; Lee *et al.*, 2020). In brief, HAC and KAD (acting as a control) laid down supine for 10 minutes, followed by standing with feet approximately six inches away from the wall, leaning back such that shoulders were touching the wall and the body was straight. Heart rate was measured by pulse oximetry on the right index finger.

Blood pressure was measured using an automated sphygmomanometer on the left arm. Measurements were taken at five and 10 minutes after commencement of laying down, and then minutely upon standing in the lean position.

Figure S1 shows there were no meaningful changes to either HAC nor KAD's blood pressure, though HAC's systolic blood pressure did elevate slightly during standing (greatest difference from 10 minutes of laying down was at 3 minutes standing, Δ 22 mmHg; comparatively the largest change for KAD was at 4 minutes standing, Δ 11 mmHg). This ruled out orthostatic hypotension. **Figure S2** shows no meaningful changes in HAC and KAD's pulse pressure (systolic minus diastolic blood pressure). **Figure S3** shows average heart rate for KAD whilst standing was 82 beats per minute (bpm), compared to 68 bpm laying down (Δ 12 bpm). Comparatively, HAC's average heart rate whilst standing was 130 bpm, *versus* 80 bpm when laying down (Δ 50 bpm). The greatest difference in heart rate compared to the measure taken at 10 minutes of laying down was at 10 minutes of standing (Δ 20 bpm) for KAD, and 8 minutes of standing for HAC (Δ 66 bpm). During standing, HAC had symptoms of mild clamminess, shakiness, and light-headedness.

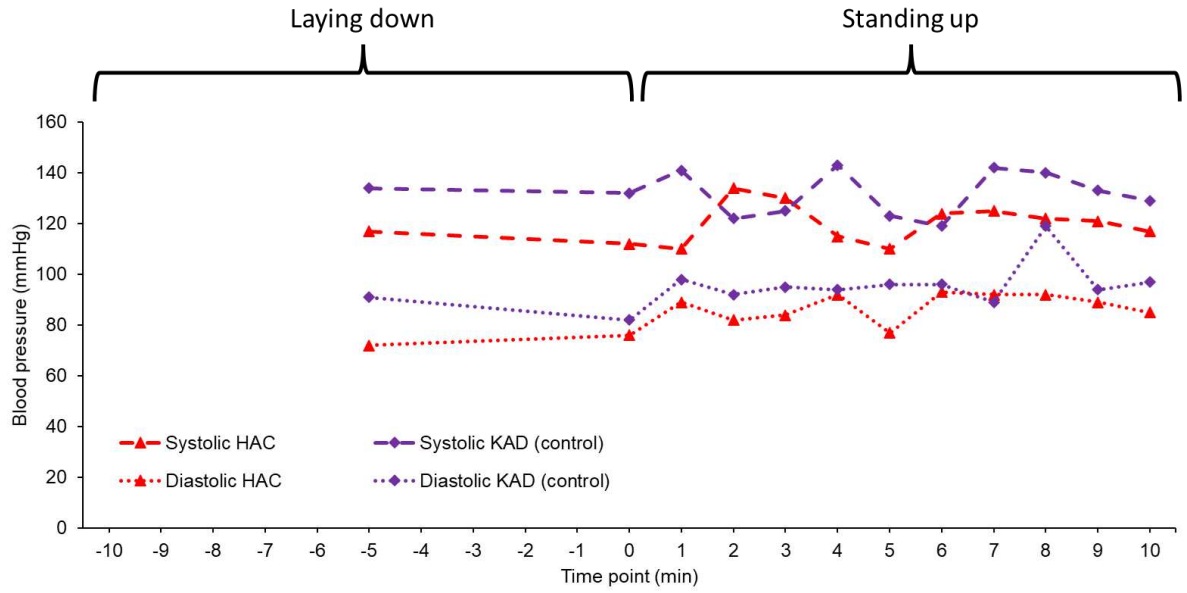

Figure S1. HAC and KAD's systolic and diastolic blood pressure through the NASA Lean Test

Prior to vaccination, HAC reported feeling a bit faint after standing or sometimes with exercise "like my blood pressure had dropped" on occasions. Often this resulted in having to sit down, but overall was not disruptive to life. After a first rib resection, scalenectomy, and pectoral minor tenotomy for thoracic outlet syndrome in 2017, HAC mentioned these symptoms to her cardiothoracic surgeon who did not seem concerned. Since COVID-19 vaccination in March 2021, these symptoms have become increasingly more apparent and disruptive, for example, having to sit down when talking to colleagues at work or whilst preparing food.

Overall, whilst perhaps not conclusive, these results indicate HAC may have POTS, supporting autonomic nervous system dysfunction as a key pathology. This may have been exacerbated by vitamin B12 deficiency.

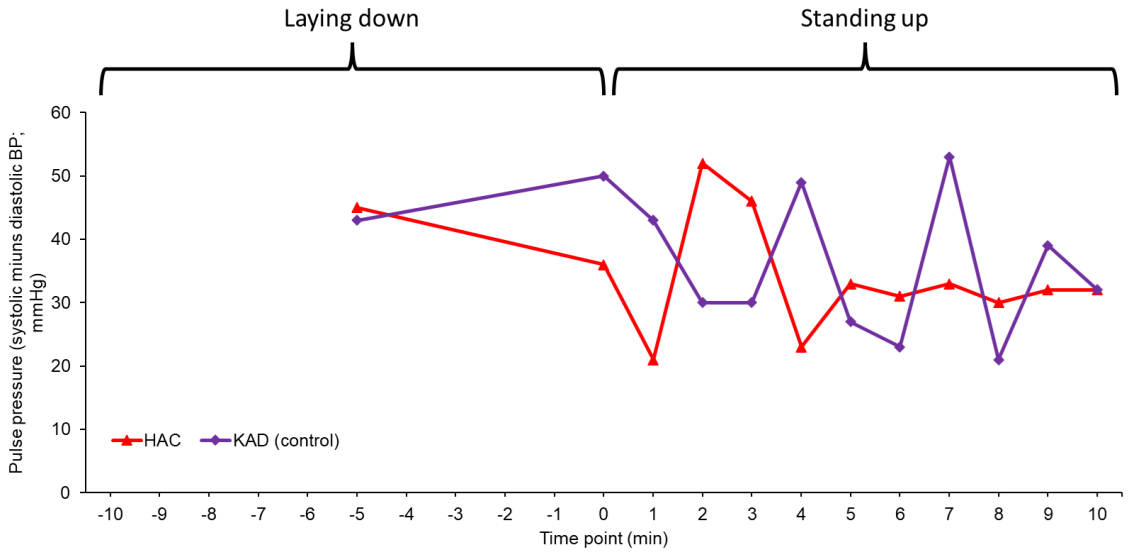

Figure S2. HAC and KAD's pulse pressure (systolic minus diastolic blood pressure) during the NASA Lean Test

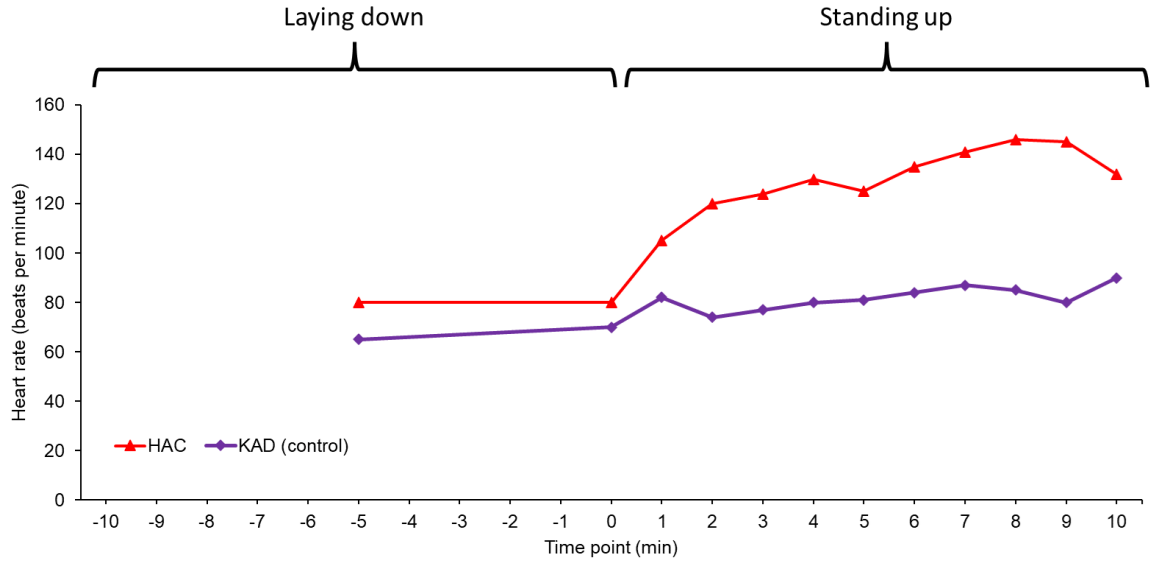

Figure S3. HAC and KAD's heart rate during the NASA Lean Test

Table S2. Blood test results for Case 2 (HAC)

	31/03/2021	13/05/2021	29/12/2021	12/01/2022	17/01/2022	10/02/2022
Full Blood Count						
Haemoglobin (g/L)	129	119	130	131	124	125
Red blood cell (x10^{12}/L)	4.3	3.8	4.2	4.3	4.0	4.0
Haematocrit (L/L)	0.39	0.36	0.40	0.41	0.38	0.38
Mean corpuscular volume (fl)	92	94	94	95	95	95
Mean corpuscular haemoglobin (pg)	30	31	31	31	31	32
Platelets (x10^{9}/L)	277	199	182	165	195	194
Mean platelet volume (fl)	10.3	11.9	12.6	13.4	12.9	12.7
White blood cell (x10^{9}/L)	7.3	7.8	5.5	5.0	5.2	6.9
Neutrophils (x10^{9}/L)	4.6	4.6	2.6	2.7	3.0	3.8
Eosinophils (x10^{9}/L)	0.06	0.19	0.07	0.06	0.03	0.07
Basophils (x10^{9}/L)	0.03	0.06	0.02	0.03	0.04	0.05
Lymphocytes (x10^{9}/L)	1.9	2.3	2.1	1.7	1.6	2.2
Monocytes (x10^{9}/L)	0.7	0.7	0.7	0.5	0.5	0.7
Haematinics						
Ferritin (μg/L)						20.9
Folate (μg/L)						11.5
Vitamin B12 (ng/L)				< 148		
Clotting Markers						
D-dimer (ng/mL)		1040	886			755
Prothrombin time (s)		11.3	11.7			11.9
INR		1.0	1.0			1.0
Activated Partial Thromboplastin Clotting Time (s)		31.3	30.8			31.3
Urea and electrolytes						
Sodium (mmol/L)	141	141	139	140	140	140
Potassium (mmol/L)	4.8	4.2	4.3	4.3	4.4	4.4

Chloride (mmol/L)	104	106	105	106	107	103
Bicarbonate (mmol/L)	35	28		29		
Urea (mmol/L)	3.2	2.4	3.4	2.7	2.8	3.2
Creatinine (μmol/L)	54	56	57	54	59	52
eGFR (mL/min/1.73m^2)	> 60	> 60	> 60	> 60	> 60	> 60
Liver Function Tests						
Alkaline phosphatase (U/L)	67	75	74	74		66
Albumin (g/L)	51	45	47	47	46	47
Total protein (g/L)	79	69	81	78	73	76
Alanine aminotransferase (U/L)	31	7	19	16		15
Aspartate aminotransferase (U/L)				20		
Gamma-glutamyl transferase (U/L)	11	8	9	13		13
Total bilirubin (μmol/L)	6	5	7	8		9
Lactate dehydrogenase (U/L)				155		
Immunoglobulins						
Serum IgG (g/L)	9.3			9.4	9.2	
Serum IgA (g/L)	3.30			3.10	3.00	
Serum IgM (g/L)	1.47			1.25	1.21	
Inflammatory Markers						
C-reactive protein (mg/L)	< 1	< 1	< 1	< 1		< 1
Interleukin-6 (pg/mL)				2.3		
Vascular endothelial growth factor (pg/mL)				460		
Endocrine Markers						
Cortisol (nmol/L)		245				
Thyroid stimulating hormone (mU/L)		1.62		1.87	2.09	
Free thyroxine (T4) (pmol/L)		9.5		10.2	11.2	

Lipid Profile					
Cholesterol (mmol/L)				4.5	
HDL cholesterol (mmol/L)				1.3	
LDL cholesterol (mmol/L)				2.7	
Non-HDL cholesterol (mmol/L)				3.2	
Triglyceride (mmol/L)				1.07	
Apolipoprotein A1 (g/L)				1.54	
Apolipoprotein B (g/L)				0.91	
Nutrition Screen					
Vitamin A (µmol/L)				1.3	
Vitamin B1 (ngTDP/gHb)				353	
RBC Vitamin B2 (nmol/gHb)				2.0	
RBC Vitamin B6 (pmol/gHb)				569	
Total Vitamin D (nmol/L)				< 8	
Vitamin D2 (nmol/L)				< 8	
Vitamin D3 (nmol/L)				< 8	
Vitamin E/cholesterol ratio (µmol/L/mmol)				4.6	
Vitamin K/triglyceride ratio (nmol/mmol)				0.66	
Zinc (µmol/L)				12.0	
Copper (µmol/L)				14.0	
Selenium (µmol/L)				1.34	
Red cell selenium (nmol/gHb)				9.1	
Manganese (nmol/L)				170	
Other biochemistry					
Adjusted Calcium (mmol/L)	2.18	2.30	2.17	2.30	2.33
Phosphate (mmol/L)	0.96	1.01	0.98	0.92	1.07
Magnesium (mmol/L)				0.92	0.84
Urate (µmol/L)				185	
Creatine kinase (U/L)			52		

Glucose (mmol/L)	4.6	4.5	
HbA1c (mmol/mol)		34	33
Serum osmolality (mmol/kg)	291		
Angiotensin converting enzyme (U/L)			30
Caeruloplasmin (g/L)			0.23
Iron (µmol/L)		27.0	
Transferrin (g/L)		3.3	
Transferrin saturation (%)		33	
Microbiology			
HIV types 1 and 2			Negative
Borrelia burgdorferi IgG			Negative
Autoantibodies			
Anti-myeloperoxidase (IU/mL)			< 0.2
Anti-proteinase 3 (IU/mL)			< 0.6
Tissue transglutaminase IgA antibody (U/mL)		0.5	
Intrinsic factor antibody		Negative	
Antinuclear antibody	Negative		

Blood film (17/01/2022): Red blood cells appear normochromic normocytic. White blood cells and platelets appear normal.
Serum electrophoresis (17/01/2022): No paraprotein visible.

Results with grey background indicate out of reference range, and the reference range for these data are explained below. Abbreviations: eGFR, estimated glomerular filtration rate; Ig, immunoglobin
Basophil reference range: 0.1-0.5 $x10^9$/L
Bicarbonate reference range: 22-29 mmol/L
Albumin reference range: 35-50 g/L
Calcium (adjusted) reference range: 2.20-2.60 mmol/L
Urea reference range: 2.5-7.8 mmol/L
D-dimer interpretation: Positive (cut-off 500 ng/mL)
Haemoglobin reference range: 120-160 g/L
Red blood cell reference range: 4.0-5.0 x 10^{12}/L
Haematocrit reference range: 0.37-0.47 L/L
Mean platelet volume reference range: 7.0-10.4 fl
Vitamin B12 reference range: 200-700 ng/L
Red cell selenium reference range: 3.0-9.0 nmol/gHb

Table S3. Case 2 (HAC) spike antibody levels

Date	Spike antibody level (AU/mL)
21/07/2021	247.30
17/08/2021	200.90
12/10/2021	179.70
10/11/2021	168.80
08/12/2021	160.10
04/01/2022	144.70
03/02/2022	103.10

Serum IgG antibodies to the receptor binding domain of the S1 subunit of the spike protein of SARS-CoV-2 were determined by qualitative chemiluminescent microparticle immunoassay on an Alinity I platform (Abbott Laboratories, UK). The cut-off for positivity is 50 AU/mL

Note: Of interest, research has suggested that the presence of autoantibodies in response to SARS-CoV-2 infection shares an inverse relationship to anti-SARS-CoV-2 antibodies (Su *et al.*, 2021). If HAC has had vaccine-induced autoimmunity, this mild antibody response to the vaccine may be in line with such research.