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Case Report

The Missing Link Between Stroke, Bone Marrow Suppression and Ataxia

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Abstract

Three interesting cases of seemingly unrelated clinical presentations and in patients of varying ages are presented to highlight the importance of a relatively common underlying problem, reversible if considered early but associated with chronic sequelae if untreated. All three cases are linked to Vitamin B12 deficiency and range in cause from dietary deficiency to abuse of a so-called legal high. This has become more significant since the COVID-19 pandemic which led to delayed presentations, increased cases of substance misuse and safeguarding related incidents.

Keywords: Stroke; Bone marrow suppression; Ataxia; Infantile ischemic stroke; Vitamin B12; COVID-19.

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Introduction

A case-series of three is presented to highlight the varied way in which vitamin B12 deficiency can present and to discuss some approaches to management. A case of infantile ischemic stroke, a 7-year-old with severe pancytopaenia and a young man's gait disturbance secondary to peripheral neuropathy ultimately shared a common pathophysiology. Pediatricians are taught to detect pathology associated with nutrient deficiency in developing youngsters, but sometimes one is surprised by the varied consequences of low levels of certain micronutrients. Something as fundamentally simple as B12 (cobalamin) depletion can have such differing effects on patients and sometimes, perhaps more puzzling, is not its depletion but its 'deactivation' which over time can lead to severe and non-reversible effects.

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Case 1

A 10-month-old boy presented to hospital after a trivial fall and minor head injury with generalized hypotonia and paucity of movements. He was born in Portugal, to non-consanguineous parents from India. He was exclusively breastfed and was thriving, with good weight and normal development. Both parents were strict vegetarians.

An MRI brain demonstrated bilateral striatal thrombotic events and hyperintensities of the basal ganglia. A diagnosis of ischaemic stroke was made, and aspirin started. A thorough thrombotic workup included cardiac, haematological, vascular, infective, vasculitic, oncological and metabolic investigations, which revealed high levels of urinary homocysteine. This would otherwise be consistent with a diagnosis of homocystinuria; however, this inherited condition is usually associated with seizures, intellectual impairment, developmental delay, and musculoskeletal and ocular abnormalities. He was lacking the usual physical phenotype.

Raised levels of urinary methylmalonic acid were also detected, suggesting depletion of vitamin B12 and likely dietary deficiency. Indeed, serum vitamin B12 levels were undetectable (<100 ng/L), and he was also iron deficient. An echocardiogram and all other investigations were normal.

He received parenteral cobalamin (B12) replacement, and this led to clinical improvement, with resolution of hypotonia and normalization of urinary homocysteine and methylmalonic acid levels over time. Aspirin was discontinued and he was prescribed regular multivitamins and iron. He now enjoys a varied diet with chicken, eggs and dairy and is growing and developing well. On follow up he has very subtle left sided weakness but no cognitive deficit.

Case 2

A 7-year-old girl presented with pallor, lethargy and abdominal pain on a background of non-bloody diarrhea and vomiting for one month. She had some weight loss over this period, detected by clothing becoming loose. There was no history of fever, no infective household contacts, and no risk factors for infective diarrhea. Parents were Kuwaiti in origin and consanguineous (cousins). She had an elder brother and younger sister who were both well. Although both parents were strict vegetarians, she had recently been diagnosed with vitamin B12 deficiency by her GP and was on oral cyanocobalamin and a diet more inclusive of meat, fish, and dairy. She was described as a 'picky eater'.

Examination revealed low body weight with conjunctival pallor but no bruising or petechiae. Initial investigations showed marked pancytopaenia; haemoglobin 47 g/L, platelets 61 x109/L, neutrophils 0.8 x109/L, but no blast cells on blood film. Subsequent flow cytometry excluded haematological malignancy. Mean corpuscular volume was 91.7 fL, suggesting borderline macrocytosis. Further haematinics revealed undetectable serum vitamin B12 level (<100 ng/L) with sufficient total iron and folate and raised ferritin and lactate dehydrogenase (LDH 1771 IU/L). Inflammatory markers were low. Liver and renal function was normal. An auto-antibody panel and viral PCRs (Parvovirus, EBV, CMV, adenovirus) and serology were

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negative. Coeliac screen was normal. Stool cultures and virology were negative.

She received a transfusion of red cells and platelets, but white blood cell count normalised slowly after intramuscular vitamin B12 replacement. She is receiving 6-monthly hydroxocobalamin injections as well as oral folate and multivitamins, and her full blood count and vitamin levels remain normal. Extensive metabolic investigation concluded that the presentation was most likely secondary to total depletion of vitamin B12.

Case 3

A joint review with adult neurologists provided encounter with a 24-year-old male with gait instability, following a four-week history of lower limb paraesthesia and significant decline in mobility. He described a two-week history of tingling in his fingers at onset, causing functional difficulties such as fastening clothing and typing. Tingling also involved his feet and gradually spread to involve the whole of the legs and trunk. He had impaired balance, requiring a walking aid, as his legs would give way. At presentation, he also complained of chest tightness. There was no tinnitus, visual, swallowing, urinary or bowel symptoms. He declared no significant medical history. He enjoyed a normal diet and denied taking illegal substances.

On examination there was normal power and tone but absent ankle deep-tendon reflexes bilaterally and impaired sensation to light touch, vibration and proprioception in his lower limbs. Investigations revealed vitamin B12 level 168 ng/L (180-1100 ng/L), Homocysteine 113.3 µmol/L (<15 µmol/L), Methylmalonic acid 6374 µmol/dL (0-28 µmol/dL) and MCV 106 fL. Suspecting dorsal column spinal pathology, targeted questioning revealed regular inhalation of nitrous oxide from small, pressurized metal containers called 'Whippits', used to charge commercial whipped cream dispensers. He was subsequently diagnosed with subacute combined degeneration of the cord (SACD) secondary to nitrous oxide abuse through its interference with vitamin B12 metabolism and its essential role in production of other B-vitamins and the process of myelination. Unfortunately, due to its prolonged use, his condition was non-reversible despite B12 replacement.

Figure 1: Image of Whippit used commonly in recreational inhalation of nitrous oxide. Taken from Addiction Center website on 15.06.2020 [1].

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Discussion

The 10-month-old boy in case 1 presented with hypotonia and was ultimately diagnosed with ischaemic stroke on MRI. It is well understood that the inherited metabolic condition homocystinuria is linked to increased risk of thrombosis likely due to the hypercoagulable state associated with raised serum levels of homocysteine. However, dietary depletion of vitamin B12 also causes transient hyperhomocysteinaemia, and subsequent hypercoagulability. Vitamin B12 deficiency has been linked to increased thrombotic risk and is proposed as the mechanism behind this boy's presentation. No inherited cause was found in this case [2].

Table 1 in appendix lists causes of stroke in children, and thus provides a loose approach to investigation.

The 7-year-old girl in our second case presented with features of bone marrow suppression secondary to deficiency of vitamin B12. She was a picky eater with vegetarian parents but was already taking oral cyanocobalamin for low B12 levels. Transient diarrheal illness could have led to malabsorption of this oral supplement. Inflammation of the intestine at the terminal ileum may impair B12 absorption and cause severe deficiency in the context of already low B12 stores, or if the malabsorptive process is prolonged.

It is worth noting that diarrhea can also be a symptom of B12 deficiency, resulting from impaired replication and maintenance of the cells lining the intestine, due to the vitamin's vital role in DNA synthesis. Hence there is diagnostic uncertainty as to the underlying cause of her diarrhea in this case [3].

Consanguinity raised suspicion of an underlying inherited metabolic condition, due to increased likelihood of offspring inheriting both defective alleles in homozygous manner. Specifically, low serum B12 is associated with both homocystinuria and methylmalonic acidemia and replacement is essential in these conditions. They involve a wide array of clinical features including neurological impairment, seizures, developmental delay and stroke. Both are inherited in an autosomal recessive pattern and are more likely in children of consanguineous parents. Another rare inherited condition predisposing to low B12 is congenital transcobalamin II deficiency which presents early with severe sequelae [4].

Again, in this second case total depletion of Vitamin B12 (despite oral replacement) was concluded, and no inherited cause was found.

The third case touched on the use of inhaled nitrous oxide recreationally, and development of subacute combined degeneration of the cord (SACD) secondary to this. Symptoms involved impaired balance and proprioception and subsequent gait disturbance. Drug abuse, even those considered to be 'legal-highs', can lead to serious complications. One such example is the interference of the B12 metabolism pathway by nitrous oxide. This can lead to inactivation of B12 and inadequate production of myelin, resulting in irreversible neuropathies and ultimately SACD. Typically, this is associated with sustained use of nitrous oxide–such as in Whippets. An important

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association, not merely because this substance is believed by many to be harmless, but also as some sequelae can be irreversible. Although commonly thought to affect adults, it is an emerging phenomenon in the paediatric literature and it is important that young people, are made aware of the implications. [5,6].

Management

Vitamin B12 is not synthesized by mammals, instead by microorganisms in the large intestine. In humans this process occurs too distally for subsequent absorption from the terminal ileum, and so it's ultimately excreted. Thus, 100% of the B12 that is required must be ingested. Ruminant animals can absorb the vitamin after it is produced within their gut and store it in their muscles and liver, and hence the most abundant sources of B12 are the meat of these animals and their dairy products; the richest sources being liver and kidney [7].

There is no consensus internationally on the exact daily requirement of vitamin B12 for adults (ranges from 1.5-2.5 μg/day), but UK government advises a stepwise increase in requirement from 0.5 μg/day for infants to 1.5 μg/day for adults. It is recommended that pregnant and lactating women target higher levels, which may be achieved with the use of multivitamin supplements. Dietary sources of vitamin B12 include meat, liver, fish, shellfish, eggs, milk, cheese and fortified cereals. Fortified breakfast cereals provide a good source of vitamin B12 for children adhering to a dietary restriction but not for breastfeeding infants [8].

When suspecting B12 deficiency, a thorough diet history from the child and family members is crucial.
Remember to explore gastroenterological symptoms, developmental milestones, wellbeing of other family members and a social history including drug and alcohol use. Construct a family-tree including asking about any consanguinity. A thorough and systematic physical assessment including a full neurodevelopmental examination is paramount.

Useful investigations alongside serum B12 include urinary organic acids specifically for elevated levels of urinary homocysteine and methylmalonic acid. Both, if present in raised quantities, indicate B12 deficiency, even when serum B12 level is within normal range. Test for coeliac disease, inflammatory bowel disease and for anti-parietal cell antibodies in cases of suspected malabsorption where the native intestine is intact. After intestinal surgery replace nutrients according to which part of the gut has been removed. In cases of depletion, B12 should be replaced parenterally initially, with the use of intramuscular hydroxocobalamin, and current guidelines suggest 1mg intramuscularly with varying initial frequency depending on indication [9]. Maintenance then depends on underlying cause. A concise summary of suggested management is summarized in Figure 2 below.

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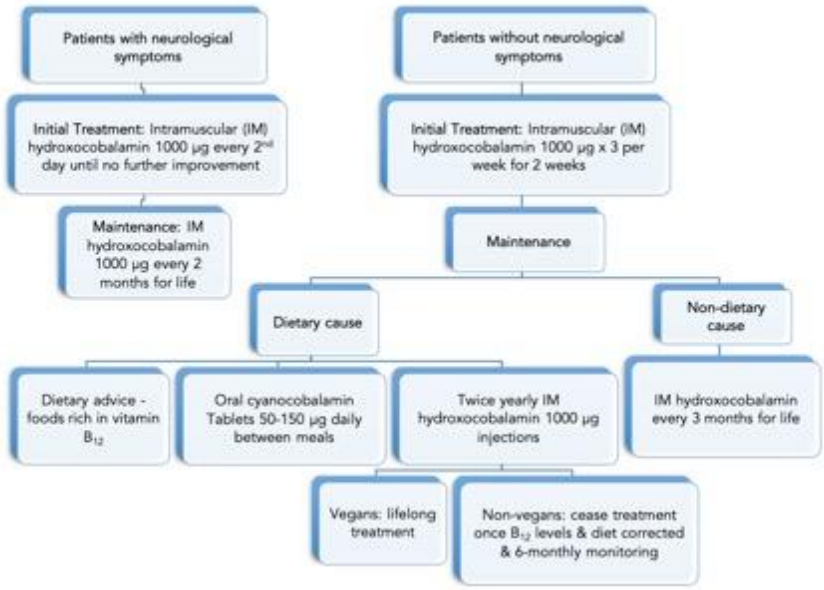

Figure 2: Summarising suggested management of Vitamin B12 replacement taken from Tan & Harris [10].

Summary

Vitamin B12 deficiency can present in a multitude of ways; from asymptomatic megaloblastic anemia to pancytopaenia and varied neurological disorders, even psychosis. Here three seemingly unrelated but significant presentations are outlined in which all three patients had low or inactivated B12 levels. It is well described that deficiency of vitamin B12, and subsequent neuropathy, occur secondary to dietary insufficiency in those with alcohol dependence. In children however, vitamin B12 deficiency commonly co-exists with other nutrient deficiencies, and is largely due to poor dietary intake following a vegan diet or breastfed infants of vegan mothers. Hence the advice in the UK for breastfeeding mothers with dietary restrictions to take multivitamins. It is important to remember that diet is just one factor in maintaining healthy levels of vitamin B12, and if deficiency remains despite adequate intake one must consider another process at play. These include intestinal malabsorption (specifically conditions affecting terminal ileum), inherited metabolic conditions or abuse of agents that interfere with key metabolic pathways in otherwise healthy individuals– such as using 'Whippits' to inhale nitrous oxide. A problem which needs increased coverage not only because of its rising use in the UK but also the potential for chronic irreversible spinal pathology and debilitation.

Alternate causes of B_{12} deficiency must be considered if a varied diet rich in meat and dairy is maintained or in presentations with seemingly unrelated neurological features. In cases of consanguinity, underlying genetic diagnosis must be considered. Commonest causes of Vitamin B12 deficiency are listed in Table 2 in appendix.

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Appendix

Cardiac	Associated with instrumentation/repair (surgery or vascular catheterisation) Long-term polycythaemic state secondary to hypoxic congenital cardiac defect Valvular defects and/or myocardial disease can lead to thrombosis Anatomically normal communications in young infants like foramen ovale can lead to paradoxical embolisation (venous thrombosis entering arterial circulation)
Haematological	Sickle cell disease can lead to microvascular occlusion of cerebral vessels Clotting factor deficiencies can be both congenital and acquired e.g. Protein S and C deficiency
Vascular / Anatomical	Arteriovenous malformations (AVM) can lead to both haemorrhagic and ischaemic stroke
Infection	Systemic infection with a variety of pathogens has been associated with a prothrombotic state
Vasculitis	Vasculitides can affect children and lead to a prothrombotic state e.g. Kawasaki disease, Henoch-Schönlein purpura (HSP) and those associated with rheumatoid arthropathies and inflammatory bowel disease
Renal	Nephrotic syndrome and glomerulonephritis can lead to significant loss of antithrombin III and dehydration and hence hypercoagulability
Oncological	Leukaemias and lymphomas can lead to hyperviscous blood and thus can be complicated by stroke, especially at diagnosis
Metabolic	Inborn errors or metabolism e.g., homocystinuria lead to the build-up of prothrombotic intermediaries and lead to increased risk of stroke
Nutritional	Vitamin B12 deficiency

Table 1: Causes of Stroke in Children. Adapted from Pediatric stroke: a review by Tsze DS, Valente JH [11].

Dietary insufficiency (strict vegan diet, and/or malabsorption)
Pernicious anaemia (autoimmune gastritis leading to loss of parietal cells and absence of intrinsic factor)
Gastrectomy or gastric bypass
Terminal ileal disease or surgical resection
Intestinal bacterial overgrowth
Fish tapeworm infection
Medications (Proton pump inhibitors or H2 receptor antagonists)
Drug abuse (nitrous oxide)
Congenital metabolic disorders (Homocystinuria, methylmalonic acidaemia)

Table 2: Causes of low Vitamin B12.

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