Beriberi following sleeve gastrectomy

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Abstract

Bariatric surgery is being undertaken more frequently in response to rising levels of obesity, but increasingly also requested as a cosmetic choice. Nutritional deficiencies are a recognised consequence of gastrectomy, with potentially severe and permanent neurological sequelae. We present two cases of acute, severe polyneuropathy following sleeve gastrectomy. Severe thiamine deficiency was considered in both cases but with delayed proof and a significant initial differential diagnosis. Neurologists must have a high index of suspicion for the peripheral as well as central presentations of thiamine deficiency to avoid permanent disability. We also call for explicit information resources warning of the risk and signs of thiamine deficiency to be provided routinely to patients after gastrectomy.

Case 1

A 25-year-old woman was referred urgently from primary care with a history of ascending paraesthesia and weakness of the lower limbs alongside numbness in the fingertips over the previous week. Bidirectional horizontal nystagmus was noted on examination. Muscle strength was globally reduced in all limbs (MRC grade 4 throughout). Reflexes were reduced in the upper limbs and absent in the lower limbs. There was no ataxia. Light touch and pin-prick sensation was reduced to the mid-thigh, and normal in the hands. Proprioception was reduced to the knees, with vibration sense reduced to the costal margin.

Three months prior she had undergone an elective laparoscopic sleeve gastrectomy. Pre-surgical weight was 106 kg (BMI 37). The operation was preceded by a preparatory diet consisting of low calorie, low protein, and low-fat foods. Post-gastrectomy supplementation recommendation was reported to be a non-prescription multivitamin, vitamin D, and calcium supplement daily and to seek a 3-monthly intramuscular B12 injection via primary care. Two months after the surgery, she was admitted to hospital with a two week history of abdominal pain and bilious vomiting, thought consistent with cholecystitis and leading to cholecystectomy. Neurological ward admission weight was 84 kg.

Guillain-Barré syndrome was initially suspected given the rapidly ascending sensorimotor symptoms and hyporeflexia. CSF analysis was acellular, with normal protein (0.27g/L). Intravenous immunoglobulin (IVIG) therapy was initiated (2g/kg split over five daily doses). She was concomitantly given six days of intravenous high-dose vitamin concentrate (Pabrinex) with resolution of nystagmus. Nerve conduction study (NCS) showed severe

symmetrical length-dependent sensorimotor axonal loss (with no demyelination) throughout both lower limbs. Electromyography (EMG) revealed profuse lower limb fasciculations without any volitional motor units. MRI brain and whole spine was normal. Routine laboratory investigations were normal, including vitamin B12 (815 ng/L), folate (>20 mcg/L), HbA1c (30 mmol/mol), immunoglobulins and serum electrophoresis, with negative HIV, syphilis, hepatitis C, and *B. burgdorferi* serologies. Anti-nuclear antibody (ANA) positivity was recorded with a titre of 1:160 and speckled patterning, with antibodies to double-stranded-DNA (46 IU/mL), Ro60 and Ro52. Complement levels were normal. Later serum copper level was returned as normal (14.7 umol/L) with negative urinary porphobilinogens. Serum tested negative for ganglioside antibodies (including anti-GQ1b), paranodal and nodal antibodies, plus neuronal surface antibodies to LGI1, CASPR2 and paraneoplastic antibodies (Hu/Yo/Ri/Ma2/CV2/Amphiphysin/Zic4/SOX1/Tr/Titin/ Recoverin).

The patient developed severe burning pain, predominantly distally, within a week of admission which was refractory to simple analgesia and lidocaine patches. A combination of nortriptyline, gabapentin and codeine achieved reasonable pain control some weeks into the hospital admission. Repeat NCS three weeks after admission showed worsening sensorimotor axonal neuropathy with reduction of upper limb sensory responses. A further 5 days of Pabrinex was given. A sural nerve biopsy was undertaken given the evidence of progression of neuropathy in the context of positive anti-Ro60 and Ro52. This showed florid acute Wallerian degeneration with frequent myelin ovoids and marked axonal loss evenly throughout the fascicles. There was focal perivascular lymphocytic inflammation interpreted as secondary given the extent of acute axonal pathology. There was no vasculitis. Biopsy of

the adjacent peroneus brevis muscle showed several swollen intramuscular nerve fibres with florid acute Wallerian degeneration and foci of perivascular lymphocytic inflammation in the adjacent muscle analogous to the findings in the nerve [Figure 1].

This was thought to be consistent with thiamine deficiency neuropathy and repeat ANA testing was negative, with initial positivity presumed to have arisen from the concurrent IVIG administration. Five weeks after her admission, the red cell thiamine result returned low (33 nmol/L, normal >66.5 nmol/L). With rehabilitation she was able to walk 25m independently one month following discharge. Pain also improved albeit with ongoing neuropathic-type pain in the feet especially with exertion.

Case 2

A hospital in-patient neurology consultation was requested for a 25-year-old woman with a four-week history of progressive bilateral leg weakness, associated with falls and ascending paraesthesia to the abdomen. She described episodes of insensate urinary incontinence. Examination revealed complete horizontal ophthalmoplegia with restricted vertical gaze and vertical nystagmus [Supplementary video 1]. She had severe proximal leg weakness (MRC grade 2) with reduced knee and absent ankle reflexes. Light touch and pin-prick sensation was reduced to the neck. Vibration sensation was absent in the legs.

Six weeks prior to onset of symptoms, she had undergone a sleeve gastrectomy in Turkey. Two weeks postoperatively she experienced intermittent difficulty tolerating food or fluids with postprandial vomiting, prompting recurrent presentations to the emergency department. She was treated with intravenous fluids, developing hypokalemia, hypomagnesaemia and progressive liver function test derangement. Ultrasound of the abdomen was normal.

Concern for nutritional deficiency led to administration of Pabrinex for 14 days. Within a week horizontal eye movements returned with residual bilateral horizontal nystagmus [Supplementary video 2] which resolved one month later. MRI brain and spinal cord were normal. The red cell thiamine result returned eight weeks into her admission (54.9 nmol/L). NCS were undertaken eight weeks from admission and were normal. She underwent further rehabilitation. One year following admission her mobility has recovered, however she

continues to experience neurocognitive fogging alongside flickering of her vision with exertion. [Supplementary video 3].

Discussion

Over 4,000 bariatric procedures were performed in the United Kingdom in 2021-2022. [1] A growing number of bariatric tourism is performed overseas, such as in Brazil and Mexico, with less rigorous pre-and-postoperative workup. [2] Sleeve gastrectomy is now the commonest procedure and involves a typically laparoscopic excision of up to 80% of the stomach, leaving a thin tube or sleeve remnant. Following bariatric surgery, there is an increased risk of vitamin deficiency due to diet restriction (the goal of surgery itself) but also gastric malabsorption. Sleeve gastrectomy has been considered to offer a lower risk of vitamin deficiencies than traditional bypass procedures. [3] Copper deficiency is a well-recognised sequelae of gastric surgery and may cause myeloneuropathy, [4] and/or polyneuropathy. [5]

There is a wide spectrum of nutritional-gastroenterological overlap with neurology. [6] Thiamine (vitamin B1) is a water-soluble vitamin which acts as an essential cofactor for normal nervous system maintenance. It is involved in mitochondrial energy production in the pentose-phosphate-glycolysis-citric acid cycle, neurotransmitter and myelin synthesis and antioxidant properties. [Figure 1] Deficiency leads to neuronal death via energy failure and demyelination. [5] In so-called Western populations, the most common cause of thiamine deficiency is alcoholism and diabetes. [5] The most common presentation is Wernicke’s encephalopathy with the triad of ophthalmoplegia, ataxia and confusion.

Traditional malnutrition-related thiamine deficiency results in beriberi, divided into ‘wet’ if presenting with heart failure, or ‘dry’ if presenting with polyneuropathy, myalgia and weakness, as in our two patients. [5] [Figure 2]

Post-gastrectomy polyneuropathy occurred in 2% of patients in a study from 2006, but this has likely increased. [7] Its presentation can mimic other causes of acute neuropathy, especially Guillain-Barré syndrome, and when there are no features to suggest Wernicke’s encephalopathy, thiamine deficiency may be easily overlooked. The pattern is often a painful, ascending sensorimotor polyneuropathy. Large and small sensory fibres are involved. Autonomic involvement can occur which can cause further confusion for Guillain-Barré syndrome. [7] A greater degree of demyelination and axonal loss has been noted in post-gastrectomy patients versus those with nutritional dry beriberi, without clinically significant differences in symptoms. [8]

Relative to iron, vitamin D and folic acid, thiamine deficiency is considered uncommon after sleeve gastrectomy. [4] The prevalence of thiamine deficiency pre-procedure has been estimated widely from 2-30% [3,4,9]. There is no recommendation to routinely test for thiamine deficiency pre-operatively. [4] High-carbohydrate diets (especially if more than 50% of dietary intake), which are common in obese patients, independently decrease the level of thiamine through multiple metabolic mechanisms. Absorption and availability is further impaired if there is significant alcohol, nicotine and caffeine intake. [10]

The absorption of thiamine occurs throughout the entire intestine, but particularly in the duodenum and proximal jejunum [5,8]. Malabsorption following sleeve gastrectomy is

multifactorial including dietary, behavioural, anatomical and absorption alterations. [5] About 30mg is stored in tissues with high metabolic demand. If it is not sufficiently and regularly replaced, these stores can be depleted within three weeks. [10] Post-surgical nausea and vomiting exacerbate risk of thiamine deficiency. [9,11] Polyneuropathy can develop within 2-12 weeks of intermittent or continuous vomiting after sleeve gastrectomy. [3,7,10] Our first patient developed polyneuropathy within two weeks of vomiting, perhaps suggesting borderline thiamine deficiency pre-surgically. There is insufficient data in the published literature to determine the likelihood of complete recovery in cases of post-gastrectomy beriberi.

The neurologist needs to be alert to patients who develop a sensorimotor neuropathy following sleeve gastrectomy, especially with a history of recurrent vomiting, empirical high-dose intravenous thiamine replacement should be initiated, even without overt signs of Wernicke's encephalopathy. The authors suggest daily parenteral thiamine until symptoms stabilise or until the red cell thiamine level is normal. We also call for more standardised and explicit warnings and post-operative advice for patients undergoing gastrectomy, given the severe, potentially permanent and sometimes even life-threatening consequences of thiamine deficiency.

Key Points

- Subacute ascending sensorimotor polyneuropathy following sleeve gastrectomy should prompt intravenous thiamine administration.
- A history of post-operative vomiting greatly increases the likelihood.
- Features of overt Wernicke's triad may be absent.
- Individuals undergoing gastrectomy should receive explicit advice to maintain thiamine levels with information and warning signs of post-operative thiamine deficiency.

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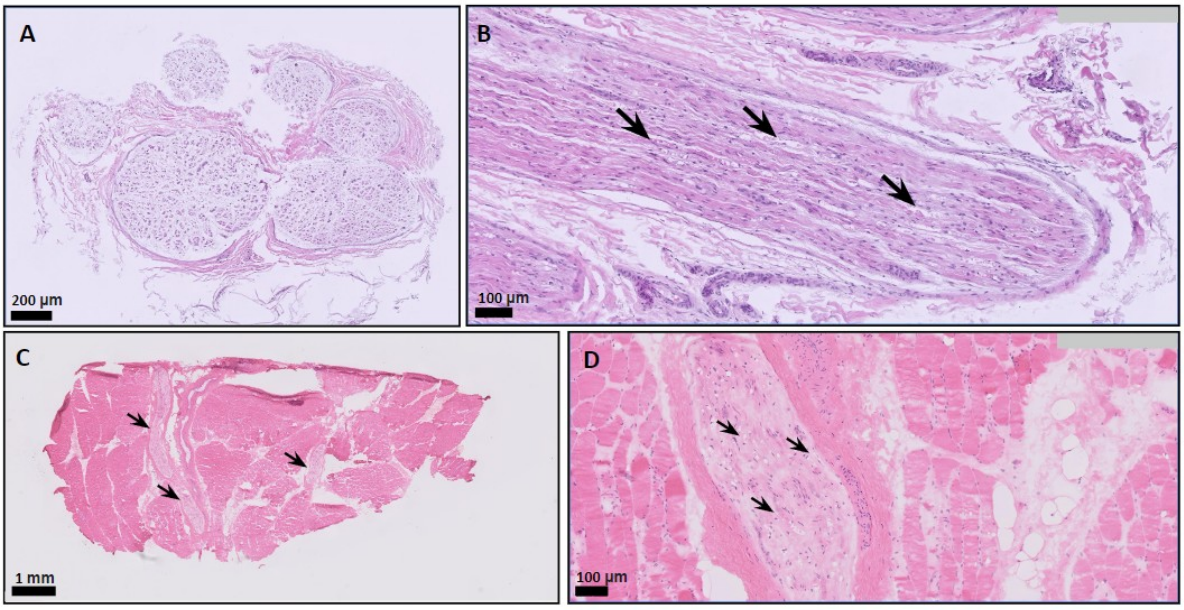

Figure 1. Left sural nerve biopsy and left peroneus muscle biopsy - representative photomicrographs (H&E staining)

A Cross-section of left sural nerve and, B, appearances consistent with active, ongoing axonal degeneration including frequent myelin ovoids (arrows). C Left peroneus muscle with prominent, swollen, intramuscular nerve fibres within the muscle (arrows) with, D, myelin ovoids within (arrows) indicative of motor nerve axonal degeneration.

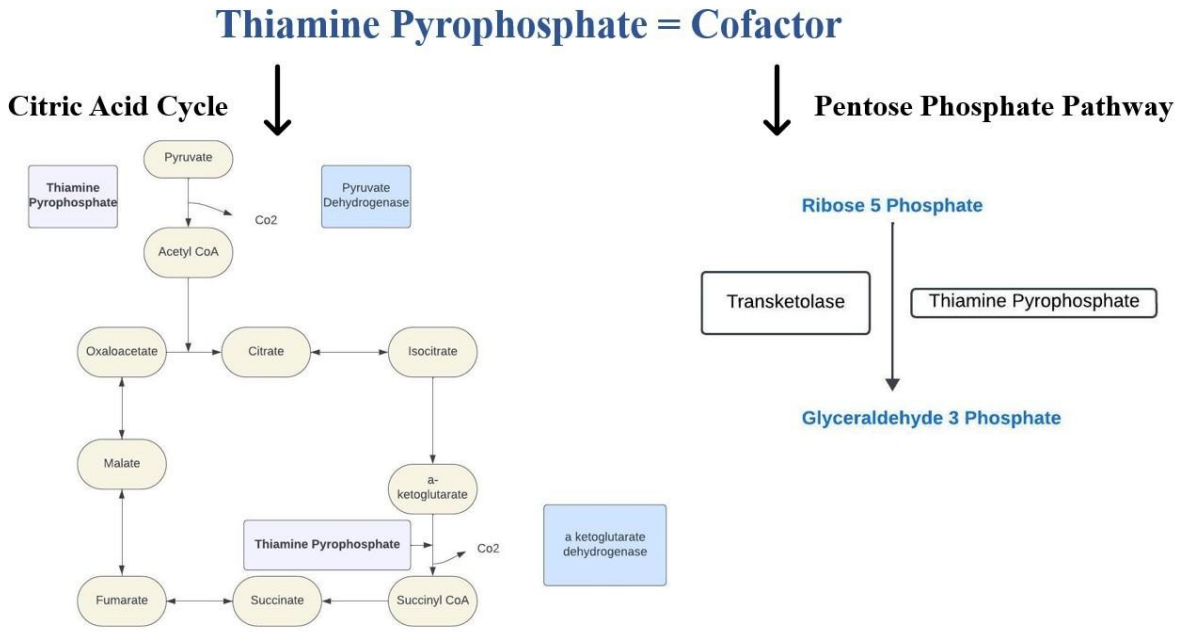

Figure 2: Thiamine as an essential cofactor in the Citric Acid Cycle and Pentose Phosphate Pathway.

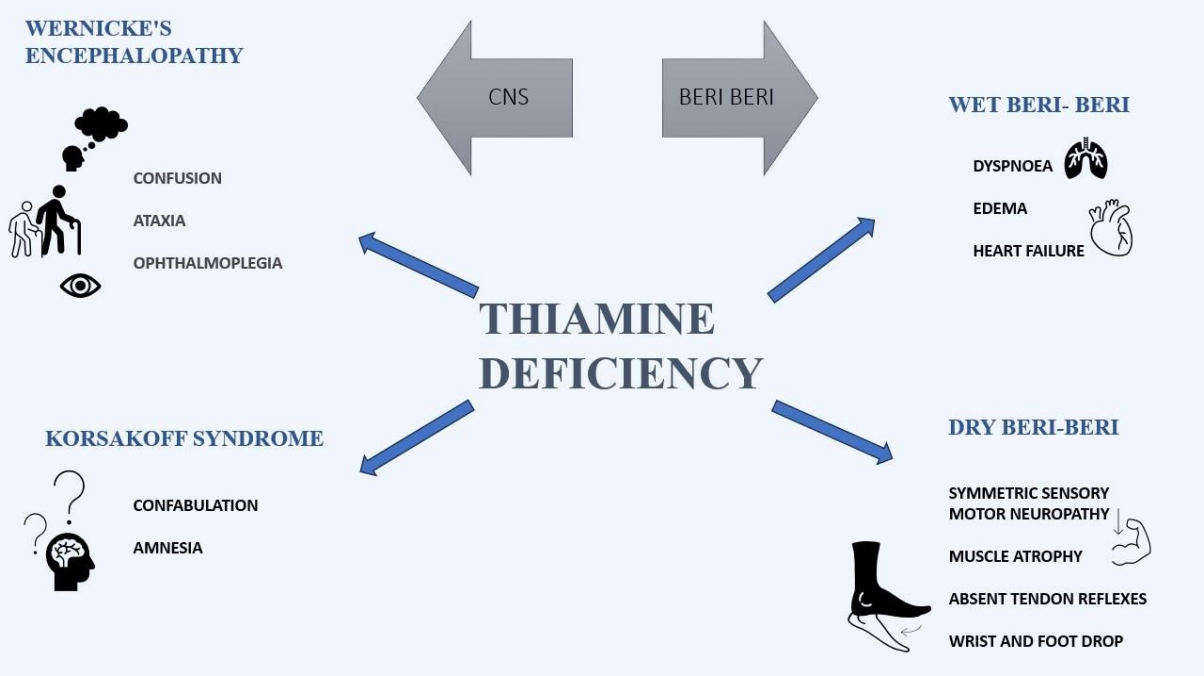

Figure 3: The clinical manifestations of thiamine deficiency in the central and peripheral nervous systems.