Nutritional neuropathy postoesophagogastrectomy

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SUMMARY

We report a case of a patient who presented complaining of a 1-week history of progressive lower limb weakness and decreased sensation bilaterally suggestive of a peripheral neuropathy, with vague associated symptoms of fluctuating concentration. Clinically, we suspected a Guillain-Barré variant. However, her functioning continued to decline despite intravenous immunoglobulin therapy, and she had normal spinal imaging studies and CSF analysis. Of note, she had a subtotal oesophagectomy and proximal gastrectomy 20 months previously for oesophageal cancer. We found her to be deficient in vitamin D, vitamin E and copper. She was treated with nutritional supplementation of these vitamins and infusion of trace elements, resulting in a gradual improvement in lower limb power, sensation and coordination, as well as improved cognition and mentation. Monthly outpatient neurology follow-up shows continued improvement in symptoms and return towards baseline functioning with regular infusions of nutritional elements and monitoring of blood levels.

BACKGROUND

Optimal functioning of the central and peripheral nervous system is dependent on a constant supply of appropriate nutrients.[1] Neuropathies due to multiple coexistent nutritional deficiencies can affect certain patient populations and have a varied presentation.[2 3] Peripheral nerves are susceptible to damage by a wide array of vitamin and trace element deficiencies. While length-dependent sensorimotor axonal peripheral neuropathy is the most common presentation, several examples present in a subacute severe fashion, mimicking Guillain-Barré Syndrome.[4] This challenging case provides an interesting example of a rapidly progressive peripheral neuropathy secondary to nutritional deficiency after upper Gastrointestinal (GI) surgery for oesophageal cancer. This case report serves to alert clinicians of the association between gastric procedures and subsequent nutritional deficiency in order to avoid diagnostic delays and to improve treatment outcomes. Accurate diagnosis can be difficult and nutritional deficiencies can go unrecognised unless specifically investigated. This is clinically significant as these conditions are often treatable and preventable.

CASE PRESENTATION

A 55-year-old woman with known history of oesophageal carcinoma presented by GP referral with a 1-week history of progressively decreasing power and coordination of her lower limbs bilaterally.

There was no pain, but subjectively her feet felt numb. She also had 2 falls during that 1-week period and noticed markedly increased sweating of hands and feet. History also revealed vague associated symptoms of poor concentration and short-term memory loss, as well as a 3-day history of intermittent confusion and disorientation, supported by collateral history from her husband.

Her story of how she arrived at this point is an interesting one. She underwent a laparotomy age 17 for small bowel obstruction secondary to impaction

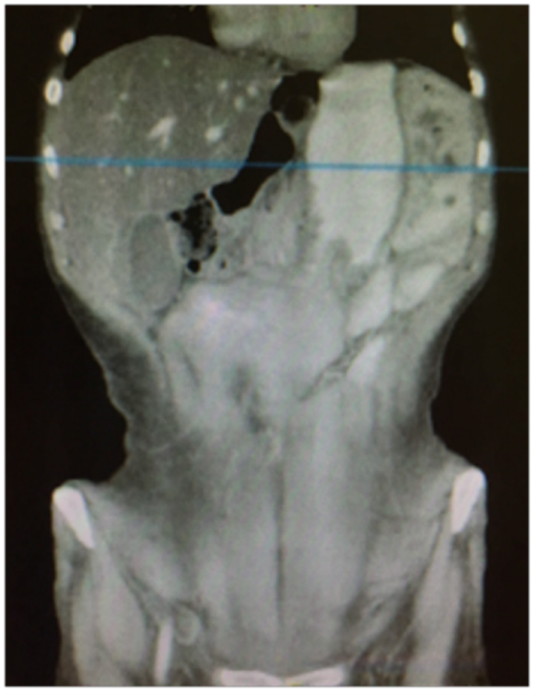

Figure 2 CT abdomen showing persistent markedly abnormal dilatation of the proximal small bowel.

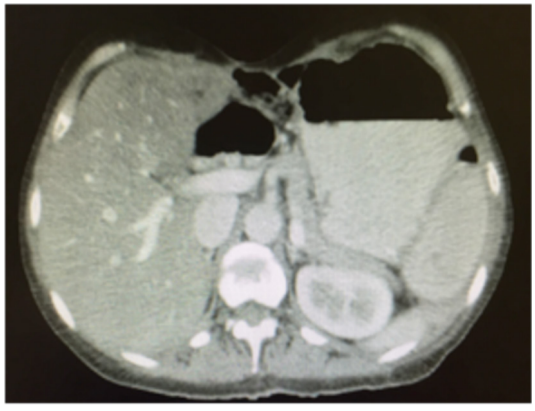

Figure 1 CT abdomen showing persistent markedly abnormal dilatation of the proximal small bowel.

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of a bezoar. She had further surgery 1 year later for division of adhesions.

At age 53, she was diagnosed with locally advanced squamous cell cancer involving the lower third and part of the middle third of the oesophagus. There was regional nodal involvement but no distant metastatic disease. She received preoperative neoadjuvant chemoradiotherapy: Paclitaxel+carboplatin weekly +23 fractions of radiotherapy (41.4 Gy) over 1 month ("CROSS regimen").[5] She then underwent subtotal oesophagectomy and proximal gastrectomy. The distal two-thirds of the oesophagus and proximal half of the stomach were removed. Histology revealed complete pathological response to the preoperative chemotherapy and radiation treatment. She was asymptomatic when she returned for routine 1-year follow-up gastroscopy. Biopsies revealed recurrence of disease adjacent to the anastomosis in the upper oesophagus.

She underwent a second CROSS regimen to the small area of cancer recurrence. Follow-up gastroscopy and biopsies were normal 2 months later. There was no radiographic evidence of any metastatic disease. The patient was clinically very well and was recommended for 6 monthly outpatient follow-up.

Social history

This woman works as a teacher and lives at home with her husband and two sons where she has excellent family support. She does not smoke or drink alcohol, and has no recent travel history.

Family History

Insignificant.

Cinical examination

- Patient alert and orientated in time, person and place but with noticeable deficits in short-term memory and attention span.
- Unsteady stepping gait.
- Cranial nerves intact.
- Upper limb examination normal despite noticeable sweating of the hands.
- Lower limb power decreased in a pyramidal distribution: 4/5 proximally, 3/5 distally.
- Proximal lower limb: decreased sensation to light touch/vibration/temperature. Decreased vibration sense up to iliac crest. Normal pin-prick test.
- Distal lower limb: absent sensation for all modalities.
- Absent reflexes in lower limbs.
- Plantars downgoing bilaterally.
- Sweaty feet noted.

INVESTIGATIONS

MRI brain and spine: normal. No metastatic or degenerative disease.

Lumbar puncture: normal (Cerebrospinal Fluid (CSF) protein 309, glucose 4.9, White Cell Count 2, Red Cell Count 216, no growth on culture).

Nerve conduction Studies were consistent with a length-dependent axonal peripheral neuropathy. Sensory responses were absent in the lower limbs with reduced peroneal motor responses bilaterally. Upper limb responses were normal.

CT abdomen showed persistent markedly abnormal dilatation of the proximal small bowel (figures 1 and 2).

Bloods

Full Blood Count, C-Reactive Protein, Erythrocyte sedimentation rate, thyroid function, renal, bone and liver profiles were all within normal limits.

There was no anaemia. Red and white cell indices on FBC were also within normal limits.

Vitamin B_{12} and serum folate levels were within normal limits.
Vitamin A: 282 µg/L (366-546 µg/L).
Vitamin B_1 (thiamine): 63 µmol/L (67–200 µmol/L).
Vitamin B_6: 118 µmol/L (35–110 µmol/L).
Vitamin C: 54 µmol/L (26–85 µmol/L).
Vitamin D: 11 nmol/L (50-125 nmol/L).
Vitamin E: 3.70 mg/L (4.29-13.30 mg/L).
Copper: 7.0 µmol/L (11.0-25.0 µmol/L).
Zinc: 14 µmol/L (11–19 µmol/L).
Lead and mercury levels were normal.
Plasma/urinary/faecal porphyrins were negative.

Angiotenin Converting Enzyme, Anti-Neutrophil Cytoplasm Antibodies, autoantibody screen/neuronal antibodies/anti-Voltage-gated Potassium Channel antibodies, Serum Protein Electrophoresis, lymphoma screen, coeliac screen, viral screen, Epstein-Barr Virus, Cytomegalovirus, Human T-cell Lymphotrophic Virus, Human Immunodeficiency Virus, syphillis, toxoplamosis, Lyme, Q fever, parvovirus B19, chlamydia, bartonella and quantiferon tests were all unremarkable/negative.

PET-CT scan was normal.

DIFFERENTIAL DIAGNOSIS

This case presented us with a diagnostic challenge. The acute nature of the presentation pointed towards a Guillain-Barré syndrome pattern. Nerve conduction studies were in keeping with an axonal form. However, her continued deterioration despite treatment with intravenous immunoglobulin paired with a normal CSF protein posed a diagnostic conundrum. Our initial considerations of common nutritional deficiencies such as B_{12} and folate which can present in this manner were tested for and excluded at the time of her initial presentation. After 4 days of progressing symptoms, we tested specifically for other vitamin and trace element deficiencies which are absorbed by the gastric mucosa. Some of these tests can take weeks to give a result so we empirically treated broadly for vitamin and nutrient deficiency based on clinical suspicion.

Given her recent history of carcinoma, we thought it possible that her symptoms were attributable to a paraneoplastic myelitis or an infiltrating radiculoneuropathy. We also wondered if there may be a cord compressive pathology or lumbosacral plexopathy. Normal spinal imaging on MRI made this unlikely. Her metbolic panel was normal. With her recent history of chemoradiotherapy, we considered if this was an iatrogenic phenomenon, possibly a side effect of a medication, or a chemotherapy-induced peripheral neuropathy. We requested input at this point from our oncology and gastroenterology colleagues. Plasma exchange was considered at this junction but given the diagnostic uncertainty and deterioration despite immunoglobulin therapy this was deferred.

After 5 days of worsening symptoms in hospital and with no clear cause identified, we were concerned about the progressive nature of her symptoms and feared that she may develop respiratory compromise and require ventilatory support. We considered rarer possible causes as evidenced by the extensive list of investigations listed above, including a vasculitic and autoimmune screen. We also wondered if her symptoms were a consequence of leptominingeal disease or indeed if they were toxin-related

and sent tests to assess for lead poisoning, mercury poisoning and porphyria.

As some of her serum vitamin levels began to return revealing deficiencies, this pointed us further in the direction of a nutritional neuropathy. Interestingly, she reported eating a well balanced diet with good portion sizes and variety and this was supported by her husband. She had never described any symptoms of malabsoprtion such as bloating or diarrhoea. Also, previous duodenal biopsy during routine follow-up gastroscopy was negative for coeliac disease aswell as negative coeliac serology. We considered possible dry beri-beri neuropathy and pellagra aswell as vitamin B6, copper and trace element deficiency. However, many of these tests would take days to weeks to return results so we empirically treated for a broad range of nutritional deficiency and subsequently correlated our results. In this sense we had a very broad differential diagnosis for this acute neurological presentation and commenced treatment, with the answer to the puzzle being confirmed later through labarotory analysis.

TREATMENT

The patient was admitted with progressive lower limb weakness of unknown cause and transfused with Intravenous Immunoglobulin (20 g once daily for 5 days) for suspected Guillain-Barre Syndrome, but displayed no clinical evidence of improvement. She was then given a trial of steroids but showed no signs of response to treatment with intravenous methylprednisolone. In the initial days following admission she displayed further progression of her lower limb weakness and she was now mobilising only with the aid of a walking frame while receiving regular physiotherapy input. The patient was started on Pabrinex on day 4, as her CT abdomen showed marked small bowel dilatation (figures 1 and 2), supporting a possible upper gastrointestinal malabsorptive pathology. She then received vitamin D and vitamin E supplementation after these levels were noted to be deficient. The role of the multidisciplinary team played an essential role in her management. Dietician and gastroenterology input were vital with regard to copper replacement and it was decided to start her on an Additrace infusion for replacement of trace elements. Her legs remained weak but showed no further evidence of worsening from this point. Over the following days, she displayed noticeable improvements in her cognition and attention. Although she became cognitively much brighter, her lower limbs remained weak with poor dorsiflexion bilaterally. Her lower limb weakness displayed a more gradual improvement within weeks of commencing replacement of nutritional deficiencies and her walking slowly became better.

OUTCOME AND FOLLOW-UP

Hypothesis

Axonal peripheral neuropathy secondary to multifactorial nutritional deficiency including copper and other trace elements.

Follow-Up

The patient was discharged home 7 weeks after her initial presentation on a tapering dose of oral steroids and vitamin D supplementation with education for regular home physiotherapy exercises. Dietician and occupational therapy follow-up were also arranged. She returns monthly for neurology review and repeat blood tests to monitor vitamin and trace element levels with appropriate subsequent replacement.

Medications on discharge

- Prednisolone 20 mg once a day (decreasing by 5 mg every 5 days until discontinuation).
- Thiamine 100 mg three times a day.
- Fortisip compact 25 mL two times per day.
- Cholecalcitrol 50 000 units once weekly for 2 weeks.
- Desunin 800 units once a day (to start after finishing cholecalcitriol).
- Esomeprazole 40 mg once a day.
- Alprazolam 500 μg once a day.
- Quetiapine 25 mg once a day.

She was most recently seen for review 4 months on from her initial presentation. All her bloods were repeated and, after discussion with dietetics, she was continued with the same infusion of vitamins and trace elements. Her weight has remained stable. On assessment, her lower limbs show continued improvement in power. She has ongoing decreased dorsiflexion, worse on the right and she continues to use a Dictus band on her right ankle as a result. She is otherwise walking without aid and is comfortable climbing stairs and performing daily household tasks including cooking. She has started to drive again in a secure area but has not yet returned to driving on public roads. She has had no further episodes of sweating of the hands or feet. She appears relaxed but reports anxiety with regards to the complete resolution of her neurological symptoms, and cites this sense of worry and decreased confidence to be the most debilitating feature of her current illness. She has a degree of ongoing difficulty with processing information and relies on family members for remembering certain details. Her husband also reports that her memory and mentation can become impaired during periods of stress. She attends physiotherapy twice a week and has excellent family support. She is very keen to return to work soon.

She will require ongoing monitoring of her vitamin and trace element levels going forward with appropriate supplementation and replacement to prevent deterioration or recurrence of symptoms. Currently, despite optimal oral nutrition, she still cannot maintain vitamin and minerals at a level that is adequate and receives regular vitamin supplementation intravenously. Following discussion, it was also decided that the patient could benefit from follow-up with a clinical psychologist with regard to coping with the psychosocial aspects of her illness.

DISCUSSION

Nutritional deficiencies can occur following procedures that remove portions of the stomach, thereby bypassing a critical absorptive surface in the gastrointestinal tract. Micronutrients most commonly depleted after gastrectomy include several water-soluble vitamins (eg, vitamin B_{12}), fat-soluble vitamins (eg, vitamins A, D, E and K) and trace minerals, including iron and calcium.[6] Vitamins are vital micronutrients that cannot be synthesised endogenously and must be ingested in appropriate quantities in the diet. Biological stores of different vitamins vary significantly, as do the biological half-lives. Because they are stored in tissue, the body retains fat-soluble vitamins for a longer time than the water-soluble vitamins. For example, thiamine is a water-soluble vitamin stored primarily in the liver; however, storage only lasts up to 18 days.[7] Consequently, thiamine deficiency can start to manifest in as little as 3 weeks.[2] Symptoms usually develop gradually over weeks to months, but sometimes they may manifest rapidly over a few days, and there have been case reports of dry beriberi mimicking Guillain-Barré syndrome.[8] By contrast, vitamin B_{12} depletion takes up to 12 months. Multivitamin supplementation should be considered for patients at risk for vitamin deficiency, such as those with alcoholism, poor-quality diets with low fruit and vegetable intake, vegan diets, malabsorption, a history of gastric surgery or some

inborn errors of metabolism.[9] An important point to make note of in this case was the timing and the rapid onset and progression of her symptoms. Her symptoms manifested 20 months postsurgery and resulted in a rapid deterioration in lower limb power and sensation over a 1-week period, having previously been asymptomatic.

Much of the existing data regarding postoperative nutritional deficiency is limited and is based on outcomes postbariatric surgery. A wide spectrum of serious neurologic conditions may develop following gastric surgery and these complications may present acutely or decades later.[10] In this case, the distal one-third of the oesophagus was resected along with the proximal two-thirds of the stomach. The type of nutritional deficiency that manifests can be related to the area of the gastrointestinal tract resected. For example, iron is mainly absorbed at the duodenum. Folate is mainly absorbed at the jejunum. Vitamin B_{12} is predominantly absorbed at the terminal ileum. Resection of a particular area of the gastrointestinal tract or indeed a malabsoprtive pathology, which affects an isolated area of the tract, can make certain deficiencies more likely.[11] The proximal half of the small intestine is the predominant site for the absorption of most vitamins and minerals. The loss of two-thirds of the absorptive surface of the stomach put our patient at increased risk of vitamin and trace element deficiency, which manifested as an acquired global malabsorption syndrome. Copper is absorbed in the stomach and proximal duodenum.[12] The acidic environment in the stomach facilitates solubilisation of copper by dissociating it from copper containing dietary macromolecules.[12] Gastric surgery is the most common cause of acquired copper deficiency, underlying approximately half of reported cases. Typically, neurological manifestations are delayed by years following gastric surgery.

This woman was found to have a variety of nutritional deficiencies on investigation. Of particular interest from a neurological point of view were copper and vitamin E. The neurological manifestations of copper deficiency include ataxia, neuropathy and cognitive deficits that can mimic vitamin B_{12} deficiency.[1 3] An isolated number of case reports describe the development of a myelopathy with neurological symptoms as a result of acquired hypocuraemia after gastric surgery.[13–15] Foregut surgery is the most common cause of acquired copper deficiency, and is likely to become even more prominent as the rate of bariatric surgery increases. Typically, neurological manifestations are delayed by years following gastric surgery but there can be a significant variation in the interval between the procedure and the manifestation of neurological symptoms. Copper deficiency should be considered in patients with a history of gastrointestinal surgery and myelopathy or new neurologic symptoms, which may mimic the more commonly described vitamin B_{12} deficiency.[1]

Achieving successful copper supplementation poses a challenge. Absorption of copper may be impaired by dietary iron, zinc or ascorbic acid. As well as normal functioning of the nervous system, copper is required for red and white blood cell production. Haematological features of copper deficiency include microcytic anaemia and neutropenia. In some cases, the findings can be mistaken for the anaemia of iron deficiency. If iron supplements are given, these can worsen copper deficiency because excess iron competes with copper and decreases net copper absorption. Excess zinc ingestion has also been identified as a cause of copper deficiency and administration of zinc in the absence of copper may cause a decrease in serum copper levels.[16] Copper supplementation is generally targeted at 2 mg daily to achieve 200% of the recommended daily allowance. This can be done with parenteral or oral copper preparations that provide 2 mg of elemental copper per day. Mild to moderate copper deficiency characterised by low haematological indices should be treated with oral copper until levels normalise. Severe deficiency, characterised by neurological symptoms should be treated with intravenous therapy until symptoms resolve.[16] Haematological abnormalities return to normal in less than 2 months with effective supplementation but resolution of neurological symptoms have been seen to be far more variable and may persist. Relapse can also occur and long-term follow-up is advised. Given the severity and acuity of symptoms in this patient, we elected to replace copper intravenously using the parenteral nutritional supplement Additrace, as guided by our dietician and gastroenterology colleagues. This formulation contains 3.4 mg of copper chloride dihydrate per 10 mL vial, which is equivalent to 1.27 mg of elemental copper daily.

The pathogenesis of vitamin E deficiency is poorly understood. Vitamin E is an antioxidant and a free radical scavenger, and it is believed that the neurological manifestations of vitamin E deficiency may relate primarily to the loss of this protective function. Fat malabsorption is the main cause of vitamin E deficiency.[2] If left untreated, patients with this disorder develop loss of vibration and proprioception, loss of deep tendon reflexes, ataxia and cerebellar degeneration as well as generalised muscle weakness.[17] Nerve conduction studies in vitamin E deficiency show a sensory predominant axonal neuropathy.[18] However, the onset of symptoms is usually slow and progressive.

An interesting case report[19] describes a 24-year-old man presenting with a form of ataxia progressive since childhood, associated with peripheral neuropathy, and was found severely deficient in serum vitamin E. He walked with bilateral aid and presented with absent deep tendon reflexes. In this patient, after 2 years of a daily supplement of high doses of vitamin E, a further progression of the disease was not observed and, moreover, the neurophysiological characteristics of his neuropathy appeared clearly improved. A longitudinal evaluation of serum vitamin E levels showed values in the normal range after 13 months of therapy. However, there is minimal data regarding postsurgical vitamin E deficiency, and the presentation of this woman's symptoms appear too acute to be attributed to vitamin E deficiency alone, but were more likely part of an overall spectrum of nutritional deficiency involving a variety of vitamins and trace elements.

Also of interest in this case was the far more gradual improvement of symptoms over the following weeks and months with appropriate replacement of her identified nutritional deficiencies. This was similar to the timescale described in the case reports regarding copper deficiency described above.[13–15] Early recognition of the underlying cause for her varied neurological symptoms and appropriate supplementation was critical to her treatment. Clinicians should be particularly mindful of the possibility of nutritional deficiencies in patients after surgery involving the upper gastrointestinal tract or indeed those with gastrointestinal absorption pathology. Nutritional counselling should be provided by an experienced dietician to educate the patient about potential long-term nutritional deficiencies after gastrectomy.[20] Supplementation should always be customised as needed to account for individual nutritional intake and nutritional status.

The direct toxic effects of chemotherapy were also a significant potential contributor to this female's malabsorption syndrome.[21] Chemoradiotherapy is not confined exclusively to malignant cells and her normal tissues may have been affected by her treatment, magnifying her postoperative nutritional deficiencies.[22] We liaised with our oncology colleagues regarding the

potential for chemotherapy-related malabsorption. Interestingly, although it is a recognised complication and potential side effect of chemoradiotherapy, there is no international recommendation to measure micronutrient and vitamin levels routinely in chemotherapy patients, although many recommend routine supplementation with a standard oral multivitamin. This could be an area for further research.

Peripheral neuropathy is not an infrequent presentation to hospital. We learnt that early consideration of patient history to elucidate if there is a history of gastrointestinal surgery or malabsorption may hint at underlying nutritional deficiency. This can potentially be treated and reversed and save the patient exposure to other treatment or investigation before progression of symptoms. This will be of particular interest to those working in the fields of neurology, upper GI surgery, dietitetics, gastroenterology and oncology. Further study is required to fully understand the pathogenesis and prevention of nutritional neuropathies.

Learning points

- Neuropathies due to multiple coexistent nutritional deficiencies can affect certain patient populations and have a varied presentation.
- Clinicians should be alert for signs and symptoms of neuropathy in patients who have had upper GI or bariatric surgery.
- Consideration of nutritional deficiency in patients presenting with symptoms of neuropathy is important as this is a potentially treatable, reversible and preventable condition. Early recognition and supplementation can prevent neurological deterioration.

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Contributors PR was involved in the clinical care of the patient in the form of follow up and review in outpatients. PR conceived and planned the case report and obtained informed consent from the patient for publication of this case report. PR reviewed the patient's chart and collected the required data and compiled the relevant results. PR designed and drafted the manuscript. PR is the primary author and is accountable for ensuring the accuracy and integrity of all aspects of the manuscript. PR responded to the reviewers comments and edited the manuscript prior to the resubmission in order to address the queries raised by reviewers. PK was involved in the clinical care of the patient in the initial assessment and management of the patient's care. PK was the consultant for the Neurology team that the patient was admitted under in hospital and coordinated investigation and treatment. PK was involved in the initial design of the report. PK reviewed the revised manuscript and proposed response to the reviewers questions. He then provided approval for the revised manuscript to be submitted to BMJ Case Reports.

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