Case Study:
An unusual case of Wernicke's encephalopathy - Thiamin deficiency in advanced gastric adenocarcinoma

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Introduction

Wernicke's encephalopathy (WE) is a neurological syndrome most commonly found in patients suffering from alcohol abuse. It is less frequently diagnosed in non-alcoholic patients. In non-alcoholic patients WE might develop due to the exclusion of upper portions of the gastrointestinal tract (e.g. after gastrectomy, gastrojejunostomy, gastric bypass surgery) or secondary to intractable vomiting, inadequate dietary intake or malabsorption.[1,2] Other described conditions in which WE may develop include HIV/AIDS, several types of malignancy (inoperable gastric cancer, leukaemia and lymphoma), prolonged periods of malnutrition (anorexia), hyperemesis gravidarum, thyroid conditions, post organ transplant as well as patients receiving dialysis and long-term dependency on parenteral nutrition (PN).[1-3,4]

WE is caused by thiamin (vitamin B_1) deficiency.[1,2] This micronutrient, a water-soluble vitamin, is absorbed primarily in the duodenum, acts as a co-factor in carbohydrate metabolism, and is important in neuron cell function.[3] The human body cannot synthesize thiamin and regular dietary intake of thiamin is essential.[3] Symptoms of a thiamin deficiency or WE include the classic triad of ophthalmoplegia/nystagmus, ataxia and encephalopathy/confusion,[1-3] although these clinical symptoms occur in only 16–25% of patients.[3,4,5] Early onset of a thiamin deficiency includes general symptoms of illness such as headaches, irritability, fatigue and abdominal discomfort.[3] Prophylactic thiamin supplementation forms part of the standard nutritional management of patients at risk of developing refeeding syndrome (RFS).[6,7] RFS, also a regularly underdiagnosed condition,[4] is characterized by the potentially fatal shift in fluids and electrolytes (decrease in phosphate, potassium and magnesium), as well as thiamin deficiency which could possibly contribute to WE.[4,6,7] These findings emphasize the importance for medical doctors as well as dietitians to be aware of the signs and symptoms of thiamin deficiency, particularly in cases with a non-alcoholic aetiology.

Case Report

A 32-year-old female was referred to the upper gastrointestinal surgical unit at Groote Schuur Hospital with a one-year history of loss of appetite, poor oral intake, intermittent postprandial vomiting and significant loss of weight. Collateral history elucidated an acute deterioration in cognitive and muscle function over the preceding month. An initial gastroscopy by the referring hospital had shown severe gastritis, a prepyloric mass and gastric outlet obstruction (GOO). An abdominal ultrasound reported an abnormally thickened appearance of the gastric mucosa. Repeat gastric biopsies were consistent with a diffuse-type gastric adenocarcinoma involving most of the distal stomach and pylorus. Staging computed tomography (CT) revealed a locally unresectable diffuse gastric cancer.

Anthropometry

The patient was unable to stand, and therefore the relevant anthropometric measurements were estimated. A body mass index (BMI) of 19 kg/m^2 and height of 1.72 m were estimated, resulting in an estimated current body weight of 56 kg. An ideal body weight of 65kg, at BMI of 22 kg/m^2, was calculated. The patient had visible temporal and deltoid wasting, with 5–10% weight loss over the preceding 6–12 months.

Biochemistry

The biochemical workup included a full blood count, serum urea, creatinine, electrolytes, calcium, magnesium, phosphate and albumin, as well as liver function tests. The relevant serial blood values are shown in Table 1. The patient had ongoing borderline hypokalaemia due to increased losses from prolonged vomiting. Serum creatinine levels reflect muscle mass as creatinine is mostly derived from the breakdown of endogenous sources, and less affected by catabolic states than urea levels.[8] Thus, the decreased creatinine levels in the patient reflected her low muscle mass, corresponding with the quadriparesis (see clinical assessment) and muscle wasting. Urea,

Table 1: Relevant cumulative biochemistry during hospital stay

	Normal values	Prior to admission	Admission		Day1	Day 2	Day 3	Day 4	Day 8	Day 11	Day 18	Day 21	Day 27
Sodium	135–147 mmol/l^{-1}	141	139	141	140	138	137	141	138	139	140	141	144
Potassium	3.3–5.3 mmol/l^{-1}	2.4	H¥	3.0	3.6	3.9	3.1	3.5	3.4	3.4	3.2	2.7	2.8
Urea	2.6–7.0 mmol/l^{-1}	3.0	3.4		4.6	5.1	3.9	4.6	3.6	3.4	6.4		9.8
Creatinine	60–120 μmol.L^{-1}	30	39		39	30	23	22		21	35		22
Haemoglobin	14.3–18.3 g/dL	10.6	13.7		11.8	9.7	10.1	9.0	7.9	8.7	10.0	9.3	9.1
WBC ¥	4–10 x 10^9/L	2.74	4.05		2.64	2.52	2.63	2.86	2.59	3.26	3.90	6.56	16.4
Calcium (corrected)	2.05–2.56 mmol/l^{-1}		2.0		1.9	1.9	2.1		2.2	2.05	2.2	2.4	2.4
Magnesium	0.65–1.1 mmol/l^{-1}		0.7		0.79	0.60	0.64		0.63		0.87	0.54	0.75
Phosphate	0.8–1.4 mmol/l^{-1}		0.84		0.68	0.8	1.02		1.56		1.14	1.15	0.62
Albumin	35–52 g/L	27	29							32	30	28	23
ALT ¥	5–40 U/L	37								42	9	<5	8
AST ¥	5–40 U/L	20								35	16	12	17
ALP ¥	40–120 U/L	48								93	85	74	130
GGT ¥	0–60 U/L	30								121	67	42	45
Vitamin B_{12}	145–569							380					
TSH ¥	0.27–4.20 mIU/L							2.84					

¥H: Haemolysed; WBC: White blood count; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphate
GGT: gamma glutamyl transpeptidase; TSH: Thyroid stimulating hormone

on the other hand, is derived from either dietary protein sources or endogenous protein sources and its formation is influenced by protein intake, increased catabolism (either due to starvation or an acute phase response), as well as the absorption of protein from blood in the gastrointestinal lumen.[8] The hypophosphatemia on day 1 was not an indication of RFS since nutritional intervention only commenced on that day, but was rather a result of increased losses and poor dietary intake. Hypomagnesemia may be attributed to poor absorption, or rather diminished nutrient delivery due to GOO, as the absorption site for magnesium is in the small intestine and colon.[10] Hypoalbuminemia is an indicator of the catabolic state due to the adenocarcinoma.[8]

Clinical

On arrival at our centre, the patient was bedridden and aphasic with a flaccid, areflexic quadriparesis, bilateral cranial nerve VI palsies, nystagmus, ptosis and encephalopathy. General wasting and fatigue with thin and weakened extremities were observed. The patient was apyrexial with stable vitals. According to collateral family history, she suffered from severe depression which was never formally diagnosed or treated, but had been fully independent and functional up until one month prior to presentation. A subsequent CT brain scan excluded metastatic disease. Psychiatry and neurology were consulted on day 1 and 4 respectively, and a subsequent diagnosis of WE due to severe thiamin deficiency was made on clinical grounds. A magnetic resonance imaging (MRI) of the brain showed no characteristic findings of WE or any other permanent lesions.

Dietary

The patient was identified as being at risk of developing RFS due to her prolonged inadequate intake and increased weight and nutrient losses. She was kept nil per os due to complete GOO, and total parenteral nutrition (PN) was initiated. An indication for PN according to European Society for Clinical Nutrition and Metabolism (ESPEN) in unresectable cancer patients includes supportive or supplementary PN, if a patient is likely to suffer from starvation prior to tumour spread, although, in most cases, the nutritional benefit is outweighed by the risk of infection, sepsis and or PN-associated liver disease with prolonged administration. Thus PN support in advanced cancer is not standard practice.[9,10]

PN support was commenced according to the National Institute for Health and Care Excellence (NICE) guidelines for the management and prevention of RFS.[9,10,11] The guidelines (Figure 1) recommend slow commencement of nutrition at 10 kcal/kg/day with an increase of 5 kcal/kg/day based on biochemical monitoring, along with intravenous (IV) thiamin supplementation and prophylactic IV phosphate, potassium and magnesium supplementation.[9,10,11] Regular repeat blood as well as glycaemic monitoring was strictly adhered to.

The patient's initial energy needs were calculated at 15 kcal/kg/day (based on estimated actual weight) due to the 330 kcal (5.8 kcal/kg/day based on estimated actual weight) that was already being received from the 5% Dextrose IV infusion @ 63 ml/hour since admission. The patient was prescribed an all-in-one PN bag, started at 60 ml/hour via central venous access. Additional IV micronutrient

solution (containing one ampule Soluvit® and one ampule Additrace® in 200 ml saline, given over 4 hours) was administered to reach daily micronutrient requirements as the whole PN bag was not used. Normal saline IV fluids with 40 mmol KPO_4 (42 ml/hour) was commenced to provide total fluids up to 40 ml/kg/day, based on estimated actual weight.

On diagnosis of gastric adenocarcinoma, the patient's goal energy and protein were adjusted to disease specific recommendations according to the ESPEN guidelines on PN: non-surgical oncology of 25–30 kcal/kg/day and protein recommendations at a minimum of 1 g/kg/day with a target range of 1.2–2 g/kg/day.[9,10] For prevention of further weight loss and/or weight gain, a total energy intake up to 40 kcal/kg/day is recommended.[12] This resulted in 1680–2240 kcal/day (based on estimated current weight) and 78–130 g/day protein (based on ideal body weight). Her fluid requirement was continued at 40 ml/kg/day to maintain her fluid balance.

Figure 1. NICE guidelines for the management of refeeding syndrome[11,12]

NICE* GUIDELINES FOR REFEEDING SYNDROME

DAY 1:	10 kcal/kg/day 5 kcal/kg/day (BMI < 14 kg/m² or nil per os for > 15days)
Day 2 to 4:	Increase by 5 kcal/kg/day Poor to no tolerance - keep to low feeding regimen or stop
Day 5 to 7:	20–30 kcal/kg/day
Day 8 to 10:	30 kcal/kg/day or increase to full requirements

Prophylactic supplementation:
Phosphate: 0.5–0.8 mmol/kg/day
Potassium: 1–3 mmol/kg/day
Magnesium: 0.3–0.4 mmol/kg/day
Sodium: restrict < 1 mmol/kg/day
IV Thiamin and B-complex 30 minutes prior to feeding till day 3 OR 200 mg once when feeding commences and 100 mg daily for 10 days
Fluid balance: maintain at a zero balance

***NICE:** National Institute for Health and Care Excellence

Medical management

The patient was initially prescribed Pantoprazole®, Clexane®, Perfalgan®, Stemetil®, and Morphine®. Prophylactic IV potassium phosphate (KPO4) and IV thiamin supplementation (200 mg immediately prior to initiation of PN and continuing 100 mg daily for 10 days) was started according to the NICE guidelines (Figure 1).[11,12] The peripherally administered 5% Dextrose infusion at 63 ml/hour was changed to normal saline with the commencement of PN. Based on the biochemical result done on day 2, IV magnesium sulphate (2 grams in 200 ml saline daily) supplementation was started.

IV thiamin supplementation was adjusted according to WE protocols on day 4 (Figure 2). It is inadvisable to prolong infusion for more than 30 minutes as it can be painful at the infusion site.[4]

Figure 2. Neurology protocols for the management of Wernicke's encephalopathy as recommended by literature[4]

European Federation of the Neurological Societies (EFNS):
200 mg Thiamine IV in 100 ml of normal saline or 5% glucose over 30 minutes three times a day until symptoms resolve

Royal College of Physicians:
Evidence based on alcoholics
500 mg Thiamine IV three times a day for three days followed by 250 mg IV daily for 5 days or until clinical improvement is no longer noted

By day 10, the patient's cognitive state improved and she was orientated to person, place and time, nystagmus resolved and she gained 3 out of 5 power in her upper limbs, although her lower limb weakness persisted. Occupational therapy was consulted and provided bilateral ankle foot orthosis (AFO) splints for foot drop.

Nutritional Management

The patient was started on PN according to the NICE guidelines for the management of RFS (Table 2). The patient tolerated the feeding regimen well and reached maximum requirements by day 4. Prophylactic supplementation of IV thiamin as well as KPO_4 was continued and, on day 4, magnesium was also added due to deficient levels. Thiamin supplementation was adjusted on day 5 and the patient volunteered an increase in appetite, although she still had nil oral tolerance.

On day 22, an uncovered 120 x 20 mm duodenal self-expanding metal stent (SEMS) was placed endoscopically, but failed to expand due to the severity of her gastric outlet stenosis and external compression from the tumor (Figure 3). As a last resort to establish an enteral feeding route, the patient was booked for a palliative open gastrojejunostomy. On commencement of her laparotomy, however, the procedure was abandoned due to the diffuse, locally-advanced nature of her disease. After extensive counselling with all family members, the patient was identified for palliative care and PN was weaned and stopped on day 27.

Table 2. Nutritional management of the patient – progress of parenteral nutrition provided

Day	Rate (mL/h)	Total Energy (kcal/kg/day)	Protein (g/kg/day)	Dextrose (mg/kg/min)	Lipids (g/kg/day)
1	60	15	1	1.2	0.9
2	60	20	1	2.2	0.9
3	62	25	1.4	3.1	0.9
4–27	66	35	1.9	3.1	0.9

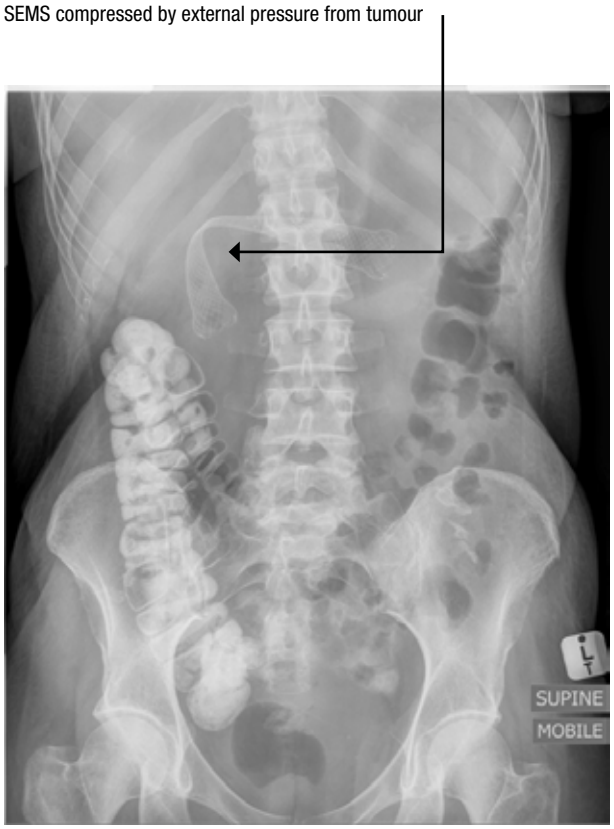

Figure 3. X-ray of failed duodenal self-expanding metal stent (SEMS)

Literature review

WE due to thiamin deficiency is common among alcoholics.[1,2] Due to this association, it is frequently underdiagnosed in non-alcoholic patients suffering from gastrointestinal cancers, HIV/AIDS, prolonged periods of malnutrition, hyperemesis gravidarum and long term total PN.[1,2] Sechi et al. found that 75–80% of WE is only diagnosed in post-mortem studies.[13] Further studies found that inadequate thiamin supplementation is administered in 40% of abdominal cancer surgery patients.[5] Symptoms of a thiamin deficiency or WE include acute mental deterioration, ophthalmoplegia, nystagmus and ataxia.[1-3,4] Onset of symptoms can be expected from two to three weeks of poor oral intake, but may also develop two to eight months after abdominal cancer surgery.[5,9]

Gastric adenocarcinoma patients may present with WE, even in the absence of gastrointestinal obstruction, due to severe malnutrition and cachexia.[1,2] Limitations to current studies include that the signs and symptoms identified to contribute to or identify risk of WE could be ascribed to other disease conditions and also a lack in sample sizes.[3] Although Restivo et al. argue a valid point with reference to the costs of IV thiamin versus an MRI – that thiamin supplementation is cheaper than having each patient at risk of WE sent for a MRI[3] – an MRI scan is considered to be the preferred diagnostic tool for WE, even though it only has a 53% sensitivity.[3,13] In this case an MRI was done to determine if the patient presented with irreversible features of WE.

Biomarkers to identify thiamin deficiency include plasma thiamin levels and, indirectly, from erythrocyte transketolase activity; the latter is not used to diagnose WE, but rather as a biomarker of an existing deficiency.[14] The additional biomarkers were not used or tested in this patient as the clinical symptoms adequately justified the initiation of thiamin treatment.

In cancer patients, factors that contribute to the development of thiamin deficiency include the consumption of thiamin by fast-growing neoplastic cells, occlusion or bypassing of the duodenal absorptive surface, poor dietary intake related to lack of appetite and nausea, significant malabsorption, and the use of specific types of chemotherapy.[3,15,16] This patient did not receive chemotherapy as the cancer was already too advanced on diagnosis, but rather developed a deficiency due to the fast growing tumour, prolonged poor intake and oral intolerance due to GOO.

Thiamin is a vital substrate in the anaerobic metabolism of carbohydrates, converting pyruvate to acetyl-CoA in the kreb cycle to produce adenosine triphosphate (ATP) or suitable energy that is transported to the brain.[11,12,17] Decreased carbohydrate metabolism and poor glucose delivery to the brain lead to poor synaptic transmission, altered DNA synthesis and neurotoxicity due to increased lactic acid and reactive oxygen species.[1-3,4,13,17] Decreased blood-brain barrier permeability due to the failed osmotic gradient has also been reported as a contributory factor.[3] Standard practice in patients who present with symptoms of confusion and delirium include dextrose IV infusion, that could lead to WE with prolonged infusion.[17] Large volumes of glucose rapidly deplete already deficient stores of thiamin in a malnourished patient, inhibiting glycolysis that result in WE.[17] Hypomagnesaemia also inhibits the metabolism of glucose to ATP, as magnesium is a co-factor that enables thiamin to bind to thiamine-dependant enzymes.[17] Recommendations include glycemic monitoring and early thiamin supplementation when a malnourished patient reaches normal glycemic levels.[17] PN is often required in these patients to deliver adequate nutrition; however, WE can also be caused by PN administration due to the increased influx of carbohydrates due to refeeding syndrome.[1,2,4]

Thiamin body stores are depleted within two to three weeks of inadequate intake/ provision and/or increased losses that may lead to brain lesions.[2,3,4,5,18] Prompt and sufficient thiamin supplementation can prevent or reverse early neurological symptoms in the initial two to three week stage of reversible biochemical lesions.[12,4] In this case the patient's neurological symptoms were partially reversed with high-dose thiamin supplementation, irrespective of the advanced stage of cancer. A lack of or delay in thiamin replacement can lead to irreversible structural lesions in the brain, permanent neurological sequelae and death.[12,4] More research is needed to determine the optimal dosage for thiamin supplementation in treating WE.[4] Side effects of parenteral thiamin supplementation include pruritus and sweating.[12,4]

Conclusion

Lack of awareness of the manifestation and clinical symptoms that present in non-alcoholic thiamin deficiency or WE increase the

fatality of the syndrome.[1-5,17,18] Gastric adenocarcinoma patients' life expectancy after diagnosis has been extended by improved treatment methods,[1,2] although all these patients suffer from poor nutritional intake and absorption that could lead to nutrient deficiencies. WE or thiamin deficiency should be considered in gastric adenocarcinoma presenting with prolonged inadequate intake and increased losses in order to ensure early supplementation and prevention of permanent neurological damage or death.

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