BMJ Endgames:

Seeing double: the Low-Carb diet

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Case History

A 38 year old Scottish-caucasian man with a background of mild learning difficulties (able to read and write but not to maintain employment) presented with a 3-day history of diplopia and agitation, following 7-days of presumed viral gastroenteritis.

On admission, he was very agitated, mildly confused, tachycardic (HR 115 regular) and tachypnoeic (RR 18). There were no chest signs or peripheral oedema. He had complete bilateral 6th cranial nerve palsies and horizontal nystagmus, with dilated, slowly-reacting pupils. Limb movements were clumsy, with moderate cerebellar signs and dysdiadochokinesis, but no tremor. He was clinically jaundiced. ECG demonstrated inferolateral T wave inversion. Heart-size was upper-limit of normal on chest X-ray.

On specific questioning, the patient gave a history of life-long alcohol avoidance, but of 34kg weight loss over the previous 3 months, corroborated by information from his parents and practice nurse. At an initial weight 127kg[BMI 42.4kg/m^2] he received 'healthy-eating' advice from his practice-nurse who described him as her "star patient", his weight falling from 123kg(4-weeks), 110kg(8-weeks), 104kg(11-weeks) to 93kg[BMI 31] on admission. Latterly, pursuing greater weight-loss, he eliminated all bread, cereals and fats, on a diet considered 'starvation' by his parents, without nutritional supplements.

Question 1. What is the most likely diagnosis?
Question 2. What definitive investigation confirms the diagnosis?
Question 3. What treatment should you start as an emergency, without confirmatory investigation results?
Question 4. Why were the ECG and chest X-ray findings alarming?
Question 5. Why did this patient become so ill, and develop jaundice, while many people follow low-carbohydrate diets without evident problems?

Short Answer 1. Concurrent agitation and cerebellar signs suggest Wernicke's encephalopathy as the most likely cause of ophthalmoplegia, with cardiac signs of vitamin B1 (thiamin) deficiency.

Long Answer 1. Bilateral abducent (6^{th}) cranial nerve palsies (**Figure 1 and video**) are uncommon. It may indicate tumours, Rathke's cleft cyst, diabetes, demyelination, subarachnoid hemorrhage, meningitis, increased intracranial pressure or Wernicke's encephalopathy(1).

The presence of agitation, cerebellar signs and ECG abnormalities suggests Wernicke's encephalopathy, from acute thiamin deficiency, as the most likely cause. Alcohol and dietary histories are vital to determining its aetiology, though inherited forms should be considered. Patients with learning difficulties may behave unexpectedly: our patient was praised for losing 4kg in the first month, and sought (and received) greater praise by trying harder.

Specific differential diagnoses observed with malnutrition include hypophosphataemia, Miller-Fischer syndrome (ophthalmoplegia/ataxia/areflexia) and central pontine myelinolysis (symmetric non-inflammatory demyelination)(1).

The signs of cardiomegaly, tachycardia and ECG abnormalities also support a diagnosis of thiamin deficiency with high-output cardiac failure.

Short Answer 2. Low red cell thiamin diphosphate (TDP) concentration.

Long Answer 2. A nutritional screen, available 10 days post-admission, confirmed thiamin deficiency, and also revealed low values for vitamins A, C, B6, folate and selenium, without a significant inflammatory response **(Table 1).**

Thiamin (vitamin B1) is a water-soluble vitamin with a 9-18 day half-life, demanding a regular dietary supply. Deficiency causes complete inhibition of carbohydrate metabolism, with acetaldehyde accumulation predominately affecting astrocytes within cranial nerve nuclei 3,4,6 and 8(2, 3). Magnesium is required for thiamin-binding to enzymes(4). The gold-standard method to assess vitamin B1 status is red-cell concentration of thiamin diphosphate (TDP), its physiologically active form, which reflects body vitamin B1 stores and concords well with transketolase functional testing(5).

Our patient had a red-cell TDP 132ng/gHb, the lowest ever recorded in our laboratory, lower than values previously reported to cause neurological impairment(6). Thus, his very strict weight-loss regimen, far beyond what had been advised, eliminated most sources of thiamin, precipitating the clinical triad of Wernicke's encephalopathy: ophthalmoplegia, ataxia, and mental confusion(7). He had no clinical features of other vitamin deficiencies despite subnormal values.

Short Answer 3. Suspected/potential thiamin deficiency, in alcoholic or other malnourished patients, demands immediate treatment with intravenous thiamin: ophalmoplegia usually resolves rapidly. Without thiamin, carbohydrate administration causes Wernicke-Korsakoff Syndrome, and permanent anterograde amnesia(7).

Long Answer 3. Presumed or potential thiamin deficiency, regardless of aetiology, demands immediate treatment with intravenous thiamin. It is commonly administered with additional water-soluble vitamins B and C as Pabrinex (Archimedes Pharma UK Ltd) providing thiamin 250mg three-times daily for three days, before switching to oral thiamine, 300mg daily (8, 9). Ophthalmoplegia usually resolves rapidly. Without sufficient thiamin, carbohydrate administration precipitates Wernicke-Korsakoff Syndrome, and permanent anterograde amnesia(7). Magnesium deficiency must also be corrected, to permit thiamin function (4). The response to thiamine administration excludes familial syndromes which can mime Wernickes encephalopathies.

Short Answer 4. Chest X-ray and echocardiographic signs of cardiomegaly, and ECG abnormalities, indicated cardiac involvement as 'wet beri-beri', a potentially fatal complication of starvation.

Long Answer 4. In addition to classical neurological signs of 'dry beri-beri', our patient had ECG and chest X-ray abnormalities indicating cardiac involvement, as 'wet beri-beri'; which untreated progresses to high-output heart failure, a cause of sudden death from starvation or anorexia nervosa(10). Out-patient echocardiogram 15 days post-admission confirmed right heart enlargement. Myocytes contain high concentrations of TDP, an essential cofactor for enzymes involved in glucose, high-energy phosphates and amino acid metabolism, activating chloride channels and regulating cholinergic neurotransmission. Although thiamin deficiency is common in alcoholics, only about 10% develop Wernicke's encephalopathy, possibly through other micronutrient imbalances or genetic predisposition(11).

Short Answer 5. Weight losses >4kg/week indicate extreme dieting (demanding micronutrient supplementation), marked muscle loss, or intercurrent illness: it is hard to ensure thiamin (found mainly in carbohydrate-rich cereals) status, and avoid gallstones, on diets below 1000kcal/day. He had several small gallstones within the gallbladder, a recognised complication of consuming under 15-30g/day of fat.

Long Answer 5. Severe dietary restriction potentially incurs nutritional insufficiency, unless specific dietary advice is adhered to, so clinical monitoring is important. This 'low-carb dieter' was unusual in his extreme, prolonged, diet restriction and weight-loss. Exactly what he ate over his 3-month dieting, or his thiamin intake, cannot be established. However he reported excluding all identifiable sources of carbohydrate, and for much of that time ate no solid food other than occasional rice-crispies and chicken nuggets, which his parents confirmed. His pre-diet food consumption was also erratic, with high consumptions of high-fat energy-dense foods like ice-cream, apple-pies, crisps and of full-sugar carbonated drinks.

Investigations suggested obstructive jaundice. Ultrasonography revealed several small gallstones within the gallbladder. Symptomatic cholelithiasis occurs in approximately 6% of patients on liquid-formula diets of 400-600kcal/day, and 30% after bariatric surgery. Weight-loss above 1.5kg/week, or >24% body-weight, increase risks: including 15-30g/day dietary fat prevents this problem(12,13). Weight-loss on food-based diets should not usually exceed about 4kg/month. More rapid rates entail extreme diets (which demand micronutrient supplementation), marked muscle loss, or intercurrent illness.

Assuming mainly loss of adipose tissue, at 7,000kcal/kg(14), a 10kg/month weight-loss requires consuming 2,500kcal/day below 24-h metabolic rate. At 93kg, with physical activity level equating to 1.4x basal metabolic rate [BMR], his estimated 24-hour metabolic rate was 2,675(± standard error 170)kcal/day(15,16,17). Thus, his energy deficit of 2,500kcal/day implies a virtual starvation diet. An adult man requires 1.0mg/day thiamin(17), achievable from, for example, 400g bread (a major source), which would provide 880kcal/day. Including 20g/day dietary fat to avoid gallstones adds 180kcal/day. Therefore, it is difficult to maintain thiamin status without supplements, and avoid gallstones, consuming <1000kcal/day. Sudden deaths, presumed cardiac, were reported with early semi-starvation 'protein-sparing-modified-fast' diets(18), possibly through thiamin deficiency. The cardiac abnormalities in the present case, which resolved after thiamin replacement, indicated an impending fatal outcome(19). Modern micronutrient-replete formula diets appear safer, without requiring close medical supervision except for patients taking insulin, sulphonylureas, antihypertensives and diuretics(20,21). However, dietary advice that results in significant weight loss should be monitored by a trained health-care professional to prevent micronutrient intake being 'forgotten'.

Patient Outcome

After starting intravenous thiamin, 250mg three-times daily for 3 days as Pabrinex, this patient resumed normal food consumption. There was no biochemical evidence of refeeding syndrome, probably because he was still obese, with adequate mineral reserves. His neurological signs resolved within 24hours. There is no clear evidence to support follow-up thiamin treatment duration or route of administration (22). Our patient was discharged five days post-admission, with normalised LFTs and ECG, on oral thiamin 300 mg/day. At outpatient follow-up on day 50, weighing 94kg, having stopped oral thiamin and continued a

normal food-based diet, no abnormal signs remained. ECG, chest X-ray and echocardiography were all normal and showed reductions in the previously elevated heart size: cardiac diameter 162 to 142 mm, right ventricle outflow tract diameter 3.0 to 2.4cms.

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Figure 1. The patient was asked to gaze to the extreme left and right

(Video for online version. Eye movements one day after thiamin replacement, showng bilateral lateral rectus paralyses, and nystagmus)

a) Left lateral gaze *b) Right lateral gaze*

Table 1: Biochemistry, Haematology and Nutritional Screen results

Result (reference range) *subnormal	Day 1	Day 2	Day 3	Day 4	Day 50
Liver Function Tests:					
Bilirubin (<20µmol/L)	48	38	35	24	16
ALKP (40-150 U/L)	140	126	130	116	93
AST (<40 U/L)	34	-	-	-	17
ALT (<50 IU/L)	70	57	59	62	18
GGT (<70 U/L)	111	86	87	74	-
Hb (13-18g/dL)	15.2	14.9	15.3	14.4	13.9
CRP (<10mg/L)	11	13	12	6.7	2.7
Albumin (32-45g/L)	40	37	38	37	41
Thiamin diphosphate: TDP (275-675ng/g Hb)	132*				453
Vitamin C (15-90 umol/L)	3*				27
Vitamin E (15-45 umol/L)	20				20
Vitamin A (1-3 umol/L)	0.5*				0.9*
RBC Vitamin B6 (250-680 pmol/g Hb)	139*				619
RBC Vitamin B2 (1.0 - 3.4 nmol/g Hb)	1.6				2.9
Copper (10.0 - 22.0 umol/L)	14.4				17.1
Manganese (70 - 280 nmol/l)	182				176
Magnesium (0.70 - 1.00 mmol/L)	0.94				0.89
Selenium (0.8-2.0 umol/L)	0.66*				0.74*
Zinc (10.7 - 18.0 umol/L)	15.1				10.8
Cholesterol (<5.00 mmol/L)	3.92				-
Calcium (adj) (2.10 - 2.60 mmol/L)	2.67‘				2.52
Vitamin B12 (200 - 900 pg/ml)	481				328
Folate (3.1-20.0 ng/ml)	1.4*				3.3
Ferritin (10.0 - 275.0 ng/ml)	224				25.0