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Cystic fibrosis associated with Wernicke's encephalopathy in an older adult

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SUMMARY

Here we report the first case of an association between cystic fibrosis and Wernicke's encephalopathy. The patient had a history of cystic fibrosis diagnosed in her early 60s associated with pancreatitis and chronic lung disease. She presented with a traumatic hip fracture requiring operative repair. On examination, she was found to have bilateral nystagmus. MRI revealed enhancement of the mammillary bodies. Laboratory results were notable for thiamine deficiency, which in context of the radiographic and physical examination findings, confirmed a diagnosis of Wernicke's encephalopathy. The cause of her low thiamine was thought to be poor dietary intake, weight loss and malabsorption associated with exocrine pancreatic insufficiency in the setting of a history of recurrent pancreatitis. The patient had complete resolution of her symptoms with the initiation of thiamine supplementation and pancreatic enzymes. Although classically associated with fat soluble vitamin deficiencies, there are increasing reports of water-soluble vitamin deficiencies associated with cystic fibrosis.

BACKGROUND

Cystic fibrosis (CF) is a common autosomal recessive disease caused by mutations in the CFTR gene, with a prevalence as high as 1 in 3000 in certain populations. Six categories of mutations have been discovered with various phenotypes. Universal newborn screening for CF started in 2010 in the USA, leaving a generation of adult patients who have not been screened and are likely underdiagnosed.¹ Its prevalence varies among racial groups but can be as frequent as 1 in 3000 in Caucasian populations.^{2,3} CF can result from 1500 different mutations in the CFTR gene that can be classified into six classes with various phenotypes.^{4,5} It is typically diagnosed by either one or more characteristic phenotypic features of CF, or a history of CF in a sibling, or a positive newborn screening test in combination with either a positive sweat chloride test, identification of two CF mutations, or demonstration of abnormal nasal epithelial ion transport.⁶ CF may evade diagnosis in part due to perceptions that CF is a disease of childhood. Additionally, older individuals are more likely to have milder phenotypes⁷ and to have inconclusive results on sweat chloride testing.^{3,8,9} With increased heterogeneity among the CF population, delays in diagnosis and longer life expectancy, it is important to better understand the complications of CF that may accumulate over a lifespan.

Pancreatic disease with associated deficiency of fat-soluble vitamins is one of the most well-described

manifestations of CF within gastrointestinal tract. Rarely, there have also been case reports of water-soluble vitamin deficiencies¹⁰ but no previously reported cases of symptomatic thiamine deficiency.

CASE PRESENTATION

A Caucasian woman in her early 60s was admitted to the internal medicine service following a left periprosthetic hip fracture sustained after falling backwards while ambulating with a walker. The patient had a history of multiple previous falls in the setting of difficulty controlling her left upper and lower extremities. History was notable for nausea, vomiting and anorexia for the previous few weeks, for which she had received a diagnosis of symptomatic cholelithiasis. She reported a 40 lb weight loss over several months. The patient also complained of diplopia, vertigo, difficulty maintaining a seated posture and gait changes.

Her medical history was significant for a diagnosis of CF 2 years prior to admission when she presented to a pulmonologist with dyspnoea, cough, wheezing and steatorrhoea and ultimately underwent testing demonstrating a CFTR mutation. She also endorsed a prior history of recurrent acute pancreatitis with the latest episode being approximately 3 months prior to presentation.

Outside of the last few weeks, the patient reported eating a well-balanced diet. She denied current alcohol use or a history of heavy alcohol consumption and had never smoked cigarettes. She had no history of gastrointestinal tract surgery.

On mental status examination, the patient was found to be disoriented with anterograde amnesia, forgetting she had a fall and unsure of her reason for being hospitalised. She had a flat affect with monotone expression. Cranial nerve and cerebellar examination revealed right beating, left beating and torsional end-upward gaze nystagmus. She was also found to have a high frequency, low amplitude action tremor of both upper extremities, worse on the left side. Finger nose-finger testing was normal except for the presence of the tremor. Left lower extremity strength, gait and balance testing was deferred due to her hip fracture.

INVESTIGATIONS

Laboratory results demonstrated mild normocytic anaemia with a haemoglobin of 84 g/L. Her initial magnesium level was low at 1.5 mg/dL (normal range 1.8–2.5 mg/dL). Liver enzymes, thyroid stimulating hormone (TSH), lipase, folate, vitamin B₁₂ and vitamin E were all within normal



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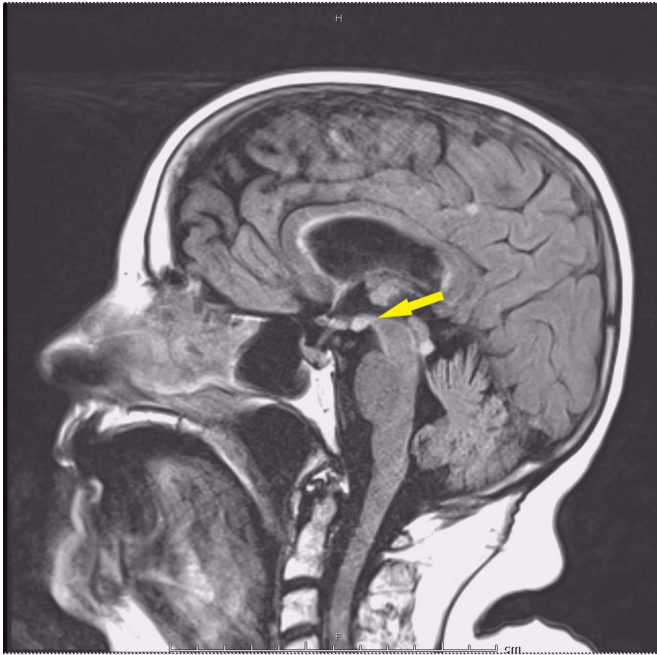


Figure 1 MRI brain with and without contrast sag T2 FLAIR showing hyperintensity lesions in bilateral mammillary bodies.

limits. Thiamine resulted at 37 nmol/L (normal range 78–185 nmol/L).

MRI/MRA was obtained, which was notable for mild cerebral and cerebellar atrophy. FLAIR hyperintensity and restricted diffusion in bilateral mammillary bodies and the tectum were also seen (figures 1–3).

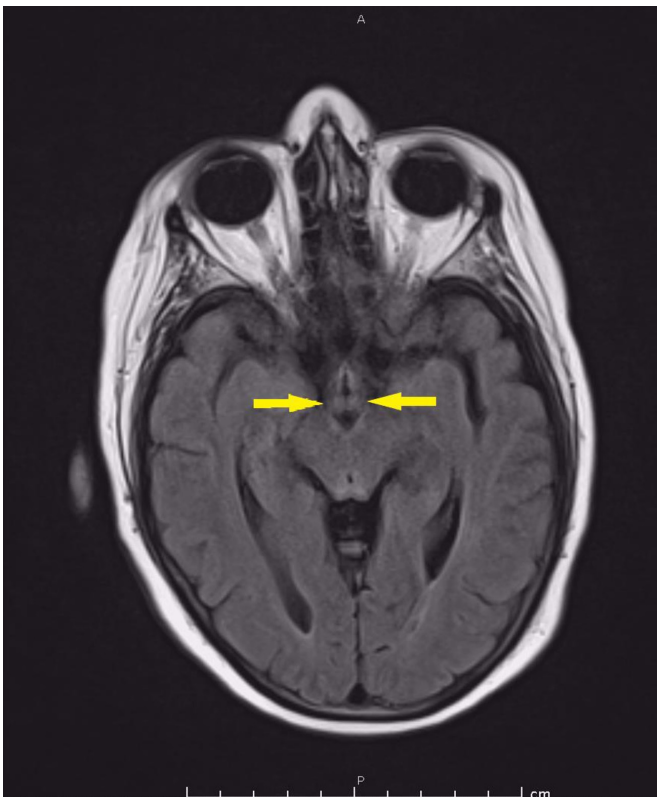


Figure 2 MRI brain with and without contrast AX T2 FLAIR showing hyperintensity lesions in bilateral mammillary bodies.

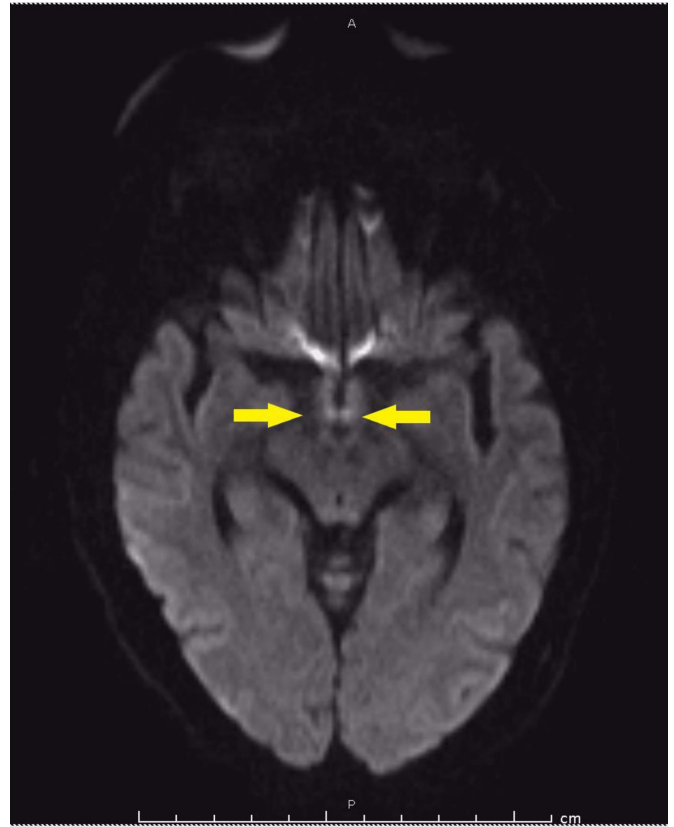


Figure 3 MRI brain with and without contrast AX DWI TR showing hyperintensity lesions in bilateral mammillary bodies.

Ultrasound of the gallbladder reviewed no evidence of gallstones or sludge. The pancreatic head was unremarkable, and the body and tail were poorly visualised.

DIFFERENTIAL DIAGNOSIS

Given her acute left-sided limb control issues, truncal instability, multidirectional nystagmus, vertical diplopia and vision fixation issues in the context of a lack of gross motor weakness, there was initial consideration of a subacute cerebellar stroke, a cerebellar mass or a mass effect on the cerebellum. Cerebellar demyelination and degeneration were also considered. However, these diagnoses were excluded once the MRI/MRA findings returned.

Hypothyroidism was also considered but discounted when the TSH returned within normal limits.

Given the patient's known CF, the investigation turned towards potential vitamin and mineral deficiencies; however, B₁₂, folate and vitamin E levels were all within normal limits.

Ultimately the clinical presentation of reported gait ataxia, nystagmus and altered mental status, combined with bilateral mammillary body oedema and the subsequent finding of thiamine deficiency cinched the diagnosis of Wernicke's encephalopathy. The presence of limb ataxia, while more atypical can also be seen in Wernicke's encephalopathy.¹¹

TREATMENT

The patient was started on intravenous thiamine 500 mg for 3 days and then transitioned to 250 mg intravenous for 2 additional days. Three tablets of pancrelipase (12 000/38 000/60 000) with meals were also started. Her magnesium was repleted. During the rest of her hospitalisation, she had progressive improvement in her mental status and resolution of her nystagmus and dysmetria,

as well as her nausea and anorexia. She was discharged with oral thiamine and pancreatic enzymes.

OUTCOME AND FOLLOW-UP

One month after discharge, the patient was noted to have resolution of her neurological deficits and had returned to her baseline mental status. One year and seven months after discharge, she reports that continues to take pancrelipase and was started on a magnesium supplement but is no longer taking thiamine.

DISCUSSION

Wernicke's encephalopathy is known by the classic triad of gait ataxia, ophthalmoplegia and altered mental status. In developed countries, it is most often associated with alcoholism but can be seen in the setting of malnutrition, malabsorption and hyperemesis, requiring a high index of suspicion when evaluating non-alcoholic patients with compatible clinical findings.¹²

In our case, a seemingly routine case of an older patient presenting with a hip fracture after a ground level fall led to the diagnosis of Wernicke's encephalopathy. We hypothesise that the patients' thiamine deficiency is related to suboptimal intake, impaired binding of nutrients, impaired conversion of thiamine due to hypomagnesaemia and malabsorption in the setting of recurrent pancreatitis and pancreatic insufficiency caused by CF. Interestingly, pancreatic insufficiency is relatively rare in patients diagnosed with CF at an older age.^{7-9 13 14}

CF is more traditionally associated with deficiencies in fat soluble vitamins due to exocrine pancreatic insufficiency,¹⁵⁻¹⁷ However, rare cases of water-soluble vitamin deficiencies (such as vitamin B₁₂) resulting in focal neurological deficits have also been reported in the literature. Thiamine deficiency has also been previously reported in multiple patients with CF though in the absence of Wernicke's encephalopathy.¹⁰ Hypomagnesaemia has been associated with CF likely due to malabsorption and as well as exposure to aminoglycoside antibiotics. Magnesium is

required for conversion of thiamine to its active form and there have been reports of Wernicke's encephalopathy refractory to thiamine administration in the setting of hypomagnesaemia.¹⁸⁻²¹ It may be the case however, that as life expectancy improves in CF, vitamin deficiencies from chronic malnutrition may accumulate over time and the clinician taking care of adult CF patients should be attentive to this.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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Learning points

- ▶ Cystic fibrosis (CF) is a genotypically and phenotypically heterogeneous condition that is underdiagnosed in the adult population.
- ▶ In addition to chronic lung disease, CF is associated with pancreatitis and pancreatic insufficiency. The clinician should keep CF on the differential when evaluating adult patients with evidence of malnutrition or malabsorption.
- ▶ Although classically associated with fat soluble vitamin deficiencies, water soluble vitamin deficiencies with and without clinical manifestations have also been associated with cystic fibrosis.
- ▶ With increased heterogeneity among the CF population, delays in diagnosis and longer life expectancy, it is important to better understand the complications of CF that may accumulate over the lifespan.

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