4. D)Primary central nervous system lymphoma

Part 2: A PET scan was subsequently performed 2 months later and FDG-avid lesions were noted in the small bowel and the left testicle. An exploratory laparotomy was performed, resulting in small bowel resection and left partial orchiectomy. Two weeks later, he returns with a headache and left sided ptosis. MRI brain revealed a large extra axial mass lesion measuring 6.2 cm x 3.0 cm x 6.4 cm in the left temporo-parietal region resulting in a mass effect and 2 mm midline shift. He undergoes a craniotomy with excisional biopsy and duraplasty for a large defect. Pathology from all the three locations mentioned above reveals primarily basophilic cells interspersed with histiocytes with abundant cytoplasm ("starry night"). What is the most likely diagnosis?

1. A) Hodgkin lymphoma
2. B) Burkitt lymphoma
3. C) Follicular lymphoma
4. D) Primary central nervous system lymphoma

Part 1: A

Explanation: Primary central nervous system lymphoma is ruled down because it is most common in patients with a CD4 count <50 cells/mm^3 and typically presents as CNS mass lesions with seizures and altered mental status. Non-Hodgkin lymphomas (NHL) are AIDS-defining cancers that are very common in HIV+ patients and commonly presents with diffuse lymphadenopathy; however, NHL does not have Reed-Sternberg cells as seen on the biopsy. Burkitt lymphoma typically presents as an extra-nodal tumor mass, which was not seen on imaging. Hodgkin lymphoma, though not an AIDS-defining malignancy, is usually common in moderately immunosuppressed patients rather than severely immunosuppressed patients, and this is consistent with the Reed-Sternberg cells seen on biopsy. Therefore, answer A is the best choice.

Part 2: B

Explanation: Hodgkin lymphoma rarely enters the testicles or CNS, which rules it down significantly, despite the previous diagnosis of Hodgkin lymphoma. Now that several extra nodal masses have been identified and have been shown to have the characteristic "starry sky" appearance, Burkitt lymphoma is much more likely.

Thiamine Deficiency: A Case Presentation and Literature Review

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Abstract

This case examines the complicated hospital course of a patient ultimately diagnosed with thiamine deficiency. The presentation, diagnostic work up, and treatment of a 53-year-old male with a history of schizoaffective disorder, pituitary adenoma status post trans-sphenoidal adenectomy, GERD, hyperlipidemia, and glaucoma are evaluated. He had lived at a care facility for over 10 years, and he was brought to an outside hospital after members of the staff found him in bed, unresponsive. They also had concerns about a one-day history of inability to sit or stand up straight and gait abnormalities. An extensive work up with chest x-ray, EKG, urinalysis, routine CBC and CMP, blood and urine cultures, head CT, MRI of the brain and spine, lumbar puncture, EEG, and various miscellaneous labs ensued. Urinalysis and urine cultures revealed evidence of Enterococcus urinary tract infection. EEG revealed evidence of encephalopathy. The patient was also hyponatremic with thiamine and pyridoxine deficiency. Thiamine deficiency was diagnosed after a dramatic improvement in gait and mentation after administration of thiamine.

Introduction

Thiamine or vitamin B1 is an essential water-soluble vitamin found in yeast, organ meat, pork, legumes, beef, whole grains, and nuts. It functions in energy generation by participating in decarboxylation of alpha-ketoacids and branched-chain amino acids. It also functions in peripheral nerve conduction through an unknown mechanism. The most common cause of thiamine deficiency worldwide is poor dietary intake. In developed countries, the most common causes are alcoholism and chronic disease (i.e. cancer). Other patients at risk include patients with poor nutritional status on parenteral glucose, patients after bariatric bypass surgery, pregnant patients with prolonged hyperemesis gravidarum, and patients on chronic diuretic therapy due to urinary losses.[1] Thiamine deficiency due to overuse of the vitamin within the body can occur in hyperthyroidism, pregnancy, lactation, or fever. Severe liver disease can impair the utilization of thiamine leading to a similar clinical picture.[3]

Early stages of thiamine deficiency manifest as anorexia and nonspecific symptoms including irritability and decreased short-term memory. When thiamine deficiency persists, patients will progress to a condition called beriberi, which is classified as wet or dry with frequent overlap between the two. Symptoms of wet and dry beriberi are pain and paresthesia. Dry beriberi presents with peripheral neuropathy of the motor and sensory systems with diminished reflexes, especially in the lower extremities. Patients with wet beriberi will also have cardiovascular manifestations such as cardiomegaly, tachycardia, high-output congestive heart failure, peripheral edema, and peripheral neuritis.[1]

Thiamine deficiency is associated with alcoholism in 90% of cases in developed countries. Alcoholic patients most commonly present with Wernicke's encephalopathy due to thiamine deficiency. Wernicke's encephalopathy is associated with a classic triad of ophthalmoplegia, cerebellar ataxia and mental impairment. However, all three, if any, of the classic signs are not often seen in patients with Wernicke's encephalopathy. Wernicke-Korsakoff syndrome is diagnosed when there is also an inability to form new memories and confabulatory psychosis. While Wernicke-Korsakoff syndrome is highly associated with alcoholism, patients with thiamine deficiency due to other causes can be diagnosed with the syndrome as well.[2]

Patients with suspected thiamine deficiency are managed with 100mg/d of IV thiamine for seven days, and 10mg/d orally everyday thereafter until there is resolution of symptoms.[1] A maintenance dose of 2.5-5 mg per day is then recommended.[3] Treatment with IV and oral thiamine is very safe, with minimal to no risk.[2] It is important to begin thiamine replacement early if thiamine deficiency is suspected, because of risk for morbidity due to permanent psychosis.[2] Administration of thiamine can even be used as a diagnostic test in cases of acute heart failure or insidious peripheral neuropathy, because of the rapid and dramatic improvement in symptoms if deficiency truly exists. Prognosis is good for patients with thiamine deficiency that has not progressed to Korsakoff syndrome.[3] In Wernicke-Korsakoff syndrome, psychosis may not improve for months and may be permanent.[1]

Case Presentation

History: S.M. is a 53-year-old male with a past medical history of schizoaffective disorder, pituitary adenoma status post trans-sphenoidal adenectomy, GERD, hyperlipidemia, and glaucoma. He presented to an outside hospital due to altered mental status and muscle weakness. History was obtained from the patient and from reports from the care facility he has lived in for over 10 years. The care facility reported that the patient had a one-day history of problems sitting upright and standing. He had several episodes of sliding off the toilet without any trauma or injuries experienced during these episodes.

On the day of admission he was found unresponsive in his bed. He responded only slightly to sternal rub. Upon arrival at the outside hospital, he was somnolent and answering questions with mumbles and garbled speech. Upon arrival at our hospital, he was more alert and able to answer questions. Staff from the care facility reported that he had been seen at the outside hospital a month ago for similar gait disturbances and decreased mentation.

His psychiatrist decreased his Clozaril dose from 350mg at bedtime to 250mg at his last presentation due to possible interactions with valproic acid and congentin. S.M's other pertinent medications include: bupropion, cabergoline, clozapine, fluoxetine, and trazodone. The patient has a history of heavy drinking for three to four years in the past, but has not drank alcohol since residing at his care facility. He smokes occasionally, but denies recreational drug use.

Review of Systems: S.M. denies any pain, headache, fever, chills, shortness of breath, cough, chest pain, abdominal pain, nausea, vomiting, diarrhea, constipation, dysuria, hematuria, hemoptysis, hematochezia. He denies recent travel, tick bites, and mosquito bites.

Physical Findings: On physical exam, he was alert and oriented and in no acute distress. Musculoskeletal and neurologic exams were significant for normal range of motion and 5/5 strength in bilateral upper and lower extremities. There were no focal neurologic deficits noted and cranial nerves II-XII were grossly intact, including normal extraocular movements. Examination of the neck did not reveal any signs of nuchal rigidity. However, he had an unsteady gait and felt unbalanced when standing. Cardiovascular exam revealed a 2/6 systolic ejection murmur, but was otherwise negative. Respiratory, skin, and abdominal exams were within normal limits.

Differential Diagnosis, Diagnostic Work Up, Hospital Course

Initial work up at the outside hospital included a chest x-ray that was negative for acute findings, negative blood cultures,, EKG revealing normal sinus rhythm, and a negative head CT. Urinalysis was positive for leukocytes and nitrites. Repeat UA was negative for nitrites, positive for a small amount of leukocytes, and positive for trace ketones. Differential diagnosis at this point included urinary tract infection, medication interactions or toxicity, dehydration and electrolyte abnormalities, and recurrent pituitary adenoma or other CNS pathology.

Labs on admission included a CBC that showed an elevated WBC count at 13.6, slightly decreased sodium at 133, and decreased potassium at 3.4. He had a slight normocytic anemia with a Hgb of 12.3 and Hct of 37.8. Albumin was low at 3.4. Together with ketones found in the urine, this may have indicated some insufficient nutrition. Prolactin and valproic acid levels were ordered and found to be within normal limits, ruling down recurrent pituitary adenoma and valproic acid toxicity. Urine and blood cultures were also ordered. Urine cultures were positive for pan-sensitive Enterococcus, confirming suspected UTI.

S.M. received fluid resuscitation, potassium replacement, and appropriate antibiotic therapy for his UTI. His WBC count appropriately trended downwards with antibiotic therapy. The patient's hyponatremia proved to be difficult to correct throughout the course of his hospital stay. Intravenous normal saline was stopped and started several times. His Clozaril dose was decreased further to 200mg at bedtime, with no improvement in symptoms.

He continued to be difficult to arouse in the mornings on hospital days 1-7. He was minimally responsive and answered a few questions with a mumbled voice. He would improve throughout the day, but continued to be unmotivated with a flat affect. However, this was consistent with his baseline according to his care facility staff. He remained unsteady on his feet, according to the

nurses that worked with him in the hospital. With no improvement in symptoms, an MRI of the brain and spine were ordered on hospital day three with no acute findings.

Neurology was consulted on hospital day four and found him to be alert and oriented with good registration, being able to repeat three objects. They noted normal sensation to soft touch, pinprick, and vibration throughout. Romberg sign was negative. Reflexes were brisk aside from the Achilles reflex, which was hypoactive. Upgoing Babinski was noted bilaterally, but without fanning of the toes. The patient exhibited an intention and postural tremor in both upper extremities, with the right being worse than the left. He also had tremulousness in his legs when trying to hold them in position. Gait was limited by this tremulousness. The tremor was attributed to multiple medications, including clozapine and Depakote. The primary team increased the patient's benztropine dose in an effort to improve the tremor.

An EEG was ordered by neurology that revealed evidence of encephalopathy with generalized slow activity and a slow posterior dominant rhythm, but no evidence of seizure activity. A metabolic encephalopathy was suspected and the neurology team suggested measuring levels of thiamine, B6, B12, folate, TSH, and copper. HIV tests to rule out HIV encephalopathy, ammonia levels to rule out hepatic encephalopathy despite negative history of liver disease, and lead levels were also ordered by the primary team. Pending results of several of these tests that would explain the patient's encephalopathy and without any improvement in symptoms, the patient underwent a lumbar puncture on hospital day seven to rule out meningitis or encephalitis. The results were negative for infection.

Vitamin B12, folate, TSH, copper, lead, ammonia, and HIV tests returned within normal limits. However, the result for the patient's thiamine (B1) level returned on hospital day seven and was found to be low at 6nmol/L, with normal being 8-30nmol/L. The patient subsequently received thiamine replacement with 100mg IV thiamine. When the patient was seen the next morning (hospital day eight), he was still difficult to arouse from sleep, but had improved mentation later in the day when compared to previous days. Thiamine was administered again, and the next morning (hospital day nine) he was found sitting in his chair eating breakfast and listening to music. He was very conversational and alert. He stated that he was feeling much better with improvement in his weakness and was requesting to be discharged and returned to his care facility. Tremor was also noted to be improved. Before he was discharged, B6 was also found to be low at 4.3nmol/L, with the normal range being 20-125nmol/L. S.M. was ultimately diagnosed with nutritional deficiencies of thiamine (B1) and pyridoxine (B6). It was believed that thiamine deficiency was the major player in the development of the patient's symptoms, given the dramatic improvement after the administration of thiamine.

Final Diagnosis and Management Plan

Clinically, thiamine deficiency can have several different presentations. Wet beriberi is not likely in this patient because he did not exhibit cardiovascular symptoms. Dry beriberi or Wernicke's encephalopathy would be more likely. According to Caine criteria for diagnosis of Wernicke's encephalopathy, which is more sensitive than the classic triad, a patient can be diagnosed if two out of four of the following are present: eye signs, cerebellar signs, mild memory impairment or confusion, and signs of malnutrition.[2] S.M. had clear evidence of altered mental status, cerebellar

signs with ataxia leading to gait disturbances, as well as evidence of malnutrition with hypoalbuminemia and ketonuria. The patient was also demonstrated to have decreased levels of thiamine in his blood, further supporting this diagnosis. Finally, all other work up that was performed during the patient's hospital stay proved to be negative.

While thiamine deficiency was concluded to be the final diagnosis, this patient presented many diagnostic challenges. There were many confounders that had to be considered in the evaluation of this patient's altered mental status and ataxia. Other diagnoses that were considered throughout the patient's hospital course included medication interactions or toxicity, acute decompensation of mental status due to infection, and acute hyponatremia. These diagnoses are possible explanations for the patient's presentation, as they are all acute processes that were also corrected during the patient's hospital stay. However, the patient improved most rapidly after the administration of thiamine.

After a nine-day hospital stay, the patient was discharged on 100mg PO thiamine daily, with plans to decrease to maintenance dose when symptoms completely resolved. His care facility was also instructed to complete his seven-day course of antibiotics for his urinary tract infection.

Discussion

According to Isenberg-Grzeda, et al., there are many misconceptions about Wernicke-Korsakoff syndrome, including the misconceptions that it is rare, exclusive to alcoholics, and likely to present with the classic triad for Wernicke's encephalopathy. On the contrary, this condition is likely under diagnosed, occurs in patients with malnutrition secondary to any cause, and rarely presents with the classic triad.[2] This case is a great example to reinforce the inaccuracy of these misconceptions. This case of thiamine deficiency occurred in a patient who was suffering from nutritional deficiencies due to decreased appetite and apathy. He had a remote history of alcohol use but had not had any alcohol for over 10 years. The patient also presented with very vague, non-specific symptoms that did not fulfill the classic triad of Wernicke's encephalopathy. However, this patient did have significant improvement in his symptoms following administration of IV thiamine. This alone is often used diagnostically and reasonably confirms the diagnosis of Thiamine deficiency.[3]

Many expensive and invasive tests were performed in the work up of this patient. If the physicians involved in the care of this patient had considered a higher degree of clinical suspicion for thiamine deficiency and administered IV thiamine, several of these tests may have been avoided. If thiamine replacement had been provided earlier in S.M.'s hospital stay, his symptoms might have resolved before several expensive and invasive tests were ordered, including the MRI of the brain and spine and lumbar puncture.

When a patient presents with any evidence of nutritional deficiency and nonspecific neurologic symptoms or acute heart failure, thiamine deficiency should be on the list of possible diagnoses. Intravenous thiamine should be administered early if there is any suspicion for thiamine deficiency. This may aid in diagnosis if rapid improvement of symptoms occurs, and also prevents the morbidity associated with Wernicke-Korsakoff syndrome in the form of permanent psychosis.[2]

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An Interesting Case of Anemia

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BACKGROUND

Cobalamin (Vitamin B12) deficiency can result in abnormalities in all cell lines which normalize after cobalamin replacement[1]. Moreover, Andres *et al.* reported hematological findings in 201 consecutive patients with vitamin B12 deficiency [2]. Approximately 10% of the patients had life threatening hematological manifestations, including symptomatic pancytopenia (5%), "pseudo"