CASE REPORT

Severe hyponatremia and MRI point to diagnosis of tuberculous meningitis in the Southwest USA

Stephanie Michelle Benson,^{1,2} Rashmi Narasimhamurthy¹

¹Department of Family Medicine, Southern New Mexico Family Medicine Residency Program, Las Cruces, New Mexico, USA

²Department of Family Medicine, University of North Carolina-Chapel Hill, Chapel Hill, North Carolina, USA

Correspondence to

Dr Stephanie Michelle Benson, stephanie.benson@lpnt.net

SUMMARY

A 21-year-old woman presented to the hospital with 3 days of headache, fever, mood disturbance and nausea. She had recently emigrated from India, and was noted to have a positive screening purified protein derivative tuberculosis skin test with normal chest x-ray. Meningeal signs were noted prompting lumbar puncture and initiation of presumptive treatment for bacterial meningitis. While tuberculous meningitis (TM) was entertained at admission, diagnosis was clouded by the rapid onset of symptoms and recent major psychosocial stressors. She developed severe hyponatremia. Brain MRI revealed tuberculomas, and she was started on treatment for TM, a diagnosis confirmed by culture. On review, several lessons were learned: (1) globalisation of society makes uncommon diagnoses present in unlikely locations, (2) hyponatremia is a common complication of TM, (3) MRI can aid in diagnosis of TM and (4) cognitive and mood changes can be prodromal symptoms of TM.

BACKGROUND

Tuberculosis (TB) remains a significant infectious disease with an estimated 8.7 million new cases and 1.4 million deaths from TB worldwide in 2011.¹ Despite this worldwide burden, it is a rare finding in the USA with a case rate of only 3.4 cases/100 000 persons in 2011 and the lowest number of reported cases since reporting began in 1953.² Tuberculous meningitis (TM) develops in 7–12% of patients with TB³ and is the most lethal form of TB.⁴ In the USA in 2011 extrapulmonary TB accounted for 21% of identified cases.¹ TM often presents with an indolent course with malaise, anorexia and headache being common presenting symptoms³ and fever, meningismus, altered consciousness and cranial nerve palsies the most common findings.^{3–5} Prognosis is largely dependent on timely diagnosis and treatment. The presence of hyponatremia, cranial nerve involvement and mental status changes are associated with worse outcomes.⁶ Diagnosis can be difficult with demonstration of acid-fast bacilli (AFB) in the cerebrospinal fluid (CSF) being the gold standard but this test has poor sensitivity.⁶ Other CSF findings can suggest TM in the context of patient history⁷ and MRI may be helpful in suspected cases.^{8–9} In this patient, prodromal symptoms presented as subtle cognitive and mood changes, hyponatremia developed as a complication, and MRI was helpful for diagnosis pending definitive laboratory confirmation.

CASE PRESENTATION

A 21-year-old female college student, who had recently emigrated from India, presented to a community hospital in southern New Mexico, USA, with a 3-day history of acute severe frontal headache, subjective fever and nausea. Four months prior to presentation she had been found to have induration of 13 mm following a purified protein derivative skin test on screening examination. Through the student health centre, she had then given three sputum samples, two of which were AFB negative and one of which was reported as indeterminate. At the time of presentation, sputum cultures were still pending, outpatient chest x-ray was normal and our local health department had planned on presumptively beginning treatment in next few days. On further questioning the patient reported a 2-month history of dry cough and a 10 pound weight loss over the previous 4 months. She denied any haemoptysis or night sweats. Her sister, who was also a student at the university, reported a decline in the patient's mood over the previous few months, which she attributed to the stressors related to her current graduate school studies, including the cultural adjustment and distance from her home and parents. On examination, at the time of admission, she was quiet and withdrawn with a very flat affect, but cooperative with history and examination. Examination revealed no focal neurological deficits but she was found to have significant nuchal rigidity, so a lumbar puncture was performed to evaluate for meningitis. She was admitted to the hospital and placed on precautionary respiratory isolation. Intravenous ceftriaxone, acyclovir and dexamethasone were started prophylactically pending her CSF results. We considered beginning empiric treatment for TM at this time as well but, because she seemed to present so acutely, the team decided to wait until further studies had been conducted.

INVESTIGATIONS

At initial presentation in the emergency department (ED), non-contrast CT of her brain was normal except for the incidental finding of a benign sub-arachnoid cyst. Initial chemistries revealed sodium level of 131 mmol/L and normal total white blood cell count with neutrophilia of 85.5% noted on differential. CSF analysis showed low glucose of 28 mg/dL and elevated protein of 58 mg/dL. CSF was found to be clear and colourless with a cell count of two red blood cells per field and 35 white blood cells per field with a differential of 12% polymorphonuclear leucocytes, 85% lymphocytes and 3% monocytes.

To cite: Benson SM, Narasimhamurthy R. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009885

CSF bacterial antigen panel, Gram stain and AFB smear were all negative. AFB culture, TB PCR, bacterial culture and herpes simplex PCR were also ordered. Over the next few days the patient's neurological status declined. While still alert and following commands, she became even more withdrawn and even disoriented at times. In discussion, with her faculty mentors within the local University, they mentioned noting a steady decline in her mood and academic functioning over the previous 2–3 months. She also developed ophthalmoplegia, specifically sixth cranial nerve palsy. At this point, an MRI of her brain was pending. We also asked for a psychiatry consult as her family and faculty mentors felt many, if not all of her symptoms, were owing to the psychological stress of being in a foreign country far from home.

On hospital day 7, the patient's sodium dropped to as low as of 114 mmol/L (see table 1 for sodium trend), and she developed tonic-clonic seizures. She was transferred to the intensive care unit and treated with intravenous 3% saline solution and antiepileptics. At that time, serum osmolality was low, urine osmolality was high and urine sodium was normal consistent with the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. An MRI with and without gadolinium enhancement was performed the same day which showed numerous ring-enhancing nodules throughout the cerebral hemispheres, cerebellum and brain stem; meningeal enhancement; and acute infarcts of bilateral frontal parietal junctions (see figures 1 and 2). Given the very likely diagnosis of TM, she was started on multidrug TB treatment. The original sputum cultures from before hospitalisation eventually became positive for *Mycobacterium tuberculosis*. An induced sputum sample obtained in hospital and the CSF AFB culture, both of which were AFB smear negative, also returned positive with pansensitive *M tuberculosis*. The CSF TB nucleic acid amplification PCR test returned negative. Other serum and CSF studies included HIV antibody testing, coccidiomycosis titres, CSF cryptococcal antigen, histoplasma urine antigen, CSF herpes simplex PCR and CSF Venereal Disease Research Laboratory test (VDRL), and all returned negative.

TREATMENT

The patient was treated with hypertonic saline for SIADH. Her hyponatremia subsequently improved, as seen in table 1. After the diagnosis was made with the aid of MRI, the patient was started on a multidrug treatment regimen for TM with rifampin, isoniazid (INH), pyrazinamide and ethambutol. During this time, she was also treated with systemic steroids and pyridoxine. Owing to TM related seizure risk, she was treated with oral levetiracetam. After the 2-month period of intensive four drug TB treatment, the pyrazinamide and ethambutol were discontinued and she continued on the rifampin and INH for an additional 10 months. This provided for a total of 12 months of anti-TB treatment. She also remained on the levetiracetam for seizure prophylaxis until the entire TB treatment course was completed.

OUTCOME AND FOLLOW-UP

Our patient was discharged home after 20 days of hospitalisation with instructions to continue the anti-TB medications.

Table 1 Blood sodium during admission

Day of hospital admission	1	4	8	8.5	9	10	11	12
Blood sodium (mmol/L)	131	138	121	114	120	126	129	131

Figure 1 Sagittal T1 MRI.

During her course of treatment, she elected to return to India, to stay with family and complete her treatment. While there, she developed medication induced hepatotoxicity. She was briefly taken off the medications until her liver enzymes reverted to normal and then restarted on the medications for an additional 9 months. After completion of her treatment, she returned to the USA to finish her graduation and was seen for follow-up in our outpatient clinic. A year after discharge from the hospital, and after completion of her multidrug treatment for TB, the patient was found to be doing well with complete return to baseline mental status, cognition and overall functionality. There was also complete resolution of her ophthalmoplegia with no neurological sequelae.

DISCUSSION

As mentioned previously, TB is an uncommon finding in the USA, and TM even rarer still. When it is seen within the USA, it is much more likely to be seen in foreign-born persons. In fact, according to the Centers for Disease Control (CDC), 62% of all reported TB cases in the USA in 2011 occurred in foreign-born persons.² The case rate in the USA among US born persons was 1.5 cases/100 000 in 2011 compared with 17.2 cases/100 000 in foreign-born persons.² The globalisation of our society allows for increased ease of travel, and can lead to, as in our case, unlikely diagnoses being seen in even small community

Figure 2 Axial T1 MRI.

hospitals. It is therefore imperative to keep these diagnoses in mind when caring for patients with increased risk.

It is well known that prognosis in TM depends on the stage of disease at time of diagnosis.³ The British Medical Research Council developed a set of clinical criteria to assess the severity of TM. In stage I, the patient is conscious with non-specific symptoms. In stage II, lethargy or cranial nerve palsies have developed. In stage III, patients have stupor, severe illness, gross paralysis, or paresthesias. Stage I disease conveys a 20% mortality risk, stage II, 30% mortality risk, and stage III, 55% mortality risk.⁶ In our case, while treatment had begun within 1 week of presentation, and our patient had an excellent outcome, there were definite signs of this diagnosis at initial presentation that, if noted and fully understood, may have allowed for even more rapid initiation of treatment.

One of the difficulties with diagnosis of TM is the vagueness of the symptoms with which these patients can present. In one recent study of 160 cases from Turkey, the most frequent symptoms observed at the time of admission were headache (86%), nausea/vomiting (64%) and altered sensorium (59%).⁸ On examination, 88% of these patients had stiff neck, although only 37% had signs of meningeal irritation.⁸ In another smaller study from Pakistan, the most common signs were meningismus (81.4%), fever (65.1%) and cranial nerve palsies (46.5%).³ Our patient presented with fever, headache, nausea and vomiting, and was noted to have meningismus on examination, which prompted the lumbar puncture. While she did have altered sensorium at presentation, which became more pronounced over the following week, and in hindsight, altered cognitive function prior to presentation, these symptoms were attributed to her recent psychosocial stressors and the depression described by her family. Her cognitive and mood changes had in fact been prodromal symptoms of her central nervous system infection. A similar case report published in 2011 points out that while slow onset, gradual cognitive changes are atypical in TM, any cognitive change in a young person warrants further investigation.⁷ In our case, a better understanding of her normal abilities and cognitive function prior to presentation, may have aided earlier diagnosis.

The development of recent onset lateral rectus palsy should also be a clue to the possible diagnosis of TM.³ In the previously mentioned study from Turkey, 24% of patients had cranial nerve palsies at admission, with the abducens (sixth) nerve being the most frequently affected.⁸ In another study, 20 of 43 patients (46.5%) had a cranial nerve palsy while 14 (32.6%) had sixth cranial nerve palsy specifically.³ Patients with sixth nerve palsy describe horizontal diplopia because the sixth cranial nerve supplies the ipsilateral lateral rectus, which is responsible for abduction of the eye.³ It is thought that the third and sixth cranial nerves are most affected because they have the longest anatomical intracranial course and exudates formed in TM settle at the base of the brain causing entrapment.³ Our patient developed sixth cranial nerve palsy during admission, which completely resolved after treatment.

According to British Infection Society guidelines, diagnosis of TM is best obtained with lumbar puncture and examination of CSF.^{10 11} Characteristic CSF findings in TM include a predominantly lymphocytic leucocytosis, a rise in CSF protein, and CSF to plasma glucose of ratio less than 50%.¹⁰ Table 2 outlines the differences seen in CSF analysis among bacterial, viral and tuberculosis meningitis. AFB may not be seen on AFB smear, so the lack of visualisation of AFB should not delay treatment if TM is suspected. A study carried out in Vietnam in 2004 with 132 adults with clinically diagnosed TM found AFB in only

Table 2 Expected disease specific CSF findings^{10 14}

	CSF-serum glucose ratio	Protein	WBC's	WBC differential
Bacterial	Decreased	Elevated	Highly elevated	Neutrophilic
Viral	Normal	Normal to elevated	Normal to slightly elevated	Lymphocytic
TB	Decreased	Elevated	Moderately elevated	Lymphocytic

CSF, cerebrospinal fluid; WBC, white blood cell count.

73/141 CSF specimens (52% sensitivity) and TB culture became positive in only 90/141 specimens (64% sensitivity), resulting in bacteriological confirmation in only 107/132 (81%) cases.¹² These results can vary greatly depending on the study reviewed. Sensitivity of AFB smear can vary from 10% to 60% and culture positivity rates vary between 25% and 75% after 2–6 weeks of incubation.⁶ Even PCR is unreliable in TM. A meta-analysis of commercial nucleic acid amplification tests (NAAT) for the diagnosis of TM published in 2003 showed overall sensitivity of only 56% (95% CI 46% to 66%) and 98% specificity (95% CI 97% to 99%).¹³ This means that while NAAT can confirm suspected cerebral tuberculosis, it should not be used to rule out the disease.^{6 11} In our case, we did eventually have bacteriological confirmation through positive sputum and CSF cultures though our TB NAAT returned negative.

Imaging may also be useful in assisting with diagnosis of TM. CT and MRI can demonstrate tuberculomas and signs of meningeal enhancement as well as complications of TM such as hydrocephalus and infarction. In our case, the presence of tuberculomas on MRI leads us to begin the treatment while waiting for biological confirmation (see figures 1 and 2). Tuberculomas typically appear as contrast enhancing ring lesions with surrounding oedema.¹¹ A few studies have examined one modality versus another. For example, in one study, MRI was performed in 27 cases and MRI was positive in 8/13 cases with normal CT.⁸ Another retrospective study reviewed 29 cases of patients diagnosed and treated in Tunisia between 1996 and 2003, who had undergone both CT and MRI, found CT was normal in 19 cases (65%) of confirmed TM, while MRI was normal in only three cases (10%).⁹ It is important to note that cryptococcal meningitis, viral encephalitis, sarcoidosis, meningeal metastases and lymphoma may also have similar radiological findings. CT and MRI cannot reliably differentiate tuberculoma from other causes of ring-enhancing lesions.^{11 14}

Hyponatremia is one of the more common complications in TM, thought to affect more than 50% of cases, and its development is associated with worse outcomes.^{4 14} Two physiological distinct conditions can lead to hyponatremia in TM, SIADH and cerebral salt wasting (CSW) syndrome.⁴ Hyponatremia in the setting of SIADH is dilutional as total body sodium remains normal while in CSW sodium is lost in the urine at a greater rate than water loss leading to a reduction in total body sodium.⁴ Each is dangerous and can lead to increased cerebral oedema, seizures and cerebral ischaemia but it may be difficult to differentiate between the two. Given that fluid restriction can be detrimental for patients with CSW, although beneficial in SIADH, most experts recommend all TM patients with hyponatremia be treated cautiously with either hypertonic saline or fludrocortisone.^{4 6} Our patient received hypertonic saline in the acute setting during initial severe hyponatremia leading to appropriately timed sodium correction (see table 1).

While there is sufficient evidence to support the current recommendations for treatment of pulmonary TB, for TM, the best regimen and optimal length of treatment has not been well established.^{11–15} Our patient was treated according to treatment guidelines which suggest 2 months of intensive four drug treatment of susceptible strains with INH, rifampin, pyrazinamide and ethambutol followed by an additional 7–10 months of INH and rifampin alone.¹⁵ We also treated her with dexamethasone, as available data shows corticosteroids, particularly dexamethasone, beneficial in decreasing mortality, though not morbidity, in HIV-negative patients with TM.^{6–15} She also received antiepileptics after her initial seizure until the completion of treatment, though her seizure was likely precipitated by her hyponatremia. It is estimated that seizures occur in half of paediatric and approximately 5% of adult cases and confer a worse prognosis as patients are likely to experience recurrent seizures if not treated with antiepileptics.⁶

Thankfully, our patient had an excellent outcome despite the combination of factors that increased her risk for poor prognosis, such as altered sensorium, advanced stage at presentation, seizures and the development of hyponatremia. Given that patients with TM, who require ICU admission, can have as high as 75% mortality,⁴ it is remarkable that not only did she recover, but went on to have no neurological sequelae. As mentioned previously, TM can be difficult to diagnose, especially if clinicians are unaccustomed to caring for these patients. Given the globalisation of our society, it would be wise to refresh our knowledge about diseases, such as TB, which, while rare in the USA, are much more common in other parts of the world. Specifically in this case, improved baseline knowledge of the characteristics findings in TM, such as CSF lymphocytosis and lateral rectus palsy, may have lead to more rapid initiation of TM treatment. With only superficial knowledge of this disease process at the time, our team was able to eventually arrive at the correct diagnosis and initiate the proper treatment. This was accomplished with the assistance of MRI findings, and resulted in an excellent outcome.

Learning points

- Globalisation of society has made diagnoses that are not commonly seen in areas of the USA much more possible, even outside of tertiary academic medical centres, and we need to consider such diagnoses earlier in our evaluation of the foreign-born or have recently travelled outside the country.
- If a patient presents with risk factors for TM but seems to present acutely, inconsistent with TM, a thorough history may reveal subtle cognitive and mood changes that could be prodromal symptoms of TM.
- Hyponatremia is a common and severe complication of TM and needs to be addressed aggressively erring towards treatment with fluid hydration and hypertonic saline rather than fluid restriction.
- While caring for a patient, for whom TM is in the differential, consider the use of early MRI.

Acknowledgements The authors would like to thank Anthony Viera, MD, MPH, for his feedback and edits on drafts of this manuscript.

Contributors SMB performed all background research, assisted with collection and assimilation of patient data, wrote the majority of the manuscript, and performed edits. RN assisted with obtaining consent, assisted with collection of patient data, wrote the treatment section, and assisted in editing.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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