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Case Report

Disseminated *Salmonella Typhi* Infection Presenting with Slurred Speech and Encephalopathy: An Unusual Presentation

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Abstract: *Salmonella enterica serovar Typhi* causes systemic infections and typhoid fever in humans, mainly affecting infants and children. It presents mostly with fever, malaise, anorexia, abdominal pain, constipation, and/or diarrhoea. Complications of the disease include intestinal perforation and haemorrhage. However, sometimes extra-intestinal complications are also reported, which rarely include encephalopathy. This report presents a case of a 28-year-old male who presented with somnolence and later developed slurred speech. A week before his current admission, he was admitted with abdominal pain and underwent a laparoscopic appendectomy, and was discharged uneventfully. Now after eight days he presented with somnolence. His neurological examination was otherwise unremarkable. Imaging studies helped to rule out ischaemic stroke. A detailed system-wise examination revealed mild right upper quadrant tenderness and hepatosplenomegaly on abdominal examination. Imaging revealed hepatosplenomegaly with gallbladder wall oedema and mesenteric lymphadenopathy. Blood culture was reviewed, revealing extensively drug-resistant (XDR) *Salmonella Typhi*. A diagnosis of XDR *Salmonella* bacteraemia leading to encephalopathy was made. The patient responded well to antibiotic therapy guided by the culture and sensitivity.

Keywords: *Salmonella*, Complicated typhoid, XDR typhoid, Food hygiene, Speech disturbance, Ischaemic stroke.

OBJECTIVE

This case report aims to document and analyse an uncommon presentation of disseminated *Salmonella Typhi* infection, characterized by slurred speech and encephalopathy in a 28-year-old male. The objective is to provide a comprehensive understanding of this atypical manifestation, emphasizing the clinical course, diagnostic challenges, and successful management strategies. Through this report, we aim to contribute valuable insights to the medical community, especially in regions endemic to *Salmonella* infections, and underscore the importance of considering *Salmonella* as a potential aetiology in adults presenting with neurological abnormalities.

INTRODUCTION

Typhoid fever is caused by infection with *Salmonella enterica serovar Typhi*. An estimated 11-21 million cases of typhoid fever occur worldwide annually causing 200,000 deaths with the highest number of cases reported in South-central and Southeast Asia [1, 2]. The most common population affected is infants and children and the most common one presenting to the hospital is children and young adults [3, 4].

Salmonella shed from carriers' faeces and urine, contaminates food and water and is thus spread through the faeco-oral route [2]. The organism disseminates from the Peyer's patches via lymph and blood and then replicates within the reticulo-endothelial system (which is the hallmark of the disease) eventually causing systemic symptoms [5]. The incubation period is typically 6 to 30 days with the disease initially, being asymptomatic and then most commonly, presenting with fever and malaise (at the onset of bacteraemia), anorexia, dull headache, abdominal pain associated with nausea/vomiting, constipation and/or diarrhoea [1, 4]. On examination, abdominal tenderness can be seen from being diffuse to being localized in nature, in which case it can mimic appendicitis. Hepatomegaly and splenomegaly usually develop and are seen on examination as well. Some people may also exhibit an erythematous blanching macular rash (Rose spots) on the chest and abdomen [5].

Although, gastrointestinal haemorrhage (10%) and intestinal perforation (3%) are the most studied and reported complications of severe *salmonella* infection, numerous extra-intestinal manifestations, including encephalopathy, can occur, especially in severe disease typically after two to three weeks of illness [1, 4, 6]. However, its pathogenesis is not known. Encephalopathy in patients is identified if he/she presents with: (a) confusion, disorientation, slurred speech, or altered mental status (AMS) or (b) Glasgow Coma Scale (GCS) < 15 without an alternative diagnosis [3]. Encephalopathy is also associated with high mortality if accompanied by shock [4].

Other neuropsychiatric complications include agitation, delirium, and meningitis, which occur mainly in children who are less than two years old [4, 7]. In fact, the term typhoid was derived

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from the word "typhus" which meant "smoky" in Greek and was used to describe patients who exhibited apathy or delirium associated with infection [5]. Some cases of peripheral neuritis, radiculitis, myelitis, cerebritis, insomnia, and acute psychotic state have been reported as well however, all these complications are rare [3,8]. The incidence of neuropsychiatric presentations after *salmonella* infection varies among countries, in endemic areas (like Southeast Asia and Africa) more frequent neurologic manifestations have been reported, with Pakistan having an incidence of less than 2% [2, 4].

Early initiation of correct antibiotic therapy protects from severe complications of typhoid fever. Multidrug-resistant (MDR) and extremely drug-resistant (XDR) strains have developed in endemic areas [2]. MDR strains are resistant to chloramphenicol, amoxicillin, and cotrimoxazole whereas XDR strains are additionally resistant to third-generation cephalosporin and ciprofloxacin as well, and have been reported from Pakistan in early 2018 [9].

In laboratory findings, leucocytosis or leukopenia can be seen with a left shift depending on the patient's age and relative anaemia could be present. If a complete metabolic profile is obtained, elevated transaminases maybe observed. Culture is used for confirmation of diagnosis. Blood and/or stool cultures can be taken which are 40-80% and 30-40% sensitive respectively. Blood cultures are most sensitive in the first week of illness. Culture of bone marrow aspirate, although invasive is the most sensitive (more than 90%) and is relatively unaffected by previous or concurrent antibiotic use [4, 10].

We considered this case interesting and unique, due to the rarity of *salmonella* bacteraemia presenting as encephalopathy, having been the first case in our country to the best of our knowledge. This case report aims to highlight a rare form of complication of *Salmonella*.

CASE SUMMARY

A 25-year-old gentleman presented to the emergency department with tiredness and feeling sleepy all the time. He had a recent history of laparoscopic appendectomy eight days ago. There were no other prior comorbidities. He was not taking any medication. There was no wound site infection and prior laparoscopy scars were completely healed. His vital observations were all within normal limits. On examination, the chest was clear. There was no evidence of a heart murmur. The abdomen was soft but mildly tender in the upper right quadrant. Neurologically his GCS was E4 M6 V5 (15/15), he was oriented but was slow and somnolent. There was no sign of meningitis. He was admitted to the medicine ward and later in the night he developed slurring of speech and his GCS dropped to 13/15 E3 V4 M6. There was no motor or sensory abnormality. There was no cranial nerve palsy on examination. The patient was shifted to the special care unit for neurologic observations and further workup. On presentation, his haemoglobin was 10.8 g/dL, white blood cells were 6.5 $\times 10^9$/L, with 85% neutrophils and Platelet count was 94 $\times 10^9$/L. Peripheral blood film showed anisocytosis and microcytic RBCs with low platelets. There was a left shift in neutrophils with toxic granulations. It was suggested that there might be a bacterial infection. Urine dip was done it was positive for leukocyte esterase and nitrites and was sent for culture and sensitivity. Blood cultures were also sent. C- Reactive protein (CRP) was 230 mg/L. Lactate was 0.6 µmol/l. Ammonia was checked it was normal (36 µmol/L). Renal function and electrolytes were all normal. Alanine transaminase was 148 IU/L and Alkaline phosphatase was 751 IU/L along with direct hyperbilirubinemia (117 µmol/L). All lab investigation results are mentioned in Table **1**.

Table 1. Laboratory Investigations of the Patient.

Laboratory Investigation	Value	Unit
Hemoglobin	10.8	g/dL
White Blood Cell	6.5	10^9/L
Platelets	94	10^9/L
Lactate	0.9	µmol/L
C-Reactive Protein	230	mg/L
Alanine Transaminase	148	IU/L
Alkaline Phosphatase	751	IU/L
Direct Bilirubin	117	µmol/L
Lactate Dehydrogenase	280	IU/L
Ammonia	36	µmol/L
Electrolytes	Normal	-
Hepatitis A, B, C, D & E , EBV, CMV, HIV Serology	Negative	-
Autoimmune Screen	Negative	-

As the patient has a recent history of surgery and blood tests were pointing toward bacterial infection, so CT Abdomen Pelvis was done to rule out any GI injury. There was no evidence of bowel injury but mild ascites with oedematous gall bladder wall. There was also hepatosplenomegaly (Fig. **1A**, **1B**) with mesenteric lymphadenopathy (Fig. **2A**, **2B**). Later in the night when the patient developed slurring of speech, an urgent MRI brain was done to rule out stroke. MRI brain did not show any evidence of acute infarct (Figs. **3A**, **3B**, **4A**, **4B**). DWI sequence and time of flight sequence were all normal on MRI brain imaging. To work up for hepatosplenomegaly, Lactate dehydrogenase was done which was 280 IU/L and viral serology for hepatitis were all negative (which included Hepatitis A, B, C, and E). Epstein - Barr virus (EBV), Cytomegalovirus (CMV) and Human Immunodeficiency Virus (HIV) serology were also tested and were negative. An autoimmune screen was also sent and it turned out to be negative. Empiric antibiotics therapy was started with Piperacillin and Tazobactem.

Based on the presentation of encephalopathy and increased infection markers. Initially, differential diagnoses included.

1. Bowel injury from a prior appendectomy.
2. Cholecystitis.
3. Ischemic stroke.
4. Sepsis of unknown origin.
5. Lymphoproliferative disorder.

Bowel injury was ruled out by CT abdomen, although it showed hepatosplenomegaly. The patient's full blood count showed anaemia and thrombocytopenia, so lymph proliferative disorder was a possibility. Due to somnolence, ammonia was checked. It was normal and viral hepatitis screen was also negative. MRI Brain was done and it was normal, therefore, stroke was ruled out. Lumber Puncture was not performed as there were no meningeal signs and there was not any meningeal enhancement on the MRI scan. Blood culture after 24 hours showed positive growth and was identified as *Salmonella Typhi* that was extensively drug-resistant (XDR), resistant to cephalosporin (Ceftriaxone, Cefixime), quinolones (Ciprofloxacin), and penicillin (Ampicillin). It was sensitive to Azithromycin (MIC 4 mcg/ml), Imipenem (MIC <0.25 mcg/ml) and Meropenem (MIC <0.25 mcg/ml). Therefore, the diagnosis of XDR Typhoid fever was established and antibiotics switched to Meropenem. Intravenous Meropenem 1g three times a day and oral azithromycin 1g once a day was started. The patient improved clinically and started to feel better after 48 hours of antibiotics therapy. Somnolence completely improved and slurring of speech improved within 36

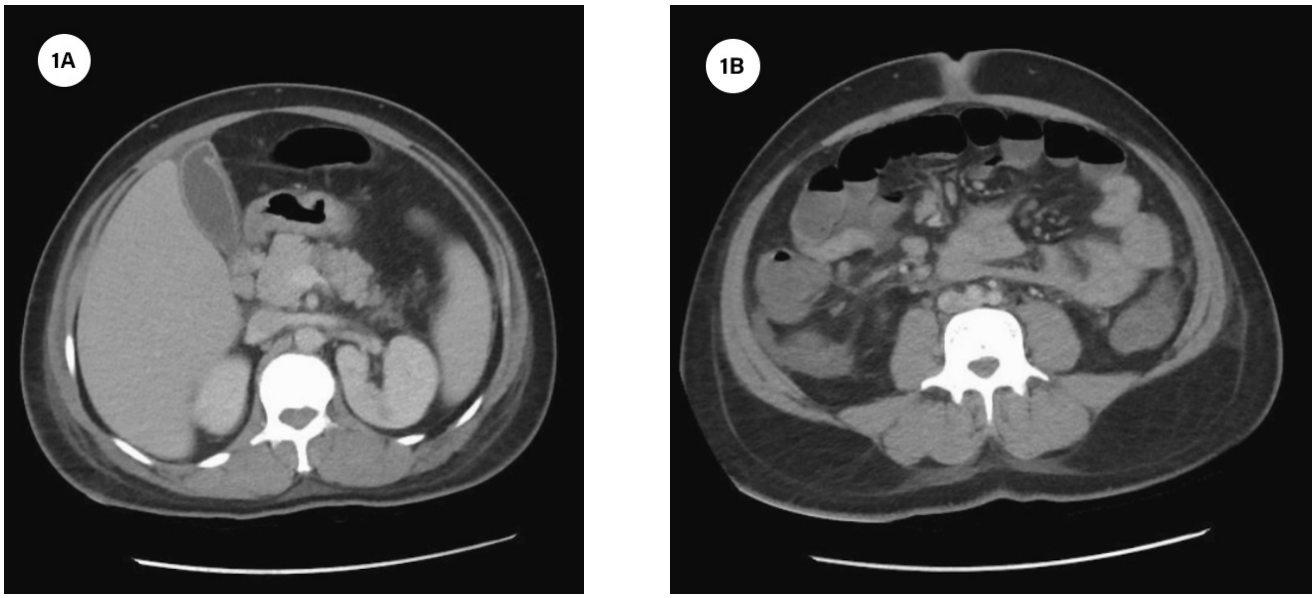

Fig. (1A & **1B**). CT Abdomen Axial (Left) and Coronal (Right) View, Liver Appears Enlarged and Spleen Appears Bulky.

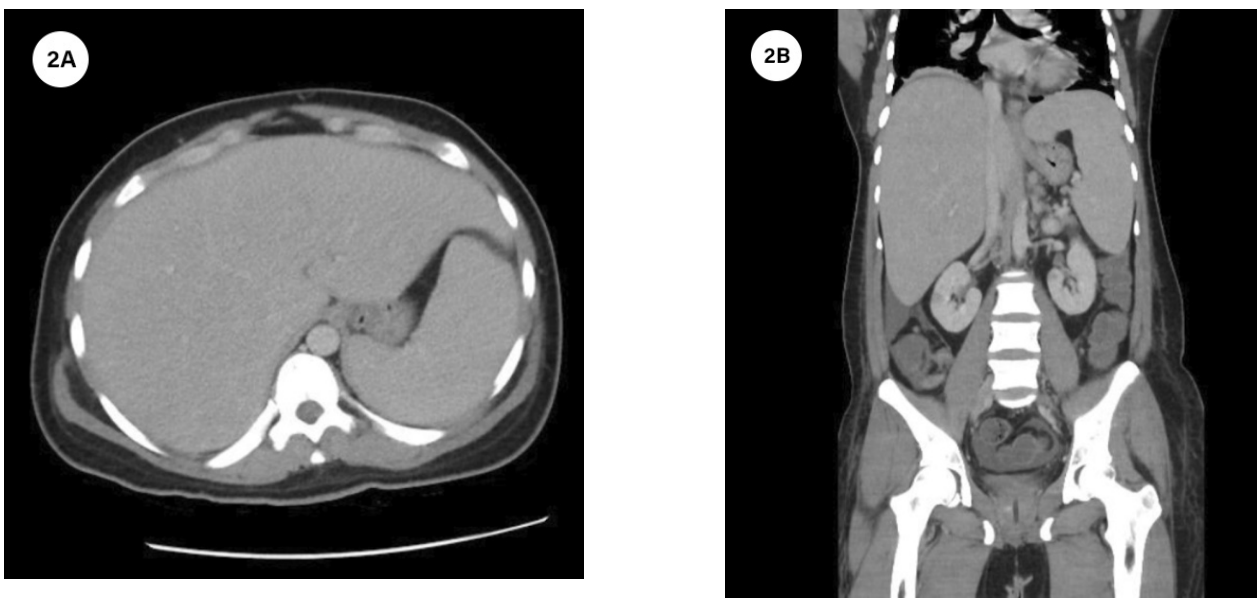

Fig. (2A & **2B**). Enlarged Peripancreatic (Left) and Precaval (Right) Lymph Nodes.

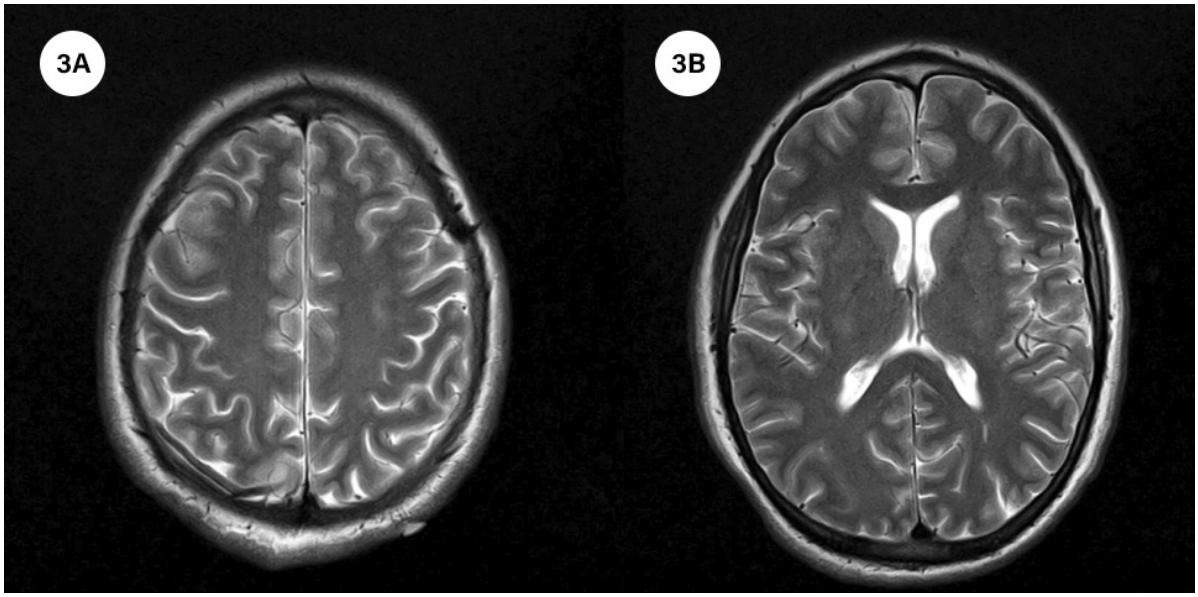

Fig. (3A & **3B**). T2 Weighted MRI Axial Sections Reveal No Significant Abnormality.

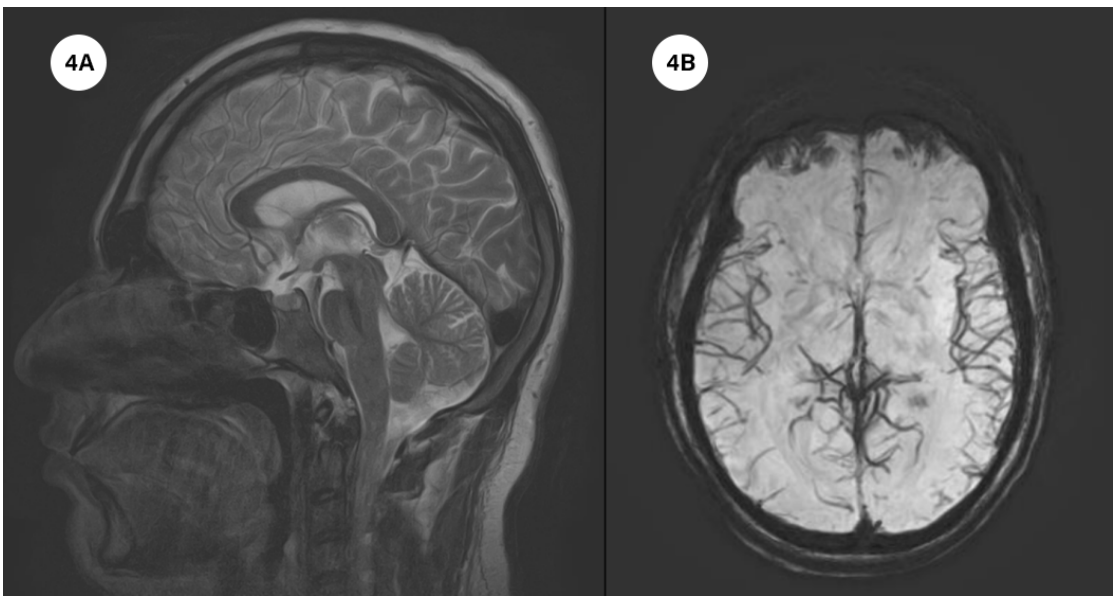

Fig. (4A & **4B**). T2 Weighted MRI Sagittal Section and Axial SWI Image Reveal No Significant Abnormality.

hours. The fever settled after four days of intravenous (IV) therapy. A repeat culture was sent after five days of therapy prior to discharge that showed clearance of bacteraemia. Its institutional protocol in the hospital is to treat all XDR typhoid with dual antibiotics therapy to prevent further resistance strains selection. Azithromycin was given for a total of five days and later he was discharged with a plan to complete 14 days of Meropenem IV in total. He was instructed by the nursing team and he self-administered remaining antibiotics' doses at home.

He was followed up in an outpatient infectious diseases clinic at end of antibiotics treatment. He was feeling completely normal. There were no B symptoms or any weight loss to warrant any underlying lymphoproliferative disorder. A follow-up CT scan was done after 3 months, it showed resolution of all lymphadenopathy, resolution of gall bladder oedema and improvement in hepato-splenomegaly

DISCUSSION

The case described corresponds to a young male, who presented with clinical findings suggestive of stroke. However, diagnostic workup showed an unusual finding of hepatosplenomegaly with mesenteric lymphadenopathy and then a review of labs revealed *Salmonella Typhi*.

Salmonella enterica serovar Typhi (*S.Typhi*) and *Paratyphi* (*S. Paratyphi*) cause typhoid fever and paratyphoid fever, respec-

tively (both also called enteric fever). It is one of the major causes of mortality and morbidity in developing countries with Asia having the highest burden of disease [2]. Typhoid fever includes gastroenteritis, where a patient commonly experiences fever along with nausea/vomiting, abdominal pain, constipation and/or diarrhoea although it is possible that these specific signs and symptoms are absent. Therefore, in endemic areas, typhoid is one of the top differentials when someone presents with one week old acute undifferentiated fever [1, 4]. It also includes bacteraemia, which is most commonly seen in children <5 years old [3] and it gives rise to the abdominal, cardiovascular, haematological, respiratory, and/or neuropsychiatric complications of typhoid fever [1, 4].

The neuropsychiatric complication of *Salmonella* infection has variable manifestations including encephalopathy, meningitis, delirium, psychotic state, impairment of coordination (e.g. ataxia), parkinsonism, dysarthria, etc [10, 11]. Typhoid encephalopathy, also called *Salmonella* -associated encephalopathy (SAE) or enteric encephalopathy, is a rare and potentially fatal complication of *Salmonella* infection [2]. It is mostly seen in children and young adults. A study compared the incidence of encephalopathy among patients from different age groups hospitalized due to *Salmonella* bacteraemia. It showed a higher incidence in older children and young adults as compared to other age groups [2]. In fact, age 10 to 24 years has been implicated as one of the risk factors of typhoid encephalopathy [10]. Our case is different as the patient's age does not lie in this age bracket.

Other than age, there are a number of risk factors associated with typhoid encephalopathy. These include severe dehydration, low oxygen saturation level, increased respiratory rate (tachypnoea), leukopenia and thrombocytopenia [1, 3]. However, in our case we did not see these risk factors. The only risk factor that was seen in our case was thrombocytopenia.

Encephalopathy with *Salmonella* infection is rare as it occurs mostly in the third week of infection, although in a study the range of appearance of neurological signs from the day of *Salmonella* infection was 1-35 days [12], in this era it is less likely that patients don't receive appropriate treatment by this time.

As described above, encephalopathy presents with confusion, disorientation, slurred speech, or GCS < 15 [3]. In some places insomnia or somnolence have also been one of the presenting features. Our case presented with somnolence and later developed slurring of speech however, rest of the neurological examination was unremarkable. In terms of imaging findings, there is limited literature regarding SAE MRI findings. Some non-specific findings such as oedema, ischemia, vasculitis, demyelination and infiltration of cells can be seen. One case was reported to have diffuse hyper intense signals in some parts of the brain including deep white matter, corpus callosum etc. on FLAIR sequence [13]. However, it is possible to have a normal MRI brain with SAE which was also seen in our case [12].

Infection with MDR *S. Typhi*, though associated with higher morbidity and mortality (according to a study conducted in Pakistan), has no association with higher risk of typhoid encephalopathy [12]. However, there is no study regarding association of XDR *S.Typhi* presenting with encephalopathy. Our patient had an infection with XDR *S.Typhi* and to our best knowledge, this is the first case of XDR *S.Typhi* associated encephalopathy being reported.

Regarding treatment of *Salmonella* associated encephalopathy, some places say that the neurological manifestations resolve over time [12] while some experts suggest the use of dexamethasone [12]. In fact, use of high dose versus low dose dexamethasone has been compared and immediate treatment with high dose dexamethasone has been suggested in cases of typhoid encephalopathy [12]. However there is no guideline as of yet regarding the use of dexamethasone in treatment. In our case, the patient responded well to the treatment without need for dexamethasone. There was resolution of somnolence and speech became normal after initiation of appropriate antibiotic treatment, with no sequelae.

Despite being a typhoid endemic area, no case of typhoid encephalopathy has been reported from Pakistan yet. With most cases of severe typhoid infection with neuropsychiatric manifestations being reported in children, our case is unique as it suggests to consider the possibility of *Salmonella* even in an adult presenting with abnormal neurological signs and symptoms.

CONCLUSION

This case underscores the significance of recognizing unusual and atypical symptoms in the diagnosis of infectious diseases, particularly in endemic regions. The patient's presentation of disseminated *Salmonella Typhi* infection with slurred speech and encephalopathy, although rare, highlights the diverse clinical spectrum of this pathogen. While typhoid fever traditionally manifests with gastrointestinal symptoms, this case emphasizes the need for clinicians to remain vigilant for less common presentations, especially in adult populations.

The diverse neurological manifestations observed in this case challenge conventional diagnostic expectations, emphasizing the importance of a thorough clinical evaluation. Such cases prompt healthcare professionals to broaden their differential diagnoses and consider infectious aetiologies even in the absence of classical symptoms. This is particularly relevant in regions with a high burden of infectious diseases, where unusual presentations may be encountered more frequently.

Furthermore, this report accentuates the emergence of extensively drug-resistant (XDR) *Salmonella Typhi* strains and the associated complications. Vigilance in identifying and promptly treating such cases is essential to prevent severe outcomes and the development of further drug resistance.

In conclusion, this case report serves as a reminder that infectious diseases can present with a wide array of symptoms, necessitating a nuanced and comprehensive diagnostic approach. Clinicians should remain attuned to the evolving nature of infectious

pathogens and be prepared to adapt their diagnostic strategies to encompass diverse clinical presentations, contributing to more timely and accurate diagnoses.

CONFLICT OF INTEREST

Declared none.

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Declared none.

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