CRCP Case Reports in Clinical Practice

Case Report

Journal Homepage: http://crcp.tums.ac.ir

Cranial Nerve Palsy and Diplopia in Typhoid Fever: Case Report

Reza Taslimi[1], Taha Bayat[2], Behshad Pazooki[3], Seyed Ali Nabipoorashrafi[4*]

1. Department of Internal Medicine, Division of Gastroenterology, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

2. Iranian Medical Students' Association (IMSA-Iran), Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences, Tehran, Iran.

3. Department of Internal Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

4. Department of Internal Medicine, Iran University of Medical Sciences, Tehran, Iran.

Use your device to scan and read the article online

Citation Taslimi R, Bayat T, Pazooki B, Nabipoorashrafi SA. Cranial Nerve Palsy and Diplopia in Typhoid Fever: Case Report. Case Reports in Clinical Practice. 2022; 7(4): 211-215.

Running Title Diplopia in Typhoid Fever

Article info:
Received: June 13, 2022
Revised: June 21, 2022
Accepted: July 29, 2022

Keywords:
Salmonella typhi;
Diplopia;
Abducens nerve;
Typhoid fever

ABSTRACT

Salmonella typhi is the cause of an acute febrile illness with high morbidity and mortality, especially in countries with poor sanitation. Neurological complications of salmonella are severe and usually under-diagnosed. This article reports an extremely rare case of a woman with typhoid fever with a history of travel and consumption of raw fish. She had no sign of meningitis but developed diplopia and sixth nerve palsy, which was ultimately resolved by antibiotic therapy.

Introduction

Salmonella typhi is a facultative anaerobic Gram-negative bacillus and a member of the Enterobacteriaceae family, which mostly causes gastroenteritis but is also associated with other conditions such as septicemia and enteric fever [1]. Salmonella typhi is most common in countries with poor economic status and inadequate sanitation. The long incubation period, various and non-specific manifestations, and reliance on culture to confirm the diagnosis make Typhoid fever difficult to diagnose and its life-threatening complications more challenging to prevent [2, 3]. Transmission of typhoidal salmonella mostly occurs through the consumption of food or water contaminated with feces or prepared by a chronic Salmonella typhi carrier [4].

*** Corresponding Author:**
Seyed Ali Nabipoorashrafi
Address: *Department of Internal Medicine, Iran University of Medical Sciences, Tehran, Iran.*
E-mail: *nabipour.sa@iums.ac.ir*

Case report

History

A 17-year-old woman presented with fever, jaundice, non-bloody diarrhea, myalgia, headache, and severe back pain in the thoracic region for one week before admission to our hospital. She was otherwise healthy until this problem. She had a history of travel to Iraq in the past month and reported frequent consumption of raw fish in her diet. On her initial examination, her temperature was 39.8ºC, blood pressure was 150/80 mm Hg, heart rate was 80/min but increased to 140/min (sinus tachycardia) in several days, respiratory rate was 16/min and her body mass index was 36 kg/m^2. In physical examination, there was RUQ tenderness in the abdomen with pain radiating to her right shoulder, there was also moderate lower limb edema, and her sclera appeared to be icteric. There was no lymphadenopathy or rash. There was tenderness in the thoracic and lumbar spine but no sign of sensory level or sphincter abnormalities. Diplopia and esotropia developed on the 3rd day of admission. In neurological examinations, left VI nerve palsy was noticed (Figure 1). Eyes' movement showed that the patient's left eye turned in toward the nose and was unable to abduct properly to the extreme left. Visual fields and acuity, pupils, and sensory function of the face were normal.

Functions of other cranial nerves appeared to be normal. There was no neck stiffness. No significant defect was seen in the mental status examination. The force of four limbs was normal. The cerebellar examination was normal. Fundoscopy was normal. Deep tendon reflexes were normal, except for the right leg which was decreased and it was probably due to the pain in that leg. The patient did not exhibit any muscular hypotonia in the limbs.

Lab data

Patient's initial laboratory report revealed low hemoglobin levels, microcytic RBCs, and high WBC count, predominantly neutrophils. Immunologic tests results were negative for hepatitis B surface antigen, hepatitis C antibody, HIV antigen, and antibody against Epstein–Barr virus and Cytomegalovirus. Antinuclear Antibodies were also negative; therefore, collagen and vascular diseases were ruled out. Her wright and *Coombs test were reported negative*. Other electrolytes and kidney function tests were normal. Urine culture was negative, and urine analysis was normal except for high levels of bilirubin. Although urine analysis showed no traces of protein, a 24-hour urine collection test indicated mild proteinuria (less than 500 mg/day). Detailed laboratory results are described in Table 1.

Abdominal and pelvic ultrasonography revealed the normal size of the liver with signs of grade I fatty liver disease. Common bile duct and portal vein were normal in diameter. The Spleen span was 166 mm, which suggested splenomegaly. The gallbladder, kidneys, and bladder also appeared normal. The chest CT scan showed mild pleural effusion in the right lung. In the thoracic MRI, subcutaneous edema in the lower thoracic region was seen, but there was no signal change in bone or cord (Figure 2). Since the patient was febrile

Table 1. Significant Laboratory results

	On admission	10 day after admission	15 days after admission (at discharge)
Na (meq/L)	137	133	137
K (meq/L)	3.8	4.6	4.6
Ca (mg/dl)	7.6	-	8.9
P (mg/dl)	3.2	-	4.8
Cr(mg/dl)	0.5	0.4	0.7
Urea (mg/dl)	13	11	12
AST (U/L)	137	172	82
ALT (U/L)	106	115	77
ALP (U/L)	269	315	789
Bilirubin Total (mg/dl)	14.5	10.4	5.3
Bilirubin Direct (mg/dl)	10.2	7.4	3.5
WBC (/mm^3)	13000	9660	7200
RBC (million/ mm^3)	4.4	3.85	3.75
Hemoglobin (g/dl)	9	8.7	8
MCV (fl)	62	62.1	66
MCH (pg)	20	22.6	21.3
RDW-CV (fl)	14.7	23.9	25.5
Platelet (*1000/ mm^3)	195	437	644
PT (sec)	16.3	13.2	12.8
INR	1.61	1.12	1.06

Fig. 1. On neurologic examination, patient was unable to abduct the left eye, indicating VI nerve paralysis.

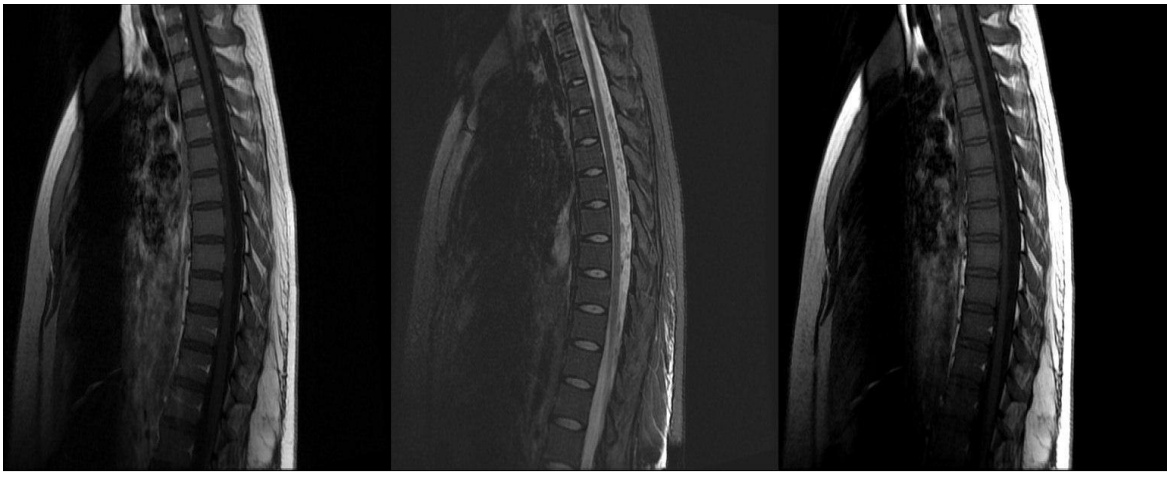

Fig. 2. Thoracic MRI with lower subcutaneous edema.

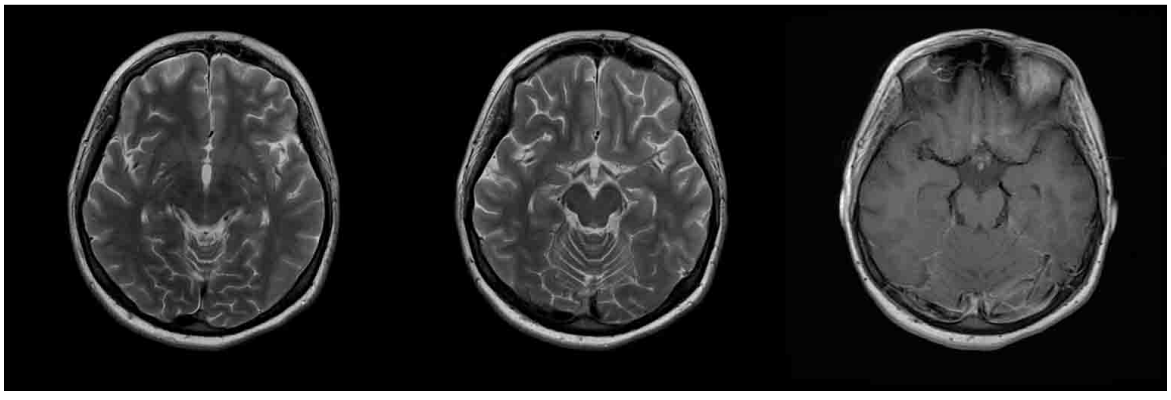

Fig. 3. Brain MRI with Patchy Dural enhancement

and tachycardic, echocardiography was performed to rule out myocarditis and endocarditis and revealed no evidence in favor of endocarditis or myocarditis.

Lumbar Puncture was not performed due to the lack of symptoms associated with meningitis in physical examinations and prolonged INR. Brain MRI revealed abnormal T2/FLAIR signal intensity with mild DWI restriction in both corticospinal tracts. Patchy Dural enhancement especially in the tentorium cerebelli was noted. Mild mucosal thickening was seen in both maxillary and sphenoid sinuses (Figure 3).

Diagnosis and treatment

Blood samples for culture were obtained on the 6th, 10th, and 12th days of admission; the first sample was negative; however, *Salmonella enterica* serovar Typhi was isolated from the second and third ones. Antimicrobial susceptibility test using disk diffusion method indicated sensitivity to ciprofloxacin, ceftriaxone, imipenem, gentamycin, ampicillin/sulbactam, and amikacin. After the results of laboratory tests revealed *Salmonella typhi,* the patient was started on intravenous ceftriaxone on the 10th day of her admission. After two days, as the fever persisted and the patient did not seem to be improving, intravenous ciprofloxacin was also added to the treatment plan. The patient received one unit of packed red blood cells due to her anemia. After five days of treatment, the fever and sixth nerve palsy resolved, and the patient was discharged.

Discussion

Typhoidal Salmonella strains are the main cause of typhoid fever [4]. Classic Typhoid triad is fever, abdominal pain and chills. There is a gradual rise in fever with chills during the first week. At this point, patients usually develop bradycardia, but it is not a consistent symptom. During the second week, symptoms include abdominal pain accompanied by skin rashes called rose spots. Abdominal pain will increase during the third week, as well as aggravated bacteremia and digestive complications such as gastrointestinal bleeding, terminal ileum perforation, and peritonitis [5-9]. This classic presentation of disease exists in a minority of patients; for instance, in a study in Indonesia, among 300 patients, only 15% presented with classic typhoid manifestations [10]. Typhoidal hepatitis causes an increase in hepatic enzymes and jaundice, but in comparison with acute viral hepatitis, patients with Typhoidal hepatitis show higher fever, lower levels of AST and ALT, and relative bradycardia [11]. Some studies report the cases of fulminant hepatitis arising from typhoid fever [12].

Clinical symptoms are variant and non-specific, making it difficult to receive an accurate diagnosis [2, 4]. The gold standard method for the diagnosis of S. Typhi is performing a culture test that requires automation or trained lab technicians [14]. Serologic tests such as ELISA and Widal test are greatly dependent on the stage of the disease and have low sensitivity and specificity during the acute phase of typhoid fever [14].

Gastrointestinal complications such as bleeding and intestinal perforation are reported to happen in 10% and 1-3% of patients, respectively. Moreover, extraintestinal complications have been reported in patients with typhoid fever; for example, Cardiovascular and pulmonary complications such as endocarditis, myocarditis, pneumonia, and empyema have also been documented [4, 15].

Besides, neurological manifestations are extraintestinal complications of typhoid fever that develop in 3–50% of patients, such as headache, encephalitic disorders, acute psychosis, cerebral edema, myelitis, cerebral abscess, cerebellar ataxia, and meningitis. Findings in favor of upper motor neuron diseases such as hyperreflexia and spasticity and clonus may be seen. The most common neurologic symptom in typhoid fever is headache, present in 44-94% of patients. The exact underlying mechanism of these complications is unknown to this day, while some speculate metabolic disturbance, hyperpyrexia, cerebral hemorrhage, or edema to be the cause [16, 17].

Isolated nerve palsies in typhoid fever are extremely rare and only a few reports of this neurological complication have been published in the medical literature to date. Gkrania-Klotsas et al. reported a 25-year-old woman with typhoid fever and a cyanosed left hand, who had recently come back from a trip to Nepal and developed sixth nerve palsy and esotropia of the left eye on the 1st day of admission, which resolved after 12 hours [18]. The case of a 7-year-old boy with typhoid fever was reported by Bhatt et al. Left-sided facial nerve palsy and bilateral sixth nerve palsy started on the eighth day of therapy and resolved after three days and two months, respectively [19]. Joshi et al. reported three cases of typhoid fever with isolated cranial nerve palsies [20].

In this case, the patient had a history of travel, but consumption of raw fish seemed to be the likely route of transmission. The patient failed to mention this dietary preference in her history and did not reveal the fact until the last days of hospitalization, which considerably delayed the diagnosis. Although the patient's fever and leukocytosis pointed to an

infection, the negative result of the first blood culture obtained on the 6th day of admission caused more confusion. Concurrent fever and jaundice also made the possibility of typical viral hepatitis unlikely; in addition, tests for hepatitis B and C were negative. Normal kidney function tests, negative urine analysis, culture tests, and normal ultrasound seem to indicate that the infection did not spread to the urinary system. Antimicrobial sensitivity testing indicated sensitivity to ceftriaxone; however, *deterioration of patient* condition suggested resistance as well as considering the patient well responded to ciprofloxacin.

Cases of isolated nerve palsies are extraordinary in their variety and rarity. Further studies on other more frequent neurological manifestations could cast light on the pathologic mechanisms of salmonella typhi and seek to explain the hidden process of isolated nerve palsies.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or nonprofit sectors.

Conflict of Interests

The authors have no conflict of interest to declare.

References

1. Smith SI, Seriki A, Ajayi A. Typhoidal and non-typhoidal Salmonella infections in Africa. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2016;35(12):1913-22. https://doi.org/10.1007/s10096-016-2760-3

2. Dougan G, Baker S. Salmonella enterica serovar Typhi and the pathogenesis of typhoid fever. Annual review of microbiology. 2014;68:317-36. https://doi.org/10.1146/annurev-micro-091313-103739

3. Darton TC, Blohmke CJ, Pollard AJ. Typhoid epidemiology, diagnostics and the human challenge model. Current opinion in gastroenterology. 2014;30(1):7-17. https://doi.org/10.1097/MOG.0000000000000021

4. Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive Salmonella Infections. Clinical Microbiology Reviews. 2015;28(4):901-37. https://doi.org/10.1128/CMR.00002-15

5. Connor BA, Schwartz E. Typhoid and paratyphoid fever in travellers. The Lancet Infectious diseases. 2005;5(10):623-8. https://doi.org/10.1016/S1473-3099(05)70239-5

6. Ostergaard L, Huniche B, Andersen PL. Relative bradycardia in infectious diseases. The Journal of infection. 1996;33(3):185-91. https://doi.org/10.1016/S0163-4453(96)92225-2

7. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid Fever. New England Journal of Medicine. 2002;347(22):1770-82. https://doi.org/10.1056/NEJMra020201

8. Scaggs Huang FA, Schlaudecker E. Fever in the Returning Traveler. Infectious Disease Clinics of North America. 2018;32(1):163-88. https://doi.org/10.1016/j.idc.2017.10.009

9. Stuart BM, Pullen RL. Typhoid; clinical analysis of 360 cases. Archives of internal medicine (Chicago, Ill : 1908). 1946;78(6):629-61.https://doi.org/10.1001/archinte.1946.00220060002001

10. Hoffman SL, Punjabi NH, Kumala S, Moechtar MA, Pulungsih SP, Rivai AR, et al. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. The New England journal of medicine. 1984;310(2):82-8. https://doi.org/10.1056/NEJM198401123100203

11. El-Newihi HM, Alamy ME, Reynolds TB. Salmonella hepatitis: analysis of 27 cases and comparison with acute viral hepatitis. Hepatology (Baltimore, Md). 1996;24(3):516-9. https://doi.org/10.1002/hep.510240308

12. Khan FY, Kamha AA, Alomary IY. Fulminant hepatic failure caused by Salmonella paratyphi A infection. World J Gastroenterol. 2006;12(32):5253-5.

13. Andrews JR, Ryan ET. Diagnostics for invasive Salmonella infections: current challenges and future directions. Vaccine. 2015;33(0 3):C8-C15. https://doi.org/10.1016/j.vaccine.2015.02.030

14. MacFadden DR, Bogoch, II, Andrews JR. Advances in diagnosis, treatment, and prevention of invasive Salmonella infections. Current opinion in infectious diseases. 2016;29(5):453-8. https://doi.org/10.1097/QCO.0000000000000302

15. Huang DB, DuPont HL. Problem pathogens: extra-intestinal complications of Salmonella enterica serotype Typhi infection. The Lancet Infectious diseases. 2005;5(6):341-8. https://doi.org/10.1016/S1473-3099(05)70138-9

16. Lakhotia M, Gehlot RS, Jain P, Sharma S, Bhargava A. Neurological manifestations of enteric fever2003. 196-9 p.

17. Lutterloh E, Likaka A, Sejvar J, Manda R, Naiene J, Monroe SS, et al. Multidrug-resistant typhoid fever with neurologic findings on the Malawi-Mozambique border. Clinical infectious diseases : an official publication of the Infectious Diseases Society of

18. Gkrania-Klotsas E, Cooke FJ, Zochios V, Lofitou N. Fever, a blue hand, and abducens nerve paralysis in a returning traveler. Journal of travel medicine. 2009;16(1):57-9. https://doi.org/10.1111/j.1708-8305.2008.00262.x

19. Bhatt GC, Dewan V, Dewan T, Yadav TP. Pseudotumour cerebri with multiple cranial nerve palsies in enteric fever. Indian journal of pediatrics. 2014;81(2):196-7. https://doi.org/10.1007/s12098-013-0965-3

20. Joshi N, Bhattacharya M, Yadav S, Rustogi D. Cranial nerve palsies in typhoid fever: report of three cases. Annals of tropical paediatrics. 2011;31(3):255-8. https://doi.org/10.1179/1465328111Y.0000000023