AUCTORES
Globalize your Research

Journal of General medicine and Clinical Practice
Richmond R Gomes*

Open Access

Case report

Enteric Encephalopathy: An Old Archenemy

Richmond R Gomes

Associate Professor, Medicine, Ad-din Women's Medical College Hospital, Dhaka, Bangladesh.

Corresponding Author: Richmond Ronald Gomes, Associate Professor, Medicine Ad-din Women's Medical College Hospital, Dhaka Bangladesh.

Received date: October 27, 2021; **Accepted date:** December 27, 2021; **Published date:** January 04, 2022

Citation: Richmond Ronald Gomes (2022). Enteric Encephalopathy: An Old Archenemy. *J. General medicine and Clinical Practice.* 5(1); DOI:10.31579/2639-4162/055

Abstract

Typhoid fever is the name given to the illness caused by the bacterium *Salmonella* Typhi, a member of the *Salmonella* family. Typhoid fever is spread through food and water contaminated by animal and human feces. Typhoid fever is very rare in the United States and other developed nations, and it is more common in underdeveloped nations, particularly Latin America, Asia, and Africa. Typhoid fever has a wide variety of presentations that range from an overwhelming multisystemic illness to relatively minor cases of diarrhea with low-grade fever. The classic presentation is fever, malaise, diffuse abdominal pain, and constipation. Untreated typhoid fever may progress to delirium, obtundation, intestinal hemorrhage, bowel perforation, and death within 1 month of onset. Survivors may be left with long-term or permanent neuropsychiatric complications. Here, we present a 30 years old nurse who presented with fever, constipation and diagnosed as typhoid fever. While on treatment, she developed abnormal behavior. CSF was sterile. Neuro imaging was normal. Considering typhoid encephalopathy she was treated with high dose pulse steroid. She showed significant improvement. Thus, all clinicians should keep in mind the possibility of typhoid encephalopathy as a rare complication of typhoid fever.

Key Words: typhoid; salmonella; encephalopathy; pulse steroid

Introduction:

Typhoid fever, also known as enteric fever, is a potentially fatal multisystemic illness caused primarily by Salmonella enteric serotype typhi and, to a lesser extent, *S enterica* serotypes *paratyphi* A, B, and C. The terms typhoid and enteric fever are commonly used to describe both major serotypes. *S typhi* has been a major human pathogen for thousands of years, thriving in conditions of poor sanitation, crowding, and social chaos. It may have been responsible for the Great Plague of Athens at the end of the Pelopennesian War. [1] The name *S typhi* is derived from the ancient Greek *typhos*, an ethereal smoke or cloud that was believed to cause disease and madness. In the advanced stages of typhoid fever, the patient's level of consciousness is truly clouded. Although antibiotics have markedly reduced the frequency of typhoid fever in the developed world, it remains endemic in developing countries. [2] Typhoid fever can feasibly be eradicated completely if advances in its diagnosis, prevention and treatment are financially supported by governments and philanthropists and if the healthcare infrastructure in regions with endemic Typhoid fever are improved [3].

Case report:

A 30 years old nurse, not known to have diabetes, hypertension, bronchial asthma presented with the complaints of high presented to us with the history of initial low grade then high grade, continued fever (maximum recorded temperature 104°F) associated with chills but not with rigor, headache, bodyache and dry cough for 4 days, vomiting for several times and severe prostration for 1 day. She denied any altered consciousness, convulsion, chest pain, palpitation, shortness of breath, abdominal pain or distension, burning micturition, joint pain or skin rash or bleeding from any site. She had no recent history of travel to malarial endemic zone. She also denied any previous history of tuberculosis or contact with any patient with active tuberculosis. On examination, she was toxic, conscious, oriented, febrile (temperature 102°F), with pulse 92 beats/min, with normal rhythm and volume, Blood pressure was 110/70 mm of Hg. There was diffuse blanching erythema. There was no signs of meningeal irritation. Fundoscopy was normal. Other systematic examination including general examination, cardiovascular system, respiratory system, alimentary system and nervous system examination revealed no abnormalities. Initial laboratory investigations is plotted in table 1.

Investigations	Results	Reference ranges
Complete Blood Count		
Hemoglobin (gm%)	12.1	12-16
Total white cell count(/cmm) with DC	4200, N: 65%, L: 32%	4-11, N:45-75, L: 20-45
Total platelet count(/cmm)	162	150-450
ESR(mm in 1st hour)	48	0-20
CRP(C reactive protein)(mg/L)	66	<5
SGPT(U/L)	72	<30
Chest X ray P/A view	normal	
Ultrasonography of whole abdomen	acalculus cholecystitis	
Urine routine examination		
Protein	trace	
Pus cell	0-2/HPF	0-5/HPF
RBC	0-1/HPF	0-5/HPF
Casts	Nil	Nil
Random blood sugar(mmol/L)	5.2	<7.8
Febrile antigen	Insignificant titer	
ICT for malaria	negative	
Blood film for malarial parasite	Not found	
Serum Electrolyte		
Sodium(mEq/L)	138	135-145
Potassium(mEq/L)	4.1	3.5-5.5

Abbreviations: DC: differential count, ADA: adenosine deaminase, ICT: immunochromatographic test

Table 1: *Initial laboratory investigations*

As she denied hospitalization, she was started tablet ceftibuten 400 mg once daily along with anti-pyretic and anti-emetic pending blood C/S report. Three days after starting antibiotics, her roommate complained of episodic irrelevant behavior with muttered speech. In the meantime, her blood C/S showed growth of salmonella typhi sensitive to ceftriaxone. She was urgently hospitalized. Injection ceftriaxone was started at the dose of 2 gram twice daily. Repeat serum electrolyte and random blood sugar result was non-significant. So CT brain and CSF analysis was done which were also noncontributory (table 2). Thus, the diagnosis of typhoid encephalopathy was considered and she was given pulse methylprednisolone 1 gram daily for 3 days along with ceftriaxone. With treatment she showed significant recovery with subsidence of fever and she became conscious oriented with normal speech. Ceftriaxone was continued for 10 days. During discharge she was hemodynamically and neurologically stable.

Investigations	Results	Reference ranges
CT scan of brain	normal	
CSF analysis		
Protein(mg/dl)	37	15-45
Glucose (mg/dl)	52	50-70
Cell count(/cmm)	03	0-5
ADA(U/L)	4.2	<10
Blood culture and sensitivity(FAN method)	Growth of salmonella typhi	
Random blood sugar(mmol/L)	5.6	<7.8
Serum Electrolyte		
Sodium(mEq/L)	140	135-145
Potassium(mEq/L)	4.6	3.5-5.5
CRP(C reactive protein)(mg/L)(on discharge)	14.2	<5
SGPT(U/L)(on discharge)	23	<30

Abbreviations: FAN (Fastidious Antibiotic Neutralizations)

Table 2: *Subsequent laboratory investigations after admission and on discharge*

Discussion:

The cause of typhoid fever is the bacterium Salmonella enterica subsp. enterica serovar Typhi growing in the intestines, peyers patches, mesenteric lymph nodes, spleen, liver, gallbladder, bone marrow and blood.[4,5] Typhoid is spread by eating or drinking food or water contaminated with the feces from an infected person.[6] Risk factors include limited access to clean drinking water, and poor sanitation.[7] Those who have not yet been exposed to the pathogen and ingest contaminated drinking water or food are most at risk for developing symptoms.[5] As far as we currently know, only humans can be infected; there are no known animal reservoirs. [6]

All pathogenic *Salmonella* species, when present in the gut are engulfed by phagocytic cells, which then pass them through the mucosa and present them to the macrophages in the lamina propria. Nontyphoidal salmonellae are phagocytized throughout the distal ileum and colon. With toll-like receptor (TLR)–5 and TLR-4/MD2/CD-14 complex, macrophages recognize pathogen-associated molecular patterns (PAMPs) such as

flagella and lipopolysaccharides. Macrophages and intestinal epithelial cells then attract T cells and neutrophils with interleukin 8 (IL-8), causing inflammation and suppressing the infection. [8,9]

In contrast to the nontyphoidal salmonellae, *S typhi* and paratyphi enter the host's system primarily through the distal ileum. *They* have specialized fimbriae that adhere to the epithelium over clusters of lymphoid tissue in the ileum (Peyer patches), the main relay point for macrophages traveling from the gut into the lymphatic system. The bacteria then induce their host macrophages to attract more macrophages. [8] *S typhi* has a Vi capsular antigen that masks PAMPs, avoiding neutrophil-based inflammation, while the most common *paratyphi* serovar, *paratyphi A*, does not. This may explain the greater infectivity of typhi compared with most of its cousins. [10]

Typhoidal salmonella co-opt the macrophages' cellular machinery for their own reproduction [11] as they are carried through the mesenteric lymph nodes to the thoracic duct and the lymphatics and then through to the reticuloendothelial tissues of the liver, spleen, bone marrow, and lymph nodes. Once there, they pause and continue to multiply until some critical density is reached. Afterward, the bacteria induce macrophage apoptosis, breaking out into the bloodstream to invade the rest of the body. [9]

The bacteria then infect the gallbladder via either bacteremia or direct extension of infected bile. The result is that the organism re-enters the gastrointestinal tract in the bile and reinfects Peyer patches. Bacteria that do not reinfect the host are typically shed in the stool and are then available to infect other hosts. [2,8]

Chronic carriers are responsible for much of the transmission of the organism. While asymptomatic, they may continue to shed bacteria in their stool for decades. The organisms sequester themselves either as a biofilm on gallstones or gallbladder epithelium or, perhaps, intracellularly, within the epithelium itself. [12] The bacteria excreted by a single carrier may have multiple genotypes, making it difficult to trace an outbreak to its origin. [13]

Typhoid fever occurs worldwide, primarily in developing nations whose sanitary conditions are poor. Typhoid fever is endemic in Asia, Africa, Latin America, the Caribbean, and Oceania, but 80% of cases come from Bangladesh, China, India, Indonesia, Laos, Nepal, Pakistan, or Vietnam.[14] Within those countries, typhoid fever is most common in underdeveloped areas. Typhoid fever infects roughly 21.6 million people (incidence of 3.6 per 1,000 population) and kills an estimated 200,000 people every year. [15]

The most common symptom is prolonged fever which occurs in about 75% of patients and can last up to four weeks if left untreated. Although abdominal pain and constipation/ diarrhoea are considered classical symptoms, they occur in only about 35% of the population.1 This patient had fever for ten days before admission to TH Jaffna and did not have any gastrointestinal symptoms. Other symptoms such as headache, chills, sweating, anorexia, arthralgia may also occur in patients with enteric fever. Around 10% can develop hepatosplenomegaly. Typical “rose spots” rash in typhoid occur in about one third of infected patients and are mostly seen in patients with a fair complexion [16].

Complications in typhoid occur in 10 to 15 percent of patients and are particularly likely in patients who have been ill for more than two weeks. Many complications have been documented, of which gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy are the most important. Other complications include meningitis, disseminated intravascular coagulation, haematophagocytic syndrome, hepatic and splenic abscesses and granulomas, pancreatitis, endocarditis, myocarditis, pericarditis, orchitis, hepatitis, glomerulonephritis, pyelonephritis and haemolytic-uremic syndrome, severe pneumonia, arthritis, osteomyelitis, and parotitis [9].

Typhoid encephalopathy, also known as “typhoid state” “muttering delirium” or “coma vigil” is observed in 2-40% of typhoid patients. Picking at the bedclothes and at imaginary objects (carphology and floccillation) are characteristic, as is muscular twitching (subsultus tendinum) [17]. Even though not previously reported in Sri Lanka, around 27% of patients diagnosed with typhoid in India are reported to have some neurological manifestation, either due to typhoid toxaemia causing delirium or as specific neurological manifestations such as encephalitis, polyneuropathy, nerve palsies or cerebellar ataxia [9].

Our patient’s behavior with abnormal gestures was more in favour of the typhoid state. The pathogenesis of typhoid encephalopathy remains unknown. In the past it was said typhoid delirium, stupor and coma carry a mortality of around 40% [18].

Typhoid fever should be suspected in any patient from the Asian sub continent with prolonged fever without an obvious focus of infection, especially in the monsoon season. Culture of the organism is the only recommended diagnostic test for typhoid. Blood culture is the widely used method but bone marrow, intestinal secretions, stool or rose spot punch biopsy can also be used to isolate the organism. Bone marrow culture has the highest sensitivity (90%) but is rarely performed [16]. Unlike the blood culture, it remains positive even after initiation of antibiotics. Other investigations (FBC, SAT) have low sensitivity and low positive predictive value as seen in this patient.

Empirical treatment for S. Typhi is with ceftriaxone 50-60 mg/kg/day for 10-14 days or azithromycin 8-10 mg/kg/day for 7 days. Ciprofloxacin is the optimal treatment for typhoid but quinolone resistance in Asia makes it a poor choice as empirical treatment. [16] Ampicillin, chloramphenicol and cotrimoxazole can also be used as treatment. There have been trials stating efficacy of high dose dexamethasone in the past with combination of chloramphenicol but no evidence with other drugs.16 It has been proposed that steroids decrease mortality in typhoid encephalopathy by reducing the production and release of prostaglandins and free oxygen species by macrophages induced by S. Typhi endotoxin. [19] However, evidence is still lacking to prove the definite benefit of steroids in typhoid delirium.

Oral live attenuated vaccine and a parenteral vaccine are available which needs booster dosing at five and two years respectively. People who travel to countries with high risk of infection are advised to get vaccinated. Proper sanitation and good personal hygiene play a main role in preventing the spread of this disease.

Conclusion:

Typhoid delirium is a known neurological complication of typhoid fever which has not been previously reported in Sri Lanka. This patient presented on day nine of fever with typical muttering delirium and picking at bedclothes and imaginary objects. The diagnosis could have easily been missed if not for the high degree of clinical suspicion. Early initiation of specific antibiotics ensured complete recovery without residual complications.

Conflict of Interest: None declared.

References:

1. Papagrigorakis MJ, Synodinos PN, Yapijakis C. Ancient typhoid epidemic reveals possible ancestral strain of Salmonella enterica serovar Typhi. *Infect Genet Evol*. 2007 Jan. 7(1):126-127.
2. Christie AB. *Infectious Diseases: Epidemiology and Clinical Practice*. 4th ed. Edinburgh, Scotland: Churchill Livingstone; 1987.
3. Pitzer VE, Meiring J, Martineau FP, Watson CH, Kang G, Basnyat B, Baker S (October 2019). "The Invisible Burden:

Diagnosing and Combatting Typhoid Fever in Asia and Africa". *Clinical Infectious Diseases*. **69** (Suppl 5): S395–S401. doi:10.1093/cid/ciz611

4. "Typhoid Fever". *cdc.gov*. May 14, 2013. Archived from the original on 6 June 2016. Retrieved 28 March 2015.
5. "Typhoid Fever". *cdc.gov. May 14, 2013.* Archived *from the original on 2 April 2015. Retrieved 28 March 2015*
6. "Typhoid vaccines: WHO position paper" *(PDF). Relevé Épidémiologique Hebdomadaire. **83** (6): 49–59. February 2008*
7. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL (March 2015). "Typhoid fever". *Lancet*. **385** (9973): 1136–1145. doi:10.1016/s0140-6736(13)62708-7
8. Raffatellu M, Chessa D, Wilson RP, Tükel C, Akçelik M, Bäumler AJ. Capsule-mediated immune evasion: a new hypothesis explaining aspects of typhoid fever pathogenesis. *Infect Immun*. 2006 Jan. 74(1):19-27.
9. Parry CM, Hien TT, Dougan G, et al. Typhoid fever. *N Engl J Med*. 2002 Nov 28. 347(22):1770-1782.
10. de Jong HK, Parry CM, van der Poll T, Wiersinga WJ. Host-pathogen interaction in invasive Salmonellosis. *PLoS Pathog*. 2012. 8(10):e1002933.
11. Ramsden AE, Mota LJ, Münter S, Shorte SL, Holden DW. The SPI-2 type III secretion system restricts motility of Salmonella-containing vacuoles. *Cell Microbiol*. 2007 Oct. 9(10):2517-2529.
12. Gonzalez-Escobedo G, Gunn JS. Gallbladder epithelium as a niche for chronic Salmonella carriage. *Infect Immun*. 2013 Aug. 81(8):2920-2930.
13. Chiou CS, Wei HL, Mu JJ, Liao YS, Liang SY, Liao CH, et al. Salmonella enterica serovar Typhi variants in long-term carriers. *J Clin Microbiol*. 2013 Feb. 51(2):669-672.
14. Chau TT, Campbell JI, Galindo CM, Van Minh Hoang N, Diep TS, Nga TT, et al. Antimicrobial drug resistance of Salmonella enterica serovar typhi in asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. *Antimicrob Agents Chemother*. 2007 Dec. 51(12):4315-4323.
15. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ*. 2004 May. 82(5):346-353.
16. Kasper L, Fauci A, Hauser S, et al. Harrison's Principles of Internal Medicine.19th ed. 2015 New York. McGraw-Hill Medical.p.1049-1053.
17. Verghese A. The "typhoid state" revisited. *Am J med*. 1985; 79(3):370-372.
18. Haque A. Neurological manifestations of enteric fever. In: Chopra JS, Sawhney IMS, editors. Neurology in tropics. 1st ed. BI Churchill Livingstone; New Delhi: 1999. pp. 506–512.
19. Leung DT, Bogetz J, Itoh M,et al. Factors associated with encephalopathy in patients with *Salmonella enterica* Serotype Typhi bacteremia presenting to a diarrheal hospital in Dhaka, Bangladesh. *Am J Trop Med Hyg.* 2012; 86(4):698–702. *doi : 10.4269/ajtmh.2012.11-0750*

DOI: 10.31579/2639-4162/055