



## RESEARCH ARTICLE

# Typhoid fever presenting as acute psychosis in a young adult: case report and literature review of typhoid psychosis

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### ABSTRACT

The rarity of acute psychosis in typhoid fever can result in delayed and misdiagnosis of the condition. We report a case of a 20-year-old man who presented with fever and acute psychotic symptoms. This was associated with headache, dizziness, and body weakness. There were no other significant symptoms. Neurological examination revealed reduced muscle tone of bilateral lower limbs but otherwise unremarkable. The computed tomography (CT) scan of his brain showed no abnormality. Blood specimens for microbiological culture grew *Salmonella* Typhi. This isolate was susceptible to chloramphenicol, ampicillin, ceftriaxone, ciprofloxacin, and trimethoprim-sulfamethoxazole. He was treated with intravenous ceftriaxone for one week and responded well. He was discharged with oral ciprofloxacin for another week. The repeated blood and stool for bacterial culture yielded no growth of *Salmonella* Typhi.

**Keywords:** Acute psychosis; bacteraemia; *Salmonella* Typhi; typhoid fever.

### INTRODUCTION

Typhoid fever is endemic in many countries in Southeast Asia. The infection is mainly transmitted through contaminated food and water supply. Exposure to unimproved or unsafe water is an important risk of acquiring the infection (Mogasale *et al.*, 2018). The clinical manifestations include gradual onset of high-grade fever followed by intestinal symptoms. However, diarrhoea is not a common feature of typhoid fever. Neurological manifestation is one of the clinical presentations of extra-intestinal typhoid fever and this can occur in up to 84% of the cases (Ali *et al.*, 1997). Nevertheless, acute psychosis is not a common clinical manifestation of typhoid fever. Thus, proper history taking will help to elucidate the diagnostic work up needed for this infection.

### CASE REPORT

A 20-year-old man with no known medical illness presented with acute onset of behavioural changes whereby he was frequently talking to himself. This was noticed by his relatives. He claimed that he was responding to the voices he heard in his head. This occurred for about five days prior to this admission. It was associated with intermittent fever, headache, dizziness, and body weakness. Apart from that, he did not have any other significant clinical symptoms. On physical examination, he was febrile with body temperature

of 39.0°C and tachycardic with pulse rate of 120 beats per minute. His blood pressure was normal at 110/80 mmHg. There was no papilledema noted. The central nervous system examination revealed only low muscle power of both lower limbs but otherwise unremarkable. The cranial nerve examination and examination of the other body systems were normal.

The initial working diagnosis was acute meningo-encephalitis and cerebral malaria. Thus, his blood was taken for several laboratory investigations including full blood count, serum electrolytes, serum creatinine, blood film malaria parasite (BFMP), and blood for bacterial culture. CT-scan of the brain was also performed which showed no evidence of increased intracranial pressure and no other abnormal findings noted. Subsequently, lumbar puncture was performed and the cerebrospinal fluid (CSF) was withdrawn and sent for related analysis including bacterial culture. He was empirically started on intravenous ceftriaxone 2 grams 12-hourly and acyclovir 500 mg 8-hourly.

The laboratory investigation results showed that his full blood count was within normal limit as shown in Table 1. His serum creatinine level at 136 mmol/L was mildly increased but serum electrolytes were within the normal range. The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also raised. The serum creatinine kinase and lactate dehydrogenase were raised at 760 u/L and 535 u/L respectively. The BFMP result was negative. His blood for bacterial culture was positive on the

**Table 1.** Blood and cerebrospinal fluid investigation results on the day of admission

Laboratory Investigations	Value	Unit	Normal Range
<b>1. Blood Count</b>			
WBC	7.92	X 10 <sup>9</sup> /L	4-10
RBC	3.75	X 10 <sup>9</sup> /UL	3.8-4.8
Haemoglobin	14.2	g/dL	12-15
Haematocrit	41	%	36-46
Platelet	172	X 10 <sup>9</sup> /L	150-410
Neutrophil	69.6	%	40-75
Lymphocyte	21.6	%	20-45
Monocyte	8.2	%	0-8
Eosinophil	0.5	%	0-5
Basophil	0.1	%	0.0-2
Neutrophil	5.5	X 10 <sup>9</sup> /L	2-7
Lymphocyte	1.7	X 10 <sup>9</sup> /L	1-3
Monocyte	0.7	X 10 <sup>9</sup> /L	0.2-1.0
Eosinophil	0.04	X 10 <sup>9</sup> /L	0.02-0.5
Basophil	0.01	X 10 <sup>9</sup> /L	0.02-0.10
<b>2. Inflammatory Markers</b>			
ESR	49	mm/h	4-20
CRP	16.71	mg/dL	<0.80
<b>3. Renal Profile</b>			
Urea	4.4	mmol/L	1.7-8.3
Sodium	136	mmol/L	135-150
Potassium	3.2	mmol/L	3.5-5.0
Creatinine	119	mmol/L	44-88
<b>4. Cerebrospinal Analysis</b>			
CSF Smear	Clear, 0 cells, No pus cell, No organism seen		
CSF culture	No growth		
CSF Bacterial antigen	Not done		
CSF Cryptococcal antigen	Negative		
CSF glucose	3.5	mmol/l	2.5-5.0
CSF protein	0.45	g/L	0.15-0.40
CSF chloride	120	mmol/l	120-130
<b>5. Other Investigations</b>			
Stool FEME	Negative ova & cyst		
Stool Culture	No enteric pathogen detected		

same incubation day. The Gram stain revealed gram-negative bacteria infection. The bacteria grew well on the blood and MacConkey agar producing non-lactose fermenter colonies on the MacConkey agar (Figure 1a). They produced hydrogen sulphide as demonstrated by black precipitate of ferrous sulphide in the triple sugar iron (Figure 1b). The O, H and Vi polyvalent tests were performed using the bacterial colonies were reactive. The bacterial isolate was identified as *Salmonella* Typhi by the VITEK® 2 (bioMérieux, France) automated identification system with an excellent identification profile. The isolate was susceptible to chloramphenicol, ampicillin, ceftriaxone, ciprofloxacin, and trimethoprim-sulfamethoxazole (Table 2). The CSF analysis showed no features of acute bacterial meningitis with normal level of glucose and protein. The CSF culture revealed no bacterial growth. Further history revealed that he just came back from Jogjakarta, Indonesia about a week prior to this admission.

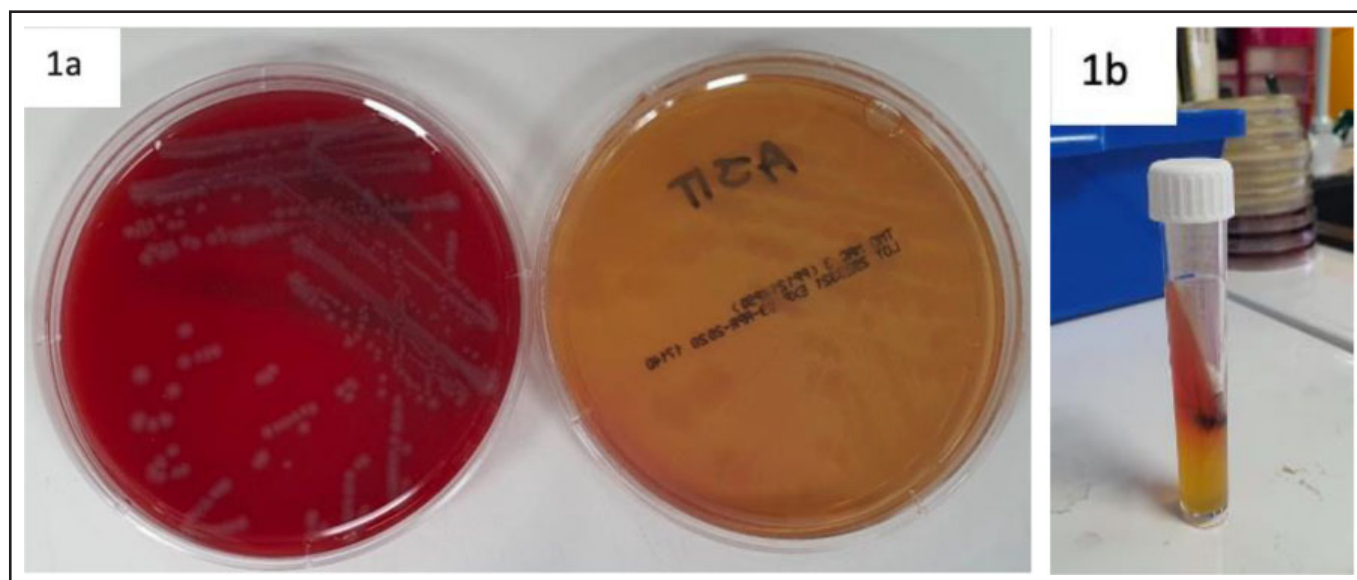
The final diagnosis of acute psychosis secondary to typhoid fever was made. He was continued with intravenous ceftriaxone 2 grams 12-hourly for one week. The psychotic symptoms improved tremendously when he was on treatment. The repeated blood culture taken on the day 5 of intravenous ceftriaxone revealed no bacterial growth. His stool sample was also sent for detection of *Salmonella* Typhi but no growth of the bacteria noted. He was then discharged

with oral ciprofloxacin for another week. His psychotic symptoms were definitely disappeared at the time of discharged.

## DISCUSSION

Globally, the incidence of typhoid fever is reducing in trend. The number of cases dropped from 26.9 million in 2010 to 11.8 million in 2016 (Crump, 2019). The bacteria, *Salmonella* Typhi is mainly transmitted through contaminated water and food. Thus, improvement in microbiologic quality of drinking water and better sanitation system leads to a reduction in typhoid fever incidence (Crump, 2019). The latest epidemiological study in Malaysia which was conducted in the most developed state in the country showed the peak incidence of 1.42 cases per 100,000 population in 2015 (Muhammad et al., 2020). Nevertheless, typhoid fever is still being reported particularly in the endemic area and the neuropsychiatric manifestation of typhoid fever continued to be reported.

The neuropsychiatric symptom is one of the clinical presentations of typhoid fever. It has a wide range of clinical presentations. It can also be part of the complications of the infection. This manifestation can be divided into two major groups which are acute onset that is characterized by delirium or confusional state without much fever and the slow insidious onset with varying degrees of temperature



**Figure 1a.** The bacteria isolated in this case were able to grow on both blood and MacConkey agar. The bacteria were non-lactose fermenter as demonstrated by the characteristic of the bacteria on MacConkey agar. **Figure 1b.** The bacteria produced hydrogen sulphide that resulted in production of ferrous sulphide demonstrated as black precipitate at the slant of the triple sugar iron.

**Table 2.** Antibiotic susceptibility testing result for this *Salmonella* Typhi isolate

Antibiotic	Diameter for test isolate (mm)	Susceptibility range (mm)*		
		Susceptible	Intermediate	Resistant
Ampicillin	28	≥ 17	14-16	≤ 13
Chloramphenicol	28	18	13-17	12
Trimethoprim-sulfamethoxazole	30	16	11-15	10
Ciprofloxacin	34	31	21-30	20
Ceftriaxone	30	23	20-22	19

\*Antibiotic susceptibility testing was performed using disk-diffusion technique and the reference range for each antibiotic was based on the CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 28<sup>th</sup> ed. CLSI supplement M100. Wayne, P.A.: Clinical and Laboratory Standard Institutes; 2018.

with toxæmia (Khosla, 2010). Although the central nervous system involvement in typhoid fever is not uncommon but acute psychosis such that experienced by the patient, in this case, is indeed very rare. This was reported to occur in only 0.63% of typhoid fever patients with neuropsychiatric manifestations (Ali *et al.*, 1997). Another earlier study in Nigeria reported only seven out of 959 patients with typhoid fever had schizophreniform psychosis (Osuntokun *et al.*, 1972). Similarly, another series analyzing the overall clinical presentation of typhoid fever in one of the areas in India demonstrated only seven out of 232 of their patients presented with psychiatric symptoms between 1999 and 2001 (Lakhotia *et al.*, 2003). Based on all these series, acute psychosis is indeed very rare among patients with typhoid fever.

Nevertheless, in all previous series of neuropsychiatric manifestations of typhoid fever, the confusional state was reported as the most common neuropsychiatry symptoms of typhoid fever (Osuntokun *et al.*, 1972; Ali *et al.*, 1997; Lakhotia *et al.*, 2003). Altered mental state among adults with typhoid fever was described in 29% of the cases and this was seen the highest in Europe and Central Asia as well as in East Asia and Pacific regions (Azmatullah *et al.*, 2015). Previously several case reports were published describing acute psychosis in typhoid fever. In one case, the patient presented with acute onset of aggressive behaviour associated with a

violent outburst (Adogu, 1990). In another case, the patient started talking irrationally, expressing inappropriate guilt and feeling of worthlessness on day three of illness (Ukwaja, 2010). Another case reported that the patient had delusions of prosecution (Nair *et al.*, 2003) and recently another case described excessive talkativeness associated with visual and auditory hallucinations (Alexander *et al.*, 2017). Importantly, in all of these cases, the onset of psychosis developed within the first three days of illness.

Thus, given the rarity of acute psychosis in typhoid fever and this manifestation may mimic psychotic disorders, appropriate laboratory investigation is needed. The isolation of the causative bacteria which is *Salmonella* Typhi can be achieved by sending the appropriate clinical sample. In most cases, the blood sample is taken for culture. However, blood culture was shown to have low sensitivity and bone marrow aspirate was considered as the gold standard for the isolation of this bacteria (Mogasale *et al.*, 2016; Antillon *et al.*, 2018; Mahler *et al.*, 2019). The overall sensitivity of blood culture was 0.59 when compared to bone marrow culture as a gold standard (Antillon *et al.*, 2018). It was also noted that the bacterial load peaked in the peripheral blood during the first week of illness (Mahler *et al.*, 2019). Blood bacterial counts were shown to reduce with increasing duration of illness (Wain *et al.*, 1998). The sensitivity of blood culture reduced remarkably by 31% after the first week of

illness (Antillon et al., 2018). Although bone marrow is said to be more sensitive than a peripheral blood sample, the procedure is invasive. Thus, it is imperative to send blood for culture as soon as typhoid fever is suspected. As demonstrated in previous case reports, *Salmonella* Typhi was successfully isolated from the blood specimens (Adogu, 1990; Nair et al., 2003; Alexander et al., 2017).

It is also important to rule out meningitis in this kind of clinical presentation of fever with acute psychosis. Thus, it is also important to send the cerebrospinal fluid sample for bacterial isolation. Interestingly, as shown in previously reported cases of acute psychosis in typhoid fever, the cerebrospinal fluid culture is often negative (Nair et al., 2003; Alexander et al., 2017). Similarly, the radiological investigation of the central nervous system such as computed tomography of the brain showed no abnormalities (Nair et al., 2003; Alexander et al., 2017). These findings indicated that acute psychosis in typhoid fever is not simply caused by the bacterial invasion into the central nervous system. Typhoid toxin was postulated to result in this manifestation and a study in rats showed that the toxin was found around the blood-brain barrier that possibly contributed to the psychotic symptoms (Chong et al., 2017).

Administration of the appropriate antimicrobial therapy resulted in complete resolution of psychotic symptoms without the need to use antipsychotic medication as shown in many cases (Adogu, 1990; Ukwaja, 2010; Alexander et al., 2017). Although there is concern about the increasing number of multidrug-resistant *Salmonella* Typhi isolated globally, local data in Malaysia showed that this isolate occurred in only 7.5% of *Salmonella* Typhi and the highest resistance rate was found in ciprofloxacin with 24.1% (Muhammad et al., 2020). The ceftriaxone which is the first line of antimicrobial used in *Salmonella* Typhi infection had a very low resistance rate at 1.6% (Muhammad et al., 2020). The bacterial isolate from our patient was sensitive to all the tested antibiotics. He was successfully treated with intravenous ceftriaxone and his psychotic symptoms completely resolved.

## CONCLUSION

Given the rarity of the acute psychosis in typhoid fever, it should be suspected in patient living in the endemic area or had recent history to the endemic area. It is prudent to take the appropriate sample for the isolation of the *Salmonella* Typhi as the yield of the laboratory diagnosis depending on the onset of the infection.

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## Conflict of interest

Authors declare no conflict of interest.

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