

## Case Report

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## Mild Encephalopathy/Encephalitis with Reversible Splenial Lesion in a Patient with Salmonella Typhi Infection: A Case Report

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### ABSTRACT

**Introduction:** Mild encephalopathy/encephalitis with the reversible splenial lesion is an uncommon complication of *Salmonella* infection. Awareness of these lesions is important as these are uncommon findings on MRI and carry an excellent prognosis.

**Case Presentation:** A previously healthy 17-year-old man was hospitalized for a 6-day history of fever and diarrhea. Physical examination of the patient showed fever. Laboratory investigations revealed elevated inflammatory markers, and two blood cultures revealed *S.typhi*. Three days later, the patient presented headaches and hallucinations. The MRI showed abnormal T2 hyperintensity in the splenium of corpus callosum showing restricted diffusion. There was no abnormal postcontrast enhancement of the lesion typical of MERS. The patient's general condition and her laboratory test results, improved after receiving treatment with ceftriaxone and corticosteroids. He received antibiotics for two weeks.

**Conclusion:** Patients with typhoid fever should be closely monitored for the development of neurological complications. Timely intervention can show signs of MERS and reduce morbidity and mortality.

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### Introduction

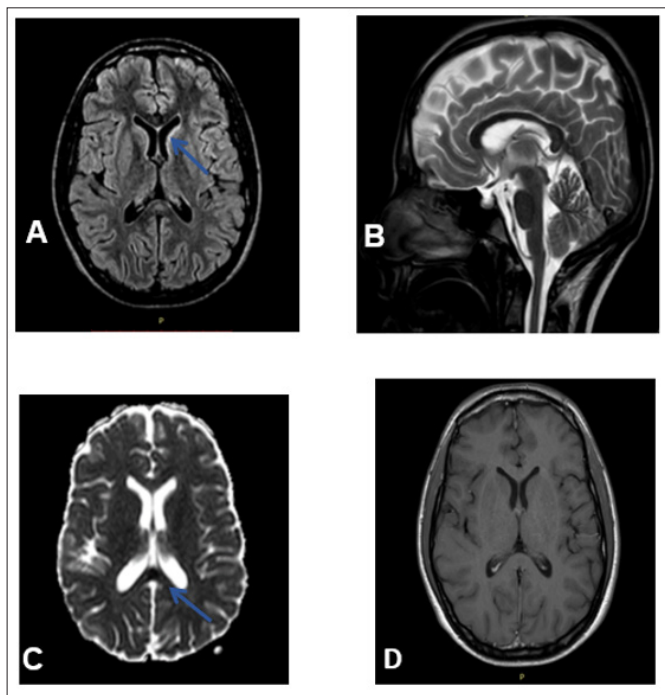
Typhoid fever is a bacterial disease caused by *Salmonella enterica* serovar *Typhi*. It is transmitted through the fecal-oral route, generally by contaminated water or food. The clinical presentation varies from low-grade fever, malaise, and slight dry cough to a severe clinical picture with multi-organ involvement [1]. These complicated forms occur in up to 10% of patients. The involvement of the central nervous system varies from 10-40%. Neurological signs described in association with typhoid fever have commonly included spasticity and clonus, ataxia, dysarthria, and less frequent, neuropsychiatric features, cerebellar dysfunction, and cranial nerve abnormalities [2]. Mild encephalopathy/encephalitis with a reversible splenial lesion (MERS) is an uncommon complication of *Salmonella* infection. In general, patients with MERS presented with consciousness disturbance, seizures, and headaches. MRI findings are typical, and patients recovered completely within a month [3]. MERS can be caused by several viral or bacterial infections or by drugs administration [3-5]. However, it was rarely attached to typhoid fever, this entity has been described earlier in a child and a 21 years old adult who both made an excellent clinical recovery [6,7]. Here, we report a case of *Salmonella typhi* encephalopathy in a young adult with culture-proven typhoid fever, who presented with reversible transient splenial lesions on MRI.

### Case Presentation

17-year-old HIV-negative men, presented with a 6-day history of

fever and diarrhea. He was previously well with no admission or illnesses until this episode. He reported no history of traveling but the consumption of palm juice. At admission, the patient had a fever of 39°C, a heart rate of 100 beats per minute, a Glasgow Coma Score of 15/15. There was a generalized abdominal tenderness but no hepatomegaly, no rebound or guarding. The cardiovascular and neurological exam was normal and there was no lymphadenopathy. Full blood count (FBC) revealed thrombocytopenia with a platelet count of 122.000/mm<sup>3</sup>. Elevated inflammatory markers were noted, with C-reactive protein levels (161 mg/L). Transaminase level was 2 times normal. Blood cultures were collected on admission. The patient was initially treated empirically with Ciprofloxacin 500 twice daily. One day later, he presented hallucinations, headaches, and confusion. He had neither meningeal syndrome nor signs of localization. Bladder and bowel function was intact. A Magnetic resonance imaging revealed a hyper signal in FLAIR and weighted sequence in diffusion (DWI), with restriction in ADC, and in iso T1-weighted sequence signal without enhancement after gadolinium injection. The lesion is an ovoid, sitting in the central portion of the splenium of the corpus callosum without affecting the periventricular white matter. (Figure1) A lumbar puncture was done and cerebrospinal fluid studies were normal. On the fourth hospital day, blood culture taken at admission grew *Salmonella Typhi*, which was subsequently found to be susceptible to ceftriaxone and ciprofloxacin. An initial Widal test was initially negative and at day 10 strongly positive with an *S. Typhi* flagellar (TH) agglutinin level of 1/640 and (TO) agglutinin level of 1/100. The patient was managed with intravenous ceftriaxone

4g daily for 14 days followed by a relay with Thiobactam for 7 days. Dexamethasone was prescribed for 7 days. The fever and neurological signs resolved by day 3. Repeat MRI performed a month later, revealed complete resolution of changes in the splenium of the corpus callosum. He was discharged from the hospital without any central nervous system impairment.



**Figure1:** Magnetic resonance images in a patient with typhoid fever and encephalopathy:

- T2-weighted axial image shows a hyperintense signal in the splenium of the corpus callosum;
- FLAIR sagittal image shows a hyperintense signal in the splenium of the corpus callosum
- Diffusion-weighted image shows hypointensity on apparent diffusion coefficient (ADC) image suggestive of restricted diffusion.
- No abnormal postcontrast enhancement was seen on contrast-enhanced T1-weighted images.

## Discussion

Typhoid fever, caused by infection with *Salmonella Typhi*, presents typically as an acute febrile illness. Complicated forms occur in up to 10% of patients and can include all systems of the body. These complications can include the central nervous system from 10-40% and manifests as toxic confusional state (57%), encephalopathy, meningism (5%), meningitis (0.2%), convulsions (1.7%), focal neurological deficits (0.5%), optic neuritis, sensorineural deafness (0.5%), and peripheral neuropathy (0.7%) [1]. A rare form of cerebellitis, as a complication of typhoid, was reported by Rajoo and Al in an 11-year old boy who presented with dysautonomia [8].

The exact pathophysiology of these neurological complications is not clear. The most accepted mechanisms are the immune-mediated process and endotoxemia [9]. Leung DT and Al studied risk factors of encephalopathy: Age (10–24 years), severe dehydration, Widal TH  $\geq 640$ , and leukopenia have been implicated as the risk factors associated with higher rates, probably reflecting prominent inflammatory response [10]. According to this study, our patient presented two risk factors: age and high rates of antibodies. Most of the neurological complications occur

during the second week but maybe the initial features. In our case, neurological signs started on the first week. Our patient presented with fever had disoriented behavior and had reversible neuroradiological findings on MRI in the splenium of the corpus callosum, consistent with MERS. MERS is most often identified in patients with seizures and/or antiepileptic drug withdrawal, and it is also associated with infections of various pathogens [4,11]. The reason for the predilection for the splenium of the corpus callosum is not clear. The restricted diffusion in MERS may occur due to cytotoxic edema, resulting from the separation of myelin layers and local infiltration of inflammatory cells. The cytotoxic edema is more pronounced in the splenium of the corpus callosum, considering the high density of neurons, astrocytes, oligodendrocytes, including cytokine and glutamate receptors in this area of the brain [12].

Infectious causes of MERS include numerous viral (adenovirus, Chikungunya virus, dengue virus, Epstein-Barr virus, influenza A and B viruses, and rotavirus, measles, herpesvirus, adenovirus, mumps, Epstein-Barr virus) and bacterial (*Enterococcus faecalis*, *Staph aureus*, and *Mycoplasma pneumonia*) pathogens [5,6,13,14]. Typically, the clinical neurological symptoms include mildly altered states of consciousness, delirium, and seizures after a range of previous viral infections but usually have complete recovery without neurological sequelae after a short disease course [15]. This entity has been rarely reported as a complication of typhoid fever [16]. Kombucha et al. previously reported a case of MERS secondary to *Salmonella enteritidis* in an eight-year-old Japanese patient [17]. Puneet et al. reported the first case of MERS in a 21 years old patient with typhoid encephalopathy. The diagnosis was made given positive blood culture, serology, and clinical features [6]. The second case of MERS secondary to typhoid fever was reported by McKenzie ED. and Al: It was a 29-year-old man presented with three days of progressive word-finding difficulty, coordination impairment, and headache in the context of a diarrheal illness. Blood and stool cultures were positive for *Salmonella typhi* [7].

In both cases, brain MRI revealed an abnormal T2 hyperintensity in the splenium of corpus callosum showing restricted diffusion. There were no hemorrhagic residues or abnormal postcontrast enhancement of the lesion. The key radiological features include T2 hyperintensity, restricted diffusion, and non-enhancing lesions located in the splenium of the corpus callosum. The MRI findings were similar in our case. Typhoid fever treatment is based on fluoroquinolones, azithromycin, and third-generation cephalosporin drugs is the main treatment, with chloramphenicol used in regions in which susceptible strains are present [18]. Our patient was treated with Ceftriaxone as the treatment of a complicated form of typhoid fever. Corticosteroids were also prescribed. The similar cases described in the literature were treated by the same antibiotic but without corticosteroids with the resolution of neurological symptoms within a week [6,7]. There is no specific treatment of MERS presentation besides treatment of the underlying cause [6]. Yuan and Al exposed in their review of the literature published in 2017 the efficiency of specific treatment of MERS: The evidence of methylprednisolone pulse therapy and IVIG's efficacy is still lacking. All patients without this additional treatment recovered clinically completely, which suggests that those treatments may not be necessary [3].

However, in case of severe typhoid fever with neurological complications, Dexamethasone may decrease the likelihood of mortality. Although the pathophysiology is not completely known, dexamethasone may work to counteract endotoxins released by

the Salmonella bacteria that ultimately stimulate the production of cytokines and free oxygen species responsible for enteric encephalopathy [19]. Nonetheless, this point is still debated. A 2003 WHO statement endorsed the use of steroids, but reviews by eminent authors in the *New England Journal of Medicine* and the *British Medical Journal* do not refer to steroids at all [18,20,21].

Chisti and al conducted a retrospective chart analysis of diarrheal patients with enteric fever and encephalopathy to examine the role of high-dose intravenous dexamethasone and it suggests high dose intravenous dexamethasone, as an adjunct to appropriate antimicrobial therapy, substantially reduces mortality. From the same point of view, Laps and al reported a case of enteric encephalopathy caused by Salmonella enterica serovar Typhi (S. Typhi) and the utility of adjunct treatment with a high dose of corticosteroids (22,23). In our case, the patient responded well to intravenous ceftriaxone and corticosteroids with the resolution of neurological symptoms within a few days.

## Conclusion

The learning point from this case is that although typhoid fever is generally a mild illness, in some circumstances it can present as a febrile neurological illness. We reported a case of an adult-onset MERS with typhoid fever. Taken together with the previously reported cases, we suggest that MERS in adults is an entity with a broad clinical-radiological spectrum and the prognosis is good. MERS can be associated with various infectious etiologies including *S. Typhi*, and awareness about this entity is important for its distinct neuroradiological features and benign prognosis.

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