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Chapter

Typhoid Fever and Its Nervous System Involvement

Atif Iqbal Ahmed Shaikh and Appasamy Thirumal Prabhakar

Abstract

Typhoid fever is a common cause of febrile illness. The causative organism S. Typhi uses special mechanisms to invade the intestines and then disseminates to the reticuloendothelial system. Thereafter, using the immune mechanism to its own advantage, it can reach the nervous system. The nervous system involvement usually occurs around the second week of fever. It usually occurs when the patient has severe sepsis. Neuropsychiatric manifestations are common, and fatigue is out of proportion to the fever. Diagnosis is often delayed, due to lack of diagnostic facilities in developing nations where it is common. In developed nations diagnosis is delayed as well, as often it is not suspected. Antibiotic therapy usually is effective, unless resistance is present, which is gradually becoming common. Early diagnosis and treatment usually leads to complete resolution of symptoms.

Keywords: Typhoid, brain, CNS

1. Introduction

The label 'enteric fever' suggests a febrile illness arising out of infection of the gut, however it is restricted to infections with *Salmonella enterica* typhi and paratyphi [*Salmonella enterica* serovar typhi and paratyphi] [1] rather than the family-enterobacteriacae itself. The nosology of 'enteric' suggests early and predominant involvement of the ileum and other parts of the gastrointestinal and biliary system in typhoid and paratyphoid fever [2]. The term typhoid is derived from the [3] Greek word *typhus*, in 1829 by a French Pathologist Louis Pierre [4]. He wanted to describe the disease by one of its prominent manifestations in those days. Typhus means 'hazy' or 'smoky' and typhoid means 'Typhus like', differentiating it from the typhus group of fevers. The 'hazy' could have been a reference to the CNS manifestation where the patient is often delirious.

Clinical manifestations: Typhoid fever to this day institutes a very significant proportion of diarrheal and febrile illnesses, especially in the developing world [5]. It has been reduced to very low levels in countries with good sanitation and accessibility to hygienic drinking water [6]. Cases in developed nations often are patients who have traveled to nations where enteric fever is endemic and these patients may have a drug resistance pattern similar to the originating country or locality [7–9].

Classical clinical features in the form of fever in a step ladder pattern, rose-spots and relative bradycardia may be less commonly seen and recognized. Typical fever patterns and classical signs may help to consider *Salmonella typhi* infection early in the disease, however, they are often not recognized [3, 10]. Enteric manifestations are common, with diarrhea, vomiting, abdominal pain and abdominal tenderness

are present in most patients. Non-enteric manifestations are common as well, and central nervous system manifestations are discussed in this chapter.

Nervous system manifestations: The nervous system manifestations usually occur later in the disease, usually by the second week. CNS manifestations are often associated with severe disease and other toxic manifestation including septicemia and septic shock. Fever with any central manifestations, always raises the possibility of meningitis, if the febrile illness has not been diagnosed earlier. Empirical antibiotics given early in the disease, impacts culture results.

Microbiological diagnosis becomes imperative to decide choice of antibiotics. Appropriate diagnostic facilities are often not available in areas where typhoid infection is common. These patients are often treated with empirical antibiotics [11]. If the choice, duration and doses are incorrect, patients are likely to develop multi-drug resistant infection, and often present late when they become toxic and have signs of severe disease. Antibiotic resistance to fluoroquinolones has become common. Resistance to third generation cephalosporins is rising as well [12, 13]. Inappropriate antibiotic usage also interferes with cultures, hence microbiological diagnosis becomes incorrect, and hence all the more risk of drug resistance and poorer clinical outcomes [14]. Incidence of multi-drug and extensively drug resistant salmonella infections, that includes resistance to extended spectrum penicillin, and carbapenems like meropenem has been reported [15, 16]. This makes it necessary for clinicians to be alert to the possibility of patients presenting with typhoid fever in all its manifestations including the eponymous one.

The earliest possible description which possibly can be typhoid fever was made by the historian Thucydides [17]. He describes 'the plague of Athens' in his writings of the Peloponnesian war in 430 BC and probably later again. The description is that of a slowly rising fever, weakness, diarrhea, muscle pain, rash of flat spots, and in extreme illness, intestinal bleeding, memory loss, and confused behavior.

Clinical studies with large patient cohorts have been described since the end of the nineteenth century and recently as well. Descriptions of neuropsychiatric manifestations, behavior and association with fever along with other classic manifestations have been described. Quite a few classic authors in the field of neurology have dabbled with typhoid and its CNS involvement. In their classic book "On peripheral neuritis- A treatise" James Ross and Judson S Bury describe 'Paralysis after typhoid fever" in detail, amongst other infective and non-infective causes of neuropathies [18]. Adolphe Gubler of Millard-Gubler syndrome fame has described patients with palatal paresis and limb paresis after presumably a bout of typhoid fever. Hermann Nothnagel has described patients with typhoid fever developing ulnar nerve palsies [19]. Even William Osler has attempted to describe and name a syndrome called 'Typhoid spine' which apparently had been used until the 1980s, however, has fallen out of use [20]. Wallenberg had reported 4 cases out of 160 cases of hemiplegia were secondary to typhoid fever. Hemiplegia was also reported by Smithies and Osler [21, 22].

Many large descriptive cohort studies have been conducted, since the beginning of the twentieth century, and later in the post-antibiotic era. CNS manifestations range from 5 to 35% in various studies [10, 23–26].

Psychiatric manifestations in the form of delirium, altered behavior are the commonest CNS manifestations. It may be difficult to differentiate from encephalopathy of sepsis and may have similar pathogenesis. Older authors describe 'scared' 'frightful' patients who worsen to become comatose and develop focal deficits. Aggressive behavior is less commonly described [19]. Memory disturbances are common and may remain persistent after the acute encephalopathy wanes off. Behavioral disturbances generally improve, however often do not resolve completely. Hallucinations, delusions and other psychotic symptoms have been described, and are less common.

Low mood and fatigue out of proportion to fever is common, and has been demonstrated in chimpanzees, who develop excessive fatigue without fever, hinting that fever and fatigue may have different pathogeneses [27].

Other less common manifestations that have been reported are stroke like presentations, cerebellar involvement, reversible extrapyramidal syndrome, myelopathy and optic neuropathy. These presentations are more commonly late presentations. Other peripheral nervous system involvement in the form of Guillain Barre syndrome has been reported. Cases of *Salmonella* brain abscess have been reported [28–30].

Diagnosis of typhoid fever, when CNS involvement is significant, can be delayed. In Mozambique, an outbreak of fever with often patients developing neurological complications was reported. Typhoid was not suspected immediately, however, later investigations revealed it to be the cause. Around 13% of patients had some neurological abnormality, with similar profile as other series, with addition. Vitamin B6 deficiency was also described to be low, however, direct comparison with patients without neurological manifestations was not done [25].

Patients who develop salmonella infection-related CNS complications generally have a more severe form of illness. Older patients, dehydration, lung involvement, thrombocytopenia and low blood counts have been found to be high risk factors for development of encephalopathy. Widal levels were found to be higher in patients with encephalopathy as compared to patients without CNS involvement [26].

Neurological manifestations have largely been reported to occur in the second week of fever, however, can be seen early in the disease as well. Early and empirical use of antibiotics may be one reason for reduced CNS manifestations of typhoid fever. However, cultures must be taken, and an appropriate microbiological diagnosis must be made.

CNS manifestations generally wane with the initiation of early antibiotics. However, some studies have noted features of encephalopathy after the patient has been treated with antibiotics. The mechanism proposed for this is endotoxin release, however, it has not been substantiated adequately. Another possible mechanism is immune mediated disease. Encephalopathy occurring after initiating antibiotics may confound the treating physician. Treatment consists of steroids as discussed later.

Non-typhoidal salmonellosis can cause CNS involvement in the form of encephalopathy and meningitis as well. This has even been reported from developed nations. Minimal brain edema, microvesicular fatty liver and severe enterocolitis was seen in the patients that expired. Focal encephalitis with seizures with frontal intermittent rhythmic delta activity (FIRDA) on electro-encephalography (EEG) has been described. Rare manifestations like cerebellar ataxia, cranial nerve palsies and Guillain Barre Syndrome have been reported [31, 32]. Non-typhoidal *Salmonella* associated meningitis has a very high mortality of around 60%.
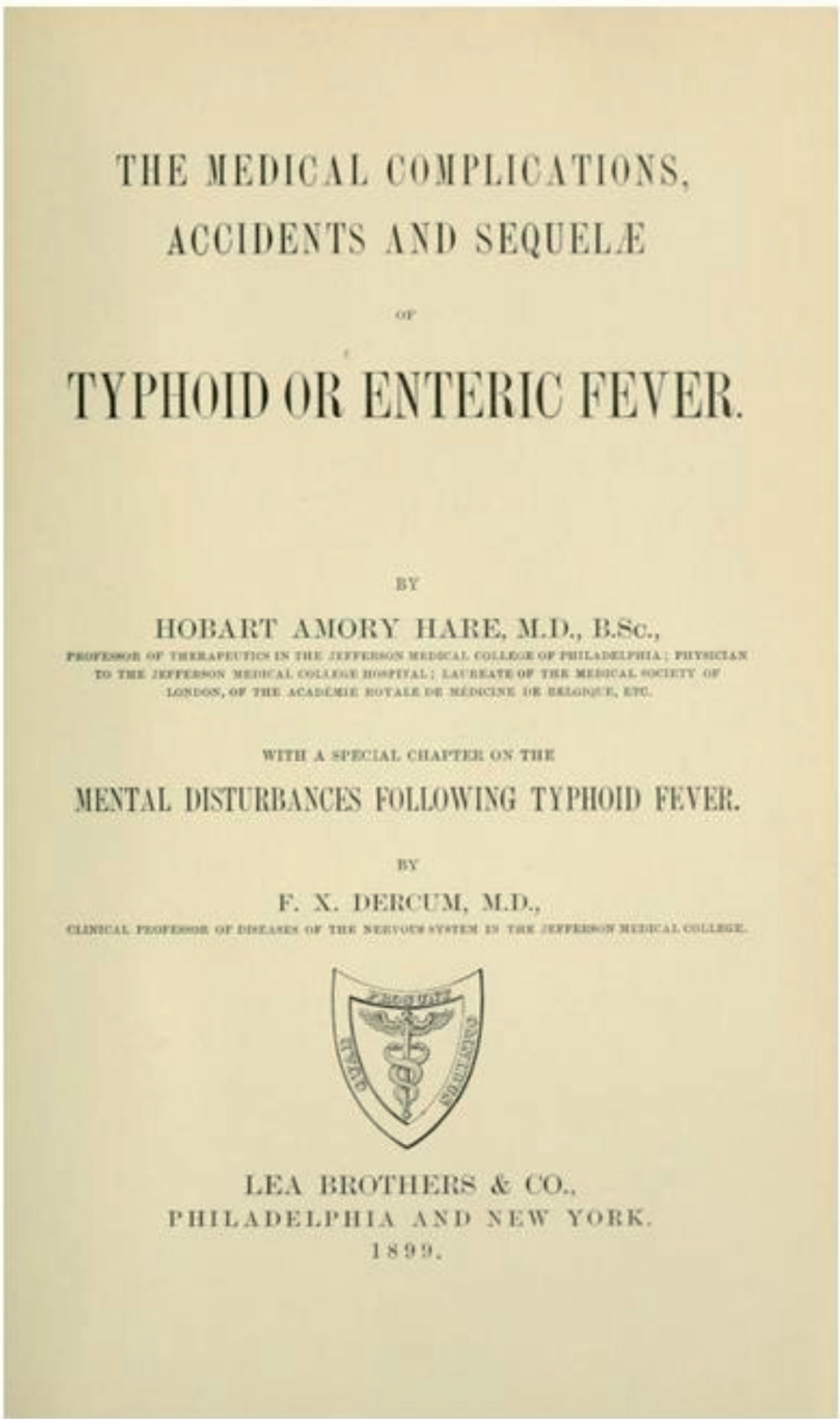
2. Immune response to salmonellae

Innate immune response is the first wall in the defense at places where the body is exposed to microorganisms. One important such site is the gastroenteric tract where a balance has to be maintained to enable absorption of nutrients and protection from plethora of organisms residing or invasive organisms [33].

The acidic pH is the one of the initial steps to reduce infections arising in the gastro-intestinal tract. Thus, conditions in which acidic pH is impaired can give rise to higher risk of contracting salmonella or severe salmonella. This includes achlorhydria, proton pump inhibitor therapy or previous gastrectomy. Additionally,

salmonellae also show increased acid tolerance, especially if previously exposed to a moderately acidic environment such as ponds or soils [34].

After passing the stomach salmonellae arrive in the intestine. The intestinal flora is one of the luminal barriers to prevent invasion. Antibiotic usage, especially ones that destroy the intestinal flora, increase chances of infection as well as give rise to a risk of severe infection [35]. Also, during an outbreak, patients who developed salmonella infection were significantly more likely to have taken antibiotics in the last one month as compared to individuals who had not taken [36, 37]. The intestinal flora provide competition for nutrients, as well as reduce pH in the intestines

THE MEDICAL COMPLICATIONS,

ACCIDENTS AND SEQUELÆ

OF

TYPHOID OR ENTERIC FEVER.

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WITH A SPECIAL CHAPTER ON THE

MENTAL DISTURBANCES FOLLOWING TYPHOID FEVER.

BY

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LEA BROTHERS & CO.,
PHILADELPHIA AND NEW YORK.
1899.

Figure 1.
A page from the classic book on typhoid fever and its manifestations called 'The Medical Complications, Accidents and Sequelae of Typhoid or Enteric Fever' by Hobart Amory Hare and F.X. Dercum. [5].

and increase volatile fatty acids. However, salmonella use a specific nutrient called ethanolamine, which is especially present when the intestines are inflamed. Therefore, a mild inflammation induced by salmonella increased chances of further infection. Additionally, inflammatory bowel diseases like Crohn's disease provide an additional risk factor for development of salmonella infection.

Salmonella enters the gut by means of antigen presenting cells or direct invasion of the epithelial cells [38, 39]. Entry is partially gained via the cystic fibrosis transmembrane conductance regulator protein, that is abnormal is cystic fibrosis. Indeed, homozygous and heterozygous mutations in this gene may have some protection against salmonella infections.

Salmonella can survive and replicate intracellularly, with a capacity to divide in different tissues. Entry into the enteric cells and later survival in macrophages and that too especially macrophages in the liver and spleen may be essential for it to gain virulence as well as seed to different organs, including the central nervous system. This stage of reticuloendothelial infection gives rise to the common clinical findings of rising fever after complaints of loose stools, and mild hepatosplenomegaly [40].

Salmonella virulence in the gut has been identified in studies that it arises from the *Salmonella* pathogenicity island loci [SPI] placed on the *Salmonella* chromosome. They produce amongst others a protein called Type-III secretion system (TTSS-1) that modulates the intracellular milieu to aid *Salmonella* uptake into the cells and replication [41, 42]. Whether the same mechanism is enough or essential is a topic of many studies. Salmonellae evade the initial response as they can survive in the macrophages. This is mediated by the Salmonella pathogenicity Island – 2 [SPI-2] encoding type three secretion system that blocks movement of
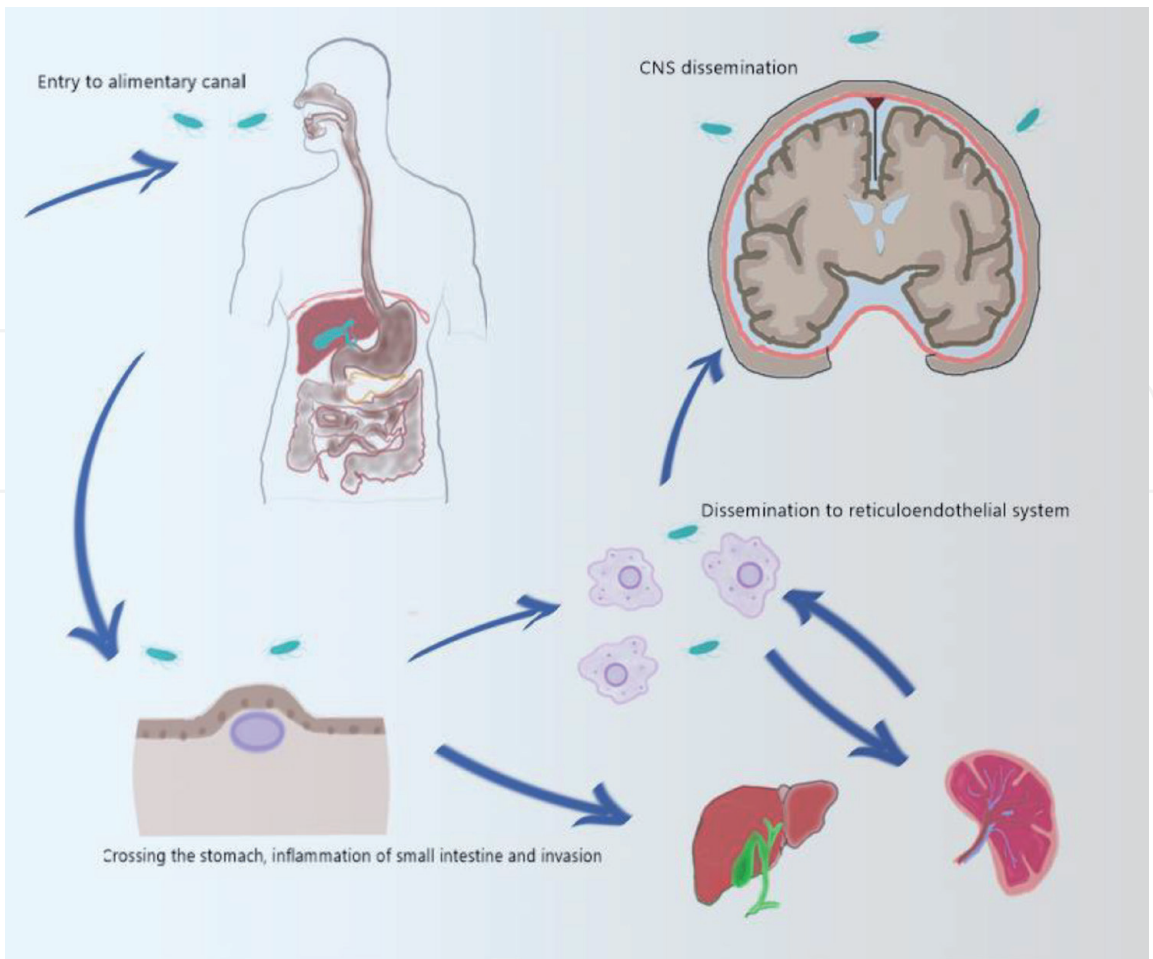
Figure 2.
Basic pathway of salmonella infection to reach the central nervous system.

reactive oxygen and nitrogen species inside the phagosome, where the salmonella survives. This initial survival against the innate immune responses is the key to systemic infection. Once the salmonellae survive in the macrophages, they can travel and multiply in other sites [33, 43]. Developing a mouse model and demonstrating *Salmonella* bacteria in the brain after oral feeding, was amongst the initial steps to study brain infections [44]. Crossing the blood–brain barrier is difficult, however eventual invasion of the neurons and later multiplication of the bacteria in the CNS is a relatively rapid process as has been demonstrated *in vitro* models by Debolina et al. [45, 46].

In the central nervous system, the presence of blood brain barrier poses an extra line of defense to most organisms including *Salmonella*. How *S. typhi* get around this is not clearly known. Most of the studies of central nervous system infection with *Salmonella* have been done with *S typhimurium*, as *S. Typhi* itself is an exclusive human pathogen. Van Sorge et al. used human brain microvascular endothelial cells to demonstrate binding and intracellular uptake of *Salmonella typhimurium* as a substitute to blood brain-barrier [45]. They showed that entry via blood–brain barrier may have additional pathogenic factors apart from the SPI associated proteins. Additionally, it has been studied in septicemia secondary to gram-negative bacteria there are structural and functional deficits in the blood–brain barrier which may give rise to sepsis-associated encephalopathy. This is a complex state with multiple players, including circulatory and microcirculatory dysfunction, cytokine storm, free radical release and oxidative damage amongst other metabolic derangements.

When salmonella interact with the blood brain barrier increased chemokines and a neutrophilic response is noted. Interactions with outer membrane protein A [often a constituent protein of cell membrane of gram negative bacteria] may be involved as ompA deficient strains when injected intraperitoneally have reduced CNS concentration even though liver and spleen concentrations remain the same [47]. OmpA has been incriminated for blood brain penetration by *E. coli* as well [48]. This additionally brings up the second mode of producing CNS manifestations mediated via non-specific toxins (**Figures 1** and **2**).

3. Pathology and pathophysiology

The clinical description of central nervous system manifestations has been described since the end of the nineteenth century. Numerous studies have been done to evaluate the pathogeneses of the same, and they continue into the twenty-first century. The early studies have described clinical manifestations in detail. Multiple mechanisms of CNS manifestations were put forward, including meningitis, toxic-mediated brain damage and dyselectrolytemia being the possible causes. Neuropsychiatric manifestations have been described in good detail by Hare and Foulerton in the late nineteenth century [31]. They document cases and reports of early mania and delusions associated with typhoid fever by multiple physicians. However, they conclude suggesting central nervous system manifestations are not common in the early stages of the disease. Studies by Foulerton and Thompson demonstrated bacterial invasion into the brain, however, attempts to demonstrate a toxin were futile [49].

In their seminal book titled 'The Medical Complications, Accidents and Sequelae of Typhoid or Enteric Fever', Hare classifies nervous system related symptoms into those arising from prodrome or early stage of the disease, in the well-developed stage of the disease and those arising in convalescence. Such a division of manifestations pushes one to consider different pathogenic mechanisms for different manifestations. These are described in **Table 1**.

Period of infection	Manifestations
Early infection or prodrome [First few days]	Confusional state, delusions, mania, meningismus often progress rapidly to coma
Well developed stage [After more than a week]	Delirium- restlessness, insomnia, confusion, apathy, delirious, vivid dreams, delusions, impaired sensorium, retrograde amnesia, melancholy, visual hallucinations, convulsions, meningitis +/− Kernigs sign with pathologically confirmed purulent meningitis involving both dura and leptomeninges, lead-pipe rigidity, cranial nerve palsies, cortical venous thrombosis, bulbar palsy, coma
Convalescence	Paralysis-LMN type- peripheral neuropathy, UMN type- Myelopathy, hemiplegia secondary to cortical involvement, thrombosis, hemorrhage, meningo-encephalitis, aphasia, cerebellar involvement, chorea

Table 1.
CNS manifestations of Salmonella *infection.*

4. Hypotheses and evaluation of pathogenic mechanisms

CNS manifestations have been suspected to result out of one or more of the following

1. *Salmonella* meningitis or meningoencephalitis: For this, the organism if entering the body orally, requires to be absorbed into the gut, get disseminated, cross the blood–brain barrier and finally cause infection of the cells of the CNS. Direct damage to the cells then causes the clinical syndrome.

2. Toxin mediated damage: where chemicals are released locally or systemically which impair the neuronal function. The toxin could be *Salmonella* specific or non-specific, for example, cytokine storm following any gram-negative septicemia.

The role of toxins in pathogenesis of clinical manifestations in Salmonella has been suspected for more than a century. However, the discovery of toxin and mechanism of actions is yet under investigation. A reason for the inability to demonstrate toxins is that toxins are produced intracellularly and causes severe disease only in humans [27, 50]. The toxins have variable effect on humans and chimpanzees. In chimpanzees, despite there being a higher concentration of bacteria, symptoms are only mild, with manifestations being severe in humans. This has been attributed to the differences in sialoglycans in humans and chimpanzees. Additionally, even though the toxin produced only a mild fever in primates, it did produce severe malaise and fatigue that is seen in patients with typhoid fever. As the malaise occurs without the fever, it is expected to probably be a CNS manifestation rather than secondary to a systemic infection [27]. A recent study indicates that typhoid toxin is not essential for typhoid infection nor may be responsible for early manifestations. The study was not adequate to negate attribution to severe manifestations or chronic disease [51]

3. Electrolyte disturbances: These could arise in typhoid commonly as a result of loose stools or vomiting. Renal impairment in severe infections causing multiple organ dysfunction syndromes can also cause metabolic derangements.

4. Immune mediated damage: Many reported syndromes can best be explained by immunological involvement, for example, Guillain Barre syndrome,

acute disseminated encephalomyelitis like presentation, cerebellitis and late manifestations.

Immune-mediated clinical syndromes associated with typhoid are often suspected and reported [52]. Another reason to suspect immune basis is that the symptoms begin well after the fever subsides, in which case autoimmune mechanisms become very likely. Resolution of symptoms with steroids helps the case further, however, specific antigens have not been conclusively described. A well-known complication of severe typhoid fever is macrophage activation syndrome. In all the series that have studied CNS manifestations, discussion regarding macrophage/microglial activation is surprisingly inadequate. This is one complication that needs further evaluation as a means of encephalopathy. This is especially important as treatment may mandate high dose steroids and carefully follow up till the macrophage activation syndrome reverses.

5. Micronutrient deficiency: Possibly postulated as secondary to intestinal involvement giving rise to difficulty in the absorption of some nutrients, and anorexia as well along with increased metabolic demand.

5. Diagnosis and evaluation

Clinical evaluation: Like any febrile illness, evaluation begins with a history and circumstantial knowledge. In an area of a high incidence of typhoid fever, there is a chance that the diagnosis will be suspected at the outset. History of any contacts with patients who had salmonella may be beneficial. An astute clinical examination in all patients presenting with acute febrile illnesses should include looking for dehydration, coated tongue, Rose spots, splenomegaly and relative bradycardia. A detailed CNS examination is a must especially in cases of manifestations, including brief cognition testing, evaluation for focal motor, or sensory deficits and neck stiffness, at the bare minimum.

Laboratory evaluation: All patients with an acute febrile illness usually have total blood counts done which may be normal or mildly reduced. Thrombocytopenia may be present. Blood cultures in all patients is mandatory before starting antibiotics. Bone marrow culture is more likely to yield a positive result; however, it is invasive in nature [14]. Stool and urine cultures may be helpful as well in the second and third weeks of fever. Serological tests like Widal or Typhidot can be done in the second week if the fever persists. In addition to getting cultures, it is imperative to check for sensitivity patterns, in view of ever-rising drug resistance. CSF is almost always done when CNS manifestations are present, importantly to rule out bacterial meningitis secondary to common organisms. CSF studies are often found to be normal. Cultures may occasionally show the presence of *Salmonella*.

Other evaluations for encephalopathy require checking of hydration status, and metabolic disorders including dys-electrolytemias, renal failure, liver disease, or acidosis.

Imaging: In the absence of florid findings on the CSF, other means to chase CNS involvement in typhoid fever is imaging. MRI findings have been described in multiple cases. They include focal white matter edema suggestive of cerebritis or diffuse vasogenic edema. There may be other focal signs in the form of single or multiple *Salmonella* associated abscesses. Reversible diffusion restriction in the white matter has been described [53–55]. Often findings of swelling of the splenium of corpus callosum have been reported, however it is a finding that can be seen when imaging is done immediately after seizures.

EEG generally shows nonspecific findings. There can be focal slowing, focal spikes, and one case showing features of FIRDA [56].

Serological testing with WIDAL is commonly conducted, as it is widely available, inexpensive and easy to conduct. A rise in titers may be more important than a single study. Although it is non-specific, patients with CNS involvement often have very high titers of antibodies, as compared to patients without CNS involvement. Also, in the same spirit, patients are often sicker, have systemic inflammatory response syndrome, low blood counts, thrombocytopenia and more likely to have pulmonary or hepatic complications [26].

6. Management

Early diagnosis is essential in cases of salmonella infections which can be difficult especially in a non-endemic clinical setting. In endemic areas blood-cultures commercial kits are often not available or may not be affordable. As the incubation period is around one to two weeks, a history of recent travel must be documented in patients. This has shown to be as much as 60 days. The classic clinical presentations of step ladder pattern fever, with loose stools, and abdominal pain, relative bradycardia, rose spots over the abdomen and occasionally chest, and coated tongue should be carefully evaluated, however, they often may be absent. Soft splenomegaly may be present. Peripheral white blood cell counts are generally on the lower side of normal, and thrombocytopenia is often present.

Definitive diagnosis however entails blood culture, especially in the first week. It can take a long time to show results. Immunological tests including WIDAL become positive only after a period of one week. Imaging and CSF analysis are often done for evaluation of differential diagnosis.

Antibiotic therapy: Antibiotic therapy is generally not as urgent as in other gram-negative septicemia. However as soon as the diagnosis is made, therapy should be initiated with help from a local microbiological guide regarding sensitivity to drugs. Empirical antibiotic therapy is to be generally avoided, however, must be started early in cases when the patient has SIRS or CNS manifestations.

Antibiotic therapy is generally advised for a period of two to three weeks. Ceftriaxone becomes a good choice of therapy especially as it has good CNS penetration. As more often *Salmonella* resistance is being reported, it is imperative to have a local drug sensitivity profile. Fluoroquinolones were sensitive, and possibly sensitivity to ciprofloxacin may still be present, however gradually increasing NARST [Nalidixic acid-resistant *S Typhi*] strains may necessitate higher doses or change in therapy. Extensively drug-resistant strains have been reported with resistance to Chloramphenicol, Trimethoprim-sulbactam, ampicillin, third-generation cephalosporin, and fluoroquinolones [57]. Resistance to Azithromycin has been reported in a single case of *S. paratyphi* who was treated with ceftriaxone [58]. However, if the patient is septic, or is in shock, injectable carbapenems like meropenem may be the treatment of choice at the outset. Therapy can be adjusted later based on drug sensitivity testing.

Steroids: Steroids are indicated in the treatment of patients with severe disease [59, 60]. The two common and most important indications are CNS disease and shock. CNS involvement in the form of encephalopathy, psychiatric manifestations, cerebellar involvement, extrapyramidal involvement, myelopathy or seizures are indications of starting steroids. Hydrocortisone, dexamethasone and pulse doses of methylprednisolone have been tried, with case reports suggesting good outcomes [61]. CNS manifestations have been recorded often to revert quickly with steroids, however, there are only case reports present. Additionally, mechanisms of how

steroids help is not explored, as also if steroids have caused poor outcomes. This aspect requires further study.

Steroids are often helpful in presumed immunologically mediated syndromes, for example, ADEM and cerebellitis. Intravenous immunoglobulin (IvIg) may be required in some cases, especially post infectious Guillain Barre syndrome.

Supportive therapy: This includes rehydration and fluid resuscitations. Dyselectrolytemia needs to be corrected promptly. If the patient has had seizures, then anti-epileptic therapy is warranted. The choice of anti-epileptic will vary from patient to patient. Phenytoin is to be avoided if cerebellar signs are present. Valproate and phenytoin are to be avoided if hepatic dysfunction is present and levetiracetam is to be avoided or doses need to be adjusted if renal failure is present.

Early and aggressive treatment with close monitoring is required to avoid long-lasting complications. Long-lasting problems known to persist are psychosis, delusions and spasticity. Extrapyramidal and cerebellar involvement generally reverts completely. Patients can have memory deficits and behavioral symptoms and hence follow up is essential.

7. Public health issues

Salmonella infection being an orally acquired infection, has major public health issues. Any such infection should assume that there is a break in the path for fecal waste disposal or contamination. CNS manifestations are assumed to be severe manifestations and hence they have a special regard.

Severe infections are common in patients who have taken antibiotics in the past one month. Widespread illogical use of broad-spectrum antibiotics should hence be controlled. With a single dose of streptomycin, the bacterial flora of the gut gets altered and leads to higher risks of infection. Additionally, drug resistant infections, especially fluoroquinolone and third generation cephalosporin resistant infections are on the rise and drug resistance to carbapenems has been reported as well. This is a huge implication in terms of management of typhoid fever.

Use of oral vaccine has been slow, but gradually increasing. The protection offered by these vaccines should reduce severe typhoid infections, and additionally so the CNS manifestations, however, this is not clearly known.

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