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Review Article

Typhoid Encephalopathy in Children: Review Article

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Abstract

Typhoid fever is very common. A large number of cases with typhoid fever have delayed presentation and many are treated inadequately resulting in admission with different complications. The most vulnerable age for enteric fever and its complication is 5 years to 10 years. Most common complications were involving the central nervous system, hepatobiliary and GIT system. Typhoid encephalopathy is the most frequent neurological complication of enteric fever. If treated early it is reversible without any long term sequelae. This is a review article about the presentation of typhoid encephalopathy.

Keywords: Typhoid; Encephalopathy; Seizure; Children

Introduction

The term 'typhoid' is derived from the Greek word 'Typhos' meaning smoke which further connotes to apathy and confusion [1]. Sir William Osler described typhoid as a semi conscious state which is characterized by a blank stare with muttering, non interactive, just arousable patient [1]. Typhoid fever is caused by *Salmonella enterica serovar typhi* (*S. Typhi*), a gram-negative bacterium. It is also caused by *Salmonella Paratyphi A, S. Paratyphi B (Schotmulleri) and S. Paratyphi C (Hirschfeldii)*. It infects 11 million to 20 million people every year in the world, resulting in 120,000 to 220,000 fatalities [2]. Its incidence is high among preschool children. South Asia has the highest number of infected people with the disease [2]. India is burdened by the disease with approximately 63,45,776 cases per year [3]. If untreated the illness - cause complications by the second to the fourth week [2]. Higher risk of complication is seen among three categories of patients. First, patients whose antibiotic treatment for typhoid was started late. Second, patients with resistant strains and third, the younger demographic [2]. In a study done in West Bengal the incidence of typhoid fever was found to be 1.4/1000/year, with mean age of 14.7 years [4]. Complications of typhoid fever have been estimated to occur in 10 % to 15% of the hospitalized patients [2]. There has been evidence of higher risk in children [2]. Overall, the complications with the highest prevalence (95% CI) reported by three studies are encephalopathy, gastrointestinal bleeding, and nephritis, with a prevalence of 7.3%, 5.7%, and 4.8% respectively is reported in a meta analysis conducted by Espinoza et.al [2]. Relapse is seen in 2% to 4% of infected children after response to treatment [5]. Low carrier state in children, seen in less than 2% of the infected children [5].

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Salmonella Typhi has an incubation period of 4 days to 14 days. Its onset is insidious without much warning. Patient in the first week experience high grade fever, coated tongue, malaise, headache, abdominal pain. Usually patient will be drowsy with arthralgia, relative bradycardia, tender abdomen and meningismus. In the second to third week patient develops rashes (rose spots) with tender hepatosplenomegaly. Complications like typhoid encephalopathy develops only by the third to fourth week. It is seen that maximum complications were of the central nervous system followed by hepatobiliary, abdominal, hematological, bones and joints, respiratory and cardiovascular system in order of frequency [6]. Among CNS complications most common was encephalopathy involving 60% of the cases [6]. Followed by febrile seizure, acute cerebellar ataxia and aphasia in 10% of the cases [6].

Bone marrow culture is 90% sensitive until upto 5 days after starting antibiotics [7]. Blood culture sensitivity is the gold standard for the diagnosis of enteric fever. It has 90% sensitivity in the first week which drops to 40% by fourth week. Widal test has a low sensitivity and specificity. The sensitivity of Nested Polymerase Chain Reaction (RTPCR) on blood was found to be 100% whereas the specificity was 76.9% [8]. Due to its high sensitivity and specificity, nested PCR can be used as an important tool to diagnose clinically suspected, culture negative cases of typhoid fever [8]. The Ig M / Ig G titre of ≥1:200 has a high sensitivity (95.50% / 96.85%) and specificity (94.69% / 94.95%). The diagnostic sensitivity of agglutination of 'O antigen" titre at titre ≥1/400 was 84.09% and specificity was 52.65% [9].

Pathogenesis of Extraintestinal Manifestations

Typhoid encephalopathy means the generalized cerebral dysfunction due to typhoid fever. Mean age for the disease is 6.7 ± 4.31 years with male preponderance (61.5%) [10]. Extraintestinal complications occur based on the size of the inoculum ingested, strain virulence, host immunity and local protective factors [11]. The virulence is dependent on its ability to cell invasion, lipopolysaccharide coat, Vi antigen and invasin [11]. After ingestion, if *S. Typhi* survives the HCL in the stomach then passes into the small intestine [11]. Here, it penetrates the M cells of the peyers patches [11]. They are taken up by the lymphoid tissue of the intestine, which disseminates *via.* the lymphatic or haematogenous route [11]. Multiplication of the bacterium takes place in the reticuloendothelial cells and

macrophages located in the lymph nodes, liver, spleen, and bone marrow [11]. The bacteria are then released into the blood leading to secondary bacteraemia [10]. During this secondary, and persistent, bacteraemia, the bacteria further spreads to additional organs, thus causing extraintestinal manifestations [11].

Typhoid Encephalopathy

Untreated patient develops high grade step ladder pattern of fever with coated tongue and rose spots. If untreated by the third week of illness patient develops features of encephalopathy [1]. Upon the central nervous system examination, the higher mental functions test reveals - subtle personality changes, inability to concentrate, progressive loss of memory, lethargy, altered mental state, and eventually progressive loss of consciousness. There is no specific cranial nerve abnormality caused by typhoid fever. Motor system examination is usually suggestive of features of upper motor neuron lesion like spasticity, hyperreflexia and clonus [12]. Sensory system remains normal. Very rarely cerebellar dysfunction - presenting as acute cerebellar ataxia, meningism, sinus thrombosis, pseudotumor cerebri, brain abscess and Guillain Barre syndrome is seen in children [13]. Spinal cord involvement has not been observed. In children less than 5 years, typhoid encephalopathy presents as febrile seizures along with upper motor neuron type of lesions [13]. In older children typhoid presents with neurologic findings without altered sensorium/ encephalopathic features thus suggesting that typhoid can produce focal as well as generalized neurologic dysfunction [10]. In CNS, the common complication are motor neuron disorders, cerebral edema, subdural empyema, Guillain-Barré syndrome, psychosis, cerebral abscess, meningitis, ventriculitis, ataxia and seizures [11]. Management of typhoid encephalopathy includes basic stabilization of airway, breathing and circulation. Raised intracranial tension is managed by osmotherapy (hypertonic saline or Mannitol), carbonic anhydrase inhibitors and steroids. Antiepileptic medications are started for prevention of seizures. CSF study and MRI brain has to be done. If reports suggestive of meningitis or encephalitis then high dose IV Ceftriaxone is to be given for 14 days. Sejavar et al. [12] who found that the due to involvement at various sites of the CNS, typhoid presents with variable neurologic manifestations. The higher seizure rate in children was more due to febrile seizures. EEG was suggestive of frontal intermittent rhythmic delta activity in typhoid encephalopathy. CSF study is usually normal with no pleocytosis or protein elevation. Britto et al. [13] said that the children present with seizure more than adults. The typhoid toxin (Neu 5AC glycoproteins) binds to mammalian gangliosides. Sejavar et al. [12] also found that encephalopathy was often accompanied by shock, which was associated with high mortality. Pary et al. [14] found that antibiotics are required for the treatment of typhoid fever. High dose dexamethasone therapy reduced the mortality and morbidity in patients with typhoid encephalopathy [15].

Other complication of the enteric fever includes cardiovascular system, pulmonary system, hepatobiliary and other systems involvement [11]. In CVS, the complications are congestive heart failure, endocarditis, myocarditis, pericarditis, arteritis and in pulmonary system mainly bronchopleural fistula, pneumonia and empyema [11]. In bone and joint mainly leads to osteomyelitis or septic arthritis. Peritonitis, paralytic ileus, cholecystitis, hepatitis, hepatic abscesses, splenic abscess occurs as part of hepatobiliary complication [11]. In genitourinary system, the complications are prostatitis, epididymitis, urinary tract infection, renal abscess, pelvic infections and testicular abscess. Rare complications are the cutaneous vasculitis, psoas abscess, and gluteal abscess and hemophagocytosis syndrome in enteric fever [11].

Conclusion

In conclusion, the incidence of typhoid fever is high in India, affecting the pediatric population very frequently. If untreated it can cause complications like typhoid encephalopathy by 3rd week of the illness. Neurologic abnormalities in most cases resolve over time, leaving very rarely a long term sequelae. Thus if managed aptly patient can recover completely from typhoid encephalopathy without any sequelae. Therefore it is necessary to identify and manage typhoid fever and look for the earliest sign of complication and manage it accordingly.

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