Article *NIMHANS Journal*

Neurological Complications of Salmonella Typhi - Clinical, Microbiological and Pathological Study

Volume: 08 Issue: 02 July 1990 Page: 111-126

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Reprints request

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Abstract

Fifty-five patients with neurological complications due to Salmonella typhi (S. typhi) infection were studied. Seven (12.7%) of them presented with pyogenic meningitis, 2(3.6%) with cerebral abscess and 46(83.6%) had neurological deficits without pyogenic meningitis. The mean age was 19.24 ± 12 years. The mean duration of illness at the time of admission was 16.4 ± 13 days. Fever was the initial and most prominent symptom in 46(83.6%) and most of them had headache, vomiting, myalgia and/or loose motions. Hepatomegaly and/or splenomegaly was present in 27(49%). The mean interval between the onset of fever and the development of neurological deficits was 9.5 ± 9 days. The neurological deficits included those of pyramidal, extrapyramidal, cerebellar, brain stem, spinal cord and/or peripheral nerves. One had polymyositis. Blood Widal was done in 45 cases and was positive in 43 (95%) of them. The S. typhi was isolated from blood in 21, CSF in 3, cerebral abscess pus in 2, and from other sources in 4. The phage and biotype of isolates was done in 17 patients. The antibiotic sensitivity studied in 25 cases revealed resistance to ampicillin in 5 and to chloramphenicol in 10, while all were sensitive to co-trimoxazole and gentamycin. The lumbar CSF analysis done in 47 patients, was abnormal in 14 (29.7%). The EEG done in 29, was abnormal in 19 (66%) and the abnormalities were subclinical in 1. The ENMG done in 7 patients, was abnormal in 4. The mean duration of hospital stay of 54 patients was 14.8 ± 14 days. At the end of hospital stay 46 of them (83.6%) recovered (completely or partially) and 9 of them (16.4%) died. Seven of them were autopsied. At autopsy, brains showed features of pyogenic meningitis in 3 cases, while the other four had degenerative changes involving the dentato-olivary pathway.

Key words -

Typhoid,

Salmonella typhi,
Pyogenic meningitis,
Cerebral abscess,
Bacterial encephalomyeloradiculopathy

Typhoid fever due to S. typhi is still a common clinical condition in the developing countries. The confusional states and altered sensorium are commonly associated with this clinical entity. Osuntokun [1] found confusional state in 57% on analysing 959 cases of typhoid fever. Pyogenic meningitis due to S. typhi has been reported infrequently [2], [3], [4], [5]. Neurological deficits without meningitis have been reported occasionally [6], [7], [8], [9], [10]. A large number of these cases, probably go undetected in the developing countries. The aim of this paper is to highlight the clinical features and the pathological changes in the autopsied cases and to focus the attention on the emergence of resistant strains of S. typhi to commonly used chemotherapeutic agents in developing countries.

Material and Methods

Fifty-two patients with neurological complications due to S typhi infection were studied from 1981 to 1989 and 3 cases admitted earlier were included in the study; These patients were referred to the department of Neurological services because of the neurological deficits they had, often with a provisional diagnosis of viral encephalitis. On investigation they were found to be secondary to S. typhi infection.

The diagnosis of S. typhi infection was based on
(i) isolation of S. typhi either from blood, CSF and other sources and/or
(ii) demonstration in serological tests of a significant 'raise in the titre for "O" agglutinin.

Investigations to exclude common infective diseases were done routinely in all. Patients who had only psychiatric features and/or altered sensorium without neurological deficits were excluded from this study. The phage typing was done according to internationally adopted phage typing scheme, at Salmonella phage typing centre, Lady Hardinge Medical College, New Delhi.

Results

The mean age of incidence in the group of 55 cases was 19.24 ± 12 years; the youngest being 3 years and the oldest 80 years. There were 33 (60%) males (Table I).

Table Ia - Results

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Table Ia - Results - Neurological Complications without Meningitis

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Table Ib - Results - Neurological Complications without Meningitis

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* Ch - Chloramphenicol
  Co - Cotrimoxazole
  Am - Ampicillin
  CP - Crystalline pencillin
  Ge - Gentamycin
  Ax - Amoxicillin
  ** CR - Complete recovery
  PR - Partial recovery
  RP - Residual pyramidal signs on left side
  SL - Shortening of left lower limb
  FD - Bilateral foot drop
  NI - Not Improved
  D - Died
  DA - Died autopsied

The duration of illness at the time of admission varied from 1 day to 60 days, with a mean period of 16 ± 13 days. Fever was the initial and most prominent symptom in 46 (83.6%). Most of them had associated headache, vomiting and myalgia. Some of them had loose stools. Twelve (21.8%) of them had hepatosplenomegaly, 6 (11%) had only splenomegaly, and 9 (16.4%) had only hepatomegaly: They regressed with clinical improvement.

The interval between the onset of fever and development of neurological deficits varied from 1 to 44 days with a mean duration of 9.5 ± 8days in 49 and it could not be ascertained in 6 (11%).

Neurological Deficits

In the series of 55 cases, 7 had meningitis. Six of these patients were comatose. Four of them had bilateral pyramidal signs, one had left hemiplegia and one had right hemiplegia. Three of them had fits.

In 46 cases without meningitis, the prominent neurological deficits were encephalomyeloradiculopathy in 5, dense hemiplegia or hemiparesis in 9, unilateral or bilateral pyramidal signs without significant weakness in 7, bilateral cerebellar signs in 9, parkinsonian features in 7, papilledema in 5, brain stem dysfunction in, right facio-brachial weakness with aphasia in one, dorsolumbar myeloradiculopathy in one and polyradiculopathy of alt four limbs in four. Eight patients had fits. The neurological deficits varied from transient, lasting for a few days to producing permanent deformities. The parkinsonian features were transient and hemiplegia was the most disabling.

Of two patients with cerebral absess, one had right hemiparesis with right motor fits becoming generalised and another had papilledema with left hemiparesis. These were in addition to their pre-existing neurological deficits. One of them was a known case of spinocerebellar degeneration (case 54) and another had undergone right STAMCA shunt for right cerebral infarction due to occlusion of right internal carotid artery at its origin 6 months back (case 55).

Investigations

Blood Widal was done in 45 (81.8%) and was positive in 43 (95%). In most of the cases it was positive in increasing and/or decreasing dilutions and the positive result in highest dilution is given in Table 1. In the remaining 2 with negative Widal test the culture was positive. CSF widal was done in 9 cases of neurological deficits without meningitis treating CSF like serum and was found negative in all and it was positive in one case of meningitis (Case 5).

Lumbar CSF analysis was done in 47 patients. In 7, the findings were in favour of meningitis and in the remaining the findings were either normal or mildly abnormal. When it was done more than once, only the first CSF analysis result is given in the table.

Bacterial culture. S. typhi was grown from different sources in 27 (49%) patients. The blood culture was positive in 21 (77%) cases, CSF in 2, cerebral abscess pus in 2, stool in 1, urine in 1, post mortem meningeal swab in 1, and the bone marrow aspirate in 1. Most of the patients had received antibiotics prior to referral to this hospital. This rendered the isolation of the organisms difficult.

Antibiotic Disc Sensitivity Test and Phage Typing

Among the 25 cultured isolates, 17 were submitted for phage typing at Salmonella phage typing centre, New Delhi, India. As indicated in Table 2, Salmonella bacilli in 16 cases had the receptor for Vi-antigen (Vi positive) and one was Vi negative (untypable). On further typing, five cases belong to "O", seven to "A", two to "", and one to UVS. In all the five, belonging to phage type "O" the organisms were found resistant to chloramphenicol, while those of phage type "A" and E1 were sensitive. Kristensen's biotype based on fermentation of xylose and Arabinose indicated type-I in 10 and type-II in 5. Among the 25 isolates, 10 were resistant to chloramphenicol, 5 were resistant to ampicillin white all were sensitive to gentamycin and co-trimoxazole.

Table II(a) - Antibiotic disc sensitivity test, phage type and biotype=25 Cases

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Table II(c) - Antibiotic disc sensitivity test, phage type and biotype=25 Cases

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S=sensitive
I=Intermediate
R=Resistant
All were sensitive to
1. * Co-trimoxazole (100%)
2. Gentamycin (100%)

EEG was done in 29 cases and was abnormal in 19 (66%) cases. The abnormalities consisted of diffuse slowing to either delta or theta range in 19 and two records contained primary generalised seizure discharges. The abnormalities were subclinical in one patient without clinical evidence of brain involvement (case 19). In one (case 26), there was only seizure discharges. In a case of abscess (case 54), there were focal slow waves in left frontotemporal region. The EEG was repeated in 13 patients and they had either reverted to normal or improved.

ENMG was done in 7 (cases 3, 19, 22, 23, 28, 42 and 52). In cases 3, 22 and 28 it was normal. In case 19, it was done on the 61st day of illness. The EMG in this case was normal but stimulation of the right common peroneal nerve evoked no motor response and sural nerve conduction was normal. In case 23, ENMG was done on the 29th day of illness. EMG was normal but the conduction velocity of the right common peroneal nerve was 36.62 m/s. (N.51.2 ± 3.7). The amplitude of the evoked motor response was decreased and its duration was increased. The right median motor conduction velocity was normal, but the duration of evoked response was prolonged. The 'F' wave latencies were within normal limits. The right median sensory and sural nerve studies revealed no abnormality. In case 42, EMG findings were suggestive of total denervation of right tibialis anterior. The nerve conduction velocities of both motor and sensory were grossly reduced in all 4 limbs. The reduced amplitude of evoked motor response from extensor digitorum brevis and abductor digiti minimi suggested associated axonopathy. Inconsistent and delayed F response from common peroneal and ulnar nerves suggested the involvement of the proximal segment of those nerves. In case 52, the latency of F response obtained from stimulation of right common peroneal nerve was delayed an obtained infrequently testing a proximal site of lesion in that nerve.

VEP studied in cases 25, 28 and 30 were normal. BAER was abnormal in case 28 and normal in case 30. Blink reflex and SSEP done in case 15, were unremarkable.

CT scanning of head was done in 4 (cases 27, 28, 29, 55) and was normal in 2 (cases 28 and 29). In case 27, who had parkinsonian features, in addition to other neurological deficits, CT showed hypodense areas over both paraventricular regions The CT in case 55 revealed an abscess

Other investigations. The total leucocyte count varied from 2,000 to 13,000/mm^3, with a mean of 6942 ± 2571. In 4 cases the count was below normal range and in 3 it was above normal range (N=4,300 - 10,000/mm^3). The differential count was unremarkable. One patient was diabetic (case 1) and the blood sugar was normal in the rest. Blood urea was normal in all. BKG showed non specific changes in some. X-ray chest showed consolidation in 2. The carotid angiogram was done in 4 (cases 1,27,54,55) and was abnormal in two cases of abscess (cases 54 and 55).

In case 8, positive LE cell phenomena and rheumatoid factor and an abnormal serum electrophoretic pattern found before therapy returned to normal after treatment. In 6 patients (cases 21, 22, 27, 29, 30 and 31) serum protein analysis and electrophoresis revealed reversal of albumin/globulin ratio and raised immunoglobulins, except in case 22. CSF electrophoresis done in 3 cases (27, 30 and 31 revealed features of hyperglobulinaemia with raised IgG levels. Similarly in two of these cases (30, 31) serum also showed significantly elevated IgG and IgA components.

In case 44 which presented with fear of polymyositis serum CPK was 1550 (N 20-170 U/L), SGOT 382 (N=0-30 U/L), SGPT 268 (N=0-30 U/L) and were normal when repeated clinical improvement.

Treatment All patients received chloramphenicol, co-trimoxazole, ampicillin and gentamycin either alone or in various combinations. Dexamethasone was used in 20 and the recovery pattern was better

in this group.

Duration of hospital stay in 54 eases varied from 1 to 65 days with a mean duration of 15 ± 14 days. 24 (44.4%) recovered completely, 29 (36%) partially (including one treated outside) and 1 did not improve at the time of discharge and was lost for followup. Nine succumbed to the disease (16%).

Follow up Of the 46 patients (including one treated outside) that survived, 24 (55%) had come for follow up. The follow up period varied from 7 to 927 days (mean 286 days). Twenty-one of them had made complete recovery. One patient (case 8) had shortening of the left leg with contracture of calf muscles and minimal spasticity of the left limbs. One of them (case 19) had bilateral foot drop and needed calipers.

Pathological Features

The resected abscess in case 54 had a thin yellowish wall, suggesting xanthomatous reaction. Histological examination revealed features of a chronic abscess bordered by gliosed brain.

Complete necropsy was performed in one case and in 6 the study was restricted to the examination of the brain alone. Three had features of frank, pyogenic meningitis, one had focal necrotising myelopathy, while in the other three the essential microscopic pathology was confined to the cerebellum and inferior olivary nuclear complex.

The three cases of the meningitis (cases 1, 2, 7) group had purulent exudate in the superolateral surface extending to the base of the brain, obscuring the vessels and the cranial nerves (Figure 1). The superficial veins revealed thrombophlebitis while the sinuses were patent. Gross evidence of ventriculitis was seen, especially in the third ventricle, extending to hypothalmic areas. Histological examination confirmed meningitis. In addition to the acute polymorphonuclear response many histiocytes with erythrophagocytosis were observed, a feature as in the ulcers in Peyer's patches of the ileum in typhoid fever. Many of the parenchymal arterioles and venules in the brain showed vasculitis and thrombosis surrounded by fibrin and haemorrhages (Figure 2A). In the deep white matter of the cerebral cortex multiple discrete zones of demyelination around necrotising vasculitis were seen. The ventricular lining was covered by the purulent material, the inflammation spilling to the subependymal areas of the parenchyma (Figure 2B). The meningeal inflammation had extended into the cranial nerves especially the optic nerves.

- ***Basal view of the brain showing thick purulent exudate in the interpeduncular fossa extending on to the temporal lobes and cerebellum. (case 2)***
- ***Periventricular parenchymal inflammation and vascular necrosis H.E. × 60 (case 1)***
- ***Inflammatory exudate in the fourth ventricular cavity, subependymal perivascular haemorrhages and inflammatory cuff. H.E. × 30 (case 1)***

Case 35 had typical typhoid lesions in small intestine and liver in addition to bronchopneumonia and toxic myocarditis. The brain was oedematous and revealed neuronal loss and astrocytic proliferation in the dentato-olivary pathway. The upper cervical cord had softened with focal necrosis involving one half of the grey horns and the lateral columns. No significant vasculitis of the spinal vessels was seen. The encephalomyelopathy noted was considered secondary to salmonella infection and toxaemia.

In three cases (case 10, 32, 33) grossly the brain was unremarkable but for oedema. There was relative paucity of inflammatory reaction. In all of them definite neuronal loss, and reactive astrocytosis was

seen in the dentate nucleus in the cerebellum and the inferior olivary complex of the medulla oblongata. The existing neurons revealed chromatolysis, cytoplasmic vacuolation and variable degree of degeneration, in both the areas (Figures 3A.B). Mild pallor and spongy change of myelin tract was noted in the hilum of the inferior olive and the dentate nucleus. In addition there was patchy loss of the Purkinje cells of cerebellum. The features indicate transynaptic degeneration in the olivary-dentate-cerebellar pathway. The other nuclear structures and fibre tracts were normal.

- ***Low power view of inferior olivary nucleus showing patchy loss of neurons and glial prominance (arrow). H.E. × 30 (case 33)***
- ***Higher magnification showing central chromatolysis, peripheral migration of nucleus and occasional cytoplasmic vacoulation of the neurons and reactive astrocytic proliferation. H.E. × 240 (case 33)***

Discussion

The genus Salmonella consists of more than 1,700 serotypes. Of these, about 100 are pathogenic to man and the most frequent of them is Salmonella typhimurium [11]. At least 23 types of Salmonella have been identified as the etiological agents in meningitis. Of these the outstanding exception is S. typhi, which is pathogenic only to man. In the present series, the characteristic clinical features in most of the patients, a positive widal test and/or a positive culture for S. typhi established an unequivocal diagnosis of typhoid infection.

In this series, 7 presented with meningitis. It is difficult to conclude as to whether the meningitis was primary or secondary to typhoid as autopsy is limited to the brain and intestine was not examined. However, in case 2, the long duration of illness, consolidation of the lung, which is found in about 10% of typhoid cases, and hepatomegaly indicate that meningitis was probably secondary to typhoid. In cases 1, 5 and 7 the short duration of illness and the absence of signs of other system involvement suggest that meningitis could be probably primary in origin. Likewise, the case 4 reported by Chanmugam [4] was probably a case of primary meningitis. In the 2 cases reported by Bayne-Jones [12] and Lantin and Morales [13] initial lumbar puncture yielded no abnormal findings, but grossly purulent CSF was found on repeat examination, 3 and 9 days later, respectively, during the third week of typhoid illness. Thus, they were cases of secondary pyogenic meningitis.

The pathogenetic mechanisms of neurological deficits without overt meningitis are probably multiple. Hyperpyrexia, dehydration, electrolyte and acid-base with balance, bacteremia and toxaemia have been incriminated as etiological factors [14]. Immune origin of inflammatory reaction, must be considered, in view of perivenous myelinoclysis and vasculitis reported by Ramachandran et al [7] and the observations in the present series in cases of clinical meningitis. The occurrence of neurological complications due to typhoid vaccine and intense immune reaction found in typhoid strongly suggest an immune origin of inflammatory reaction. Osuntokun [1] has also suggested that the transient nature of parkinsonian features may result from interference of endotoxin with cholinergic and dopaminergic pathways in the nervous system.

Pre-existing disease was present in both the cases of brain abscess, one had hereditary ataxia (case 54) and the other had a stroke due to occlusion of internal carotid artery for which he had undergone STA-MCA shunt (case 55). The devitalised cerebral parenchyma appears to have become a favourable nidus for the circulating S. typhi organisms resulting in an abscess.

We feel during the natural history of typhoid infection the incidence of neurological complications with normal CSF is fairly common. Similar neurological complications due to other systemic bacterial infections have been reported in literature [15].

Acknowledgements

We are grateful to Prof. K. B. Sharma, Department of Microbiology, Lady Hardinge Medical College and Salmonella Phage Typing Centre, New Delhi for typing the isolates. We also thank Mr. M. V. Srinivasan for secretarial help.

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