Neuroleptospirosis - revisited: experience from a tertiary care neurological centre from south India


Departments of Neurology, *Neuropathology, **Neuromicrobiology & + Biostatistics National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India

Received September 7, 2005

Background & objectives: Leptospirosis is a zoonotic disease commonly reported from south India. Neurological manifestations seen in about 10-15 per cent of cases, are protean and remain unrecognized and diverse. We evaluated the pattern of nervous system involvement in leptospirosis, among patients presenting to the emergency services of a tertiary care neurological centre in south India, and also analysed the outcome and prognostic indicators.

Methods: The diagnosis of neuroleptospirosis was based on clinical and laboratory evidence of hepatorenal syndrome, and serum or CSF positivity for antileptospira antibody by a macroscopic agglutination test (MAT) and by ELISA in a limited number of samples.

Results: A total of 31 patients (M:F 27:4, age range 6-68 yr, mean 36.4 ± 14.3 yr) were treated during the five year period. Acute fever with chills and rigors, headache and vomiting were the presenting manifestations; 25 patients (81%) had altered sensorium for a period ranging from 1-8 days, four (12.9%) being deeply comatose. Eleven (35.5%) had acute symptomatic seizures at the time of presentation. Conjunctival congestion with or without haemorrhage was seen in 12 patients (38.7%), icterus in 14 (45%) and mild hepatosplenomegaly in 11 (35.5%). Early papilloedema was observed in three. Only three patients had localizing deficits. CT scan was normal in 18 of 27 (67%), while 7 (26%) had diffuse cerebral oedema. CSF pleocytosis with lymphocytic predominance (mean 50 cells/µl) and elevated protein levels (mean 115.5 ± 67.5 mg %) were noted. Leptospira antibody was detected in serum of all, and 5 of 22 in CSF samples. Eight patients (26%) succumbed. Deep altered sensorium at presentation and raised CSF protein were two poor prognostic indicators. Pathological study of brain in five cases revealed encephalitic features and in addition immune mediated acute disseminated encephalomyelitis (ADEM) like pathology in two cases.

Interpretation & conclusion: Neuroleptospirosis should be considered in the differential diagnosis of neuroinfections associated with hepatorenal dysfunction, in endemic areas. Leptospira antibody can be detected in CSF also in some cases. Deep altered sensorium at presentation indicates poor prognosis.

Key words Leptospirosis - macroscopic agglutination test - neurological manifestations - prognostic factors
Leptospirosis in humans is a common zoonotic disease, transmitted through rats and is found all over the world, more so in the developing and underdeveloped countries. It is observed both in urban and rural settings in tropical and temperate climates. The animal hosts and carriers of this infection are household rats, bandicoots, pigs, cats, dogs and cattle, which also act as reservoirs for many endemic viral, bacterial and parasitic diseases, transmitting them to the human host by contact.

In developing countries such as India, leptospirosis is often underdiagnosed because of protean clinical manifestations, leading to significant morbidity and mortality. The clinical spectrum can range from an asymptomatic, subclinical infection to a fatal hepatorenal syndrome (Weil’s disease). Though physicians and internists in tropical countries are sensitized to diagnose a patient with characteristic clinical features, sometimes the diagnosis is missed because of atypical presentation, especially when associated with neurological manifestations. This subgroup of patients are empirically treated for cerebral malaria, dengue fever, tuberculous meningitis, hepatic encephalopathy, viral encephalitis, etc., based on seasonal prevalence, endemicity of the infective agent and clinical bias. They are referred to a tertiary care hospital, following poor therapeutic response, often in a moribund state. Hence, it is essential to be aware of these uncommon manifestations of leptospirosis, especially with neurological deficits. Early intervention in such cases will be rewarding.

We undertook this study to evaluate the clinical features and laboratory profile of patients presenting with various neurological manifestations, following leptospiral infection (neuroleptospirosis) in a tertiary care neurological centre in south India [National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, located in a temperate zone, with significant rodent population in the environment. There were only 5 cases in the retrospective period and the remaining 26 cases were prospectively studied from November 2000 to November 2003. The patients presenting with symptoms and signs referable to nervous system involvement, biochemical evidence of hepatorenal dysfunction, and serological evidence of leptospiral infection by macroscopic agglutination test (MAT) were analyzed. Patients with similar neurological manifestations but diagnosed to have cerebral malaria, enteric encephalopathy, viral encephalitis, tuberculous meningitis, dengue fever with neurological manifestations, or septicaemia were excluded from the study by relevant bacteriological, haematological and serological tests and CSF evaluation.

All patients were evaluated by detailed clinical history obtained from the patient or close relatives living with the patient sharing the household, and meticulous physical examination including detailed nervous system examination. Routine haematological, bacteriological and biochemical investigations of the peripheral blood were carried out, including examination for malarial parasite, renal and liver function tests, blood culture and Widal test. Lumbar CSF was collected after a cranial CT (computed tomographic) scan unless contraindicated by raised intracranial tension or poor neurological status of the patient. Serum (n=30) and CSF (n=22) samples were subjected to antileptospira antibody assay by the MAT, available in the hospital. A limited number of serum and CSF samples were tested by ELISA for leptospira specific IgM at the Regional Reference Laboratory, Bangalore. Patients strongly suspected to have leptospirosis clinically, received crystalline pencillin even before the laboratory confirmation of the diagnosis.
Partial autopsy confined to the examination of the brain was carried out in four cases, while needle biopsy of the liver (n=5) and transnasal brain biopsy through cribriform plate in one case were carried out in the patients who succumbed to the disease, after obtaining informed written consent from the close relatives. Representative tissue sections were processed for paraffin embedding and histological evaluation.

**Statistical analysis:** The clinical data collected were entered in the SPSS-10 software package for descriptive and analytical statistics. Results of the study were expressed as mean with standard deviation and range for continuous variables and as percentages for discrete variables. The clinical and laboratory characteristics of the patients who succumbed to the illness were compared with those who recovered, to determine the prognostic factors. The independent sample ‘t’ test was used to compare the means between the two groups of patients recovered and expired, where the variables were quantitative. For categorical variables, where the sample size was small, Fisher’s exact probability test was used.

**Results**

During the study period (1998-2003), 31 cases fulfilling the inclusion criteria were evaluated. All the cases were positive for serum antileptospira antibody, 30 by MAT and one by ELISA (IgM antibody). In addition, 5 of 22 CSF samples tested by MAT were positive for antileptospira antibody. The mean age of the cohort was 36.4 ± 14.3 yr (range 6-68 yr). Majority of patients were in the age group of 20-40 yr; 27 patients (87.1%) were males. In a 40 yr old male, with 6 days of illness, both serum and CSF had antileptospira antibody (IgM) and in addition in both the samples motile spirochetes could be demonstrated by dark ground microscopy. This patient also had IgM antibody of significant titre to Japanese encephalitis (JE) virus in CSF.

Majority of patients were farmers (51.6%) and manual labourers (22.6%) by occupation, living in low socio-economic conditions. Leptospiral infection showed a definite seasonal association, majority of cases (84%) presenting during the months of October to January.

All except one patient had fever (30 cases), 22 (71%) had headache and 20 had vomiting (64.5%) at the onset of illness. Mean duration of fever was 9.5 ± 4.2 days, headache 8.7 ± 4.5 days and vomiting 6.3 ± 4.5 days. Fever was of high grade in 19 (61%) and mild to moderate in the remaining patients. History of jaundice was reported only in 3 patients (9.7%). Of the 31 patients, 25 (81%) had impaired sensorium for a period ranging from 1 to 8 days (mean 1.9 ± 1.7 days). About one third of the cases had history of seizures, 10 manifesting generalized tonic clonic seizures (GTCS) and one had multifocal seizures.

Examination of the bulbar conjunctiva revealed icterus in 14 (45.2%), conjunctival suffusion in 7 (22.6%) and conjunctival haemorrhage in 5 patients (16%). Mild hepatomegaly was noticed in 7 patients (22.6%), while splenomegaly was detected in 4 (12.9%). Of the 25 patients with altered sensorium, 21 (84%) were in a drowsy to stuporous state and four in deep coma. Papilloedema was observed in three patients. Examination of the motor system did not reveal any focal deficits in 28 patients (90%) while left sided hemiparesis was noted in 3 (9.7%). Bilateral facial weakness and bilateral lateral rectus palsy was noted in one patient each. Neck stiffness was present in two-thirds of patients (67.7%).

Mean haemoglobin level was 12.5 ± 1.9 g%, leukocytosis was seen in 17 of 28 (61%) patients, with a mean WBC count of 11288 ± 4643 cells/µl (range 4600 to 22300 cells/µl) and neutrophilic leucocytosis was noted in 16 (96%) patients. Platelet counts ranged from 1.6 to 3.4 x 10³ cells/µl (mean 1.3 ± 0.98 cells/µl). Renal function tests were deranged in 20 (64.5%) patients; mean blood urea was 84.5 ± 58.5 mg per cent, serum creatinine 1.8 ±1.3 mg per cent, serum sodium 137 ± 6.5 meq/l and serum potassium 4.42 ± 0.9 meq/l. Liver function tests revealed elevated hepatic enzymes in all and abnormal serum bilirubin in 23 patients (74%). Mean serum bilirubin was 3.5 ± 2.5 mg per cent, serum
glutamate-oxaloacetate transaminase 524 ± 1068 u/l and glutamate-pyruvate transaminase 503 ± 1453 u/l. Hepatic dysfunction was evident in all patients at the time of admission, while renal dysfunction was evident only in 20/31 (64.5%) of the patients.

Lumbar puncture was deferred in six patients due to poor neurological status and diffuse cerebral oedema. Mean CSF cell count was 50.2 ± 72 cells/µl (range 1 to 350 cells/µl); 7 of 25 patients (28%) had normal CSF cell count (≤5 cells/µl). Lymphocytic pleocytosis was noted in 13 of 18 patients (72%) while neutrophilic predominance in remaining patients. CSF protein was elevated in 22 patients (88%) and normal in 3 patients. Mean CSF protein was 115.5 ± 67.5 mg per cent with a range of 5-323 mg per cent. Six patients (24%) had CSF sugar less than 60 mg per cent and only one had sugar ≤ 40 mg per cent.

Cranial CT scan was normal in 18 of 27 (67%) patients, diffuse cerebral oedema was noted in 7 (23%) patients, right middle cerebral artery territory (MCA) infarct in one and a lacunar infarct in the left internal capsule in one another patient. In the patient with MCA infarction, the magnetic resonance imaging (MRI) (n=1) brain (Fig. 1A) confirmed the anatomical location of the infarct but MR angiogram was normal (Fig. 1B) with no evidence of vascular occlusion.

**Outcome:** Of the 31 patients, eight (26%) succumbed to the infection. Remaining patients were either discharged and/or referred to general hospital after the general condition improved. The whole cohort of patients with neurological manifestations was divided into two groups- those who survived (group A, n=23) and those who succumbed (group B, n=8). All clinical and laboratory parameters were compared between the two groups, to evaluate the prognostic factors associated with mortality (Table). The two statistically significant parameters for poor prognosis observed were elevated CSF protein and the degree of altered sensorium at the time of admission. CSF protein concentration was significantly (P<0.001) higher in group B (183.3 ± 73.2 mg %) in contrast to those who survived (group A, 90.6 ± 45.72 mg %). One fourth of cases who succumbed were in deep coma, while only 8.7 per cent were comatose in group A (P < 0.037 - Fisher’s exact test). Patients who succumbed were younger than those who survived. Neutrophilic leukocytosis, thrombocytopenia and hepatorenal dysfunction were more marked in group B, but did not reach statistical significance because of the small sample size.

![Fig. 1. (A) Magnetic resonance imaging (MRI) scan demonstrating right middle cerebral artery infarct in neuroleptospirosis. (B). Normal magnetic resonance angiography (MRA) of the same patient [shown in Fig. 1 (A)].](image-url)
Pathological features: Among eight patients who succumbed, whole brain was examined in four and linear bits of brain biopsy in one case, while liver biopsy was available in five cases. The liver biopsy revealed focal hepatocyte necrosis and infiltration by polymorphs, lymphocytes and histiocytes (Fig. 2). The Kupffer cells were prominent with erythrophagocytosis.

Table. Prognostic factors in the patients with neurological manifestation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients survived (n=23)</th>
<th>Patients expired (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37.6 ± 16.2</td>
<td>33.0 ± 5.98</td>
</tr>
<tr>
<td>Seizures (%)</td>
<td>30.4</td>
<td>50</td>
</tr>
<tr>
<td>Icterus (%)</td>
<td>47.8</td>
<td>37.5</td>
</tr>
<tr>
<td>Total WBC count (cells/µl)</td>
<td>10693 ± 4459</td>
<td>12775 ± 5063</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>68.2 ± 14.9</td>
<td>75.9 ± 9.8</td>
</tr>
<tr>
<td>Platelet count (cells/µl)</td>
<td>142266 ± 106688</td>
<td>86400 ± 54454</td>
</tr>
<tr>
<td>Blood urea (mg %)</td>
<td>76.4 ± 61</td>
<td>107.8 ± 46.4</td>
</tr>
<tr>
<td>Serum creatinine (mg %)</td>
<td>1.69 ± 1.28</td>
<td>2.19 ± 1.17</td>
</tr>
<tr>
<td><em>SGOT (u/l)</em></td>
<td>146</td>
<td>236</td>
</tr>
<tr>
<td><em>SGPT (u/l)</em></td>
<td>116</td>
<td>171.5</td>
</tr>
<tr>
<td>CSF protein (mg %)</td>
<td>90.6 ± 45.7</td>
<td>183.3 ± 73.2*</td>
</tr>
<tr>
<td>Deep coma (%)</td>
<td>8.7</td>
<td>25**</td>
</tr>
</tbody>
</table>

* Values are given as median
* Values are given as median
*SGOT, serum glutamate-oxaloacetate transaminase
*SGPT, serum glutamate-pyruvate transaminase
*P < 0.001 compared to group A (t test)
**P < 0.037 compared to group B (Fisher’s exact test)

Fig. 3. Sparse lymphohistiocytic infiltrates in the subarachnoid space. (HE x 40). Inset: The histiocytes in the subarachnoid space show vacuolation following erythrophagocytosis. (HE x 300).

Fig. 4. Microglial nodules in basal ganglia, indicative of encephalitis process. (HE x 240).

The brain biopsy, on microscopic examination revealed, oedema and microglial prominence at places forming aggregates. The features are rather non specific, but suggestive of an encephalitic process.

The brains collected at autopsy (four cases) were oedematous and congested. The meninges covering had sparse inflammatory infiltrate, an admixture of histiocytes with erythrophagocytosis (Fig. 3), lymphocytes and plasma cells. Perivascular lymphocytic cuffing was not prominent except in two cases. A notable feature was the presence of microglial nodules (Fig. 4) in multiple areas of the brain variably involving the cerebral cortex, basal ganglia, thalamus, substantia nigra in midbrain, pons, molecular layer and dentate nucleus of cerebellum.
and inferior olivary nucleus in medulla oblongata. The trigeminal ganglia were densely infiltrated by the histiocytes, extending along the nerve roots.

In two cases, perivenous haemorrhages and zones of demyelination were seen in thalamus, basal ganglia, and cortical white matter, especially in the parietal and occipital lobes (Fig. 5 A-F). Variable degree of perivascular lymphohistiocytic infiltration, and transudation of fibrin and inflammatory cells from the venular walls in the midst of fresh and dehaemoglobinized haemorrhage were observed (Fig. 5 D-F). These features of perivenous demyelination and haemorrhage are characteristic of postinfectious immune mediated acute disseminated encephalomyelitis (ADEM). The cervical cord was histologically normal in all cases.

The case where MRI revealed right MCA territory infarct, permission for autopsy was not available,
hence pathological features could not be established. Interestingly, in one of the cases (40 yr old man), who presented with 6 days of neurological illness, on cranial CT scan, thalamic hypodensities were noted. In view of endemicity, CSF was tested and found to have IgM antibody to JE. In addition, serum and CSF had IgM antibody to leptospira and by dark ground microscopy characteristic motile leptospira were detected in the blood, thus establishing co-existing infection (double infection). On pathological examination of the brain multiple, rarified, acellular necrolytic lesions, characteristic of JE were found in the cerebral cortex, basal ganglia, thalamus and mid brain, though meningitis was not evident.

Discussion

In the present study, clinically detectable jaundice was noted in 45 per cent of subjects while conjunctival congestion/haemorrhage was present only in 38.7 per cent of patients. This indicates that icterus and conjunctival changes are not universal and their absence should not be taken as evidence against the diagnosis of leptospiral infection. Neurological manifestations are seen in about 10-15 per cent of patients with leptospiral infection and often remain unrecognized.

The commonest neurological presentation, in the present study was altered sensorium, followed by seizures. Pure meningitic presentation was noted in four patients (13%), pure encephalitic presentation in 8 (26%) and a meningoencephalitic picture in 17 (55%) patients. Though the commonest neurological abnormality reported in literature was aseptic meningitis, majority of patients presented with altered sensorium (encephalitic picture). This may be due to a referral bias, as only very sick and seriously ill patients are referred to the tertiary care neurological centre. In a general hospital setting the number of patients with aseptic meningitis could be higher. Seizure as a predominant manifestation of leptospirosis is hitherto not reported in the literature. Hence one needs to consider neuroleptospirosis in the differential diagnosis, whenever a diagnosis of viral encephalitis is made, especially in endemic areas with seasonal prevalence. The exact mechanism of seizures in neuroleptospirosis is unknown. The seizures could be secondary to diffuse encephalitis following leptospiral infection or due to metabolic dysfunction related to hepatorenal syndrome. Except for alteration in sensorium, neurological examination did not reveal any focal neurological deficits in majority of the patients and only 3 (9.7%) patients had hemiparesis. In a study by Heath et al, among 235 cases with neurologic manifestations only one had hemiplegia and in this patient, meningitis was demonstrated at autopsy. Unlike the cases reported by Panicker et al, none of our patients presented with myelitis or myeloradiculopathy.

CSF leptospiral antibody was assayed by the same technique, used to detect serum leptospiral antibody. Though serum was positive in all cases, CSF antileptospiral antibody was positive only in 23 per cent of cases. To the best of our knowledge, CSF leptospiral antibody has not been assayed in any of the previous clinical studies. The significance of this finding requires further evaluation in a larger sample, to establish if intrathecal synthesis of antibody occurs, influencing the course of the disease.

Cranial CT scan was normal in most of the patients. The commonest abnormality detected was diffuse cerebral oedema, similar to acute viral encephalitis or cerebral malaria.

The prognosis of neuroleptospirosis is largely unknown. Most of the studies report mortality rates for systemic leptospirosis, varying from 5-15 per cent. In the study by Singh et al, mortality rate was 24.1 per cent and the major cause of mortality was pulmonary involvement. In the study of Heath et al, which included patients with neurological and non neurological manifestations, the mortality was 7 per cent. In this study, 26 per cent of patients succumbed to the infection. This high mortality could be because of late referral and consequent delay in management.

Information on prognostic factors in patients with neuroleptospirosis is not available in the literature. Raised CSF protein concentration and severity of altered sensorium at the time of admission were found to be responsible for poor prognosis.
Neutrophilic leukocytosis, thrombocytopenia and hepatorenal dysfunction were more marked in those who succumbed, but these did not reach statistical significance, probably due to small sample size and hence needs further evaluation.

Another important aspect of the present study is, pathological examination of the brain tissue was available in 5 of 8 patients who died. Limited pathological studies of the brain published in the literature in cases of neuroleptospirosis, considered the features to be non-specific. Most common finding reported was meningeal and perivascular mononuclear cell inflammatory infiltrates. In the present study, histological feature of parenchymal microglial nodule, characteristic of encephalitic process was noted in addition to mild meningitic picture. Without haematological and serological corroboration, the cases cannot be distinguished from endemic viral encephalitis. The perivascular ring haemorrhages and demyelination observed in two cases could represent immune mediated pathology like ADEM. Similar pathology has been noted by us in cases of cerebral malaria as well (unpublished data). These could have contributed to poor prognosis and mortality following leptospira meningoencephalitis.

An early diagnosis of neuroleptospirosis is mandatory, as effective and specific treatment is available and neurological sequelae are unusual, unlike acute Japanese encephalitis or Herpes encephalitis which lead to significant morbidity and mortality. The role of steroids in the treatment of leptospirosis during the immune phase is controversial. Trivedi et al evaluated the role of high dose steroids in patients with pulmonary involvement secondary to leptospirosis. Though the number of patients in their study was small, they found less mortality among patients receiving steroids. The role of steroids in patients with neuroleptospirosis is not known and needs to be evaluated in future studies.

In conclusion, neuroleptospirosis should be considered in the differential diagnosis of all neuroinfections with hepatorenal dysfunction especially in endemic areas during the winter season. High index of suspicion is needed for proper diagnosis and early institution of treatment. Raised CSF protein and deep altered sensorium are associated with an increased risk for mortality.

References


Reprint requests: Dr P. Satishchandra, Professor, Department of Neurology, National Institute of Mental Health & Neuro Sciences (NIMHANS), Bangalore 560029, India
e-mail: psatish@nimhans.kar.nic.in