Rabies viral encephalitis: clinical determinants in diagnosis with special reference to paralytic form

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ABSTRACT

Background Rabies is an important public health problem in developing countries such as India where an alarmingly high incidence of the infection is reported every year despite the availability of highly effective, potent and safe vaccines. In clinical practice, diagnosis of the furious (encephalitic) form of rabies poses little difficulty. In contrast, the paralytic form poses a diagnostic dilemma, to distinguish it from Guillain–Barré syndrome. The problem is further compounded in the absence of a history of dog bite, clinical features resembling a psychiatric syndrome.

Method The present study analysed the spectrum of neurological manifestations in 47 cases of rabies encephalitis (34 paralytic, six encephalitic, and seven psychiatric manifestations) from two hospitals in south India, confirmed at post-mortem by demonstration of a viral antigen in the brain. A history of dog bite was elicited in 33 patients and fox bite in one. Twenty-two patients received postexposure prophylaxis. The incubation period ranged from 7 days to 4 years. Clinical features were analysed, looking for any clinical pointers that provide clues to a diagnosis of paralytic rabies.

Results and discussion Fever, distal paresthaesias, fasciculation, alteration in sensorium, rapid progression of symptoms and pleocytosis in cerebrospinal fluid should alert the neurologist to consider rabies encephalomyelitis. Detection of the viral antigen in the corneal smear and a skin biopsy from the nape of the neck had limited usefulness in the ante-mortem diagnosis. Although a few clinical signs may help indicate rabies encephalomyelitis antemortem, confirmation requires neuropathological/neurovirological assistance. The preponderance of atypical/paralytic cases in this series suggests that neurologists and psychiatrists need to have a high index of clinical suspicion, particularly in the absence of a history of dog bite.

INTRODUCTION

Rabies is a viral zoonosis. Infection of humans usually follows bites by rabid animals and is almost invariably fatal once the signs of the disease manifest. It is estimated that each year at least 55 000 people die from rabies, of which 20 000 are from India.[1] Human rabies continues to be endemic in India except for the islands of Andaman, Nicobar and Lakshadweep. The annual incidence of rabies in India is 2/100 000 population.[2] Atypical/paralytic cases constitute about 20% of these cases. The animal responsible for bites in India is the dog (96.2%) followed by several other species.

Two distinct clinical syndromes, furious and paralytic rabies, have been recognised in humans. Rabies is well recognised in its classical furious form with predominant limbic symptoms, hydrophobia, aerophobia and phobic or inspiratory spasms. There is a paucity of information on the clinical features of rabies presenting in the paralytic form. These cases are often clinically, electrophysiologically and pathologically indistinguishable from Guillain–Barré (GB) syndrome.[3] The situation is further compounded by the unavailability of a definitive diagnostic test for GB syndrome and limited availability of ante-mortem tests for rabies. It is possible that many cases of paralytic rabies are misdiagnosed as GB syndrome and empirically treated for the same.

Rapid diagnosis of rabies is important for appropriate infection control and public health measures to be instituted, as rabies is a notifiable disease. Although no well-documented cases of transmission between humans following a bite from an infected individual have been reported (with the exception of organ transplants), barrier nursing is used, and pre-exposure prophylactic vaccination is offered to the relatives and treating clinical and nursing staff. In addition, specimens sent to non-specialist laboratories may need to be tracked down for accurate case detection and epidemiological data.[4]

Patients referred to a neurologist are more likely to have a paralytic/atypical form of rabies rather than the classical form, and most of the time, diagnosis is not certain at presentation. This leads to utilising intensive care unit facilities necessitating proper disinfection for this dreaded neurotrophic viral infection especially in endemic countries.

Though this disease has been recognised for more than a century, and with India having the distinction of reporting the highest number of human rabies deaths, there are no large case series in the literature highlighting the spectrum of neurological manifestations of rabies and determining clinical pointers, if any, that could differentiate from GB syndrome. Hence, this retrospective study has been undertaken in two tertiary care hospitals from South India.

MATERIAL AND METHODS

There were a total of 47 cases of rabies in the clinical records of neurological services and neuropathology at NIMHANS, Bangalore for the past 30 years (two cases were managed at Nizam's Institute of Medical Sciences, Hyderabad and referred for definitive diagnosis).

Among these, a definitive diagnosis of rabies was established by post-mortem examination of

the brain/spinal cord and immunohistochemical localisation of rabies viral antigen in 42 cases by the indirect immunoperoxidase technique using polyclonal antibody directed against rabies viral nucleocapsid (1:1500 dilution, developed in house and validated by SDS polyacrylamide gel electrophoresis). One case was diagnosed on the basis of clinical suspicion and rising cerebrospinal fluid (CSF) antibody titres, and four were suspected cases based on characteristic clinical picture including hydrophobia, rapid progression and prior history of dog bite.

The clinical records of these patients were reviewed for epidemiological factors, clinical presentation, neuroimaging features, electrophysiological findings, cerebrospinal fluid picture, course of illness and neuropathological findings at autopsy. The study was approved by the Institutional Scientific Ethics Committee.

RESULTS

Out of 47 patients, in the present cohort, 36 were males and 11 females. The mean age of the patients was 31.6±18.1 years (range 3–70 years). A history of dog bite was available in 33 of 47 patients, while one patient had a history of fox bite. Thirteen patients were unaware of any animal bites. In these cases, there was no evidence to suspect bat rabies, as all these patients were from high-population areas that bats normally do not inhabit. The median incubation period between the animal bite and development of symptoms was 2 months (range 7 days to 4 years). The mean duration of illness at presentation was 5.4±3.1 days (range 1 to 15 days). The median duration of illness from onset of symptoms until death was 11 days (range 2 days to 6 months). One patient had partial recovery and survived for 1 year. Prodromal symptoms consisted of fever in 24 (51%) and headache in 11 (23%) patients. Fasciculations were noted in 11 (23%) patients. Thirty-four patients (72%) had paralytic onset of symptoms, while 13 (28%) had alteration in sensorium or psychiatric symptoms (n=6) as the first presenting feature.

Patients in the paralytic onset rabies group who were clinically at presentation diagnosed as GB syndrome (n=17), encephalomyeloradiculopathy (acute disseminated encephalomyelitis (ADEM), n=10), lumbosacral polyradiculopathy (n=5) or myelomeningitis (n=2) developed rapidly progressive weakness of limbs with early bulbar involvement which occurred within the first week of onset of symptoms in most cases (median 4 days; range 1–12 days). All these patients developed alterations in the sensorium during their hospital stay, and none were conscious during the terminal stage. Patients who were diagnosed as having ADEM (n=10) developed weakness as the first symptom followed by encephalon involvement, which usually developed prior to arrival at the hospital. Analysing these retrospectively, these two groups (GB syndrome and ADEM) may be the same, the only difference being the temporal evolution of encephalon involvement, being a terminal event in cases with a GB syndrome-like presentation, whereas it was the initial manifestation in cases presenting as ADEM. The evidence of encephalon involvement in these two groups was mainly in the form of progressive deterioration in the level of sensorium. Only two patients developed hallucinations, and five developed aerophobia or hydrophobia during the course of illness. More detailed clinical and demographic information of the cohort of paralytic rabies cases is provided in table 1.

Among 34 patients with paralytic symptoms, a history of dog bite was available in 26 cases (table 1). Of these, 10 received postexposure prophylaxis (Semple Sheep Brain Vaccine—9 (one to 14 doses), and Verorab in one (four doses)). A full course of Semple vaccine was received in only one case (case 23, table 1). This patient, however, did not receive passive immunisation. Nine cases did not receive vaccination due to logistic reasons, and in seven cases, details of vaccination were not available in the clinical records. Eleven patients were treated with plasmapheresis, as the clinical diagnosis considered was GB syndrome.

Six patients had encephalitic features at onset and did not develop paralysis during the course. Three of these six patients had classical features of furious rabies terminally. Another cohort of six patients were initially diagnosed to have psychiatric disorders such as schizophrenia, delirium tremens, acute psychosis, hypomania and hysteria, and were managed by the psychiatric services of our institute and succumbed to terminally manifesting symptoms and signs of rabies (reported earlier).[5] One patient presented with altered sensorium following acute chest pain and was diagnosed as having coronary artery disease with anterior-wall myocardial infarction and ventricular tachycardia. Altered sensorium was thought to be due to hypoxic encephalopathy. Autopsy confirmed the diagnosis of rabies manifesting with cardiac symptoms.

Haematological investigations of the cases revealed a mean WBC count of 14 066/mm^3 (range 4000–30 000). A CSF analysis was carried out within 48 h of hospital admission (7.4±3 days of onset of illness). CSF cell counts were normal in 11 and increased in 18 patients with mean cell count of 66 cells/mm^3 (range 0–700 cells/mm^3). CSF protein was normal in eight patients and raised in 21 (mean protein 115 mg/dl; range 19–480 mg/dl).

Neuroimaging

Cranial CT with contrast enhancement was carried out in seven patients and was considered normal in all. In one patient with a diagnosis of lumbosacral polyradiculopathy (case 13), MRI of the spine revealed signal-intensity changes in the conus medullaris. MRI of the brain in two patients (cases 27 and 32) showed signal intensity changes in bilateral basal ganglia, thalami and cerebral peduncles (case 27, figure 1A–C).

Electrophysiology

Electrmyography (EMG) was carried out during the second week of illness in three patients who had paralytic onset of symptoms. In one patient, a nerve-conduction study (NCS) was reported to be normal, while the EMG showed evidence of denervation. In the other two patients, NCS showed evidence of motor sensory axonal and demyelinating neuropathy and EMG showed denervation changes. In one of them, serial nerve-conduction studies carried out over a gap of 2 days showed progressive reduction in CMAP amplitude suggestive of ongoing axonal damage.

CSF immunology

An antigen-capture ELISA using monoclonal antibodies to rabies nucleoprotein (N) and glycoprotein (G) developed in house to detect immune complexes to rabies N and G proteins[6] in CSF showed the presence of immune complexes to both rabies N and G proteins in 23 of 30 cases tested (76.6%). None of the negative controls and CSF from other viral infections were positive. Thus, the results were 100% specific, and the sensitivity of this test was 76.6%. Neutralising IgG antibody to rabies by the Rapid Fluorescence Focus Inhibition Test technique was detectable in CSF in 40% of cases. In one patient, a diagnosis of rabies was made on the basis of the clinical picture and rising CSF antirabies antibody titres (IgG). The immunofluorescent test for rabies

Table 1 Clinical and laboratory parameters of cases with paralytic rabies

Serial No.	Age/ gender	History of dog bite and incubation period	Vaccination	Prodromal symptoms	Onset of weakness	Neurological localisation and diagnosis at presentation	Paresth. Fascicu. Hydroph	Cerebrospinal fluid analysis	Paralysis (day of onset)	Brainstem signs (day of onset)	Encephalon signs (day of onset)	Duration of illness until death
1	25/M	Yes, Rt. LL 7 days	Yes	None	All four limbs	Polyradiculopathy GBS	Pares.	Cells 0 Proteins 24 Glucose 36	1	3	4	D4
2	18/M	Yes, 6 months	Yes	Fever	B/L LL	Polyradiculopathy GBS	None	Not available	1	1	4	D4
3	22/M	No		None	B/L LL	Polyradiculopathy GBS	None	Cell: 17 (L16, P1) Proteins 285 Glucose 107	1	7	7	D20
4	45/M	Yes, Rt UL, 7 days	Yes	None	Rt UL	Polyradiculopathy GBS	None	Cells 4, L Proteins 94 Glucose 199	1	1	7	D12
5	3/F	Yes, 90 days	Not taken	Fever	All four limbs	Polyradiculopathy GBS	None	Cells 5,L Proteins 32 Glucose 140	2	2	4	D4
6	35/M	Yes	Not taken	Fever	All four limbs	Polyradiculopathy GBS	Fasci.	Cells 18, L Proteins 32 Glucose 73	3	6	18	D18
7	20/M	no		None	B/L LL	Polyradiculopathy GBS	Pares.	Cells 0 Protein 36 Glucose 88	1	7	10	D18
8	17/M	Yes, 4 years	Yes	Fever, Vomiting	B/L LL	Polyradiculopathy GBS	None	Cells 0 Protein 104 Glucose 30	7	7	12	D14
9	35/F	Yes	Not taken	Fever	Rt LL	Polyradiculopathy GBS	None	Cells 28, L Protein 62 Glucose 64	3	3	7	D14
10	19/M	Yes, 7 months	Not taken	Fever	Rt LL	Polyradiculopathy GBS	None	Cells 250 (L50, P200) Protein 451 Glucose 16	2	3	2	D17
11	33/M	Yes, 2 years	Not taken	Fever	All four limbs	Polyradiculopathy GBS	Hydro	Cells 4, L Protein 95 Glucose 71	8	12	10	D24
12	11/M	No		None	B/L LL	Polyradiculopathy GBS	None	Cells 0 Protein 19 Glucose 148	1	6	6	D15
13	38/F	Yes, 4 months	Not taken	None	Lt. LL	Polyradiculopathy GBS	None	Not done	1	4	14	D14
14	40/M	Yes, Rt LL, 1 year	Yes	None	B/L LL	Polyradiculopathy GBS	None	Cells 50, L Protein 45 Glucose 90	1	2	8	D14
15	70/M	Yes, 18 days	Not taken	None	Rt LL	Polyradiculopathy GBS	None	Not done	1	2	3	D11
16	7/F	Yes, Rt UL, 6 months	Yes	Fever, Vomiting	B/L LL	Polyradiculopathy GBS	None	Cells 22 (14L, 8P) Protein 151 Glucose 237	2	5	13	D13
17	15/M	No		Fever, Headache	B/L LL	Polyradiculopathy GBS	Pares.	Cells 4, L Protein 120 Glucose 48	1	3	7	D16

Continued

Table 1 Continued

Serial No.	Age/ gender	History of dog bite and incubation period	Vaccination	Prodromal symptoms	Onset of weakness	Neurological localisation and diagnosis at presentation	Paresth. Fascicu. Hydroph	Cerebrospinal fluid analysis	Paralysis (day of onset)	Brainstem signs (day of onset)	Encephalon signs (day of onset)	Duration of illness until death
18	12/F	Yes, 6 months	Yes	None	B/L LL	Lumbosacral polyradiculopathy	None	Not done	1	1	4	D4
19	60/M	No		None	Rt LL	Lumbosacral polyradiculopathy	None	Cells 2, L Proteins 27 Glucose 84	1	4	4	D15
20	21/M	No		Fever	Lt LL	Lumbosacral polyradiculopathy	None	Cells 8,L Proteins 38 Glucose 58	2		12	D23
21	13/M	Yes, Lt LL, 26 days	Yes	Fever	Lt LL	Lumbosacral polyradiculopathy	None	Cells 80 (L64, P16) Proteins 118 Glucose 55	4	9	6	D13
22	30/M	Yes, Rt LL, 18 days	Yes	None	Rt LL	Lumbosacral polyradiculopathy	Pares.Fasci.	Cells 122,L Proteins 312 Glucose 68	1	7	8	D8
23	7/M	Yes, Rt LL, 20 days	Yes	Fever, Headache, Vomiting	B/L LL	Myelomeningitis	Fasci.	Cells 220 (L40, P180) Proteins 43 Glucose 55	1	4	7	D15
24	30/M	Yes, Lt LL, 10 days	Yes	Fever, Headache, Vomiting	B/L LL	Myelomeningitis	Pares.	Cells 700 (L140, P560) Proteins 480 Glucose 40	3		5	D8
25	40/M	Yes, Lt LL, 27 days	Yes	Fever	Lt LL	Encephaloradiculopathy (ADEM)	Pares, Fasci.	Cells 110 (L99, P11) Protein 88 Glucose 56	1		2	D5
26	11/M	Yes, 15 days	Not taken	None	All four limbs	Encephaloradiculopathy (ADEM)	Hydro	Not available	2		1	D5
27	6/F	Yes, face & neck, 14 days	Yes	Fever, Vomiting	All four limbs		None	Cells 11, L Protein 33 Glucose 67	2		1	1 year
28	30/M	Yes, 1 year	Not taken	None	B/L LL	Encephaloradiculopathy (ADEM)	Fasci. Hydro	Not available	6	4	1	D6
29	13/M	Yes, 4 months	Yes	Fever	Lt. LL	Encephaloradiculopathy (ADEM)	Hydro	10, L Protein 57 Glucose 30	7	8	8	D8
30	60/M	No		Fever, vomiting	Rt LL	Encephaloradiculopathy (ADEM)	None	Cells 30,(L3, P 27) Protein 64 Glucose 30	5	6	6	D8
31	45/M	No		None	Rt UL	Encephaloradiculopathy (ADEM)	Pares. Fasci.	Cells 5 (L3, P 2) Protein 60 Glucose 59	1	3	7	D13
32	39/F	Yes, 2 months	Yes	None	B/L LL	Encephaloradiculopathy (ADEM)	None	Cells 16,L Protein 114 Glucose 81	1		7	D25
33	50/M	Yes, Lt LL, 5 months	Yes	None	B/L LL	Encephaloradiculopathy (ADEM)	Pares Fasci	Cells 120 (L 108, P12) Protein 214 Glucose 55	1		2	D7
34	30/M	Yes, Rt UL, 1 month	Yes	None	Rt UL	Encephaloradiculopathy (ADEM)	Pares. Fasci	Not done	1	3	5	D11

ADEM, acute disseminated encephalomyelitis; B/L, bilateral; D, day of illness from onset; F, female; Fascicu, fasciculation; GBS, Guillain–Barré Syndrome; Hydroph, hydrophobia; L, lymphocytes; LL, lower limb; Lt, left; M, male; paresth, limb paresthaesias; P, polymorphs; Rt, right; UL, upper limb.

on corneal smears and nuchal skin biopsy was not consistent and hence not found to be useful for diagnosis.

Neuropathological findings

An autopsy confined to the examination of the brain was conducted in 42/47 cases, following informed consent from close relatives. In addition, in seven cases with a paralytic form of rabies, the whole length of the spinal cord was available for examination. A small portion of fresh tissue from cerebellum and hippocampus was used for immunofluorescence using a polyclonal antibody to the rabies virus for rapid diagnosis. The brain and spinal cord, after fixing in 10% buffered formalin for 3 weeks, was sectioned, and representative tissue blocks from different neuroanatomical areas were processed for paraffin embedding and histological evaluation. Sections from the frontal cortex, amygdala, hippocampus, basal ganglia, thalamus, insular cortex, cerebellum, midbrain, medulla oblongata and spinal cord were immunostained using polyclonal antibody to nuclear protein of the rabies virus.

The histological evaluation of the brain revealed minimal inflammatory response in most of the anatomical areas in cases of paralytic rabies. A microglial response was evident with variable neuronophagia in lower cranial nerve nuclei and anterior horn neurons of cervical cord and less in cerebellum in cases of the encephalitic form of rabies. Negri bodies were more easily demonstrable with an increase in incubation period in different anatomical areas, prominent in the cerebellum (figure 2A), hippocampus, frontal and temporal cortex and amygdala, within large neurons. In vaccinated individuals, perivascular lymphocytic cuffing was prominent compared with the non-vaccinated group. Immunostaining, however, revealed the presence of viral antigen in most of the neurons (figure 2B) in a stippled form or as large discrete aggregates in both large and small neurons with extensive dendritic spread and occasional astrocytes in the white matter. Rabies viral antigen and/or Negri bodies were found in all the 42 cases where a histological immunohistochemical evaluation was carried out. No distinct differences were evident between the paralytic and encephalitic forms of rabies in viral antigen distribution in the various neuroanatomical regions of the brain studied.

Pathological examination of the whole length of the spinal cord available in seven cases of paralytic rabies showed variable inflammation, microglial nodules (figure 3A) and neuronophagia signifying ongoing encephalomyelitis. Negri bodies were not evident except in one case, where small intracytoplasmic eosinophillic inclusions (Negri bodies) were discernible within the ganglion cells of the dorsal root ganglion representing sites of viral replication (figure 3B). Neurons appeared surprisingly well preserved with minimal signs of degeneration despite significant neuronal loss in some cases. The radicals of spinal roots showed variable inflammation (figure 3C) and focal demyelination (figure 3D,E) reminiscent of Guillain–Barré syndrome. Demyelination was also seen to involve the posterior and lateral columns of the spinal cord corresponding to the clinical symptomatology (figure 3C).

Immunohistochemistry revealed abundant viral nucleocapsid antigen within the neurons (figure 2C,D) of anterior and posterior horns in diffuse or speckled patterns (figure 2D, inset). Dendritic spread of viral antigen was prominent in some cases. Focal spread of viral antigen was also evident in spinal nerve roots. A caudocranial gradient in distribution of viral antigen and inflammation was noted in the spinal cord with maximal changes evident in lumbosacral segments in comparison with the cervical segment. A detailed morphological study of the spinal cord and immunophenotyping of the inflammatory cells is being communicated separately. A correlation of spinal cord pathology with temporal evolution of the paralytic symptoms was difficult, as the pathology seen represented terminal changes at autopsy.

DISCUSSION

Subjects of all age groups are susceptible to rabies, though it is more common among children below the age of 15 years (especially males of low socio-economic groups) because of their exposure to street dogs while playing. Nearly 30–50% receive postexposure vaccination.[1] In the current study also, the age of the patients ranged from 3 to 70 years, while 13 patients (28%) were younger than 15 years of age. Thirteen patients (28%) were not aware of any animal bite, and hence the absence of history of dog bite does not rule out the diagnosis of rabies. This is particularly important in countries where rabies is endemic, and a high index of clinical suspicion should be maintained for appropriate therapy.

Only 22/47 patients (46.8%) received vaccination, which was inadequate in most of the cases. Out of these 22 patients, 10 received Semple vaccine, which is a nerve-tissue-based vaccine with high risk of developing allergic encephalomyelitis and polyneuritis. Furthermore, nerve-tissue-based vaccines are less potent and require a higher number of doses. A lack of early and

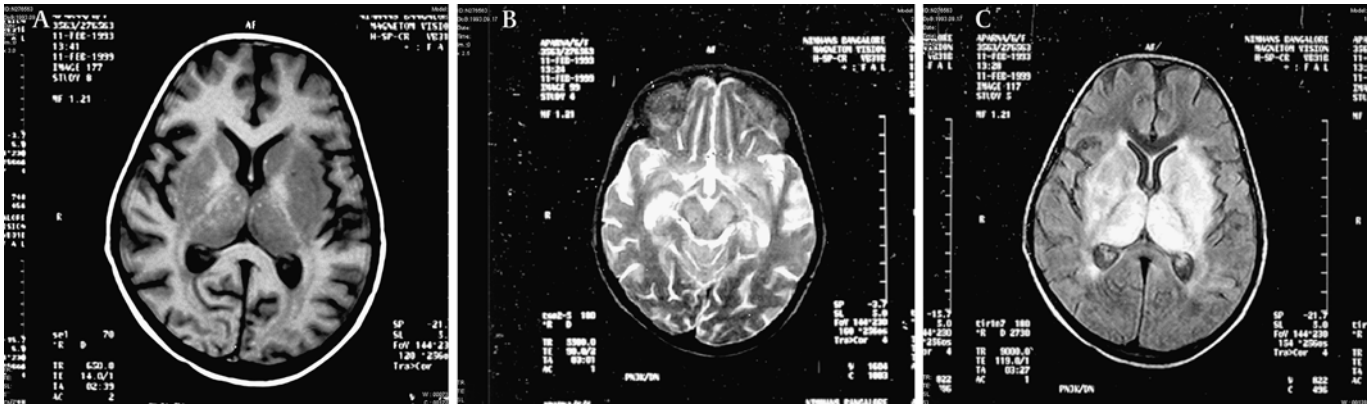

Figure 1 (A–C) MRI (brain): T1 weighted, T2 weighted and fluid-attenuated inversion recovery sequences show lesions in bilateral basal ganglia, thalami and cerebral peduncle which are hypointense on T1 and hyperintense on T2 and fluid-attenuated inversion recovery sequences (case 27, 6 years/female, paralytic rabies, duration of illness 14 days).

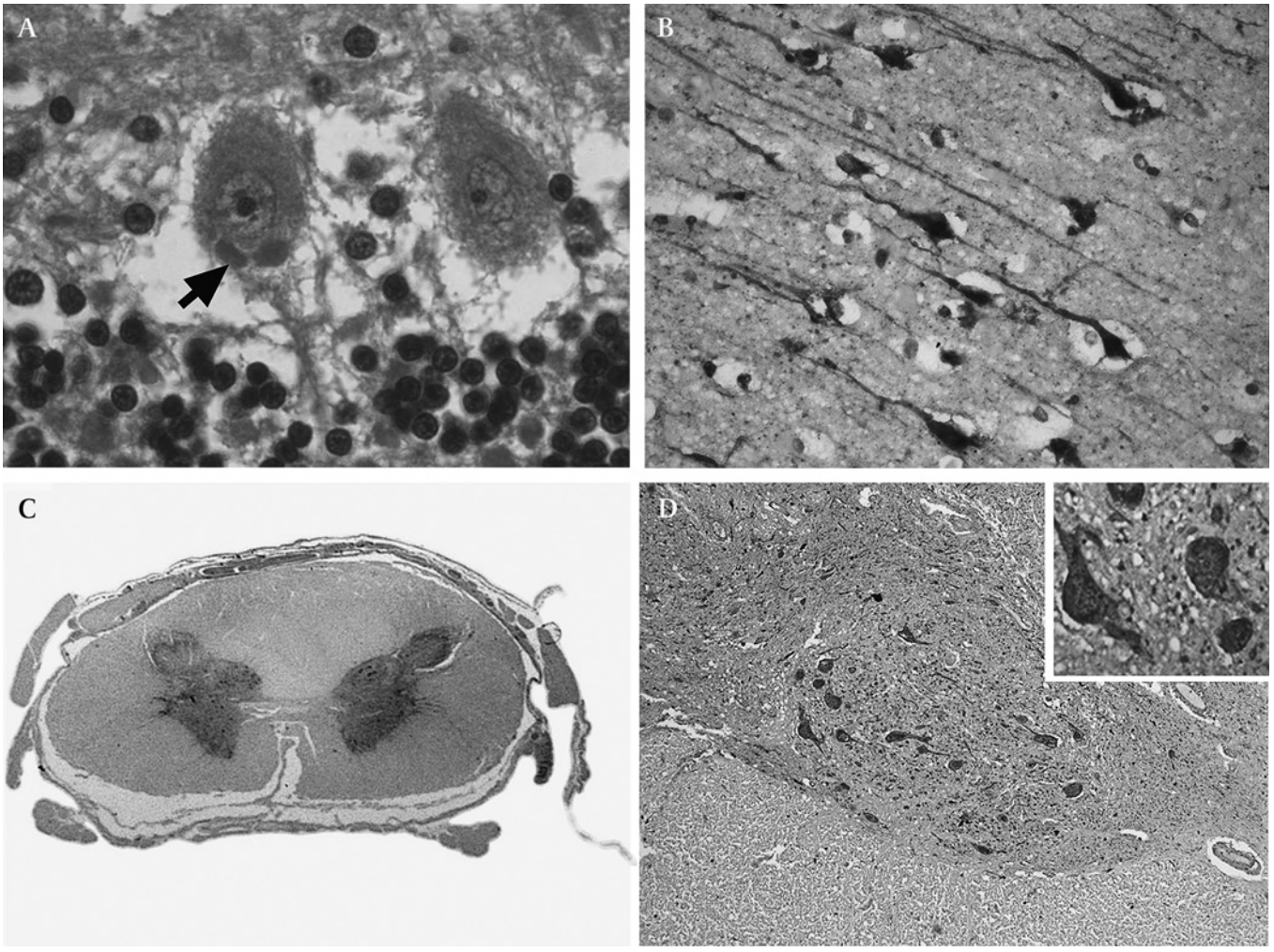

Figure 2 Intracytoplasmic eosinophillic inclusions (Negri bodies) seen within cerebellar Purkinje neurons (A, arrows). Abundant viral nucleocapsid antigen is demonstrated by immunochemistry within the cortical neurons exhibiting dendritic spread (B). Viral antigen is also seen within anterior and posterior horn cells of cervical segment of spinal cord (C). Higher magnification of anterior horn shows diffuse to speckled deposits of viral antigen in the motor neurons (D, and inset). (A] H&E ×800; (B) immunoperoxidase ×240; (C) immunoperoxidase ×8; (D) immunoperoxidase ×80; (D, inset) immunoperoxidase ×320 (case 8, 17 years/male, paralytic rabies, duration of illness 14 days).

adequate postexposure vaccination is the most important cause of mortality.

In human cases, the incubation period typically ranges from weeks to several months but may vary from less than a week to more than a year. The length of the incubation period depends upon factors such as the amount of viral inoculum, the degree of innervation at the site of viral entry, the severity of the bite, the age and immune status of the host, and the proximity of the bite to the central nervous system.[7] In the current study, the median incubation period between the animal bite and the development of symptoms was 2 months (range 7 days–4 years).

In the paralytic group, the mean duration of illness until death was 13.4 days (range 4–24 days), while in the encephalitic group it was 7 days, comparable with earlier studies. One patient survived for 1 year (published earlier).[8] Rare cases of long-term survivors have also been reported in the literature.[9]

In the current study, 34 patients had paralytic onset, seven patients had abnormal behaviour as the presenting symptom, while only six patients had the encephalitic form. Although furious rabies comprises 80% of rabies cases in the community, most of these cases are managed in the peripheral Infectious Disease hospitals and are not referred to a neurologist. Hence, the preponderance of atypical/paralytic cases seen in our series suggests a referral bias. At the same time, it also reflects the fact that neurologists see more atypical cases, and hence a high index of clinical suspicion is required. The clinical distinction between paralytic rabies and GB syndrome can be made with reasonable certainty, based on suggested criteria (table 2).[7 10]

Course of illness

All 34 patients in the paralytic group developed a progressive deterioration in the level of sensorium, and none were conscious at the time of death. Only two patients developed hallucinations, and five (11%) developed aerophobia or hydrophobia during the terminal course of the illness, which led to a suspicion of rabies. The deterioration of sensorium in the rest of the patients was thought to be due to hypoxia following respiratory involvement, iatrogenic meningitis, electrolyte disturbance, etc. This is similar to cases reported in the literature which are often clinically, electrophysiologically and pathologically indistinguishable from GB syndrome.[4 11–13]

The proportion of patients with the well-known and pathognomonic hydrophobia or aerophobia varies markedly from one

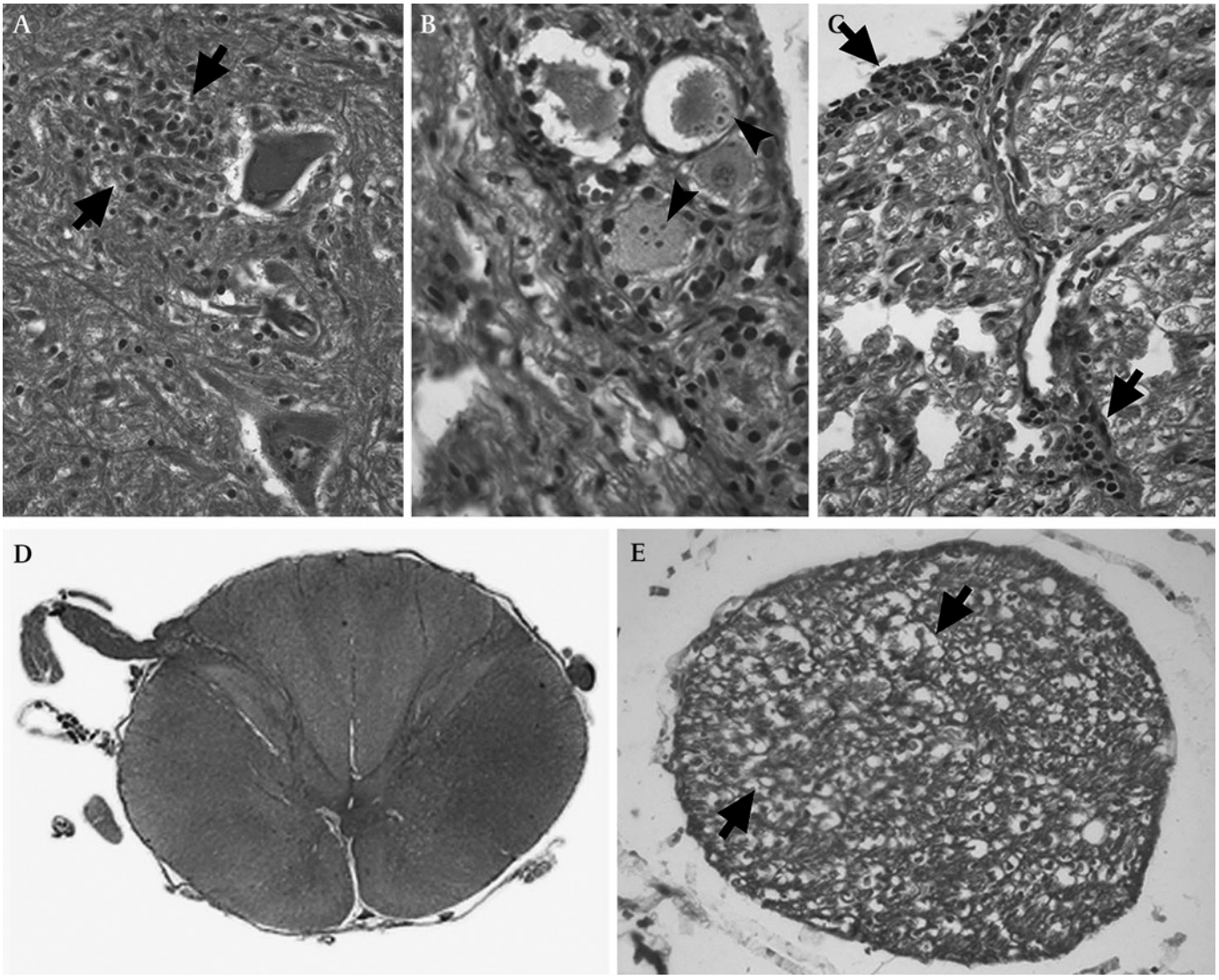

Figure 3 Thoracolumbar segment of spinal cord with focal microglial response forming nodules in anterior horn (A, arrows) signifying encephalomyelitis. Occasional small intracytoplasmic eosinophillic inclusions are demonstrable in dorsal root ganglion cells (B, arrowheads). The radicals of spinal roots show inflammation (C, arrows) and focal demyelination (D, E, arrows) reminiscent of Guillain–Barré syndrome. Demyelination is seen in posterior and lateral columns of the thoracic segment of spinal cord on whole mount preparation (C). (A) H&E ×320; (B) H&E ×320; (C) H&E ×320; (D) Luxol Fast Blue ×8; (E) Luxol Fast Blue ×160 (case 12, 11 years/male, paralytic rabies, duration of illness 15 days).

series to other. Hydrophobia was reported in 17% of patients in a series from Sri Lanka, 32% from USA and 80% from Thailand.[7] In a case series from India describing only paralytic rabies, hydrophobia was absent in all the 11 patients.[13] In the current study, among patients with paralytic onset, hydrophobia or aerophobia was present at the terminal stage in five patients (11%), compared with nine of 13 patients (69%) in patients with encephalitic/psychiatric manifestations. This demonstrates that although the presence of hydrophobia is helpful in diagnosing rabies, it is more likely to be absent in the paralytic form of rabies.

Among patients with encephalitic onset, only three out of six had classical features of rabies. Other patients had features of unexplained encephalitis. Hence, rabies must be considered in any unexplained acute encephalitis, which progresses to coma or death within 1–2 weeks. Apart from hydrophobia, the presence of paraesthesia, fasciculation and autonomic instability are important clues which should lead to further investigations for rabies. Six patients in this series were initially diagnosed as having psychiatric disorders such as schizophrenia, delirium tremens, acute psychosis, hypomania and hysteria.[5] Rabies masquerading as psychiatric syndromes has been reported infrequently in the literature, and hence clinicians in India and other endemic areas should remain alert as to the possibility of this viral infection mimicking psychiatric disorders.

Haematological profiles in cases of rabies may be normal or show mild leucocytosis. In the current series, the mean WBC count was 14 066/mm^3 (range 4000–30 000). CSF abnormality has been noted in 66% patients during the first week and in 90% patients thereafter as mild CSF pleocytosis, and an increase in proteins (generally <200 mg/dl).[7] In the present study, a CSF analysis revealed pleocytosis in 18 patients (62%, mean cell count: 66 cells/mm^3 range 0–700 cells/mm^3) and raised CSF protein in 21 cases (mean of 115 mg/dl (range 19–480 mg/dl)).

Neuroimaging studies

There have been only anecdotal reports of neuroimaging in human rabies. This may be due to the technical difficulty in

Table 2 Comparison of clinical features between Guillain–Barré Syndrome (GBS)[10] and paralytic rabies[7]

GBS[10]	Paralytic rabies[7]
Features required for diagnosis	Four clinical patterns described
1. Progressive weakness of more than one limb	1. Paresthaesia and flaccid weakness confined to bitten extremity
2. Areflexia	2. Quadriplegic form
	3. Resembling transverse myelitis
	4. Symmetrical ascending paralysis like GBS
Clinical features supportive of diagnosis	
1. Progression over days to 1–4 weeks	1. More rapid progression
2. Relative symmetry of neurological deficits	2. The extremity with the bite may be more affected
3. Mild sensory symptoms or signs	3. Severe paraesthesia, fasciculation and myoedema in the extremity with bite
4. Recovery beginning 2–4 weeks after progression ceases	4. Rapidly progressive course with eventual CNS involvement and death; hydrophobia or aerophobia is pathognomonic if present
5. Absence of fever at onset	5. Fever is common, during prodromal phase
6. Cranial nerve involvement does occur	6. Cranial nerve involvement common as in GBS
7. Autonomic dysfunction common	7. Autonomic dysfunction is common as in GBS
Laboratory features supportive of diagnosis	
1. Elevated cerebrospinal fluid protein with <10 cells	1. Elevated cerebrospinal fluid protein with varying pleocytosis
2. Electrodiagnostic features of nerve conduction slowing or block	2. Peripheral nerve demyelination or axonal degeneration

performing the study, especially in cases of encephalitic rabies. Preferential involvement of the brainstem, thalamus, basal ganglia and spinal cord has been reported.[14] Awasthi *et al* reported hyperintensities in the globus pallidi, putamen and thalami bilaterally on both T1 and T2 weighted images in a case of rabies encephalitis diagnosed antermortem.[15] They attribute the hyperintensity on the T1 image to extracellular methaemoglobin. Pathological findings in their patient are not available, but necropsy of the brain in rabies may show scattered petechial haemorrhages. Mani *et al* described hyperintensities in thalami, basal ganglia and pons in the T2 and FLAIR images. These MRI findings corresponded with the non-haemorrhagic lesions in the brain at necropsy.[16] Desai *et al* suggest that selective involvement of the grey matter could be used to differentiate paralytic rabies from postvaccinial ADEM.[17] In postvaccinial ADEM, discrete T2 weighted hyperintensities in the white matter of the brain and spinal cord are reported.[18] In the current study, a brain MRI carried out in two patients with paralytic rabies showed signal intensity changes (hypointense on T1 and hyperintense on T2) in bilateral basal ganglia, thalami and cerebral peduncles. The usefulness of imaging studies in cases of rabies appears to be of limited value, and features appear to be immune-mediated.

Electrophysiological and pathological features of human rabies have been investigated in a few studies. In paralytic rabies, evidence of peripheral nerve demyelination or axonal degeneration has been demonstrated, while in furious rabies changes suggesting anterior horn cell dysfunction were noted.[11 13] It is hypothesised that an immune phenomenon may be responsible for nerve injury in paralytic rabies, while the anterior horn cell loss in furious rabies may be due to the direct effect of the virus. In the current study, electrophysiological data in three patients with paralytic onset showed demyelinating and axonal neuropathy. Ongoing axonal damage was demonstrated in one patient by serial nerve-conduction studies.

The diagnosis of rabies can be established by detecting neutralising antibody to rabies virus in the serum or CSF in a person who has not been vaccinated. Neutralising antibody in serum is rarely detectable in the first week of illness but is found in majority of patients surviving past the second week and appears even later in CSF and therefore is less useful early in the course of the disease.[7] In the current study, neutralising antibody in CSF was detected in only 40% of patients by the Rapid Fluoescence Focus Inhibition Test when tested 7–10 days after the onset of illness. In one patient, its presence and rise in titres helped in the diagnosis.[8] A more sensitive ELISA technique was developed to detect immune complexes to rabies N and G proteins, which was 100% specific and 76.6% sensitive in our centre.[6] This may help in early diagnosis, prognostication and institution of appropriate infection control and public health measures. Also, as new therapies emerge, early diagnosis may help in early institution of treatment before the development of secondary complications.

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Competing interests None.

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