Clinicopathological Conference Report—PM 23965

Rabies Meningoencephalomyelitis presenting as Guillain Barré Syndrome

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This case ( PM 23965) was discussed on 19th November 2012 as a student clinicopathological exercise at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

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Clinical details

A 20-year-old male, hailing from Haryana, presented to medicine emergency in the month of October, with 5 days history of acute onset paralysis of all four limbs, worsening to involve the respiratory and truncal muscles. Illness was preceded by fever lasting for 3 days. He had history of dog bite with inadequate postexposure vaccination, 3 months prior to the current illness. On examination, there was hypotonia, areflexic quadriparesis along with respiratory, bifacial, palatal, neck and truncal muscle weakness. He developed photophobia, neck stiffness, worsening sensorium and respiratory efforts, for which he was managed with mechanical ventilation in intensive care unit (ICU) setting. Investigations revealed mild leukocytosis (TLC: 12,800) and normal electrolytes, renal function test, chest X-ray and ECG. CSF revealed neutrophilic pleocytosis (100 cells P70 L30) and elevated protein with normal sugars (Pr/S: 120/60; corresponding blood sugar (CBS): 97 mg/dl). Human immunodeficiency virus (HIV) serology was negative, X-ray chest was within normal limits. Nerve conduction study was suggestive of sensorimotor axonal polyradiculopathy [Rt median CMAP reduced, Rt ulnar, peroneal, tibial were nonstimulable, Rt median and ulnar sensory nerve action potential (SNAP) was reduced]. Corneal smear was negative for rabies antigen and contrast-enhanced magnetic resonance imaging (CE-MRI) brain was planned. A clinical possibility of Landry Guillain-Barré syndrome (LGBS) and rabies was kept. The patient could not afford intravenous immunoglobulins (IVIG) or plasmapheresis, and so he was started on injection methylprednisolone, 1 gm bolus once a day and empirically covered for bacterial meningitis with antibiotics. Other supportive measures continued. During the stay, he also had fluctuations in blood pressures with minimum of 110/70 to maximum of 150/90 mm Hg. On day third patient’s sensorium further worsened and cardiac monitor showed bradycardia, following which he sustained a cardiac arrest and could not be revived.

Case discussion

The acute flaccid paresis can result from pathology (Table 1) involving the brainstem, anterior horn cell, spinal cord, radicles and nerves, neuromuscular junction and muscle. Metabolic factors like hypokalemia, hypophosphatemia and ICU related weakness come lower down in the list. In the presence of altered sensorium, bulbar palsy, areflexia, prior history of dog bite, inadequate vaccination and cerebrospinal fluid (CSF) pleocytosis, a possibility of rabies remains high on cards as in our case. Other possibilities may include neurotropic viruses like cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), varicella zoster virus (VZV), measles, mumps and HIV presenting with GBS like clinical syndrome. However, the odd features for them were presence of altered sensorium,
early bladder involvement, neck stiffness, photophobia and CSF pleocytosis. Odd points for CMV and HIV was normal sugars in CSF and HIV negative status. Odd points for EBV was presence of weakness, followed by altered sensorium, absence of lymphadenopathy, rash and splenomegaly. Odd points for paralytic polio was paralysis followed by altered sensorium, symmetric involvement, progression of paralysis after 48 hours, absence of fasciculations, absence of fever, myalgias at onset and progressive fatal outcome. Odd point for nonpolio enterovirus was severe fulminant course and bulbar involvement.

Rabies can manifest in adults as furious or paralytic form. Paralytic form usually mimics the presentation of LGBS as in our case. Paralytic rabies1 presents with prodrome of fever in one-third cases, phobic spasms in half of cases, altered sensorium, ascending paresis and may involve respiratory and bulbar muscles with a rapid devastating course, culminating in death. Median survival in paralytic rabies is 11 days vs 6 days in furious rabies. The natural history of paralytic rabies (Fig. 1) starts form median incubation period of 20 to 90 days following inoculation of virus into body followed by prodromal phase of 2 to 10 days and following which patients develop the first neurological sign. This neurological phase lasts 2 to 7 days which ends in coma and finally terminating to death or recovery. Predisposing factors for paralytic rabies include bites by bat, bites on lower limb, unsuccessful post exposure immunization and corneal transplants.2 Mild CSF pleocytosis is seen in 60% of patients in the first week (usually <1000 cells). There are clinical, electrophysiological and pathological indications that peripheral nerve dysfunction is responsible for weakness in paralytic rabies.1 In rabies, viral involvement at the sinus or atrioventricular node, myocarditis, changes in the cardiac rhythm and function and hormonal aberrations may happen, which ultimately contribute to the demise of the patient.3,4 This patient had clinical evidence of dysautonomia in the form of fluctuating blood pressures and cardiac arrhythmia, bradycardia prior to demise which corroborates with the literature.

Table 1: Etiology of acute flaccid paresis

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Syndrome</th>
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<tbody>
<tr>
<td>Brainstem Stroke</td>
<td>Stroke, brainstem encephalitis</td>
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<tr>
<td>Disease of anterior horn cell</td>
<td>Polio, nonpolio enterovirus, VAPP</td>
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<tr>
<td>Neurotropic viruses</td>
<td>Rabies, VZV, JE virus</td>
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<tr>
<td>Disease of spinal cord</td>
<td>ATM, epidural abscess, compression-trauma</td>
</tr>
<tr>
<td>Disease of radicles and nerves</td>
<td>LGBS, CMV, toxin of diphtheria, botulism, tick bite, lyme disease, traumatic, AIP, vasculitis, lymphoma</td>
</tr>
<tr>
<td>Disease of neuromuscular junction</td>
<td>Myasthenia gravis, nondepolarising neuromuscular blocker</td>
</tr>
<tr>
<td>Disease of muscle</td>
<td>Viral myositis, rhabdomyolysis</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hypokalemia, hypophosphatemia, gossypol, licorice</td>
</tr>
<tr>
<td>ICU weakness</td>
<td>Critical illness polyneuropathy, thick filament myopathy</td>
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Fig. 1: Natural history of rabies
A complete autopsy was performed on this 20 years old male with a history of dog bite and clinical possibilities of Guillain-Barre syndrome/pyogenic meningitis/rabies encephalitis. On examination, the deceased was moderately built and had pectus carinatum. The autopsy was performed by bitemporal and mid line thoracoabdominal incisions. All the serous cavities were unremarkable. The brain weighed 1200 gm. On gross examination, the meningeal blood vessels were congested but no meningeal exudates were found. The cerebral gyral blood vessels were unremarkable and the cerebellum showed minimal prominence of the tonsils. Serial coronal slicing of the brain revealed no obvious gross pathology, except for narrowing of both the lateral ventricles. Microscopic examination showed lymphocytic meningitis. The parenchymal blood vessels showed extensive perivascular lymphocytic cuffing (Fig. 2A). The cerebral cortex showed extensive lymphohistiocytic infiltration, neuronophagia and microglial nodules (Figs 2B and C). These lesions were found extensively in the hippocampi and cerebellum. The cerebellum also showed paucity of Purkinje cells (Fig. 2D). Further examination of the brain sections revealed many neurons with intracytoplasmic, round to oval, eosinophilic inclusions (Figs 3A and B). These inclusions were found extensively in the neurons of hippocampus, cerebellum, mid brain, pons, medulla oblongata and the cervical cord. With respect to the clinical presentation and topography of the viral encephalitis and their morphology, these inclusions were identified as Negri bodies and the diagnosis of Rabies-meningoencephalomyelitis was made. There was widespread distribution of rabies viral antigen in neurons and neurophil on immunohistochemistry which further confirmed the diagnosis (Fig. 3C). The pleural aspect of both the lungs were dull and the lungs were firm to feel. No exudates or focal lesions were identified grossly. Multiple sections examined from both the lungs showed bronchopneumonia (Fig. 4A). No fungal profiles or bacterial colonies were seen. The heart weighed 220 gm. On gross examination, the heart revealed reduction of epicardial pad of fat along with unremarkable inflow and outflow tracts on both the sides. No other
grossly identifiable pathology was noted. On microscopic examination, the epicardial nerves showed dense lymphocytic infiltration (Fig. 4B). However, no Negri bodies was found in the ganglion cells. The myocardium showed mild interstitial excess of lymphocytes, but no definite evidence of myocarditis was noted. Sections examined from the adrenals showed expanded medulla with extensive lymphocytic infiltration. Both the kidneys showed features of acute tubular necrosis. The hepatobiliary system, pancreas, spleen and gastrointestinal systems were unremarkable.

**FINAL AUTOPSY DIAGNOSIS—20 YEARS MALE WITH HISTORY OF DOG BITE**

- Rabies meningoencephalomyelitis
- Bilateral bronchopneumonia
- Adrenal medullitis.

**Comments by Prof BD Radotra**

Rabies is a rapidly progressive, acute infectious fatal disease of central nervous system. It is caused by a neurotropic RNA viruses transmitted usually by the bite of a rabid dog although other animal bites, such as monkeys, bats, mongoose, foxes and jackals can also infect humans. Rabies encephalomyelitis continues to be a significant health hazard in South East Asia particularly in the Indian subcontinent. Some countries in the world, such as UK, Sweden, Ireland, Portugal, Australia, New Zealand and Japan are free of rabies. In India, Lakshadweep, Andaman and Nicobar Islands are also free of rabies. According to a WHO report (2013), more than 60,000 deaths occur due to rabies worldwide and 55% are contributed from Asia, (mainly from Indian subcontinent), whereas 45% occur in Africa. In our experience, 50% victims are children.

Human rabies can manifest in two neurological forms: Around 70 to 80% patients develop encephalitic type of rabies also known as furious rabies, whereas 20 to 30% develop paralytic rabies, also known as dumb rabies. The two forms may overlap. The former is characterized by episodes of agitation, insomnia, aggressive behavior that may include biting. Other symptoms are hallucinations, hypersalivation, piloerection, pupillary dilatation and hydrophobia. There may be brain stem dysfunction including dysphagia, dys-

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Figs 3A to C: (A and B) Microphotograph from the hippocampus and cerebellum showing Negri Bodies in the neurons, (C) immunohistochemistry with rabies antibody revealed positivity in the neurones and their processes
arthria, nystagmus and cardiorespiratory disturbances. The paralytic type is characterized by paralysis of one or more limbs and sometimes ascending paralysis simulating Guillain-Barre syndrome (GBS). Sensory loss and incontinence are other symptoms. These acute neurological manifestations of the disease progress to stupor, coma, and death over a period of 1 to 2 weeks. The average length of survival in encephalitic form is about 5 days, whereas in paralytic type, it is about 2 weeks, although we do encounter cases with a more protracted course lasting over a month.

In our experience at PGIMER, Chandigarh, in about 50% cases of human rabies, there is no forthcoming history of dog bite. Multiple factors are responsible for this phenomenon. Firstly, diagnosis of rabies is not clinically suspected particularly in paralytic type where patients present with ascending paralysis (Guillain-Barre syndrome like picture) and therefore the history of dog bite is not specifically elicited at the time of clinical examination. The diagnosis in such cases is only made at autopsy. Secondly, in many instances, the patient is brought to the hospital in a comatose state and the attendants may not exactly know about history of dog bite. Additionally, small dog bites or animal bites by other pets, such as cats may be ignored, particularly by subjects who hail from rural background. It is only when clinical symptoms, such as hydrophobia, restlessness (hyperactivity), excessive salivation and convulsions develop the possibility of rabies is thought (Furious or encephalitic type). Therefore, it is important to remember that paralytic rabies is a differential diagnosis of GBS. We suspect all cases of GBS syndrome as potentially rabies cases at PGIMER and many of them have turned out to be rabies encephalomyelitis at autopsy. The other differential diagnosis in such cases is post-infectious acute demyelinating encephalomyelitis (ADEM) which generally manifests as acute perivenous demyelination. Although, there is an overlap of clinical symptomatology, ADEM is easily differentiated at autopsy by the presence of perivascular demyelination of white matter and absence of grey matter pathology. Additionally, ADEM does not show presence of rabies virus antigen in brain by immunohistochemistry. Current imaging techniques have been reported to differentiate radiculoneuritic form of rabies and acute disseminated encephalomyelitis.

In this indexed case, the neuropathological examination revealed all features of rabies viral encephalitis, such as extensive perivascular lymphocytic cuffing, lymphohistiocytic infiltration, neuronophagia, microglial nodules and Negri bodies. In about 20% cases, Negri bodies may not be found even on extensive search and in those cases the diagnosis is established only by demonstration of rabies viral antigen in neurons and neuropil, otherwise it remains unknown. It is interesting to note that in some cases, there are hardly any obvious histological changes in the brain yet there are profound functional disturbances. The mechanism by which such profound dysfunction occurs without significant morphological evidence of cell destruction and inflammation remains a mystery. Some investigators believe that neuronal death in rabies is not a direct result of virus-induced structural damage but rather a functional alteration of neurons. Cytokines, such as TNF-α and Interleukins have been blamed for this neuronal damage. Regional imbalance of neurotransmitters and neuromodulators leading to neurophysiological impairment has been proposed.

It has not been clearly understood as to why some people develop paralytic type of disease, whereas others develop encephalitic type of disease following exposure to rabies virus. Transmitting animal hosts are probably not an important determinant because, in reported cases of human paralytic rabies, most subjects have been either bitten by dogs or other pets (cats) and the same is true for encephalitic disease. The type of virus strain also does not seem to be a decisive factor, since the same rabid dog transmitted paralytic rabies in one patient and furious rabies in another human. Previous
neuropathological and immunohistochemical studies have not been able to demonstrate any differences in regional distribution of rabies viral distribution between two subtypes of human rabies and thalami and brain stem showed maximum rabies viral antigen regardless of the clinical form.\(^6,15\)

Unsuccessful immunization attempts were thought to be a predisposing factor for paralytic rabies, but this proposition was not supported by facts. In some series, only 4/18 and in others 1/3 patients had received postexposure vaccination. The association of paralytic rabies with vampire bite, cat bite, squirrel bite may suggest that there may be alterations in virus properties by passage in these animals. Recently, Shuangshoti et al\(^16\) have demonstrated reduced rabies viral antigen in cerebral hemispheres of paralytic form of canine rabies compared to furious rabies. The paralytic rabies was also associated with prominent brainstem inflammation. The authors suggested that marked brain stem inflammation could lead to neuronal death and impaired viral dissemination toward cerebral hemispheres. However, these results are conflicting with previous studies and thus it is not clear which subject will develop furious or paralytic rabies. Therefore, it has been suggested that the development of clinical type may be related to immune response of the host.

REFERENCES