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Case Report Open Access

Paralytic Rabies Misdiagnosed as Guillain-Barre Syndrome in a Guest Worker: A Case Report

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Background

Animal rabies is still endemic in Israel, with an average of 35 laboratory-confirmed cases per year during 2002-2012 [1]. Nevertheless, human rabies is extremely rare in Israel, with only 4 human cases diagnosed since 1961; the last was reported in 2003 [2]. All were autochthonous, one was bitten by a cat and the other two were bitten or scratched by an unidentified small mammal [3]. Paralytic rabies, an atypical presentation of rabies manifested initially by an ascending pure motor weakness, may lead to late or misdiagnosis of rabies [4], and has never been reported from Israel.

Israel has a large and diverse migrant population; many arrive from countries with endemic rabies. We present a case of paralytic-type human rabies in a foreign guest worker, misdiagnosed initially as Guillain-Barré syndrome (GBS) variant and mistreated as such.

Case Report

A previously healthy 32-year-old female from India arrived in Israel on September 23rd 2014 to nurse an elderly couple. Upon arrival, she appeared ill, and was fired from her work after 5 days because of outbursts of rage and emotional instability. On October 1st she was examined by a general practitioner because of sore throat, abdominal pain, vomiting, diarrhea and leg weakness. On October 13th she was brought by an ambulance to the emergency room (ER) with fever, diffuse muscle pain, dizziness, diarrhea, vomiting and severe back pain. Initial vital signs were temperature of 36.8ºC, heart rate of 100 bpm and blood pressure of 122/84 mmHg. Physical examination was normal except for diffuse abdominal tenderness. Complete blood count showed 6,400 white blood cells per microliter and platelets of 154,000 K/μL. Liver and kidney function were normal and she had mild hyperglobulinemia.

Venous blood gases were normal. She was treated with metoclopramide and intramuscular ibuprofen and discharged with a diagnosis of acute gastroenteritis. The following day she returned to the ER because of severe lower back and neck pain, recurrent vomiting and episodic dyspnea. She was admitted to an internal medicine ward. On admission she was afebrile and had normal vital signs. Physical examination was normal except for anxiety and agitation. An episode of choking while trying to drink water was noted but there was no hydrophobia. Blood count and chemistry were similar to the previous tests. On the following day, neurological examination found repeated episodes of rapid breathing and motor agitation; she was observed trying to sit in bed, crying and desperate. She was alert oriented to self and place but not to time.

There was no neck stiffness and cranial nerves were intact. Tone was overall flaccid, with normal strength in arms and reduced strength in her right leg, especially in the proximal muscles. Areflexia of all four limbs was noted. Plantar reflexes were normal. The summary of the neurologist examination was psychomotor agitation and acute generalized areflexia with hypotonia. Meningoencephalitis with central and peripheral involvement was suspected and emergency brain computerized tomography (CT) followed by a diagnostic lumbar puncture were ordered. CT was normal except for suspected lacunar infarcts in the lower left basal ganglia.

There were 6 white blood cells (WBCs) and 100 red blood cells in the cerebrospinal fluid (CSF), protein level was 35 mg/dL and glucose was 82 mg/dL. Gram stain of the CSF was negative. On the third hospitalization day (HD3) she was febrile, developed respiratory failure and needed intubation, during which trismus was noted. She was transferred to the intensive care unit. The presumptive diagnosis of postinfectious neurologic syndrome (GBS or Bickerstaff brainstem encephalitis) was made. Intravenous immunoglobulins (IVIG) were administered. Ceftriaxone was empirically administered due to fever and right lung infiltrate. Infectious diseases physicians were consulted on HD4 and treatment was changed to include also acyclovir, azithromycin and doxycycline.

From HD4 on, the patient was in a comatose state with Glasgow coma scale (GCS) of 3. On HD6 eyes were open, fixed in midline position, pupils were 4 mm and non-reactive to light, and there were weak corneal reflexes. Paralysis of four limbs was noted, but jerk-like repeated movements of the jaw and neck hyperextension were seen occasionally. Electroencephalography (EEG) showed nonspecific encephalopathy pattern with no seizure activity. Herpes simplex virus, varicella zoster virus, enterovirus polymerase chain reactions (PCRs) and West-Nile virus IgM in CSF were negative. Epstein Barr virus and cytomegalovirus serology showed past infection. HIV serology was negative. Poikilothermia was noted on HD7. A repeat lumbar puncture done on HD7 showed 10 WBCs and no red blood cells. CSF Glucose was 54 mg/dL and protein 503 mg/dL. After completing 5 days of IVIG, pulse steroid therapy was given (HD8) for the alternative diagnosis of acute disseminated encephalomyelitis (ADEM). This

treatment was stopped on HD9 when rabies was suspected. Central diabetes insipidus developed on HD9, for which she was treated with desmopressin. No cardiac arrhythmias were documented.

Saliva, serum, urine, CSF and nape skin biopsy were sent to the Israeli Rabies Laboratory in Kimron Veterinary Institute, Bet Dagan, Israel. Skin and saliva were positive for canine rabies virus species 1 using real time reverse transcriptase (RT) PCR. The patient was treated with ketamine, midazolam, amantadine and insulin-glucose infusion according to the Milwaukee Protocol V.4. (www.mcw.edu/rabies). Neutralizing rabies antibodies were detected in serum on HD9 and in the CSF on HD14, but not on the first sample from HD4 (Table 1).

Real time RT-PCR	**RFFIT**			
PCR for rabies virus genotype 1	CSF (IU/ML)	Sera (IU/ML)	Hospital Day (HD)	Date
ND	< 0.04	0.07	4	17/10/14
ND	ND	0.27	8	21/10/14
Saliva*: Positive ct 29,30,31 Skin Biopsy: Positive ct 31	ND	3.71, 3.06, 3.39	9	22/10/14
Saliva: Positive ct 31	ND	6.31	13	26/10/14
CSF: Positive ct 29	1.21	ND	14	27/10/14
Saliva: low positive at ct 35	ND	ND	15	28/10/14
Saliva: Negative	ND	41.4, 25.8	20	2/11/2014
Death			21	3/11/2014
RFFIT - rapid fluorescent focus inhibition test, RT-PCR – reverse transcription polymerase chain reaction, CSF – cerebrospinal fluid, ND – not done, ct – cycle threshold,*results of three different collections.				

Table 1: Neutralizing antibodies and RT-PCR results

Sedation was stopped on HD13. At this point the patient had fixed dilated pupils and EEG was non-reactive with no measurable cortical electric activity. On HD16 she developed paralytic ileus. A CT head and CT-perfusion demonstrated severe brain edema and no cerebral perfusion (HD19). The patient died on HD21, 42 days after her first clinical signs. Post mortem autopsy was not conducted. No recollection of a dog bite surfaced, even after inquiring her family in India.

Fifteen medical staff were given post-exposure prophylaxis (PEP) out of 95 interviewed (16%). Only 3 healthcare workers had possible unprotected contact with the patients' secretions (the doctor who intubated the patient, the neurologist who examined the fundi, and a nurse who sustained a splash of fluid to the eye during bathing the patient). The other 12 demanded PEP although no real exposure was documented. In the community, 23 out of 33 (70%) exposed received PEP. Most were the members of the family that employed her, and her close friends and roommates.

Discussion

We diagnosed rabies *ante mortem* in a recent immigrant from India to Israel. Rabies is a major cause of morbidity and mortality worldwide, accounting for 59,000 human deaths annually [5]. The migrant population in Israel 2015 is estimated to include 180,000 workers from Thailand, the Philippines, the former Soviet Union, China, India and other countries as well as 44,599 African asylum seekers – all countries with endemic or emergent rabies [1]. The prolonged incubation period for rabies in humans, ranging from 2 weeks up to 9 years, facilitates travel and consequent imported cases [6,7]. A transplant-associated outbreak of rabies from a guest worker ex-India was recently reported from two other Middle Eastern countries (Elsiesy H. abstract presentation in Rabies In The Americas (RITA) XXVI conference, Fort Collins, Colorado, USA, 2015).

Human rabies remains a diagnostic challenge in non-endemic countries, particularly when a history of animal exposure is lacking. Our patient with paralytic rabies was initially misdiagnosed as having a demyelinating polyneuropathy and treated as such. Axonal neuropathies from rabies have also been described [8]. Paralytic (dumb) rabies occurs in about a fifth of rabies patients, and often lacks the hallmark features of hydrophobia, aerophobia and inspiratory spasms characteristic of encephalitic (furious) type rabies. Paralytic rabies presents as ascending pure motor weakness without loss of consciousness. This presentation overlaps other, more common neurological disorders, such as GBS, ADEM, conversion disorder, and acute flaccid paralysis syndromes from Campylobacter, West Nile virus and enterovirus D68 infection [9,10]. Features of paralytic rabies that may distinguish it from GBS are fever, autonomic dysfunction – including bowel and bladder - and percussion myoedema. Nerve conduction velocities, neuroimaging and molecular diagnostic tests assist with the differential diagnosis.

Early differentiation of rabies from GBS, ADEM, and acute flaccid paralysis syndromes is crucial for optimal medical care and to maintain the public health. Close family or medical contacts of the patient and associated victims of the animal bite require post-exposure prophylaxis. Medically, treatments for the infections and autoimmune neurological disorders vary and can be mutually antagonistic. While treatment of rabies remains anecdotal, survivors of rabies are increasingly reported and a continuum of disease severity from rabies infection has been hypothesized [11]. Early administration of IVIG and corticosteroids may hamper the development of neutralizing antibodies which are required for clearance of rabies virus [12]. Newer, broad spectrum antivirals active against the rabies virus may soon be marketed [13].

To conclude, countries such as Israel, Kuwait and Saudi Arabia with proportionately large guest worker and migrant populations from rabies endemic countries are likely to encounter further rabies cases. European countries facing migration waves from rabies endemic regions face a similar threat. Rabies should be considered regularly in the differential diagnosis of acute encephalitis and paresis syndromes. Differentiating between paralytic rabies and other paralytic syndromes in a timely fashion is challenging, but can be facilitated by noting differentiating clinical features. Broad spectrum antiviral drugs in late clinical development for ebolavirus that also inhibit rabies virus, entero viruses, and West Nile virus further heighten the need for consideration of imported agents before initiation of therapy.

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