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Is initial preservation of deep tendon reflexes in West Nile Virus paralysis a good prognostic sign?

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Abstract

Typical West Nile virus paralysis is characterized by muscle weakness, decreased tone, and loss of deep tendon reflexes attributed to destruction of anterior horn cells. Two cases in which deep tendon reflexes were initially preserved in the presence of profound and persistent muscle weakness are presented here. In both cases, deep tendon reflexes were later severely attenuated or lost, while weakness of the involved muscles remained profound and unchanged. Both patients showed good motor recovery at 6 months. Initial preservation of deep tendon reflexes in the presence of persistent muscle weakness indicates that in the early stages of disease, the muscle weakness in these two cases was not caused by destruction of anterior horn cells. Pathology involving anterior horns preceding AHC destruction could potentially disrupt upper motor neuron pathways to anterior horn cells, causing weakness with initial preserved deep tendon reflexes.

INTRODUCTION

Nearly 20% of West Nile virus (WNV) -infected patients develop West Nile fever, while < 1% develop WNV neuroinvasive disease[1] consisting of meningitis (~40%) and/or encephalitis (~60%). Some patients also develop WNV paralysis/ poliomyelitis[1] characterized by flaccid paralysis with loss of deep tendon reflexes (DTRs), which is a risk factor for predicting death.[2,3] Two cases presented here developed meningo-encephalitis, profound weakness with initial brisk DTRs which then progressed to diminished reflexes or complete areflexia in the affected limbs.

CASE REPORTS

Patient 1

Four days before examination, a 57-year-old Caucasian male developed arthralgia and myalgia that in 2 days progressed to severe nausea, vomiting, dizziness, drowsiness, slight pain on head-flexion and mild headache without photophobia or phonophobia, and then in another day to altered mental status and fever (T_{max}: 40°C). Initial vital signs were: temperature 39°C, blood pressure 128/72 mmHg, pulse 84 bpm, respirations 18/min. The patient had slight tenderness on neck-flexion, dry oral mucosa, and faint macular erythema in patches along his anterior chest, abdomen and both feet. Patient was drowsy, delirious, slow in responding but oriented. No focal deficits were observed on cranial nerve and sensory examination. The patient had severe weakness in bilateral deltoid muscle (1/5), weak left biceps (4/5) and reduced left hand grip with preserved muscle strength in his lower extremities. Deep tendon reflexes were + 2, symmetric throughout. The patient had intact bilateral heel-to-shin test and rapid alternating movements on his right upper extremity. Tests for co-ordination of his upper extremity were limited by profound weakness. His laboratory investigation results were significant for leukocytosis (11.6 X $10^3/\mu L$) and hemoconcentration (hemoglobin:17.9 g/dL; hematocrit: 52.8%), raised CK (4037 mg/dL), normal CKMB, normal troponin I and negative urine toxicological screen. Cerebrospinal fluid (CSF) showed raised WNV IgM titers, raised RBC's, relative neutrophilic pleocytosis and elevated protein (Table 1). The blood, urine, and CSF cultures were negative. No abnormality was detected in the MRI of the brain and cervical spine, or magnetic resonance venography of the brain.

The patient was empirically started on vancomycin, ceftriaxone, ampicillin, and acyclovir

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Table 1: CSF finding in the 2 cases of West Nile parlysis

	Patient 1	Patient 2
CSF Color	Colorless	Colorless
CSF Clarity	Clear	Clear
RBC Count	290	5 cells/μL
WBC Count	615	225 cells/μL
Neutrophils	80	35%
Lymphocytes	19	56%
Monocytes	1	9%
Eosinophils	0	0%
Basophils	0	0%
Bands	0	0%
CSF Glucose Level	78	46 mg/dL
CSF Protein	111	164 mg/dL
West Nile IgG CSF	< 1.30	1.15 Index
West Nile IgM CSF	5.99	6.74 Index
HSV-1 DNA	NOT DETECTED	NOT DETECTED
HSV 2 DNA	NOT DETECTED	NOT DETECTED
St. Louis IgG	NOT DETECTED	NOT DETECTED
St. Louis IgM	NOT DETECTED	NOT DETECTED

for bacterial or viral meningitis of unknown etiology, and was given aggressive IV hydration for suspected rhabdomyolysis. The patient's nausea, vomiting and neck pain subsided in a day. He was afebrile, non-arthralgic and non-myalgic by day 2. On day 3 he developed "Red Man syndrome" causing stoppage of vancomycin, followed by slow restart the next day. Mentation improved over the next 5 days. On day 8 after symptom onset, the patient's muscle weakness remained unchanged, but his DTRs on the left upper extremity were diminished compared to the right side (biceps: +1, triceps: +1, brachioradialis: 0). The patient was back to baseline cognitive function, full muscle strength, and equal brisk deep tendon reflexes in both upper extremities at 6 months.

Patient 2

Three weeks before admission, a 69-year-old Hispanic male developed fever (38°C), disorientation, mild headache and drowsiness that resolved in a week. One and half weeks later, he developed malaise, myalgia, and weakness affecting lower and upper extremities. Four days before admission the patient was bed-bound because of paraparesis. Patient denied photophobia or phonophobia. Vital signs on admission were: blood pressure 144/80 mmHg, heart rate 102 bpm, respirations 21/min and temperature (36°C). Patient had warm skin, slight tenderness on neck-flexion, was fully oriented, and displayed good memory. Cranial nerve and sensory examination were unremarkable. Motor examination (day 4 of weakness onset) showed 3/5 weakness in bilateral hip flexion, knee extension and knee flexion with preservation of ankle and toe muscle power. The patient had good muscle bulk throughout but 1/5 muscle weakness on left deltoid, 3/5 muscle weakness on left elbow flexion and 4/5 left handgrip weakness. On his right upper extremity he had 4/5 weakness in right deltoid on abduction. The patient had cog-wheel rigidity and resting tremor in his right upper extremity, though all other extremity muscles displayed normal tone. DTRs were +2, symmetric except for an areflexic left biceps reflex. Plantar reflexes were down-going. Laboratory investigation results showed leukocytosis (19 X 10^3/μL), mild hypokalemia (3.4 mg/dL), raised CRP (13.4 mg/dL), and normal CK levels. CSF findings showed raised WNV IgG and IgM titers, raised RBCs, lymphocytic pleocytosis and elevated protein (Table 1). MRI of the brain, cervical, thoracic and lumbar spine, as well as blood, urine, and CSF cultures, were negative. Patient was empirically started on a course of vancomycin, ceftriaxone, and acyclovir. He remained afebrile throughout. On day 6 of admission (~ 2 ½ weeks from onset) weakness in the affected muscle groups remained unchanged, resting tremor and cogwheel rigidity of his right upper extremity disappeared, but he

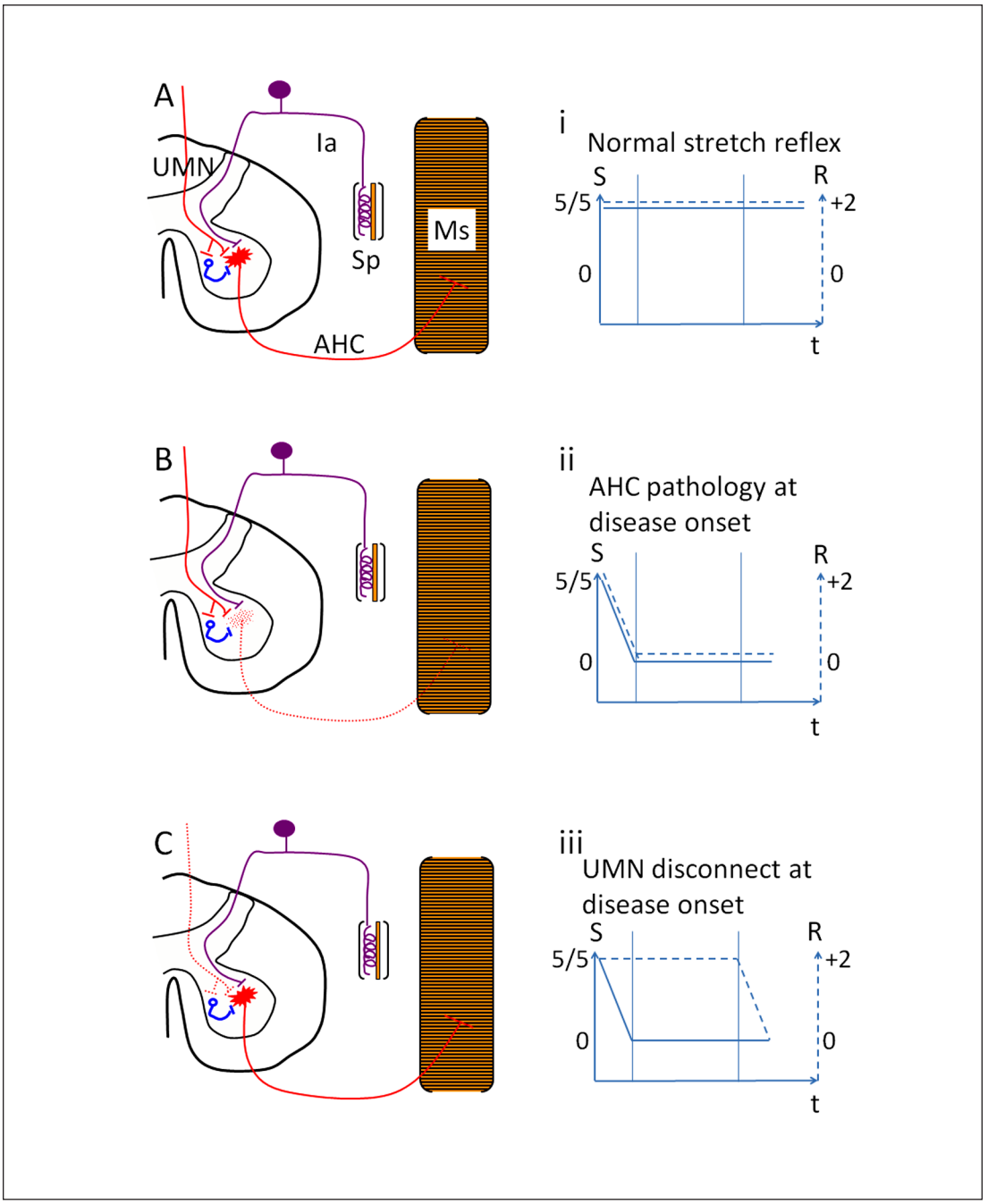

Figure 1: A: Diagram of normal stretch reflex with intact upper motor neuron and AHC function. Magnitudes of baseline muscle strength (S: solid line) and deep tendon reflex (R: dashed line) of the affected muscle group are shown as a function of time since disease onset (t). B: AHC pathology at disease onset should produce a concomitant decrease in S and R magnitudes over time. C: Upper motor neuron pathology at disease onset should produce a decrease in S, while R may be initially preserved in this scenario. UMN: Upper Motor Neuron; AHC: Anterior Horn Cell; Ia: Ia sensory neuron; Sp: muscle spindle; Ms: muscle (extrafusal fibres). Red: excitatory motor neuron; Blue: inhibitory interneuron. Violet: sensory neuron. The vertical lines indicate the time period of initial preservation of deep tendon reflexes in the presence of muscle paralysis. The magnitude of muscle strength (S) is graded qualitatively as 5/5 indicating full muscle strength to 0 indicating complete paralysis. Magnitude of deep tendon reflexes is qualitatively graded from +2 indicating preserved refexes to 0 indicating areflexia.

was found to be areflexic in his left upper extremity and bilateral lower extremity. Patient was able to walk without assistance at 6 months.

DISCUSSION

Both patients discussed eventually manifested typical WNV paralysis characterized by asymmetric flaccid limb plegia/palsy associated with absent or diminished DTRs in the affected muscles.[4,5] Patient 1 presented with acute WNV paralysis[6] whereas Patient 2 had delayed paralysis[7], transitory cog-wheel rigidity and resting tremor in the affected extremity, consistent with previous reports of reversible Parkinsonian features.[8] Both patients were admitted with weakness in certain limbs with preserved DTRs which later decreased or became areflexic in the presence of unchanged profound muscle weakness. Consistent with previous reports neither patient showed MRI changes.[1]

In WNV anterior poliomyelitis, paralysis of the involved muscles is expected to occur commensurate with loss of DTRs (Figure 1 B, ii). The initial preservation of DTRs indicates sparing of AHCs at this stage. We suggest that withdrawal of UMN influence on AHCs without a disconnect in the monosynaptic reflex arc could occur in early WNV paralysis (Figure 1 C, iii). Initial mild myelitis with spinal cord edema could disrupt UMN influence on the AHCs in the earlier stages of WNV paralysis.[9] Human autopsy in cases of WNV paralysis show cuffs of lymphocytes surrounding blood vessels in spinal gray matter extending into the nearby white matter[10] whereas, perivascular inflammation in the cord occurs before focal neuronal degeneration in experimentally induced WNV neuroinvasive disease.[11] In addition, initial glutamate reuptake failure resulting in excitotoxic injury is suggested by decreased expression of the excitatory amino acid transporter and prominent local inflammation, as well as loss of both pre- and post-synaptic dendritic proteins in spinal cords of patients with WNV paralysis[12]; and glutamate excitotoxicity in the spinal cord with associated hind-limb paralysis in alphavirus-induced encephalomyelitis in mice.[13-15] Disruption of AHC synapses before cell death could cause non-concomitant loss of motor function and DTRs. Finally, axonal spread of WNV independent of the CNS seeding from initial viremia[16] can cause sequential involvement of upper then lower motor neurons.

Evidence that destruction of AHCs may not be a *sine qua non* for WNV paresis comes from the Patient 1 and other case reports documenting reversible WNV paralysis[9] with preserved[17] or reduced[8] DTRs . To the best of our knowledge, initial preservation of DTRs followed by their loss in muscle groups has not been reported previously, and may be a good prognostic sign.

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DISCLOSURE

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