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Recovery and prognosticators of paralysis in West Nile virus infection

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Abstract

Previous studies have demonstrated that lesions of the anterior horn motor neurons are the primary pathology in patients with paralysis due to West Nile virus (WNV) infection. To characterize recovery and identify prognostic factors for the recovery of paralysis, we investigated 11 patients with electrophysiology testing and muscle biopsy, and one with autopsy. We found that limb weakness was markedly asymmetric and differed between upper and lower extremities, suggesting focal or segmental involvement of the spinal cord anterior horn. This was supported by segmental depletion of spinal motor neurons at autopsy. Clinical recovery was variable during a 21-month follow-up period. To explain variability, we performed motor unit number estimation (MUNE) in six patients. MUNE values and strength were correlated in tested muscles. We also detected motor nerve terminal damages in muscle biopsies, suggesting another possible mechanism for transient weakness and variable recovery. We conclude that the type of pathological lesions may vary in paralytic WNV infection, and different degrees or combinations of motor neuron loss and motor nerve terminal changes may account for the observed degrees of weakness and recovery.

Keywords: West Nile virus; Acute flaccid paralysis; Autopsy; Motor unit number estimation; Recovery; Muscle biopsy

1. Introduction

West Nile virus (WNV) is a single-stranded RNA virus that belongs to the Flaviviridae family, which includes the St. Louis, Kunjin, Murray Valley and Japanese encephalitis viruses [1]. Since the first epidemic in North America in the summer of 1999 [2], WNV has quickly spread across the United States [1]. Flaccid paralysis occurs in about 10% of the patients who are hospitalized for WNV infection [2]. We and others have recently characterized the acute and asymmetric paralysis in WNV infection, and localized the neurological lesion to the anterior horn motor neurons [3–9]. However, the extent of recovery of paralysis and prognostic factors remain unstudied.

Selective involvement of anterior horn motor neurons occurs in several neurological disorders, such as Polio-virus paralysis, amyotrophic lateral sclerosis (ALS), and spinal muscular atrophy (SMA). Compensation of motor neuron loss and muscle weakness mainly relies on reinnervation from collateral branch sprouting of surviving motor axons [10–12]. Because the reinnervation capacity of each motor unit is limited, it is reasonable to assume that the more surviving motor units that are available to participate in reinnervation the better recovery will be. Indeed, surviving motor unit numbers has been shown to be the major determinant of the final outcome in some of these motor neuron diseases [10,11]. In this study, we sought to characterize the recovery of paralysis in WNV infection and to evaluate whether recovery in muscle weakness is correlated with surviving motor unit numbers that are estimated by motor unit number estimation (MUNE) technique. We have also investigated whether paralysis could be explained by lesions at other anatomical sites, such as muscles or motor nerve terminals.

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2. Materials and methods

2.1. Patients and clinical assessment

Twelve patients (Table 1) diagnosed by CDC criteria were studied [13,14]. Six have been described in a previous report [3]. Electrophysiological studies were performed in all patients, muscle biopsies in five, and post-mortem study in one. Three patients were followed clinically for 21 months, five were contacted periodically by telephone, two had one clinic visit at the 20th month, and one was lost to follow-up after 6 weeks. This study was approved by Wayne State University human investigational committee and appropriate consents were obtained.

Muscle strength was assessed by the Medical Research Council (MRC) scale [15] and overall motor function was evaluated by the Amyotrophic Lateral Sclerosis Functional Rating Score (ALSFRS) since these patients shared similar neurological lesions with ALS patients [3–6,16]. ALSFRS consists of 10 questions related to motor functions, with cumulative score ranging from 40 (normal) to 0 (no motor function) [16]. For the four patients who did not return to our clinic after initial hospitalization (Table 1), the ALSFRS was collected over the telephone.

2.2. Electrophysiological studies

All patients had a full initial electrophysiological study, and nerve conduction studies (NCS) were repeated in some patients. Motor unit number estimation (MUNE) was performed using the spike-trigger averaging (STA) technique to estimate the degree of motor unit loss in six patients (Table 1). The methodology of STA has been detailed in previous studies [17,18].

2.3. Muscle pathology, immunohistochemistry and electron microscopy

Muscle biopsies were obtained from the symptomatic limbs (Table 1). In four patients, they were performed within 3 weeks from symptom onset, and in one 6 months after onset. Muscle specimens were examined with H&E, trichrome, myofibrillar ATPase, and NADH-tetrazolium reductase stains, and with transmission electron microscopy (EM). Immunohistochemistry was used to differentiate inflammatory cells. Fresh frozen muscle sections were fixed in 100% acetone for 10 min, followed by an incubation with primary antibodies against lymphocytic surface markers (CD2, dilution 1:20; CD3, 1:40; CD4, 1:40; CD8, 1:50, Becton Dickinson, CA; B cocktail, 1:20, Dako, CA; and CD68, 1:70, Dako, CA). Sections were further reacted with secondary antibodies (anti-mouse, 1:200; Vector laboratories, CA) that were conjugated with ABC complex. In addition, muscle specimens from two cases were stained with antibodies against the Japanese Encephalitis virus (JEV) antigen [19], which also reacts with WNV antigen.

2.4. Autopsy study

Autopsy material from an 86-year-old female included the spinal cord and roots, examined with light microscopy, immunohistochemistry, and EM.

Table 1
Patients' demographics and laboratory tests

Pt[a]	Sex/Age	Onset	WNV IgM	First EMG[b]	MUNE	Muscle Bx	F/U[c] method
A	F/52	8/23	+in CSF and serum	4 days, D.D.[d]	Yes, 1/per 12 weeks	24 weeks, R Biceps	Clinic visit
B	M/48	8/23	+in serum	2 weeks, D.D.	ND[e]	ND	Phone
C	M/27	9/2	+in CSF	4 days, D.D.	ND	2 weeks, L Deltoid	Phone
D	M/63	8/17	+in serum and neutra	15 weeks, D.D.	ND	3 weeks, L rectus femoris	Phone
E	M/35	8/14	+in CSF	6 weeks, D.D.	Twice	ND	Clinic visit
F	M/44	9/7	+in CSF	7 weeks, D.D.	Yes, 1/per 12 weeks	ND	Clinic visit
G	F/36	8/25	+in CSF	2 days D.D.	Yes, 1/per 12 weeks	12 days, L peroneus brevis	Clinic visit
H	F/69	8/19	+in serum	3 weeks, D.D.	ND	ND	Phone+clinic
I	M/39	8/21	+in serum	2 weeks, D.D.	ND	3 weeks, L rectus femoris	Phone
J	F/86	8/31	+in CSF	1 weeks, no D.D.	ND	ND	N/A[f]
K	M/51	8/10	+in CSF	11 days, D.D.	Yes, at 18th month	ND	One clinic visit at 18th month
L	F/50	8/30	+in CSF	at 18th month, D.D.	Yes, at 18th month	ND	One clinic visit at 18th month

[a] Pt=patient.
[b] Duration from the onset of weakness to the first EMG.
[c] F/U=follow-up.
[d] D.D.=diffuse denervation in symptomatic limbs and corresponding paraspinal muscles.
[e] ND=not done.
[f] N/A=not applicable.