Clinical Characteristic and Function Outcomes of West Nile Neuroinvasive Disease: A Case Series

Chad Swank, PhD, PT1,2; Rachel Burns, DPT2; Joanna Weakley, MPT2; Robert Suter, DO3

Texas Woman's University1; Baylor Institute for Rehabilitation2; Methodist Health System3

KEYWORDS:
West Nile Virus
West Nile Neuroinvasive Disease
Rehabilitation outcomes
Immunosuppression

For individuals with West Nile Virus (WNV) who develop West Nile Neuroinvasive Disease (WNND) symptoms of fatigue, muscle pain, muscle weakness persist > 90 days. Recovery of physical health, cognitive health, and functional health is achieved in only one-third of individuals at 18 months. The characteristics of WNND may impact long term outcomes. Specifically, recovery potential varies between WNND subtypes. This case series describes the functional outcomes for 7 individuals with various WNND clinical presentations. Each of our patients was either immunosuppressed, immunocompromised or of older age at the onset of WNV infection. For 6 cases, both pre-existing conditions were present. Recovery for each patient was restricted by profound muscle weakness and persistent fatigue despite slow progressive return of function. Impairments persisted post-rehabilitation limiting functional outcomes for each individual.

INTRODUCTION

West Nile Virus (WNV) is an arborvirus belonging to the genus Flavivirus transmitted to humans by the bite of an infected mosquito and was first isolated in the West Nile district of Uganda in 1937. The virus was first identified in the USA in 1999 during an outbreak of meningitis and encephalitis in the New York City area1 and is responsible for the three largest arboviral neuroinvasive disease outbreaks.2 Though WNV infection typically peaks in the summer season, July thru September, both Canada and the United States have experienced considerable human disease incidence.3 WNV infection usually presents with three clinical syndromes: asymptomatic infection, mild febrile syndrome (WNV Fever), and WNND. The majority of individuals are asymptomatic and only 20% exhibit WNV Fever symptoms.4 After acute illness 20-50% of people with clinically diagnosed WNV infection report persistent sequelae including somatic symptoms, cognitive and memory problems, depression, and balance and mobility difficulties.5 Though symptoms can vary among people with WNV, muscle weakness, difficulty walking, insomnia and fatigue were the most common symptoms reported.6

During the summer of 2012, the Centers for Disease Control registered the highest number of cases of WNV reported since 2003, with a total of 5,674 human cases of WNV disease reported across 48 states. Less than 1% of individuals with WNV infection develop West Nile Neuroinvasive Disease (WNND).4 However, in 2012 nearly half of the cases reported in Texas were classified as WNND.7 For individuals who develop WNND, symptoms of fatigue, muscle pain, and muscle weakness persist longer than 90 days. Full recovery of physical health, cognitive function, and functional capacity is achieved in only one-third of individuals with WNND after one year.4

Because outcomes for people with WNND are significantly worse, identification of those most at risk is critical. Weakness was a positive predictor of death.1,8,9 Age, gender6,10 and exposure to outdoor activities,11 are key risk factors. Furthermore, a weakened immune system is a well-documented risk factor for susceptibility for WNND. Immunosuppression from transplant rejection medications has been reported to be a risk for WNND.12 The role of other underlying primary or secondary immunodeficiencies and their interaction with comorbid conditions such as hypertension and diabetes has been associated with increased severity of illness and persistence of symptoms.5

The role of the immune system in preventing the progression of WNV to WNND remains incompletely elucidated. Though WNND can be divided into three subtypes: West Nile (WN) Meningitis, WN Encephalitis, and WN Poliomyelitis,13 the three subtypes vary on timelines for recovery and long term potential outcomes. Our case series describes the various clinical characteristics and functional outcomes for seven individuals with WNND.

Address correspondence to: Chad Swank, PhD, PT, Texas Woman's University, School of Physical Therapy, 5500 Southwestern Medical Ave., Dallas, TX 75235; Phone: 214-689-7714; Fax: 214-689-7703; Email: cswank@twu.edu

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METHODS
This study is a retrospective review of medical records for seven patients with a confirmed diagnosis of WNND admitted to the outpatient physical therapy department of a hospital system. Diagnosis of WNND was confirmed by the presence of WNV-specific IgM antibody in serum or cerebrospinal fluid as documented in the medical record for each patient. Each patient was identified because either the initial medical management or inpatient rehabilitation occurred within the same hospital system, allowing for a thorough review of the medical record. In some cases, the patient was followed throughout the continuum of care from acute care, inpatient rehabilitation, and outpatient rehabilitation. Patients were excluded from review if they were less than 18 years old or died while in the hospital. Institutional Review Board approval was obtained for this retrospective review.

CASE PRESENTATIONS
Refer to tables 1 through 3 for additional description of cases.

**Case #1:** A 59 year old male accountant with a history of alcoholism, tobacco abuse, and GERD when diagnosed with WN Encephalitis. His total therapy treatment time encapsulated 19 months, and his primary impairments involved muscle weakness, fatigue, and cognitive impairment. One month after initial onset, he required maximal assist with activities of daily living (ADLs) and all mobility. By the ninth month post-onset, he was able to ambulate independently using an ankle foot orthosis and had returned to work at 20% of premorbid capacity. After 10 months, he began mowing his lawn and returned to work at 40% of premorbid capacity. At 18 months, he walked within age and gender normal velocity over community distances. At 19 months post-onset, he was able to go up and down stairs with a reciprocal step pattern and handrail.

**Case #2:** A 63 year old male physician with a history of reactive airway disease and BPH when diagnosed with WN Encephalitis. His therapy treatment time totaled 33 months and his primary impairments included muscle weakness, fatigue, vestibular and visual impairment. One month after onset, he was able to perform bed mobility with minimal assist, transfers with moderate assist, and ambulation for 20 feet with a rolling walker. He required minimal assistance for ADLs but was dependent for dressing. After 10 months, he was able to work part-time and ambulate in the community independently without an assistive device. After 27 months post-onset, he was able to perform about 40% of his premorbid work activities and 70% premorbid leisure activities.

**Case #3:** A 63 year old male engineer with previous medical history of a liver transplant and polio when diagnosed with WNND. His total rehabilitation time was 30 months and involved 2 separate admissions to inpatient and outpatient rehabilitation. His primary impairments were muscle weakness, fatigue, and cognitive impairment. By four months he was able to complete basic transfers and was modified independent with ADLs. He did not become a household ambulator until 24 months. When he finished rehabilitation he was considered a modified independent community ambulator.

**Case #4:** A 38 year old male carpenter with previous medical history of alcoholism and tobacco abuse prior to developing WN Meningitis. He received four months total of therapy. The primary impairments were muscle weakness, ataxia, cognitive and visual impairment. Upon admission to rehabilitation, he required maximal to dependent assist for all ADLs. After two months of rehabilitation, he was independent with bed mobility and able to ambulate 300 feet with minimal assist without an assistive device. After four months, he was independently ambulating at 75% of age and gender normal velocity over community distances. He could climb stairs with minimal assist. He returned to his preferred leisure activity of playing golf but experienced two falls.

**Case #5:** A 59 year old female retired schoolteacher with a medical history of heart transplant, and breast cancer with double mastectomy before developing WN Encephalitis. The primary impairments found were muscle weakness, ataxia, fatigue, central and peripheral vestibular disorder, and visual impairments. Her total therapy time entailed 27 months, but she spent the first four months in acute care and skilled nursing facility. After 13 months, she ambulated at 45% of age and gender normal velocity over community distances with minimal assist. At 23 months she required stand-by assist for stairs and level surface ambulation due to her high risk for falls. She failed to achieve independence or modified independence with basic ADLs and mobility (see Table 1).

**Case #6:** A 56 year old female nurse practitioner with a history of rheumatoid arthritis and psoriasis diagnosed with WN Encephalitis. Her primary impairments of muscle weakness and fatigue were compounded by cognitive impairment due to encephalopathy. Her total rehabilitation time was nine months. After six months she was modified independent with transfers and ambulated at 20% of age and gender normal velocity over community distances with a walker and supervision. She required maximal assist for stairs. At nine months, her walking progressed to 40% of age and gender normal velocity over community distances with a cane, and she was modified independent with stairs.
Case #7: A 45 year old disabled female with a medical history that included type II diabetes, renal failure, herpes, and coronary artery disease status post bypass surgery diagnosed with undifferentiated WNND. Her primary complaints were fatigue and profound muscle weakness associated with lower extremity flaccidity. She received therapy for nine months. She recovered her ability to perform basic transfers and ADLs from a wheelchair level after four months of rehabilitation with stand by assist. By nine months she had achieved modified independence with ADLs and transfers at a wheelchair level but was unable to ambulate.

**DISCUSSION**

This case series describes various clinical characteristics and functional outcomes for seven individuals with WNND. Of our seven cases, four were diagnosed with WN Encephalitis, one with WN Meningitis, and two with undifferentiated WNND. Those with WN Encephalitis continued to make slow functional gains for an average of 22 months post-onset.

Each progressed from primary use of a wheelchair to being a supervised or independent community ambulator. Two individuals resumed part-time employment. The individual with WN Meningitis returned to his hobbies at four months post-onset. Our two patients with undifferentiated WNND had significant functional limitations requiring a wheelchair or an assistive device and orthosis for mobility. The limited recovery appears to most closely resemble WN Poliomyelitis outcomes.²

In all seven cases the initial medical management was marked by severe morbidity. Cognitive impairment experienced in three cases resolved by the end of inpatient rehabilitation and did not appear to adversely impact outpatient recovery. However, two cases with brainstem dysfunction had visual and vestibular impairments persisting throughout the course of treatment. Rehabilitation for each individual was limited by profound muscle weakness and persistent fatigue with slow progressive return of function. While acute inpatient rehabilitation length of stay was typically around 35 days,
outpatient rehabilitation varied greatly according to WNND subtype. Impairments persisted post-rehabilitation limiting functional outcomes for each individual.

Each of our patients was either immunosuppressed (n=2) or immunocompromised (n=5) at the onset of WNV infection. Consistent with the literature, immunosuppression in our two patients was due to transplant\textsuperscript{12} and cancer-related medications.\textsuperscript{1} Medical co-morbidities contributing to immunocompromise in our patients included cardiopulmonary disorders\textsuperscript{14,15} and diabetes.\textsuperscript{1,14} Lifestyle factors contributing to immunocompromise (alcohol abuse and habitual smoking)\textsuperscript{14, 15} were also seen in our patients.

One individual in this review was diagnosed with two autoimmune disorders of rheumatoid arthritis and psoriasis. Bode et al.\textsuperscript{15} identified the presence of autoimmune disorders in 30 of their 221 patients. However, when viewed statistically through odds ratios, the presence of autoimmune disorders did not increase risk of acquiring WNND. Nevertheless, in our patient, her age of 56 years and presence of two autoimmune disorders appear to be her only identifiable risk factors. Although a singular risk factor such as diabetes or transplantation outweighs the risk associated with autoimmune disorders, the presence of multiple low risk factors (autoimmune disorders) may increase the odds of acquiring WNND.

Another case had a diagnosis of reactive airway disease. It is possible that immunosuppression in this individual was due to the use of prednisone.\textsuperscript{1} Susceptibility to WNV and subsequent WNND may have also been due to his age of 63 years. For five of our cases older age (>50 years) was a concurrent risk factor. Nash et al.\textsuperscript{1} reported that individuals older than 50 years were 20 times more likely to experience signs of clinical infection than those younger than 50 years. Our patients older than 59 years, though requiring increased length of stay in rehabilitation compared to those younger patients, demonstrated improved functional outcomes. A study in Ohio observed that though children were 4.5 times more likely to test positive for WNV infection, adults older than 65 years of age were 110 times more likely to experience WNND.\textsuperscript{16}

**CONCLUSION**

It is important to identify patients at higher risk of WNND at initial diagnosis of WNV. Many patients with WNV-related illnesses are unrecognized clinically. During one well-publicized outbreak, only 40% of patients with clinically compatible meningitis or encephalitis were tested for WNV.\textsuperscript{17} Proper diagnosis and correlation of comorbidities can help health care providers understand the long term functional outcomes for the WNND population. Our seven cases had outcomes ranging from assistance required for basic mobility and ADL’s to independence with mobility and return to vocation and driving. Despite the improvements made, fatigue seemed to be a lingering complaint. The presence of immunosuppressing and immunocompromising comorbidities coupled with older age placed our patients at higher risk of developing WNND. Specifically, we observed transplantation, cancer, alcohol abuse, cardiopulmonary disease, and autoimmune disorders to be significant contributing factors for our patients.
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