CASE PRESENTATION - Dr. Julia Keith

A 76-year-old woman presented to London Health Sciences Centre in August with progressive leg weakness and general malaise. Her leg strength was deteriorating rapidly, and she had last walked two or three days prior. For the past 36 hours she felt unwell with nausea and a poor appetite. Her husband had noticed a decrease in her verbal output. She denied neck or back pain.

Her past medical history included stable Crohn’s disease, diagnosed in 2002. Her medications included prednisone 40 mg a day and Imovane 7.5 mg as needed at bedtime. She was a smoker with a 55 pack year history, but denied alcohol use. She was a retired retail worker, and her husband described her having an “active” lifestyle; the past few days had been a significant decline from her baseline.

On initial examination her heart rate was 108/min, blood pressure 130/90 mmHg, respiratory rate 26/min and temperature 39°C. She was described as being mute and staring “blankly”. Her cardiac exam revealed a 3/6 systolic murmur. Important points noted on her initial neurological exam by the admitting medical team included leg weakness. She was admitted and started on Ceftriaxone 2 g IV every 12 hours and Acyclovir 700 mg every 8 hours. The neurology service saw her in consultation the following day.

The consultant neurological examination the following day noted her to be vocalizing more. She was oriented to time and person but not to place, able to follow three step commands, and had ‘reasonable comprehension’. The cranial nerves were normal. Her arms were mildly weak with no specific pattern given, and legs much weaker in a pattern of symmetric involvement of quadriceps to about the same degree as hamstrings, suggesting that this was not solely a “pyramidal pattern” weakness. An important observation was that some deep tendon reflexes were hyperreflexic (biceps and ankles, where there was clonus), but

DISCUSSANT - Dr. Michael Nicolle

The history is that of a 76-year-old woman with a three day history of progressive leg weakness, decreased verbal output and fever. Pertinent details of her past medical history include the fact that she had an autoimmune disease (Crohn’s) and was iatrogenically immunosuppressed, although the duration of prednisone treatment was not provided. She was a 55 pack-year smoker, increasing her chances of having an underlying malignancy. She was also described as having an “active” lifestyle, perhaps increasing her exposure to environmental factors, and she presented in August, which may be of further relevance.

The initial examination by the medicine team revealed a cardiac murmur and a fever, for which she was started on Ceftriaxone and Acyclovir. No mention was made of any retinal or skin lesions. She was noted by the admitting team to be “staring blankly”, although whether this was continuous, as might be expected in an encephalitic or encephalopathic process, or was intermittent, suggesting the possibility of underlying subclinical seizures, was not further described.

The neurological examination the following day disclosed that she was “vocalizing more”, able to follow commands with reasonable comprehension and oriented to time and person, but not to place. The cranial nerves were normal. Her arms were mildly weak with no specific pattern given, and legs much weaker in a pattern of symmetric involvement of quadriceps to about the same degree as hamstrings, suggesting that this was not solely a “pyramidal pattern” weakness. An important observation was that some deep tendon reflexes were hyperreflexic (biceps and ankles, where there was clonus), but

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others were diminished (notably at the knees). Although the possibility that reflexes were diminished acutely on the basis of “spinal shock” could be considered as an academic exercise, the degree of her weakness was mild (MRC 4/5) apart from the more significant (MRC 1/5) weakness of hip flexion, and her ankle reflexes were brisk. The sensory exam described “diminished proprioception in the lower extremities”. It is difficult to determine whether this was truly abnormal or was simply a “normal” degree of proprioceptive loss at this age. The presence of significant sensory dysfunction would be very important in refining the differential diagnosis.

Information that might have been useful includes whether or not she had any constitutional symptoms such as a weight loss or cough to suggest an underlying malignancy, whether the cardiac murmur had been noted previously, and whether she complained of headaches or anything else to suggest an infection of the central nervous system.

Although her initial presentation with confusion and reduced verbal output raises the possibility of an aphasia, the subsequent examination by the neurology team suggested this was not the case, with normal comprehension, and no specific comment about problems with repetition or fluency. Although her tone was described as being decreased in both arms and legs, her toes were upgoing, providing evidence for involvement of the central nervous system.

The preliminary localization must include a process affecting both the central and peripheral nervous systems. Central nervous system involvement is evident by the involvement of her cognitive function, and by the finding that some deep tendon reflexes were brisk and that the plantar responses were bilaterally upgoing. In the absence of focal or lateralizing features, localization within the central nervous system should include a diffuse process affecting cortex, the ventricles (hydrocephalus) or frontal lobes. The latter two are areas that could produce a disturbance in the level of consciousness with remarkably few focal findings. Involvement of the descending corticospinal tracts could also be invoked to explain prominent leg weakness, although there was nothing specifically to suggest this. Although she had clonus at the ankles, deep tendon reflexes at the knees were diminished and tone in the legs reduced. However, there is also evidence for peripheral nervous system involvement. Despite her prominent proximal leg weakness, deep tendon reflexes at the knees were diminished and the tone decreased. Within the peripheral nervous system the localization remains broad and includes a process affecting the anterior horn cells, lumbosacral roots, lumbosacral plexus or peripheral nerves.

This localization can be further refined by the assumption that the sensory involvement was minimal, if any. With prominent leg weakness and no significant sensory involvement, a disorder of neuromuscular transmission should be briefly considered. Although the pattern of weakness is not consistent with an acquired post-synaptic disorder of neuromuscular transmission (myasthenia gravis), the Lambert Eaton Myasthenic Syndrome (LEMS) could cause leg weakness and deep tendon reflexes that were diminished. However, some of her deep tendon reflexes were brisk, which virtually excludes LEMS on clinical grounds. Although the pattern of weakness is not consistent with an inflammatory myopathy, specifically dermatomyositis as part of a paraneoplastic process, would need to be considered. However, there was no rash, although in some cases the characteristic rash of dermatomyositis may be missed or may not be present, and a specific diagnosis of dermatomyositis only reached after a review of the muscle histopathology. Although she had been on prednisone for her Crohn’s disease, the acuity of presentation and the severity of her hip flexor weakness would be very much against a steroid myopathy.

With involvement of both the central and peripheral nervous systems, in a woman who is immunosuppressed, systemically unwell and febrile, several etiological possibilities should be considered. The first would be an infectious process, including viral and other opportunistic infections. If the cardiac murmur was new, bacterial endocarditis might reasonably be considered although there was nothing lateralizing or particularly focal on either the history or on the examination and no mention of skin or retinal lesions. An underlying malignancy with direct involvement of the spinal cord and meninges (either carcinomatous or lymphomatous), or the indirect results of malignancy through a paraneoplastic process, are worth including in the differential. Inflammatory conditions such as a vasculitic process with involvement of both central and peripheral nervous system, or of sarcoid, would also remain, albeit remotely, in the differential at this stage.

**Dr. Keith**

Initial bloodwork was as follows: Na 134 mmol/L, K 3.7 mmol/L, Calcium 2.05 mmol/L (serum albumin 26 g/L), Magnesium 0.65 mmol/L, Creatinine 0.52 mmol/L (6 weeks previously it was 1.14 mmol/L), urea 8.8 mmol/L, WBC 11.5 x 10^9/L, Hb 155 g/L, and platelets 37 x 10^9/L (121 x 10^9/L 6 weeks previously). Liver function tests and cardiac enzymes were normal. CSF analysis demonstrated a glucose of 2.8 mmol/L (serum glucose 11.9 mmol/L ), protein of 495 mg/L and 28 nucleated cells/mm^3 (61 % neutrophils, 18 % lymphocytes). CSF was not sent for cytology. Immunological markers including complement were normal, and Anti-nuclear antibodies (ANA), (perinuclear) Anti-neutrophil Cytoplasmic Antibodies (pANCA) and (diffuse cytoplasmic) Anti-neutrophil Cytoplasmic Antibodies (cANCA) negative. A carotid doppler ultrasound arranged by the medical team showed no significant carotid stenosis. A CT head was unremarkable. An MRI without gadolinium administration was performed of her spine, which demonstrated multilevel spondylosis, most pronounced in the cervical spine, which resulted in mild contouring of the adjacent cord but no significant compromise of the cord, no signal change and no abnormalities of exiting cervical or lumbar roots.

**Dr. Nicolle**

Pertinent laboratory results include hyponatremia, not enough to produce CNS dysfunction. In the absence of medications that could cause this, the possibility of syndrome of inappropriate antidiuretic hormone (SIADH) should be considered and her urinary electrolyte levels assessed. The mild peripheral leukocytosis in someone on prednisone wasn’t striking. She was acutely thrombocytopenic. Possible causes for this include a primary autoimmune disorder such as idiopathic thrombo-cytopenic purpura, the secondary toxic effects of medications including acetylcol, disorders of hemopoiesis such as thrombotic thrombocytopenic purpura or bone marrow suppression as a result of infection.
The CSF analysis showed a mild elevation in the protein level. There was a mild increase in the nucleated cell count, the majority of which were neutrophils. However this analysis was done early in her course, when a number of infectious organisms can produce an initial neutrophil predominant pleocytosis, which later on converts to a more characteristic “aseptic” pattern of lymphocytic predominance. There was no description of atypical cells, although cytological analysis was not specifically performed to look for evidence of a malignant process. The CSF pleocytosis suggests either an infectious, inflammatory or neoplastic process.

A CT of her head was remarkable for its near normality. This suggests that there was no significant structural, ischemic or embolic process to explain her deficits. An MRI of her spine showed no lesions, excluding a structural lesion to explain her leg weakness. No gadolinium was given, which would facilitate recognition of a neoplastic meningitis by demonstration of meningeal or root enhancement. An MRI of the brain would have been useful as many of the processes in the differential might produce lesions below the resolution of a CT scan.

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Over the next 48 hours the patient’s speech fluctuated from fluent, to garbled, to near mutism. Thereafter her breathing became irregular with intermittent Cheyne-Stokes patterns. Additional laboratory results became available: CSF viral polymerase chain reaction (PCR) was negative for HSV1 and HSV2 and urine and blood cultures were negative.

The following day her level of consciousness was further depressed (GCS 10). She was discovered to be in respiratory acidosis and rapid atrial fibrillation, the latter treated with diltiazem. A brain CT scan showed no new findings. Ten hours later, three days after admission, the patient was found without vital signs. Next of kin gave consent for a full autopsy.

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Although the patient deteriorated, there were still no significant focal or lateralizing features. The CSF viral PCR was negative for both HSV1 and HSV2 and a repeat CT scan of the head shortly before death showed no evidence of a focal or structural process to explain her clinical presentation.

The localization must again consider a process affecting the central nervous system diffusely. Although no new information is given, the initial presentation also suggests peripheral nervous system involvement by a process that is purely or predominantly motor in nature, producing a symmetric flaccid paralysis affecting proximal legs much more than arms.

Etiological considerations would have to explain a rapidly progressive disorder affecting both the central and peripheral nervous systems which was associated with a fever and a low grade CSF pleocytosis and which did not respond to either antiviral or antibiotic treatment. The fact that she was a smoker, immunosuppressed, developed renal failure, had a cardiac murmur and developed atrial fibrillation may also be of relevance.

The differential at this stage includes a viral encephalitis. The lack of focal features and of seizures would be somewhat unusual for herpes simplex encephalitis (HSE) and negative results of HSV PCR go a long way to excluding this as the specific viral agent. Moreover peripheral nervous system involvement is not in keeping with an HSE. Other viral agents deserving consideration include Flaviviruses, notably West Nile Virus (WNV), which could cause both an encephalitis and poliomyelitis.

In the setting of a possibly new cardiac murmur and atrial fibrillation, a bacterial endocarditis with septic emboli should also be considered. However there were no retinal or skin manifestations, there were no focal features and the imaging was normal. This would not exclude multiple microemboli to the brain which had not produced clinically apparent focal signs, and which were below the resolution of the CT scan. However, bacterial endocarditis would not explain involvement of the peripheral nervous system. Moreover urine and blood cultures were negative, which if collected prior to the institution of antibiotic therapy, suggest that a bacterial infection was not the explanation for her clinical presentation. Other possibilities in someone who is immunosuppressed include other opportunistic infections. Her CSF white count was not high enough to suggest a bacterial infection, although she is immunosuppressed, and the clinical picture is more encephalitic than meningitic. Infections with tuberculosis, cryptococcus, toxoplasmosis, histoplasmosis, other fungal agents, as well as syphilis, should be briefly considered in the differential. However, again the clinical picture is more encephalitic, the CSF abnormalities don’t fit most of these infectious processes, and none of these would easily explain the flaccid paralysis which appears to be on the basis of peripheral nervous system involvement.

A vasculitic process affecting both the central and peripheral nervous systems should be considered although there was no evidence for systemic involvement (excepting perhaps her renal failure), there were no focal features, and the process producing her leg weakness was pure motor and painless. Peripheral nerve involvement as a result of a vasculitic process almost always affects both motor and sensory fibres and is painful. Thus I think a vasculitic process is improbable.

Another inflammatory process such as sarcoid could explain both involvement of the central and peripheral nervous systems. However, no chest x-ray abnormalities were described and neurosarcoidosis is rare without known systemic sarcoid. The most common manifestation of neurosarcoidosis affecting the peripheral nervous system is involvement of the cranial nerves, not present in this case. The rate of progression in this case is also much faster than I would expect with sarcoid. Thus I think sarcoid is unlikely.

In a long time smoker who is systemically unwell the possibility of a malignancy directly or indirectly affecting the nervous system remains in the differential. Either carcinomatous meningitis or lymphomatous meningitis could produce some aspects of her clinical presentation, although there was no mention of any atypical cells in the CSF and the pattern in the CSF doesn’t fit particularly well with malignant involvement of the meninges. There was no known primary (with breast or lung being the most likely in someone with a carcinomatous meningitis) and no description of back or extremity pain. An MRI of her spine did not show any meningeal or nerve root thickening, although the administration of gadolinium would increase the sensitivity of the MRI for this. A paraneoplastic process should also be considered. An underlying small cell
There is evidence that toll-like receptor 3 stimulation and elevated TNF-alpha facilitate CNS invasion by increasing blood-brain barrier permeability. Like receptor 3 stimulation and elevated TNF-alpha facilitate CNS invasion by increasing blood-brain barrier permeability. Although occasional human to human infections have been reported, the virus persists in an enzootic cycle principally involving birds and Culex mosquitoes. Infections in North America are seasonal owing to the life cycle of the mosquito in a temperate climate. North American strains are particularly virulent in raptors owing to the life cycle of the mosquito in a temperate climate.

Investigations that would have been useful during the course of her admission include a careful examination of her CSF for signs of iatrogenic immunosuppression in the general population. She was described as having an “active” lifestyle, which I took to mean that she was physically active and likely outdoors, potentially exposing herself to virus-bearing mosquitoes. She also presented in the late summer, when the risk of exposure to WNV infected mosquitoes is highest. Thereafter the Public Health Department reported positive serology for WNV IgM from the postmortem blood sample. Finally, anti-WNV immunohistochemistry performed by Ms. Beverly Young at Sunnybrook Hospital (polyclonal rabbit anti-WNV antibodies, 1:50 dilution, generously provided by Dr. Keith Young at Sunnybrook Hospital) confirmed the presence of West Nile Viral antigen in neuronal cell bodies and processes in affected areas (Figure d,e,f).

DISCUSSION

West Nile Virus is an encapsulated ssRNA flavivirus. The virus persists in an enzootic cycle principally involving birds and Culex mosquitoes. Infections in North America are seasonal owing to the life cycle of the mosquito in a temperate climate. North American strains are particularly virulent in raptors (crows, jays, etc.) which act as primary reservoirs. In humans, virus is believed to replicate at the site of inoculation, spreading hematogenously and by lymphatics. There is evidence that toll-like receptor 3 stimulation and elevated TNF-alpha facilitate CNS invasion by increasing blood-brain barrier permeability. Although occasional human to human infections have been
documented (breast milk, transplacental, organ donation) humans are not functionally significant reservoirs, presumably because of relatively low viremia.

Two major WNV genetic lineages are recognized. North American cases (lineage 1) having a common origin with those in Europe, Africa, Asia and Australia. Viral DNA homology suggests that North American isolates, first encountered during the 1999 New York City outbreak, likely originated from the Middle East. Since 1999, the virus has been successful in propagating across North America and in late summer 2002 the first Canadian outbreak occurred in the Toronto region, part of what remains the largest WNV outbreak documented and the largest arboviral outbreak in the Western hemisphere. The present case was among the first recognized infections in the London region and the first documented fatality at the London Health Sciences Centre. Based on worldwide epidemiological

**Figure:** a) Perivascular lymphocytic cuff (arrow) and microglial nodule formation (arrowhead), substantia nigra, H&E, bar = 50 μm. b) Neuronophagia, anterior horn, lumbar cord, H&E, bar = 20 μm. c) Microglial activation with HLADR expression and neuronophagia (arrow), dentate nucleus, cerebellum, anti-HLADR immunohistochemistry, bar = 20 μm. d) Neuronal expression of WNV antigen, thalamus, anti-WNV immunoperoxidase, bar = 50 μm. e) Motor neuron expression of WNV antigen, lumbar cord, anti-WNV immunoperoxidase, bar = 20 μm. f) Purkinje cell expression of WNV antigen, cerebellum, anti-WNV immunoperoxidase, bar = 20 μm.
data, Petersen and Roehrig suggested that WNV virus in humans was becoming more frequent and more severe.\(^6\) Interestingly and in contrast, WNV is widely disseminated in Mexico but, despite evidence of derivation from North American strains, human cases have been remarkably rare.\(^7\) These observations in Mexico have sparked considerable public health interest but the reason for the low human case load remains unknown. The possibility that reduced virulence may be due to viral genetic drift, host or environmental factors exists but disease recognition and reporting patterns may also have influenced case recognition.

**Clinical Presentation**

Most WNV infections are asymptomatic especially where background levels of immunity in the population are high.\(^8\) The incubation period is from three days to two weeks. Approximately 20% of individuals infected with WNV develop “West Nile Fever” which may include fever, headache, back pain, myalgias, arthralgias, nausea, vomiting, lymphadenopathy and a morbilliform or maculopapular rash. Less than 1% of WNV infections progress to neurological involvement but such cases carry a substantial burden of long-term disability and a mortality rate approaching 10%.\(^3,8\) The risk of neuroinvasive disease and mortality is greater in elderly and immunocompromised individuals.\(^3,5,9\) Occasional rapidly fatal cases like the present case have been reported, typically with prominent brainstem and spinal cord involvement.\(^9,11\)

**Neurological Features**

The central and peripheral nervous systems are both targets of WNV, with aseptic meningitis, encephalitis or poliomyelitis reported alone or in combination.\(^3,5,8,12\)

West Nile encephalitis is heralded by the febrile prodrome that may precede neurological signs and symptoms by several days. Evolution to encephalitis is suggested by a decreased level of consciousness, with 15% of individuals progressing to coma. WNE is associated with poliomyelitis in up to 50% of individuals. In contrast to herpes simplex encephalitis, seizures and other focal neurological symptoms are uncommon. Hints that a West Nile infection is the cause of neurological dysfunction include its frequent association with extrapyramidal features including a tremor, dyskinesias or myoclonus, as well as the behavioural consequences of an encephalitic process.\(^3,12\) Focal or highly asymmetric weakness with areflexia or hyporeflexia is suggestive of involvement of the anterior horn cells (poliomyelitis), as is sparing of the sensory system.

West Nile Virus infection is now the leading cause of poliomyelitis although other Flavivirus infections can also cause poliomyelitis. The clinical presentation includes an acute, sometimes suddenly over several hours, presentation of headache, fever, myalgia, back pain and then diffuse symmetric, often proximal, or asymmetric limb weakness with areflexia or hyporeflexia. In some cases a single limb can be affected. As a result of this the deep tendon reflexes are reduced or absent, and if anterior horn cells in the cervical cord are affected, respiratory failure can occur.\(^13,14\) Phrenic nerve or cervical cord segment involvement has been described.\(^3,5\) There is no pain or sensory involvement. In contrast to poliomyelitis secondary to poliovirus, bowel and bladder involvement is quite common with WNV.\(^12,13,15\)

Neuromuscular involvement was recorded in 11/26 patients admitted with WNV infection to Toronto region hospitals in late summer 2002. Three of these patients developed peripheral neuropathy, with one case interpreted as a possible Guillain-Barré type illness.\(^9,11\) Acute demyelinating peripheral neuropathy is uncommonly reported in association with WNV infection and its distinction from a pure motor poliomyelitis can be challenging. The incidence of neuromuscular complications rose to over 80% (9/11) in cases with encephalitis.\(^9\)

**Laboratory Investigations**

The CSF is usually abnormal with a wide range of white cell counts up to several hundred x 10\(^6\) per L, typically lymphocytic but occasionally with early neutrophil predominance.\(^3,5,11,16\) The protein level is usually elevated and glucose normal.

In cases with poliomyelitis, electrophysiological studies eventually will demonstrate involvement of the anterior horn cells and/or ventral roots, suggested by involvement of the proximal limbs and paraspinal muscles, with sparing of sensory nerves.\(^9,12,14\)

Serology should be sought from blood and/or CSF with the detection of specific IgM providing strong evidence of WNV infection.\(^3,5\) However, because WNV-specific IgM has been detected in some individuals more than a year after infection, the presence of IgM does not always indicate current infection. Given the widespread distribution of WNV and the fact that the vast majority of cases are asymptomatic, detection of specific IgG is of lesser diagnostic value. Viral cultures have a very low yield. By comparison, nucleic acid amplification tests are more sensitive (with CSF having a greater yield than serum) but still limited by the low viremia of most patients thereby making PCR a relatively poor screening tool.\(^3,17,18\) Hence, paired serological tests appear to be the most widely recommended.\(^3,19\)

Recent imaging studies have demonstrated a variety of findings. Although the timing and sequences of the examinations varied, there are a significant number of longitudinal studies judged to be normal or with abnormalities only visible on diffusion weighted images, both of which were associated with better prognoses.\(^20,21\) T2 and FLAIR hyperintensities in cerebrum, cerebellum and brainstem with variable or no enhancement were associated with less favourable outcomes. Gadolinium-enhanced imaging is recommended.\(^9\) Meningeal or nerve root enhancement is occasionally seen.\(^20\)

There has been relatively less experience in spinal imaging in WNV infection. Regions of T2 and FLAIR hyperintensity are again described as well as variable enhancement of parenchyma, nerve roots and leptomeninges.\(^20,21\)

Pathological examination reveals nonspecific features of an encephalitic process; microglial activation, perivascular lymphocytic infiltrates and neuronophagia.\(^3,10,19\) In cases coming to autopsy, these changes are typically most prominent in deep gray matter, brainstem, cerebellum and spinal cord. Inclusions are not evident, but immunohistochemistry for WNV antigens can be useful. Viral antigen expression tends to be focal and heaviest in neurons and their processes, especially in deep gray matter, cerebellum, brainstem and spinal cord as with the present case. Viral load and antigen expression tends to be greater in cases with a duration of illness of one week or less.\(^19\)
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TREATMENT

The value of specific treatments such as ribavirin, interferon, anti-WNV IgG and vaccination await proper clinical trials. Clearly, preventative measures remain paramount including exposure avoidance, mosquito repellants and larvicides.

SUMMARY

The present case was typical in many respects for neuroinvasive WNV infection. The differential diagnosis considered was appropriately comprehensive. The present case also reminds us that little or no abnormalities will be seen on imaging in many cases, and that initial serology may be negative and should be repeated beyond the acute phase ante- or postmortem. Fortunately, specific antibodies are also now available for identification of viral proteins in tissue although sensitivity of the latter may be affected by the stage of infection and sampling of areas bearing a higher viral load.

West Nile Virus, along with other emerging infections, serves notice of the health care implications of humanity’s globalization of ecosystems.

Final Diagnosis: West Nile Virus Encephalomyelitis

REFERENCES