

Electro-clinical evolution of refractory non-convulsive status epilepticus caused by West Nile virus encephalitis

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ABSTRACT – West Nile virus (WNV) has re-emerged with a much wider geographic distribution and a higher incidence than ever. In spite of some recent reports on the neurological manifestations and EEG changes caused by WNV encephalitis, there are few data on the incidence of seizures, status epilepticus or post-encephalitic epilepsy. There is also no systematic review of EEG changes caused by WNV encephalitis that is based on a large series of patients. Here, we review the pertinent literature, and report the electroclinical evolution and therapeutic complexity of a patient with WNV encephalitis who developed refractory, non-convulsive status epilepticus.

Key words: West Nile virus (WNV), seizure, status epilepticus, encephalitis, arbovirus, chronic lymphocytic leukemia, nonconvulsive status epilepticus

The mosquito-borne subgroup of arboviruses began to play a more prominent role in US clinical practice since West Nile Virus (WNV) was identified for the first time in the Western Hemisphere during the 1999 New York outbreak (Nash *et al.* 2001). Only five years later, it reemerged with a much wider geographic distribution and with exponentially increasing incidence (<http://www.cdc.gov/od/oc/media/wncount.htm>). Despite this rapid increase, we are still consolidating direct clinical experience in the management of WNV infections, and the incidence of associated seizures, status epilepticus (SE) or post-encephalitic epilepsy is uncertain. Whereas EEG changes caused by the acute form of the disease have been

somewhat better elucidated recently (Gandelman-Marton *et al.* 2003), there is only limited literature on WNV SE (Bosanko *et al.* 2003). The purpose of this paper is to present a review of the available literature on WNV central nervous system (CNS) infections as they relate to seizures, electrographic changes, and SE, and to report the electroclinical evolution in a patient with WNV encephalitis who developed refractory NCSE.

EEG changes, seizures and status epilepticus in patients with WNV

Some of the earliest reports indicated that convulsions occurred in approximately 30% of patients with WNVE,

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[The first author participated in a published case conference prompted by this case. However, the published article (Gea-Banachloche J, Johnson RT, Bagic A, Butman JA, Murray PR, Agrawal AG. West Nile Virus: Pathogenesis and Therapeutic Options. *Ann Intern Med* 2004; 140: 545-553) centers on WNV itself and the general aspects of its CNS infection. The elements of this case most interesting to a neurologist-epileptologist (neurological and EEG evolution, etc.) were not addressed.]

with EEGs showing diffuse, high amplitude theta or delta waves (Pruzanski & Altman 1962). Seizures were present in 9% of patients in the Israel report (Klein *et al.* 2002) and in 3% in the NY report (Nash *et al.* 2001), but were absent in cohorts of 326 hospitalized patients with WNV fever (Chowers *et al.* 2001) and 32 elderly, hospitalized patients (Berner *et al.* 2002). Klein (2002) found seizures in two patients with “pure” encephalitis and normal CSF findings, an abnormal EEG in 88% of patients with meningitis or meningo-encephalitis and in 74% with any neurological involvement. The most frequent abnormality was symmetric generalized slowing with frontal predominance. However, there were cases in which the slowing was more evident in the temporal regions bilaterally or the frontal regions asymmetrically. The most detailed report thus far (Gandelman-Marton *et al.* 2003) on EEG changes caused by WNV involved 18 adult patients, 13 of whom had EEGs performed. Generalized slowing that was more prominent over the anterior regions was found in eight of these patients, and prominent temporal slowing in three patients that was not associated with epileptiform discharges (unlike in patients with SLE (Wasay *et al.* 2000). Anteriorly prominent, diffuse slowing was reported in various infectious and non-infectious conditions (reviewed in Gandelman-Marton *et al.* 2003), including frontal amplitude prominence in a child with JEV infection (Misra *et al.* 1994), and frontally prominent slowing in a 70-year-old man with WNV encephalitis (Gandelman-Marton *et al.* 2003).

Case description

A 55-year-old white male who was immunosuppressed secondary to the experimental treatment (EPOCH-F: etoposide, prednisone, vincristine, cyclophosphamide, and fludarabine) of his refractory, chronic lymphocytic leukemia (CLL), but who had no previously known cerebral pathology, was admitted to hospital complaining of chills

Abbreviations:

CBZ : carbamazepine
 CNS : central nervous system
 FPHT : fosphenytoin
 HSV : Herpes simplex virus
 JEV : Japanese encephalitis virus
 NCSE : non-convulsive status epilepticus
 PHT : phenytoin
 PLEDS : periodic lateralized epileptiform discharges
 PCR : polymerase chain reaction
 PRIS : propofol infusion syndrome
 SE : status epilepticus
 SLE : St Louis encephalitis
 VPA : valproic acid
 WNV : West Nile virus

and fever. Three days later, he began experiencing double vision and malaise. Neurological evaluation revealed neither evident focal abnormalities nor cognitive changes. Brain MRI was normal (*figure 1A, E*), and CSF (white blood cells $125 \times 10^6/L$, proteins 590 mg/L, and low glucose 3.44 mmol/L) (Gea-Banachloche *et al.* 2004) was most suggestive of possible leptomeningitis (in a patient with CLL, although unlikely with normal MRI) or infection (fungal, viral or bacterial, in the context of immunosuppression), while other possibilities were considered less likely. Thus, empiric treatment with broad-spectrum antibiotic coverage (ceftriaxone, vancomycin, ampicillin) and acyclovir were started.

The patient declined rapidly over the following 2-3 days (asymmetric leg weakness, dysphagia, double vision) despite the antimicrobial treatment. On day 6 drowsiness, coarse tremor and difficulty with ambulation developed, and were followed by dysphagia and dysarthria on day 7. This led to the transfer to the ICU where intubation was required for airway protection on day 8. Meanwhile, a CSF polymerase chain reaction (PCR) test and serology (WNV-specific IgG) confirmed WNV encephalitis.

At this point, the EEG revealed moderate diffuse slowing consistent with a global cerebral process (*figure 2A*). A follow-up MRI (*figure 1B, F*), performed one day after the initial EEG, demonstrated abnormalities in the left caudate, thalamus, and the midbrain. On the fourteenth day of his illness, the patient was noted to have “fast eye movements with eyelid flickering” that responded, albeit incompletely, to 10 milligrams of lorazepam administered by the ICU staff for presumed seizures. EEG monitoring was initiated, revealing electrical status epilepticus with a polyspike pattern (*figure 2B*). A complex medication regimen (in order of use: fosphenytoin, phenobarbital, propofol, valproic acid, carbamazepine), with multiple medication adjustments and close monitoring of their free and total levels, was gradually implemented over several days before the patient’s refractory electrical SE resolved (*figure 2C-D*). A follow-up MRI (*figure 2C, G*), demonstrated progression of the earlier noted lesions, in a symmetric manner, to involve the thalamus, substantia nigra, central pons, and dentate nuclei of the cerebellum. Finally, over the next several days, the EEG normalized further (data not shown), without any noticeable change in the level of consciousness, and the monitoring was discontinued. The patient died three weeks later.

Discussion

Seizures have been reported less frequently in more recent WNV epidemics than past ones (Bosanko *et al.* 2003, Gandelman-Marton *et al.* 2003, Klein *et al.* 2002, Nash *et al.* 2001, Petersen and Marfin 2002, Pruzanski and Atman 1962, Sejvar *et al.* 2003, Tsai *et al.* 1998). It is uncertain whether this difference is due to variations in the affected

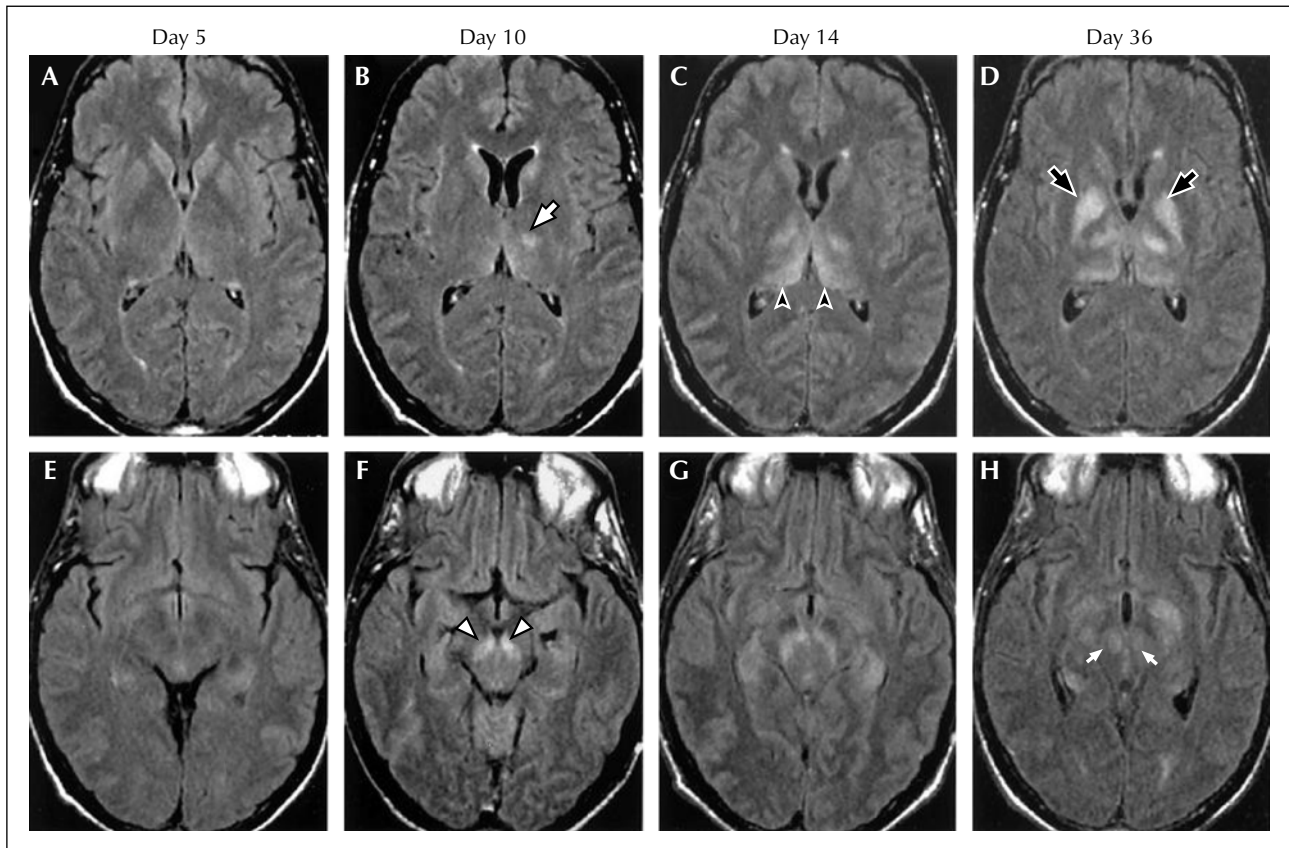


Figure 1. Progression of West Nile virus encephalitis in the deep gray nuclei. Serial, fluid-attenuated inversion recovery magnetic resonance images at the level of the basal ganglia (top, **A-D**) and midbrain (bottom, **E-H**). Day 5 is normal. Day 10 shows lesions in left thalamus (**B**) and substantia nigra (**F**). Day 18 shows progression of thalamic lesions (**C**). Day 36 shows globus pallidus (**D**) and red nuclei (**H**) lesions. (Reproduced with permission from the American College of Physicians. Source: Gea-Banachloche J, Johnson RT, Bagic A, Butman JA, Murray PR, Agrawal AG. West Nile Virus: Pathogenesis and Therapeutic Options. *Ann Intern Med* 2004; 140: 545-553.).

populations, the clinical studies performed, or changes in the infection itself. In the three most recent epidemics (Klein *et al.* 2002, Nash *et al.* 2001, Tsai *et al.* 1998), there was no single reported case of seizures as an initial presentation (Petersen and Marfin, 2002) and our patient did not have a seizure until the 14th day of his illness. This relatively low incidence of seizures (0–9%) (Bosanko *et al.* 2003, Feki *et al.* 2005, Gandelman-Marton *et al.* 2003, Klein *et al.* 2002, Nash *et al.* 2001, Petersen and Marfin 2002, Pruzanski and Atman, 1962, Sejvar *et al.* 2003, Tsai *et al.* 1998), along with the high incidence of cranial nerve abnormalities (22%) (Klein *et al.* 2002, Nash *et al.* 2001), (also seen in our case) reflects a WNV predilection for brain stem involvement (Bosanko *et al.* 2003, Tyler 2001, Wasay *et al.* 2000).

Additionally, in a complex clinical context as reported here, one has to consider the importance of at least three possible confounding factors: role of fludarabine (Zabernigg *et al.* 1994), the seizure-lowering effect of antibiotics (Walker *et al.* 1945), and the effects of propofol (Cremer *et al.* 2001).

Fludarabine may cause neurotoxicity with late-onset encephalopathy and sub-cortical white matter demyelination (Zabernigg *et al.* 1994). However, electro-clinically, this patient was clearly in NCSE (*figure 2*) and his MRI findings resembled the patterns previously seen in the encephalitis caused by the flaviviruses, with no white matter involvement and with a selective destruction of neurons in the subcortical gray matter structures (*figure 1*) (Gea-Benaholche *et al.* 2004). While this patient's immunosuppression may have led to a decreased inflammatory response that could account for the delayed nature and subtle appearance of the MRI abnormalities (Gea-Benaholche *et al.* 2004), the pattern of MRI findings was compatible with WNV encephalitis in the context of confirmatory microbial diagnostics.

The seizure-lowering effects of antibiotics have been known for many decades (Walker *et al.* 1945, Schliamser *et al.* 1991), and cephalosporins have been directly implicated in several cases of NCSE in patients with (Klion *et al.* 1994) and without (Maganti *et al.* 2006) renal impairment. While the role of antibiotics in precipitating this patient's

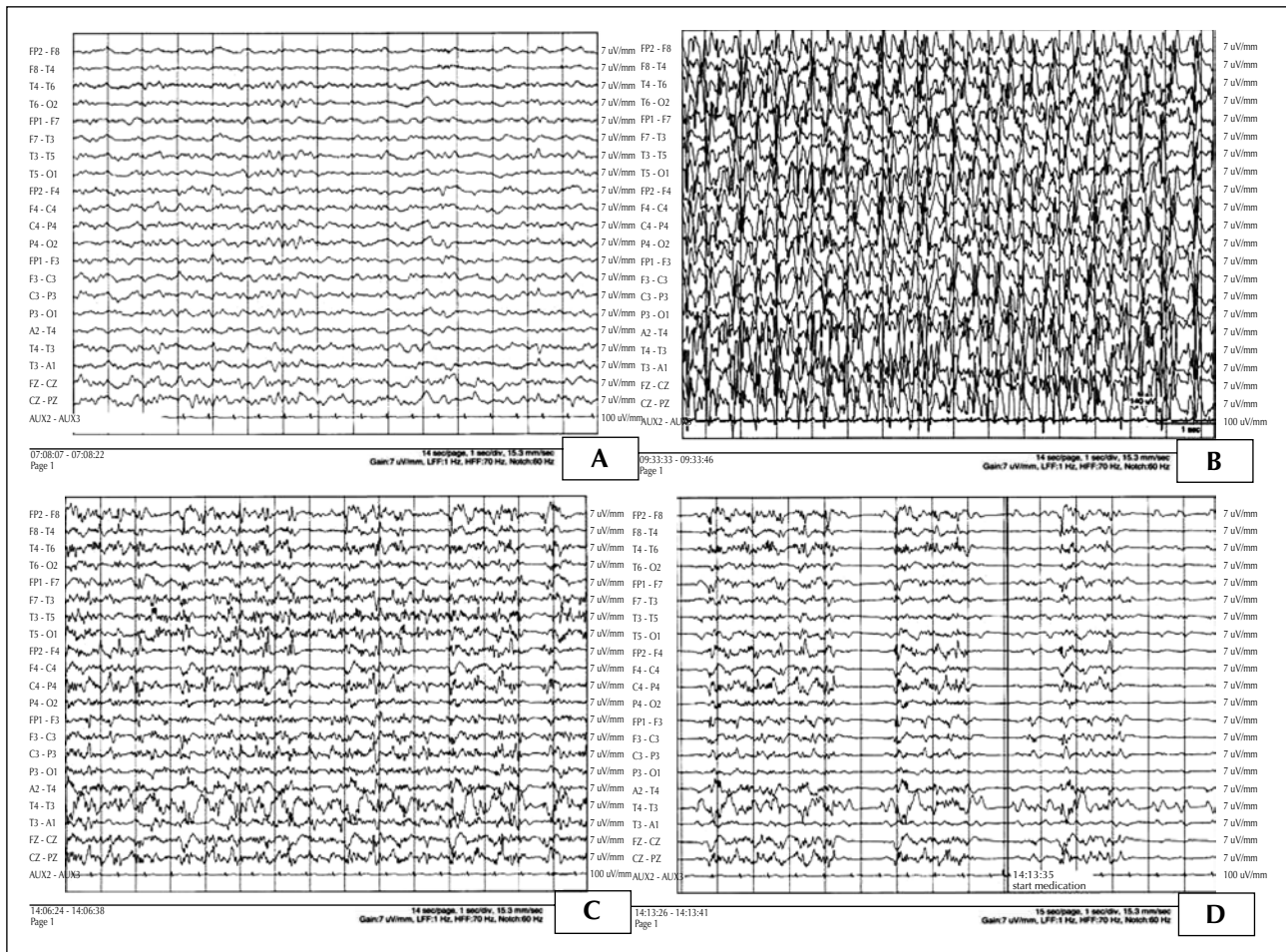


Figure 2. Representative EEG tracings indicating progression from diffuse slowing to refractory status epilepticus. **A)** EEG obtained on day 8 of patient's illness showing diffuse, irregular background slowing (2-3 Hz delta) intermixed with a short run of diffuse rhythmical activity of 4-5 Hz, suggesting a sleep-state. Amplitude predominance in the right hemisphere, and no epileptiform discharges observed, (patient is stuporous). **B)** EEG obtained on day 14 of patient's illness after clinical seizures were suspected; minimal response to i.v. lorazepam. Tracing shows polyspike wave activity, 1-2/s occurring diffusely in the right hemisphere, with an increasing tendency for spread to the left hemisphere, (patient is comatose, without clinical seizures, but in electrical SE). **C)** This tracing represents continuation of EEG monitoring, following the patient's lack of response to Lorazepam, DPH and VPA; the propofol load was followed with a drip. This tracing shows short runs of mixed delta (2-3 Hz) plus theta (4-5 Hz) with periodic polyspiking in the right hemisphere interspersed with short segments of electrodecremental periods. Towards the end of the sheet, propofol was started and its effect is visible in transient suppression of background as well as discharges, but with one discharge remaining, (patient remains comatose). **D)** EEG tracing obtained 24 hours after the initial clinical seizure, and after 19 hours of propofol drip. It shows polyspike-wave discharges occurring with a frequency of 1/s, with diffuse distribution. Patient shows no signs of clinical seizures, but electrical status epilepticus remains resistant to the treatment, (patient remains comatose).

NCSE can not be completely excluded, the entire clinical context, including MRI/MRS (*figure 1*) and EEG (*figure 2*) findings, supported by microbial studies, points to the WNV-related structural abnormalities as the cause of the patient's prolonged and refractory seizure. Fourteen years after the first published case (Parke 1992) and six years after its syndromic designation (Bray 1998), propofol infusion syndrome (PRIS: cardiac failure, rhabdomyolysis, severe metabolic acidosis and renal failure) (Vasile *et al.* 2003) remains incompletely understood. While it appears to predominantly affect younger patients

(Vasile *et al.* 2003), the PRIS is now an accepted entity in adults too (Vasile *et al.* 2003, Kumar *et al.* 2005). It is postulated to occur with a prolonged propofol infusion (> 48 hrs), at high doses (> 5mg/kg/hr), in patients suffering from acute neurological or inflammatory disease (Vasile *et al.* 2003). Thus, in this complex clinical context, PRIS should be considered as a potential contributing cause of the patient's decline since infusion rates up to 12 mg/kg/h were used over >48 hrs (Cremer *et al.* 2001, Vasile *et al.* 2003). However, the lack of obvious initial cardiac failure and rhabdomyolysis, plus the electroclinical correlation of

NCSE and demonstrated progression of the intracranial process, makes it a less likely cardinal contributor.

The EEG is abnormal in the vast majority of patients with encephalitis, and most frequently shows diffuse, generalized high amplitude delta (the most common) or theta waves, with occasional asymmetric distribution (Feki *et al.* 2005, Pruzanski and Altman 1962, Schmolck *et al.* 2005, Vas and Cracco 1997, Westmoreland 1987). However, periodic discharges, such as periodic, lateralized epileptiform discharges (PLEDs), are typically associated with HSV encephalitis (Vas and Cracco 1997), but curiously, have also been reported in cases of St Louis encephalitis (SLE) infection (Wasay *et al.* 2000) and several other conditions, including those that were non-infectious (Vas and Cracco 1997, Westmoreland 1987). It is presumed that involvement of both cortical and subcortical areas may contribute to a periodic discharge pattern (Brenner and Schaul 1990). Prominent involvement of subcortical structures has been demonstrated in SLE infection patients (Brinker *et al.* 1979, Wasay *et al.* 2000) and recently, in a patient with WNV infection (Bosanko *et al.* 2003) including this case. Curiously, the EEG changes are different and are also non-specific in those patients with WNV infections (Schmolck *et al.* 2005). Epileptiform abnormalities are rare, and their presence is usually suggestive of encephalitis. While frontally prominent slowing in patients with WNV CNS infections has been reported earlier (Klein *et al.* 2002), its occurrence has only recently been emphasized (Gandelman-Marton *et al.* 2003).

In our case, the initial EEG showed irregular background slowing in the theta range (5 Hz), intermixed with 2-3 Hz delta activity. The degree of slowing was not as dramatic as the patient's clinical decline owing to the prominent involvement of the subcortical structures, which became discernible on a subsequent MRI. Presumably, the ensuing diffuse, well-formed, complex (polymorphic delta) discharges may have originated in these structures (Brenner and Schaul 1990). Interestingly, involvement of the substantia nigra was reported in a case of WNV (Bosanko *et al.* 2003) and SLE infection (Wasay *et al.* 2000). Some reports (Hosoya *et al.* 2002) show that low-voltage EEG activity during the acute phase of encephalitis predicts an unfavorable neurological outcome, including intractable, post-encephalitic epilepsy, within one year. In our case, there was no prominent low voltage activity registered during the entire course of the six weeks, but the outcome was nevertheless fatal. The risk of post-encephalitic epilepsy occurring may not be as great in those cases without seizures during the acute phase, and the risk itself may correlate with the degree of impairment of consciousness (Hosoya *et al.* 2002, Misra and Kalita 2001, Tiroumourougane *et al.* 2002). There is insufficient evidence at this time for projecting the risk of seizure and post-encephalitic epilepsy in patients with WNV.

To our knowledge, this is the first specific and detailed report of NCSE caused by WNV, including the therapeutic

complexity it may pose and its complex electrographic changes, which further elucidates the clinical and electrographic spectrum of WNV encephalitis. The fact that WNV affects the sub-cortical gray structures along with the cortex distinguishes it from purely cortical viral syndromes. The literature suggests that there is a probable reason to include SLE infection in the differential diagnosis of PLEDs, and to include WNV in the differential diagnosis of anteriorly prominent, diffuse EEG changes. However, large and systematic structural imaging and EEG studies are necessary to establish the specific radiographic and electroencephalographic patterns associated with WNV CNS infections. □

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