International Journal of Family Medicine and Primary Care

Case Report
Published: 14 Jul, 2020

West Nile Virus Encephalitis Causing Sinus Bradycardia

Raziq Fazal I*

Department of Internal Medicine, Michigan State University College of Human Medicine, USA

Abstract

A case of seventy-five years old male presented to the Emergency Department (ED) with a cough, persistent hiccups, altered mental status, difficulty finding words and generalized weakness for 5 days. ECG showed bradycardia in background of fever. He had positive IgM antibodies which were specific for WNV. The aim of this case report is to highlight the relative bradycardia in the patient of *West Nile virus* (WNV) encephalitis.

Introduction

Fever, a manifestation of infection/inflammation, is generally associated with tachycardia. However, there are certain diseases in which there is dissociation between heart rate and temperature. Here we present a case of *West Nile virus* Encephalitis where fever is not directly associated with increased heart rate (a condition known as relative bradycardia).

Case Presentation

A 75-year-old male presented to the Emergency Department (ED) with a cough, persistent hiccups, altered mental status, difficulty finding words and generalized weakness for 5 days.

The patient had a past medical history of hypertension and hyperlipidemia and was on lisinopril and atorvastatin at home. The patient travelled to Wisconsin 2 weeks before the presentation and had an episode of fever there which resolved on its own. The history was negative for chest pain, loss of consciousness and focal neurological deficit.

Neurological examination was negative except for some drooping on the left side of his face as well as decreased strength in the bilateral lower extremities.

Investigations

In the ED, a stroke alert was called Computerized Tomography (CT) of the head was negative for any acute pathology. Heart rate was 51 (normal 60 to 100 beats per minute), blood pressure was 142/71 (Normal 120/80 to 140/90). The patient did not have any history of heart block or any other cardiac arrhythmia and was not taking any heart rate-controlling medications. The patient was febrile with maximum temperature (Tmax) of 101 degrees Fahrenheit.

Electrocardiogram EKG showed sinus bradycardia and labs showed Na (sodium) 121 (normal: 135 to 145 mEq/L), troponins <0.03 (normal <0.03), WBC count 11.9 (between 4,000 and 11,000) with neutrophilic predominance. Chest X-Ray (CXR) showed bilateral lower lobe infiltrates. He was started on 0.9% normal saline, ceftriaxone and azithromycin for a possible Community-Acquired Pneumonia (CAP) and septic workup were sent. The patient was transferred to the step-down unit for a provisional diagnosis of Acute Encephalopathy secondary to CAP.

Electrocardiogram (EKG) on presentation is given in Figure 1. *Influenza* A, B, and *Respiratory Syncytial virus*, *Streptococcus Pneumonia* IgM, Legionella IgM, Mycoplasma PCR were negative. After transfer to the step down the patient was more confused. Heart rate was consistently in the '50s (normal 60 to 100 beats per minute).

Treatment

The patient was started on 3% NaCl (at 5ml/h) and Basic Metabolic Panel (BMP) Q2 and work up for Syndrome of Inappropriate Anti-Diuretic Hormone Secretion (SIADH) was ordered. Na level improved to 130 (normal: 135 to 145 mEq/L) but the patient started becoming more confused and lost orientation to time, place and person and started feeling more weakness in bilateral lower extremities. Hence, he was transferred to the ICU. Heart rate dropped down to 45 (normal 60 to 100 beats per min). Troponins were persistently <0.03 and EKG was unchanged from the admission. Labs confirmed SIADH and Na level plateaued at 130 (baseline of the patient 134-138) on 3% NaCl.

OPEN ACCESS

Correspondence:
Raziq Fazal I, Department of Internal Medicine, Michigan State University College of Human Medicine, USA, E-mail: iraziq.fazal462@gmail.com

Received Date: *23 Jun 2020*
Accepted Date: *09 Jul 2020*
Published Date: *14 Jul 2020*

Citation:
Raziq Fazal I. West Nile Virus Encephalitis Causing Sinus Bradycardia. Int J Fam Med Prim Care. 2020; 1(3): 1014.

The patient continued to spike a fever of 102.8 Tmax with HR of 50 (normal 60 to 100 beats per min). Hence Metronidazole was added for anaerobic coverage along with ceftriaxone and Azithromycin. After a total of 5 days of Antibiotics, the patient's CAP resolved. However, the encephalopathy and sinus bradycardia did not resolve despite ruling out all the infective and metabolic causes of encephalopathy. At this point, Magnetic Resonance Imaging (MRI) was ordered azithromycin and metronidazole was discontinued and vancomycin, acyclovir, and ceftriaxone were started for possible bacterial/viral encephalitis and patient was scheduled for a Lumbar Puncture (LP). MRI of the head did not show any acute findings. LP was done which Showed Protein 72, Glucose 61, WBC 112, Neutrophil 68% and Lymphocytes 32%. CSF didn't show organisms, and nothing grew on Cerebrospinal Fluid (CSF) Culture. Thus, it was inconclusive, and workup was sent for bacterial culture, fungal culture, Histoplasma antigen, *Cryptococcus*, *Influenza* Polymerase Chain Reaction (PCR), Lyme antibodies, paraneoplastic panel, *West Nile*, *Enterovirus*, Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), *Cytomegalovirus* (CMV), *Adenovirus*, autoimmune encephalitis and syphilis. Day 9 of the admission workup came back positive for *West Nile virus* IgM. All antibiotics were stopped. Na was still at 130 (normal: 135 to 145 mEq/L) and HR in the 50s (normal 60 to 100 beats per min). At this point, Nephrology was consulted and 1 dose of tolvaptan was given and Na level normalized to the patient's baseline of 138. The patient's altered mental status improved slowly by day 12 of the admission and HR returned to normal of 78 beats per minute (normal 60 to 100 beats per minute) by day 13 of the admission. Repeat EKG was done which showed Sinus rhythm and slight left axis deviation with normal PR and QT intervals. The patient remained Afebrile for >48 h and transferred to the Floor.

Results

The patient was discharged home to follow up with his primary care doctor.

Discussion

West Nile virus (WNV) is endemic in United States (US) which was first discovered in North America in New York City, 1999 [1]. It remains asymptomatic in 80% of the cases. Commonly, the common symptomatic condition is systemic febrile illness. Less than 1 % of all infected people develop neuroinvasive condition [2]. This includes afebrile meningitis (West Nile meningitis, WNM), encephalitis (West Nile encephalitis, WNE) and poliomyelitis-like syndrome (West Nile poliomyelitis, WNP) [3]. WNV has a bird-mosquito-bird transmission cycle. *Culex* mosquito spreads it to humans including *Culex pipiens* (northern house mosquito) in northern US, *Culex quinquefasciatus* in southern states and *Culex tarsalis* in western states [4]. Humans can't infect mosquitoes owing to lower viral titers in serum and thus considers as dead-end hosts [5,6]. Other less common causes of WNV transmission includes blood and serum transfusions as well as different organ transplantations [6,7]. Moreover, breast milk, dialysis mediated, and conjunctival laboratory exposure transmission has also been reported [8].

Fever, a manifestation of infection/inflammation, is generally associated with tachycardia. However, there are certain diseases in which there is dissociation between heart rate and temperature [9]. Here we present a case of *West Nile Virus* Encephalitis where fever is not directly associated with increased heart rate (a condition known as relative bradycardia).

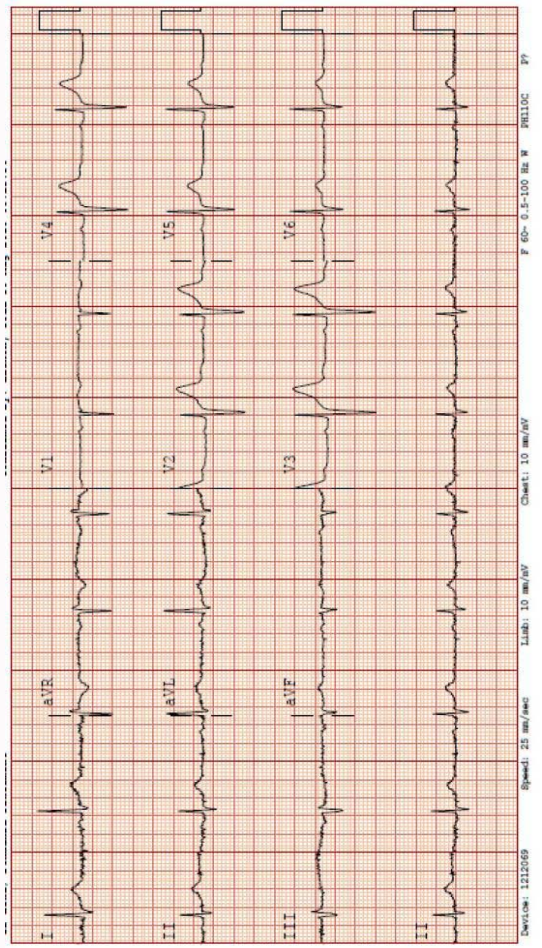

Figure 1: EKG on Presentation showing sinus bradycardia with normal PR and QT intervals.

Table 1: The expected rise in the heart rate with increased temperature.

Temperature (°F)	Heart rate (beats/min)
101	100
102	110
103	120
104	130
105	140
106	150

WNV is an arboviral infection, transmitted through mosquitoes, and is prevalent in Northern and Southern US [4]. It is common in summers (July till September) and tropical areas owing to high-temperature division of mosquitoes and increased pathogenicity coupled with short incubation period promotes the spread of infection. In our case, we suspect an insect bite in Wisconsin. Rare factors responsible for this viral epidemic include agricultural areas [10], rainfall [11], socioeconomic status [12] and poorly maintained swimming pools [13].

WNV fever, with no inclination to advanced age, presents flu-like symptoms (headache, myalgia, weakness and low-grade fever) and maculopapular rash. Sometimes, arthralgia, chills and Lymphadenopathy (LAD) are also present [14]. Neuroinvasive WNV has inclination to advanced age as mentioned about in this

Table 2: Non-infective causes of fever with relative bradycardia.

Cause	Comment
Drug Fever [25]	Common causes are antimicrobials, anticonvulsants, and antiarrhythmic medications. Range can be from 102- 104 Fahrenheit. Patient typically looks relatively well with respect to the degree of fever. The most common mechanism is a hypersensitivity reaction. Typical findings on labs include a mild transaminitis, leukocytosis with a left shift and eosinophilia, and an elevated ESR.
Cyclic Neutropenia [26]	TNF α, IL 1 and 6 increase vagal tone which decreases heart rate. Increased levels of cytokines cause bradycardia.
Lymphoma [26]	Fevers of unknown origin. Presence of relative bradycardia as a possible diagnostic tool but it does not appear to be a common manifestation
Drugs causing slow heart rate [27]	These drugs slow sinus nodal automaticity and atrio-ventricular conduction. This includes antiarrhythmic (digoxin and amlodipine), beta blockers and non-dihydropyridine calcium channel blockers (verapamil and diltiazem).
Factitious fever [26]	
CNS lesion (could not find its reference. Please find it otherwise remove it).	Marked by rapid onset secondary to damage to the hypothalamus, for example, in stroke. Typically resolves within a week, depending on the lesion.
Adrenal Insufficiency	

Table 3: Infective causes of fever with relative bradycardia.

Disease	Causative Organism	Comments
Typhoid fever [28]	*Salmonella* genus	Route of transmission is oral-fecal. Incubation period is up to 3 weeks. Stepwise progression of fever, diarrhea, and hepatomegaly/splenomegaly
Psittacosis [29]	*Chlamydia psittaci*	From infected birds to humans. Clinical manifestations include a mononucleosis-like illness, a typhoidal type illness, or an atypical pneumonia
Legionellosis [30]	*Legionella pneumophila*	Presents as pneumonia. Can present with hyponatremia, watery diarrhea, and pleuritic chest pain.
Babesiosis [31]	*Babesia microti*	A silent infection to a fulminant, malaria-like disease leading to severe hemolysis. Has a typical lymphocytes on blood smear
Q fever [32]	*Coxiella burnetii*	Presents as a pneumonia or hepatitis
Leptospirosis [33]	Leptospira	May present as fever, chills, myalgia and headache. Weil's syndrome is the most severe form of leptospirosis with renal failure, hemoptysis, myocarditis, and multiple organ failure
Rocky Mountain Spotted Fever (RMSF) [31]	*Rickettsia rickettsia*	Presents with the maculopapular rash that starts in the periphery and travels to the trunk. Rash may turn petechial in nature and associated with thrombocytopenia
Ebola/Marburg [34]	Virus	Onset with fever, headache, abdominal pain, and myalgia/arthralgia. May be associated with bloody diarrhea but is often accompanied by severe edema of the upper airway
Dengue [35]	*(Flaviviridae*)	Individual case reports made a connection dengue hemorrhagic fever and viral myocarditis/decreased ejection fraction. Also reported cases with associated bradycardia

case. WNV meningitis presents with sudden onset meningeal signs (nuchal rigidity, photophobia and headache) [14]. WNV encephalitis presents with altered state of consciousness and personality change for more than 1 day as is seen in our patient with altered levels of consciousness for 5 days [15]. It could also cause other neurologic symptoms like extra-pyramidal symptoms [16], coarse tremors [17], cerebellar symptoms [18] and seizures [19]. Acute flaccid paralysis occurs in combination with neuroinvasive WNV in 80 percent of the cases and we think that it is also the case in this scenario.

Fever has been associated with tachycardia and tachypnea in the majority of the cases. It has been proposed that for each one-degree Celsius increase in temperature above 38.3ºC (101F), the heart rate increases by approximately 10 beats per min [20-22]. Table 1 below depicts the expected rise in the heart rate with increased temperature.

The paradoxical relationship between body temperature and heart rate is termed as relative bradycardia. It is also called pulse-temperature dissociation (deficit) or Faget's sign [22].

Before the term "relative bradycardia" is used to establish a diagnosis, conditions causing bradycardia, such as pacemaker-induced rhythms, 3rd-degree heart block, history of arrhythmia or any treatment affecting conduction, should be excluded. It should be noted that none of these were present in our patient.

Depicted below in Table 2 are various non-infective causes of fever with relative bradycardia. Depicted below is Table 3 that shows various infective causes of fever with relative bradycardia [26-33].

It is thought that relative bradycardia is due to the release of pro-inflammatory cytokines, increased vagal tone and electrolyte abnormalities (hyponatremia, hypokalemia and hyperkalemia) [34,35]. The proinflammatory cytokines include Interleukin (IL) 1α, 2, 4, 5, 6, 10 and 17, Tumor Necrotic Factor alpha (TNF α) and granulocyte colony stimulating factors [34]. TNF α, IL 1 and 6 increase vagal tone which decreases heart rate [35].

Here, the pathogenesis of neuroinvasive WNV includes increased virus permeability to blood-brain barrier due to increased levels of inflammatory cytokines and axonal transport of virus to the central nervous system via peripheral nerves [36].

Relative bradycardia in this patient is thought to be due to infectious process due to WNV and an electrolyte abnormality i.e. hyponatremia. This report highlights that whenever a case of relative bradycardia is presented, physicians should consider WNV neuroencephalitis as one of the causes.

WNV encephalitis can be diagnosed by IgM specific antibody in cerebrospinal fluid or serum. It might be absent in immune compromised patients so Nucleic Acid Amplification Test (NAAT) is used to diagnose in these patients [37]. We used IgM as a diagnostic test for WNV encephalitis.

The treatment is largely supportive. Gyure and Beasley separately investigated the effects of gamma (γ) globulin, corticosteroids, ribavirin, interferon 2 alpha b (IFN 2αb) and WNV neutralizing antibodies [38,39]. However, there is no appreciable efficacy for these drugs. We used tolvaptan for treating hyponatremia and now the patient is on follow up.

West Nile virus can cause bradycardia that may resolve with the resolution of the infection. Hence, prior to making a decision of an intervention such as pacemaker implantation, physicians should wait for the resolution of infection if possible, which in most cases may lead to resolution of bradycardia. *West Nile virus* encephalitis, however, should be included in differentials in any patient presenting with fever, altered mental status, and relative bradycardia along with others given in the tables above.

References

1. Nash D, Mostashari F, Fine A, J Miller, D O'Leary, K Murray, et al. The outbreak of *West Nile virus* infection in the New York City area in 1999. N Engl J Med. 2001;344(24):1807-14.
2. Campbell GL, Marfin AA, Lanciotti RS, Gubler DJ. *West Nile virus*. Lancet Infect Dis. 2002;2(9):519-29.
3. Granwehr BP, Lillibridge KM, Higgs S, Mason PW, Aronson JF, Campbell GA, et al. *West Nile virus*: Where are we now? Lancet Infect Dis. 2004;4(9):547-56.
4. Kilpatrick AM, Daszak P, JonesMJ, Marra PP, Kramer LD. Host heterogeneity dominates *West Nile virus* transmission. Proc Biol Sci. 2006;273(1599):2327-33.
5. Zou S, Foster GA, Dodd RY, Petersen LR, Stramer SL. West Nile fever characteristics among viremic persons identified through blood donor screening. J Infect Dis. 2010;202(9):1354-61.
6. Pealer LN, Marfin AA, Petersen LR, Lanciotti RS, Page PL, Stramer SL, et al. Transmission of *West Nile virus* through blood transfusion in the United States in 2002. N Engl J Med. 2003;349(13):1236-45.
7. Nett RJ, Kuehnert MJ, Ison MG, Orlowski JP, Fischer M, Staples JE. Current practices and evaluation of screening solid organ donors for *West Nile virus*. Transpl Infect Dis. 2012;14(3):268-77.
8. Petersen LR, Hayes EB. *West Nile virus* in the Americas. Med Clin North Am. 2008;92(6):1307-22.
9. Mittal J, Estiverne C, Kothari N, Reddi A. Fever and relative Bradycardia: A case presentation and review of the literature. Int J Case Rep Short Rev. 2015;1(1):004-008.
10. Bowden SE, Magori K, Drake JM. Regional differences in the association between land cover and *West Nile virus* disease incidence in humans in the United States. Am J Trop Med Hyg. 2011;84(2):234-38.
11. LandesmanWJ, Allan BF, Langerhans RB, Knight TM, Chase JM. Inter-annual associations between precipitation and human incidence of *West Nile virus* in the United States. Vector Borne Zoonotic Dis. 2007;7(3):337-43.
12. Ruiz MO, Walker ED, Foster ES, Haramis LD, Kitron UD. Association of *West Nile virus* illness and urban landscapes in Chicago and Detroit. Int J Health Geogr. 2007;6:10.
13. Reisen WK, Takahashi RM, Carroll BD, Quiring R. Delinquent mortgages, neglected swimming pools, and *West Nile virus*, California. Emerg Infect Dis. 2008;14(11):1747-49.
14. Sejvar JJ, Curns AT, Welburg L, Jones JF, Lundgren LM, Capuron L, et al. Neurocognitive and functional outcomes in persons recovering from *West Nile virus* illness. J Neuropsychol. 2008;2(pt 2):477-499.
15. Sejvar JJ, Haddad MB, Tierney BC, Campbell GL, Marfin AA, Gerpan JAV, et al. Neurologic manifestations and outcome of *West Nile virus* infection. JAMA. 2003;290(4):511-15.
16. Pepperell C, Rau N, Krajden S, Kern R, Humar A, Mederski B, et al. *West Nile virus* infection in 2002: Morbidity and mortality among patients admitted to hospital in south central Ontario. CMAJ. 2003;168(11):1399-405.
17. Burton JM, Kern RZ, Halliday W, Mikulis D, Brunton J, Fearon M, et al. Neurological manifestations of *West Nile virus* infection. Can J Neurol Sci. 2004;31(2):185-193.
18. Sayao AL, Suchowersky O, Al-Khathaami A, Klassen B, Katz NR, Sevick R, et al. Calgary experience with *West Nile virus* neurological syndrome during the late summer of 2003. Can J Neurol Sci. 2004;31(2):194-203.
19. Kanagarajan K, Ganesh S, Alakhras M, Go ES, Recco RA, Zaman MM, et al. *West Nile virus* infection presenting as cerebellar ataxia and fever. South Med J. 2003;96(6):600-01.
20. Seneta E, Seif FJ, Liebermeister H, Dietz K. Carl Liebermeister (1833-1901): A pioneer of the investigation and treatment of fever and the developer of a statistical test. J Med Biogr. 2004;12(4):215-21.
21. Cunha BA. The diagnostic significance of relative bradycardia in infectious disease. Clin Microbiol Infect. 2000;6(12):633-34.
22. Chua KS, Kong KH, Tan ES. Paroxysmal hypertension in a C4 spinal cord injury—a case report. Ann Acad Med Singapore. 1995;24(3):470-72.
23. Mackowiak PA, LeMaistre CF. Drug fever: A critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. Ann Intern Med. 1987;106(5):728-33.
24. Cunha BA, Nausheen S. Fever of Unknown Origin (FUO) due to cyclic neutropenia with relative bradycardia. Heart Lung. 2009;38(4):350-53.
25. Peter S, Hulme O, Deuse T, Vrtovec B, Fearon WF, Hunt S, et al. ST-elevation myocardial infarction following heart transplantation as an unusual presentation of coronary allograft vasculopathy: A case report. Transplant Proc. 2013;45(2):787-91.
26. Hosoglu S, Geyik MF, Akalin S, Ayaz C, Kokoglu OF, Loeb M. A simple validated prediction rule to diagnose typhoid fever in Turkey. Trans R Soc Trop Med Hyg. 2006;100(11):1068-74.
27. Kay RS. Psittacosis in Egypt: A case study. J Travel Med. 1997;4 (1):48-49.
28. Hung YP, Wu CJ, Chen CZ, Lee HS, Chang CM, Lee NY, et al. Comparisons of clinical characters in patients with pneumococcal and Legionella pneumonia. J Microbiol Immunol Infect. 2010;43(3):215-21.
29. Kim N, Rosenbaum GS, Cunha BA. Relative bradycardia and lymphopenia in patients with babesiosis. Clin Infect Dis. 1998;26(5):1218-19.
30. Chang K, Lee NY, Chen YH, Lee CH, Lu PL, Chang CM, et al. Acute Q fever in southern Taiwan: atypical manifestations of hyperbilirubinemia and prolonged fever. Diagn Microbiol Infect Dis. 2008;60(2):211-16.
31. Assimakopoulos SF, Michalopoulou S, Papakonstantinou C, Lekkou A, Syrokosta I, Gogos C. A case of severe sinus bradycardia complicating anicteric leptospirosis. Am J Med Sci. 2007;333(6):381-83.
32. Peter S, Hulme O, Deuse T, Vrtovec B, Fearon WF, Hunt S, et al. ST-elevation myocardial infarction following heart transplantation as an unusual presentation of coronary allograft vasculopathy: A case report. Transplant Proc. 2013;45(2):787-91.
33. Lateef A, Fisher DA, Tambyah PA. Dengue and relative bradycardia. Emerg Infect Dis. 2007;13(4):650-51.
34. Golusinski LL, Blount BW. Clonidine-induced bradycardia. J Fam Pract. 1995;41(4):399-401.
35. Ostergaard L, Huniche B, Andersen PL. Relative bradycardia in infectious diseases. J Infect. 1996;33(3):185-91.
36. Cho H, Diamond MS. Immune responses to *West Nile virus* infection in the central nervous system. Viruses. 2012;4(12):3812-30.
37. Busch MP, Kleinman SH, Tobler LH, Kamel HT, Norris PJ, Walsh I, et al. Virus and antibody dynamics in acute *West Nile virus* infection. J Infect Dis. 2008;198(7):984-93.

38. Beasley DW. Vaccines and immunotherapeutics for the prevention and treatment of infections with *West Nile virus*. Immunotherapy. 2011;3(2):269-85.

39. Diamond MS. Progress on the development of therapeutics against *West Nile virus*. Antiviral Res. 2009;83(3):214-27.