

International Journal of Case Reports & Short Reviews

Case Report

Fever and Relative Bradycardia: A Case Presentation and Review of the Literature - @

Jaimie Mittal, Christopher Estiverne, Neil Kothari, Alluru Reddi*

Department of Medicine, Rutgers New Jersey Medical School, 185 South Orange Avenue, Newark, NJ, USA

*Address for Correspondence: Alluru Reddi, MD, Department of Medicine, Rutgers New Jersey Medical School, 185 South Orange Avenue, Newark, NJ, USA, Tel: 973-972-6052; E-mail: Reddias@ njms.rutgers.edu

Submitted: 30 October, 2015; Approved: 27 November, 2015; Published: 17 December, 2015

Citation this article: 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.

Copyright: © 2015 Mittal J, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Fever is defined as an elevation in core body temperature. It is a common presentation in patients with infection, and is associated with increased heart rate. In certain infectious conditions, however, there is dissociation between temperature and heart rate. This pulse-temperature deficit is called relative bradycardia, which is referred to as Faget's sign. Here we present a case of 45-year-old man with West Nile virus and a temperature of 1030 F with a heart rate of 66 beats per minute. With the case discussion, we provide a review of various causes of fever that are associated with bradycardia. In certain clinical situations, relative bradycardia should be used as a vital clinical clue to narrow down not only the differential diagnosis but also to provide guidance for appropriate management.

KEYWORDS: Fever, Relative Bradycardia, Faget's sign

INTRODUCTION

Fever is defined as an elevation in core body temperature. It is a common presentation in patients with infection, those taking prescribed or over the counter medications, neoplastic diseases, rheumatic diseases, central nervous system (CNS) lesions, and traumatic injuries. The core body temperature is regulated via thermoregulatory centers located in the hypothalamus, which receive input from hot and cold thermoreceptors located throughout the body. This input is integrated and a response is sent to the body either to conserve or dissipate heat. These changes in heat occur around a set point in the hypothalamus that maintains core body temperature within normal range [1]. Whenever the set point is increased, fever occurs.

The induction of fever by an infectious agent is mediated by the release of endogenous pyrogenic cytokines, such as tumor necrosis factor- α , interleukin (IL)-1, and IL-6 [2]. These mediators reach the CNS and induce prostaglandin release to raise core body temperature. The most common associated symptoms with fever are malaise, anorexia, myalgia, fatigue, headache, diaphoresis, sweating, and arthralgia. Certain physiologic changes also occur with fever, including increased heart and respiratory rates. In certain infectious conditions that present with fever, there is dissociation between temperature and heart rate. More specifically, the phenomenon of relative bradycardia can be appreciated. Here we present a case that illustrates this dissociation, and demonstrates its use as a clinical clue in creating a differential diagnosis.

CASE REPORT

A 45-year-old African American man with no significant medical history and not on any medications presented to the Emergency Department in the summer with a two-day history of bilateral upper extremity weakness and fever. On further questioning, the patient stated that the weakness was sudden in onset and first affected his left arm then progressed to his right arm. The morning of presentation, he was unable to grip objects with either hand. He also complained of bilateral arm tingling, gait instability, neck pain, and subjective fevers. He was born in the United States, and has worked as a landscaper for the last 15 years. After initial interview, the patient developed acute respiratory distress, requiring intubation. His vital signs were: temperature 103°F, BP 151/87 mm Hg, pulse 66 beats per

Cite this Article: 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. minuteand respiratory rate of 18 per minute. Pertinent findings on physical examination included decreased muscle strength, muscle tone and sensation in upper extremities. He was areflexic in the upper extremities and hyporeflexic in the lower extremities.

His complete blood count, electrolytes, creatinine, glucose, calcium, and liver function tests were normal, except for an elevated total protein of 9.7 g/dl. Urinalysis was also normal. Electrocardiogram Figure 1 showed marked sinus bradycardia with a shortened PR interval and normal QT interval. Chest x-ray and CT of the head without contrast were normal. Analysis of cerebrospinal fluidrevealed a WBC count of 147 cells with predominant lymphocytes.IgM and IgG titers for West Nile virus were positive. An MRI of the head showed microvascular changes and increased signal intensity involving the anterior horns of the spinal cord from the obex to T1. The patient was started empirically on a 5-day course of intravenous IgG. Despite this treatment, the patient's condition did not improve. He required tracheostomy, and he was subsequently discharged to a long-term care facility for continued management. The final diagnosis was neuroinvasive disease due toWest Nile virus.

DISCUSSION

West Nile virus was introduced into the United States in 1999. Although 60% to 80% are asymptomatic, about 20% of infected persons develop fever with influenza-like symptoms [3]. In one survey of patients with West Nile virus fever, 30% required hospitalization [3]. In comparison, neuroinvasive disease develops in \leq 1% of patients, which is characterized by encephalitis, meningitis, or acute flaccid paralysis. Neuroinvasive disease is not commonly seen in the Northeast area of the United States. According to the Centers for Disease Control and Prevention (CDC), 207 cases of West Nile virus have been reported in New Jersey from 1999 to 2014 and the incidence rate for neuroinvasive disease during this time period was 0.01 to 0.24 per 100,000 cases [4].In 2003, Colorado reported 2,947 cases of West Nile virus infection to the CDC, and of these 621 cases had neuroinvasive disease [5,6].

In general, fever is accompanied by an increase in both heart and respiratory rates.

Early studies have shown that for each degree increase above normal body temperature, the heart rate increases by an average of 8.5 beats per minute [7]. However, it has been proposed that for each one degree Fahrenheit increase, the heart rate increases by approximately 10 beats per minute, and an increase of less than 10 beats per minute is usually considered relative bradycardia. Table 1 provides the relationship between temperature and expected rise in heart rate [8].

In many noninfectious and infectious conditions, the heart rate does not increase with a rise in temperature. This phenomenon is called pulse-temperature deficit which many clinicians refer to as relative bradycardia. A caveat to this rule is that a patient must have a temperature of at least 102°F in order to better appreciate this pulse-



Table 1: Expected elevation in heart rate with increase in body temperature.		
Temperature °C (°F)	Heart rate (beats/min)	
38.3 (101)	100	
38.9 (102)	110	
39.4 (103)	120	
40.0 (104)	130	
40.6 (105)	140	
41.1 (106)	150	

temperature relationship [8]. This pulse-temperature deficit is also known as Faget's sign and is attributed to a 19th century physician by the name of Jean-Charles Faget [9]. He was analyzing yellow fever in New Orleans in the 1860s, when he noted that there was a consistent relationship between a relatively slow heart rate despite the high fevers of his patients.

Before the term relative bradycardia is used to make a diagnosis, one must rule out conditions that cause bradycardia, such as pacemakerinduced rhythms, 3rd degree heart block, history of arrhythmias, or any therapy that affects AV nodal conduction. It should be noted that none of these were present in our patient. Some of the noninfectious conditions that cause relative bradycardia in febrile patients are listed in (Table 2). With respect to infectious etiologies of fever, Faget's sign can be applied primarily to Gram negative intracellular bacteria, intracellular parasites and viruses responsible for hemorrhagic fever. One exception to this rule is Leptospira, which is a Gram negative extracellular organism associated with relative bradycardia. Table 3 is

Cite this Article: 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. a summary of infectious agents that have been associated with fever and relative bradycardia.

The mechanisms for fever-induced bradycardia are not completely understood. It is well known that many infectious agents can cause acute myocarditis and induce cardiac conduction abnormalities. A study by Ostergaard et al. [10] suggested that relative bradycardia due to a specific disease has no predictive value in making a diagnosis. However, a study by Wittesjö et al. [11] suggests that relative bradycardia in a single patient can be helpful in arriving at a tentative diagnosis. After our patient encounter and review of the literature, we agree with the latter statement. Early recognition of our patient's diagnosis would likely not have changed his ultimate clinical outcome; however, earlier recognition in this case could have affected timely reporting of this disease in our area and prompt public health interventions.

In our patient with confirmed West Nile virus fever, the heart rate did not increase proportionately to the rise in temperature. Although such pulse-temperature deficit has not been reported in some studies of West Nile virus fever, Vyas et al. [12] observed relative bradycardia in a patient with West Nile virus infection and encephalitis. Our observation of relative bradycardia is consistent with this report. Brady and tachycardias were also reported by Bode and colleagues [6]. Acute flaccid paralysishas been described with anterior horn cell involvement. Our patient's upper extremities weaknessand MRI findings suggest neuroinvasive disease due to West Nile virus infection.

In conclusion, it is suggested that the epidemiology of various infectious diseases has changed dramatically due to rapid transcontinental travel. When diagnosing potentially fatal diseases, time is of the essence, and we firmly believe a pulse-temperature deficit should be seen as a vital clinical clue in the management of seriously ill patients. If used in the correct clinical context, it can focus a broad differential diagnosis for fever and guide as well as narrow clinical management choices.

Table 2: Noninfectious causes of fever and relative bradycardia.				
Cause	Comment			
Drug Fever	Commonly implicated agents are antimicrobials, anticonvulsants, and antiarrhythmics. Typically, the temperature range can be from 102- 104°F, though temperatures as high as 108°F have been recorded (13). A clinical clue in establishing this diagnosis includes a patient that looks relatively well with respect to the degree of fever (14). Typical time between onset of causative agent and fever is 7-10 days. The most common mechanism is a hypersensitivity reaction, with presence of a drug rash upwards of 25% of the time. Typical findings on labs include a mild transaminitis, leukocytosis with a left shift and eosinophilia, and an elevated ESR			
CNS lesions (central fever)	Marked by rapid onset and hyperpyrexia (15). One common mechanism is through damage to the hypothalamus, for example in stroke. Central fevers typically have a course that resolves within a week, depending on the lesion			
Lymphoma	Many case studies describe the initial presentation of lymphomas as fevers of unknown origin (16,17). Individual case studies have mentioned the presence of relative bradycardia as a possible diagnostic tool but it does not appear to be a common manifestation.			

Table 3: Infectious causes of fever and relative bradycardia.		
Disease	Causative Organism	Comments
Typhoid fever	Salmonella genus	Route of transmission is primarily oral-fecal. Incubation period is up to 3 weeks. Clinically has a step-wise progression of fever, diarrhea, and hepatomegaly/splenomegaly (18,19)
Psittacosis	Chlamydia psittaci	Typical method of transmission is from infected birds to humans. Clinical manifestations include but are not limited to: a mononucleosis-like illness, a typhoidal type illness, or most commonly an atypical pneumonia (20)
Legionellosis	Legionella pneumophilia	Usually presents as pneumonia. Can present with hyponatremia, watery diarrhea, and pleuritic chest pain. Can alternatively cause a flu-like sickness called "Pontiac Fever"
Scrub typhus	Orientiatsutsugamushi	Main route of transmission is through infected mites. Typically has a non-specific presentation but is seen primarily in rural Asia and the western Pacific islands. Can present with regional lymphadenopathy and eschar formation (21)
Babesiosis	Babesiamicroti	Can range in clinical presentation from a silent infection to a fulminant, malaria-like disease leading to severe hemolysis. Cases have been reported of babesiosis presenting with atypical lymphocytes on blood smear (22)
Brucellosis	Brucella	Presents with fever, night sweats, arthralgias, muscle aches, leukocytosis, transaminitis, and elevated bilirubin
Q fever	Coxiellaburnetii	Presents as a pneumonia or hepatitis (8)
Leptospirosis	Leptospira	May present as acute flu-like illness with fever, chills, myalgia and headache. Weil's syndrome is the most severe form of leptospirosis with renal failure, hemoptysis, myocarditis, and other organ failure (20)
RMSF	Rickettsia rickettsia	Presents with the maculopapular rash that starts in the periphery and travels to the trunk. Rash may turn petechial in nature and infection can be often associated with thrombocytopenia (20)
West Nile	West Nile Virus	Typically presents as a meningitis or encephalitis. In a subset of patients, can also present as an acute flaccid paralysis, with damage to anterior horn cells that can be seen on MRI. (12)
Ebola/Marburg	Ebola/Marburg Virus	Has an incubation of up to 2 weeks before 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 (23)
Dengue	(Flaviviridae)	Individual case reports made a connection between the presence of dengue hemorrhagic fever and viral myocarditis/decreased ejection fraction (24,25). A link has been made between Dengue hemorrhagic fever and relative bradycardia but the precise mechanism remains unknown.
Yellow Fever	Yellow Fever Virus (Flaviviridae)	Similar in presentation to Dengue hemorrhagic fever. Greater association with scleral icterus and jaundice secondary to hepatic dysfunction (26)

REFERENCES

- Nakamura K. Central circuitries for body temperature and fever. Am J PhysiolRegIntegr Comp Physiol 2011; 301: 1207-1228.
- Netea MG, Kullber BJ. Circulating cytokines as mediators of fever. Clin Infect Dis 2000; 31:178-184.
- Hart J, Tillman G, Kraut MA, Chiang HS, Strain JF, et al. West Nile virus neuroinvasive disease: Neurological manifestations and prospective longitudinal outcomes. BMC Infect Dis 2014; 14:248.
- 4. West Nile virus statistics. Centers for Disease Control and Prevention. Accessed online on October 29, 2015.

Cite this Article: 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.

- Colorado Department of Public Health and Enviroment, Disease Control and Environmental Epidemiology Division. West Nile virus: human West Nile virus infections: Colorado 2003; 7 April 2004.
- Bode AV, Sejvar JJ, Pape WJ, Campbell GL, Marfin AA. West Nile virus disease:a descriptive study of 228 patients hospitalized in a 4-county region of Colorado in2003. Fever and cardiac rhythm. Arch Inter Med 1986; 146:1169-171.
- Cunha BA. The diagnostic significance of relative bradycardia in infectious disease. Clinmicrobiol infect 2000; 6:633-634.
- Duffy J. French influence on the development of medicine in Louisiana. Biomed pharmacother 1990; 44:147-152.
- Ostergaard L, Huniche B, Andersen PL. Relative bradycardia in infectious diseases. J Infect 1996; 33:185-191.
- Wittesjo B, Bjornham A, Eitrem R. Relative bradycardia in infectious diseases. J Infect 1999; 39: 246-247.
- Vyas JM, Gonzalez RG, Pierce VM. Case 12-2013: A 76-year-old man with fever, worsening renal function, and altered mental status. N Engl J Med 2013; 368:1919-1927.

SCIRES Literature - Volume 1 Issue 1 - www.scireslit.com Page - 007

12. Patel RA, Gallagher JC. Drug fever. Pharmacotherapy 2010; 30:57-69.

International Journal of Case Reports & Short Reviews

- 13. Tabor PA. Drug-induced fever. Drug Intel Clinical Pharm 1986; 20:413-420.
- Yu KW, Huang YH, Lin CL, Hong CZ, Chou LW. Effectively managing intractable central hyperthermia in a stroke patient by bromocriptine: a case report. NeuropsychDis Treat 2013; 9:605-608.
- Cunha BA, Mohan S, Parchuri S. Fever of unknown origin: chronic lymphatic leukemia versus lymphoma (Richter's transformation). Heart Lung 2005; 34:437-441.
- Landman RE1, Wardlaw SL, McConnell RJ, Khandji AG, Bruce JN, et al. Pituitary lymphoma presenting as fever of unknown origin. J ClinEndocrinolMetab2001; 86: 1470-1476.
- Hoffner RJ, Slaven E, Perez J, Magana RN, Henderson SO. Emergency department presentations of typhoid fever. JEmerg Med 2000; 19:317-321.
- Jamil B. Enteric fever in adult patients: clinical features, outcome and antibiotic susceptibility patterns. Infect Dis J Pakistan. 2004:13: 68-72.
- 19. Cunha BA. Clinical approach to fever in the critical care unit. In Cunha (ed)

Infectious Diseases in Critical Care Medicine. 2nd ed. New York: Informa Healthcare; 2007; pp 41-72.

- 20. Aronoff DM, Watt G. Prevalence of relative bradycardia in Orientiatsutsugamushi infection. Am JTrop MedHyg 2003; 68: 477-479.
- 21. Kim N, Rosenbaum GS, Cunha BA. Relative bradycardia and lymphopenia in patients with babesiosis. Clin Infect Dis 1998; 26:1218-1219.
- Isaacson M. Viral hemorrhagic fever hazards for travelers in Africa. ClinInfect Dis 2001; 33: 1707-1712.
- 23. Arif SM. Dengue hemorrhagic fever with bradycardia. J Med 2009; 10: 36-37.
- 24. Kaushik JS, Gupta P, Rajpal S, Bhatt S. Spontaneous resolution of sinoatrial exit block and atrioventricular dissociation in a child with dengue fever. Singapore Med J 2010; 51:146-148.
- 25. Reiter P. Yellow fever and dengue: a threat to Europe? Euro surveillance: bulletin Eur Commun Dis Bull 2010; 15:195-209.

Cite this Article: 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.