

Malignant Neurocardiogenic Syncope: Recognition and Management within the Dental Operator

Abstract

Neurocardiogenic Syncope is a form of Dysautonomia which commonly occurs in children. It carries with it a potential for a range of responses from syncope to cardiac arrest. Because of these recurring events, this condition has a significant impact on their quality of life and causes them to alter daily routine living events. This report details the symptoms, pathophysiology, malignant vasovagal syncope, treatments, dental considerations, emergency management and highlights a case report featuring a history of cardiac arrest in a patient with multiple dental needs. The case outlines the efforts taken to avoid a repeat of complications from this condition and the difficulties encountered when disagreements exist among professionals. The perils of this condition are masked by their average appearance at presentation and emphasize the importance of an accurate medical history.

Keywords: Neurocardiogenic syncope; Neuromediated faint; Vasovagal syncope; Postural orthostatic hypotension; Neurally mediated syncope; Primary dysautonomia; Electrocardiogram; Autonomic nervous system; Head-up tilt table test; Chronic fatigue syndrome

Abbreviations: NCS: Neuro Cardiogenic Syncope; WS: Vasovagal Syncope; NMS: Neurally Mediated Syncope; ECG: Electrocardiogram; HUTTT: Head-Up Tilt Table Test; CFS: Chronic Fatigue Syndrome

Introduction

Dysautonomia is a general term for any medical condition involving a dysregulation of the autonomic nervous system. Although there are numerous types of dysautonomia, including Shy-Drager syndrome and pure autonomic failure, a form commonly found in pediatric patients is Neurocardiogenic Syncope (NCS), which is also synonymous with vasovagal syncope (WS) or neurally mediated syncope (NMS) [1]. The purpose of this paper is to raise awareness of the primarily pediatric condition and provide clinicians with a basic framework to recognize evaluate and properly manage patients within the dental setting. A case study is included that illustrates the difficulties associated with treatment. Neurocardiogenic Syncope, or Vasovagal Syncope, is the most common form of syncope comprising approximately fifty percent of cases [2]. Syncope, otherwise known as “fainting,” “passing out,” or “blacking out” is the most prevalent systemic complication in dentistry [3,4]. Females have a higher incidence than males, with a peak incidence within the 15-19 year-old age group [5]. It is merely a symptom not a disease, which can be defined by a rapid onset, transient loss of consciousness with loss of postural control resulting from an insufficient supply of oxygen to the brain [6]. Syncope is then classified according to the underlying cause: neurological, psychiatric, metabolic and cardiac [7]. Neurocardiogenic syncope is classified as having a non-arrhythmic, cardiac origin. Usually, neurocardiogenic syncope is of a short duration with spontaneous recovery, although cases of prolonged cardio inhibition leading to a systolic cardiac arrest have been reported [6]. The significance of neurocardiogenic syncope lies in the fact that the presentation and spectrum of the condition vary immensely, ranging from patients having periodic syncopal episodes to recurrent, non refractory syncopal events

leading to a disabling condition with potential for cardiac arrest.

Symptoms

Neurocardiogenic Syncope may be abrupt or be associated with a variety of prodromal symptoms including, but not limited to lightheadedness, dizziness, abdominal discomfort, diaphoresis, augmented hearing, visual changes, headaches, palpitations and pallor [7-10]. If an adolescent has a syncopal event while driving, participating in sports, or operating machinery, the result could be trauma or even death. Therefore, many states suspend drivers and pilots license after such events [6]. Often, prodromal symptoms have specific triggers including pain, anxiety, dehydration and phobic stress that usually occur while standing or sitting [11]. Many of the triggers can be initiated during routine dentistry. Due to the highly variable nature of the condition, many patients with recurrent syncope have profound impairment, in both physical and psychosocial functioning. The quality of life of individuals that suffer from recurrent neurocardiogenic syncope is diminished due to debilitating symptoms, misdiagnosis, or ineffective treatment. It is not uncommon for individuals with severe NCS to miss substantial amounts of school, work and extracurricular activities [12].

Pathophysiology

Although the exact mechanism of Neurocardiogenic Syncope remains unclear, the most widely accepted mechanism of action will be discussed. It is thought to occur due to an imbalance of the autonomic nervous system. A disconnect occurs between the autonomic nervous system and cardiovascular system. Three separate phases occur. Initially, a stress occurs to the cardiovascular system that reduces blood volume. During this first phase, the reduction in blood volume caused by venous pooling leads to an increase in sympathetic nervous system activity, which subsequently increases heart rate and peripheral resistance to maintain adequate blood pressure. The second phase then begins; the vigorous contractions of a relatively empty

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left ventricle, causes activation of ventricular mechanoreceptors. The activation of the vagal C fiber mechanoreceptors and other baroreceptors cause the brain to receive conflicting information on blood pressure. The brain then assumes the body to be in a hypertensive crisis, which produces a compensatory mechanism [13]. The third phase then occurs, resulting in a reflex bradycardia (cardio inhibitory syncope) and/or an abnormal decrease in blood pressure (vasodepressor syncope). These actions are the end result of excessive parasympathetic activation combined with sympathetic withdrawal [14].

Diagnosis

A diagnosis of neurocardiogenic syncope is obtained through a series of evaluations including physical, neurological and electrophysical, which includes an electrocardiogram (ECG). If the ECG and cardiac testing results are normal, a head-up tilt table test (HUTTT) may be ordered. Recently, debate has begun regarding the efficacy of the once gold standard test for diagnosis of neurocardiogenic syncope, the head-up tilt table test. Excessive false-positive and false-negative results in children and adolescents provide a source of debate amongst cardiologists [15,16]. The first documented use of a tilt test was in the nineteenth century [17]. Later, this tool was used by NASA to evaluate physiological changes with change in posture [18]. Currently, the purpose of the HUTTT is to assess the function of the autonomic nervous system by eliminating the body's compensatory mechanism of skeletal muscle contraction, which preserves venous return [19,20].

After a period of fasting, individuals are placed on a tilt table with a foot plate support. Restraining belts are placed over the chest and thighs. The HUTTT begins after a 10 minute period of supine observation. The individual is placed in a 70-degree upright tilt and maintained for a period of 30-45 minutes, during which time heart rate, rhythm and blood pressure are monitored continually. If no symptoms or syncope occurs during the time interval allotted, pharmacologic agents are used to try to reproduce the triggering incident normally, just prior to spontaneous vasovagal syncope, serum concentrations of catecholamines increase. To simulate this catecholamine release, isoproterenol, which stimulates B-adrenergic receptors, is infused in an effort to provoke a syncopal event [21]. Other pharmacologic agents used to provoke vasovagal syncope during a head-up tilt table test include adenosine, nitroglycerin and edrophonium [22-26]. In general, a HUTTT response is considered positive for vasovagal syncope if syncopal symptoms are reproduced by provoking hypotension or bradycardia, or both, as a result of the procedure [27].

Although chronic fatigue syndrome (CFS) is an incompletely understood disorder, there appears to be an association between NCS and CFS. The profile of both NCS and CFS individuals are similar in regards to gender, age and clinical presentation. When using a HUTTT to evaluate patients with CFS, more than 60% have abnormal blood pressure or heart rate responses with abrupt hypotension or severe bradycardia and a subsequent decreased level of consciousness [28-31]. Other studies have shown CFS patients to benefit from combination therapy including fludrocortisones along with increased sodium intake [29].

Malignant vasovagal syncope

As the severity and recurrence rates of vasovagal syncope

increases, a description of malignant vasovagal syncope is assigned [32]. Individuals with malignant vasovagal syncope have been reported to have episodes of prolonged asystole during the HUTTT. One study suggested that systolic cardiac arrest may occur in patients with this extreme form of vasovagal syncope [33]. Another study of patients with vasovagal syncope found that bradycardia and asystole occurred in up to 15% of patients undergoing HUTTT, with the longest asystolic pause lasting 73 seconds [34,35]. There is limited knowledge on the prognosis of malignant vasovagal syncope. Understanding the existence and severity of this extreme form of vasovagal syncope is paramount.

Treatments

Education and non pharmacologic interventions are the first-line treatments of neurocardiogenic syncope. Both the patient and family are educated as to the mechanism of vasovagal syncope and individual triggers or situations that are to be avoided. Patients are then taught to journal and recognize their prodromal symptoms that could alert them to an impending syncopal or near syncopal episode. Another cornerstone of non-pharmacologic treatment includes increasing blood volume by adequate hydration, supplemental sodium and exercise. Eight to ten sixteen ounce glasses of water and an increased sodium intake by 200 mEq per day is required. Exercise recommendations include combinations of aerobic and resistance training three times per week for a duration of 30 minutes per session. Elastic support stockings that provide 30-40 mm Hg counter pressure prove useful in minimizing venous pooling [36]. Unfortunately, non pharmacologic interventions are often inadequate and pharmacologic management is required [37]. Neurocardiogenic syncope can be mitigated by the use of mediators that will increase blood pressure, such as midodrine. This medication acts by stimulating alpha-1 adrenergic receptors to constrict blood vessels and raise blood pressure within 30 minutes and lasts approximately 4-5 hours [38]. It has proven to be the most effective medication to prevent recurrent WS [39]. Low dose B-blockers including atenolol, metoprolol, propranolol and nadolol were once prescribed as first-line pharmacologic therapy for WS. Recently, studies have shown little to no positive results while implementing B-blockers [40]. Another medication, fludrocortisones, which enhances the sensitivity of the vasculature to circulating catecholamines and causes sodium retention, can be used to bolster the circulatory fluid levels. A randomized placebo-controlled study in children revealed fludrocortisones to be ineffective in preventing pre syncope and syncope [41].

Pacemaker placement is reserved for a select group of NCS patients and its placement is controversial. After all non pharmacologic and pharmacologic methods of treatment have been exhausted without success, pacing may be considered. Since a fall in blood pressure precedes bradycardia in most people with neurocardiogenic syncope, pacing may be ineffective in a majority of the patients. If NCS is caused by a large cardio inhibitory component, dual chamber pacing may be effective in reducing symptoms and preventing subsequent syncopal events [42]. Specific indications for permanent pacing in patients with NCS have been developed by the American Heart Association. One indication for pacemaker placement includes patients with malignant vasovagal syncope and asystole that is provoked in electrophysiological studies [43].

Dental considerations and recommendations

Undergoing dental procedures evokes a range of bodily responses that requires the autonomic nervous system to be functioning properly at all times. Patients with a history of neurocardiogenic syncope present with no immediately evident pathognomonic clinical characteristics, but when treated without precaution, a patient's inability to respond to stress appropriately can result in syncope or life threatening conditions including asystolic cardiac arrest. To manage patients with neurocardiogenic syncope, specific measures must be taken to ensure the patient's safety throughout treatment. Symptoms are typically exacerbated by a multitude of triggers including emotional stress, pain and dehydration. Dental procedures inherently produce these specific triggers that could produce a syncopal event in a number of individuals. First and foremost, a thorough medical history must be obtained including examining triggers, last syncopal or near syncope event, frequency and duration of symptoms, diagnostic testing performed with results, medications and overall medical management. During the inquiry regarding a syncopal event, attempt to glean insight into three areas: the circumstances before symptoms arise; prodromal symptoms; and how the patient felt during the recovery period. Known risk factors for recurrent neurocardiogenic syncope include female gender and the number of previous syncopal spells [44]. Consultations from all specialists including cardiologist and neurologist must be obtained prior to beginning treatment. A collaborative effort must be made when determining the safest treatment modality. If in-office treatment is considered, precautions should be taken to prevent a syncopal episode. Individual triggers should be identified and avoided. Discourage morning appointments if possible, as blood pressure is at its lowest in the early morning hours. Prior to the appointment, request the patient to wear loose fit clothing. Also, encourage the patient to maximize oral fluid intake and minimize physical activity 24 hours prior to the dental appointment to prevent dehydration [45]. During the appointment, attempt to limit strong, noxious, sensory stimuli and avoid overheating the dental operatory. Baseline vitals should be recorded and continuous monitoring considered. Administering local anesthetics with epinephrine should be considered carefully only after a thorough pharmacological review. During administration of local anesthetic, frequent aspirations are encouraged to prevent inadvertent intravenous administration. Adequate anesthesia is required to prevent pain from triggering a syncopal event [46]. At the completion of treatment, raise the dental chair incrementally and demand that the patient stay seated for 5 minutes to allow the body to equilibrate to the change in posture. To manage the highly anxious NCS dental patient, that may otherwise trigger a syncopal event, nitrous oxide alone or in combination with sedation may prove to be a valid treatment modality in specific mild forms of NCS. Careful patient selection is critical. If a collaborative decision to sedate the patient is made, fluid restrictions must be minimized. Appropriate monitoring including an ECG and emergency resuscitation must be available.

NCS patients would benefit from implementing a caries prevention plan, due to the tendencies toward polypharmacy, possible xerostomia, fatigue that could possibly contribute to unsatisfactory oral hygiene regimens and a frequent, high cariogenic diet. It would be prudent to consider increasing the frequency of recall appointments and prescribing a highly

fluoridated dentifrice.

Emergency management of a neurocardiogenic syncopal event

Essential ingredients to effective emergency management in the event of neurocardiogenic syncope include protecting and maintaining an open airway, proper positioning and closely observing vitals. If a patient loses consciousness, the operator must immediately cease treatment, remove foreign objects from the oral cavity and activate predetermined office emergency management protocol. Vital signs should be verified. Due to the variability of presentation, severe cases may lead to neurocardiogenic shock, resulting in a weak pulse, less than 60 beats/min. When the systolic blood pressure is reduced to 50mm Hg, a pulse will be difficult to palpate. After confirming hypotension, the patient should then be placed in a Trendelenburg position. With the patients legs slightly elevated, an increase in cerebral perfusion will be achieved. During the unconscious state, a patient's airway is at risk of obstruction. Techniques to ensure an open, patent airway include performing a head tilt chin lift or jaw thrust. Additional airway management includes administering supplemental oxygen at a flow rate of 6 L/min [47]. The patient must be escorted upon dismissal and must not drive an automobile [45]. If the episode is not self-limiting, activate emergency medical services. Continue to monitor the patient's vitals, administer atropine intravenously and begin CPR if necessary in the event of persistent, excessive vagal tone [48]. At the conclusion of the event, a referral is mandated.

Description of Case

An eighteen year old female presented to the dental clinic with a history significant for neurocardiogenic syncope and adverse reactions to Propofol and Fosphenytoin. This patient's history indicated that during a colonoscopy approximately two years prior to presentation for dental care, she experienced a significant loss of blood pressure and was treated for bradycardia. The patient was given epinephrine in a "rescue" dose and arrested. After several days in a coma, she was revived and recovered uneventfully. Because of this history and the need for dental treatment on teeth that were having pain, it was decided to proceed for treatment under general anesthesia. Consultations were sent to cardiology, anesthesia and neurology. The patient was taking Midodrine, Zolof, Prilosec, Sinemet and Propranolol. There was much disagreement among the specialists as to the proper method of treatment; i.e. outpatient vs. inpatient. The dentist performing the treatment did not want to proceed as an outpatient due to the possibility of a recurrence of blood pressure reduction and the possibility of instability. After nearly a year of delay due to parent and physician delays, the case was admitted to the hospital for treatment. On the morning of treatment, the patient was hydrated with sterile saline using an IV and taken to the operating room with the following treatment plan: The patient received fifteen various restorations of anterior and posterior teeth, many restored as a result of lesions occurring during orthodontic treatment (Figures 1-7). The third molars were removed by oral surgery as they were mesio-angular on panoramic radiography the patient tolerated the procedures well and was sent to recovery in improved condition. She was seen in five days for a post-operative review with no sequelae medically and a needed coverage of an open margin, dentally.



Figure 1: Facial appearance.



Figure 5: Panoramic radiograph.



Figure 2: Maxilla.

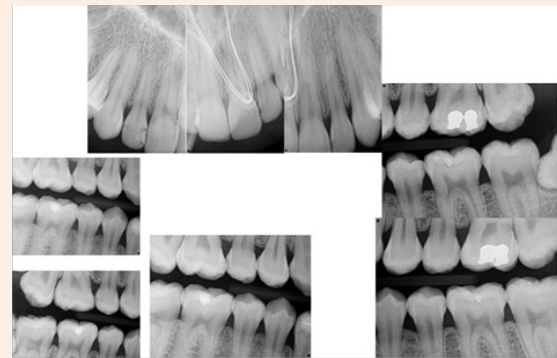


Figure 6: Bitewing radiographs.



Figure 3: Mandible.

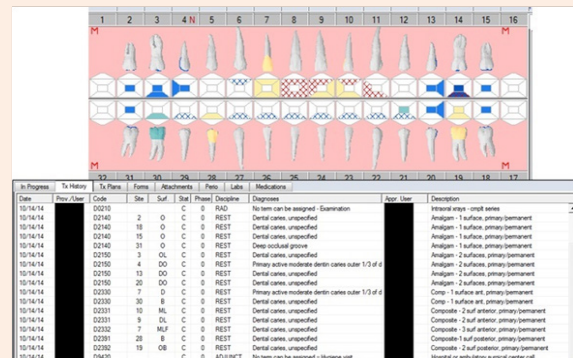


Figure 7: Completed dental treatment.



Figure 4: Dental occlusion.

Discussion

Patients with neurocardiogenic syncope present with unsuspected underlying conditions that require significant awareness. Without proper supervision, untoward events may occur that can be life-threatening. A thorough medical history is essential to prevent medical emergencies. Disagreement by medical specialists as to treatment modalities may complicate efficient treatments. Triggers for the patients included exertion, pain, supine positioning and dehydration. The constant irregularity of the symptoms interfered with daily activities and quality of life. Maintaining hydration and using Midodrine to control blood pressure as well as pressure apparel to the lower extremities helped control symptoms. During the hospitalization, the patient did not exhibit any of the suspected urgent situations anticipated and recovered well.

Conclusion

Neurocardiogenic syncope is an unsuspected medical condition that requires overriding consideration before beginning dental treatment. It is a condition that interferes with the daily activities of living. Proper precautions are necessary to prevent untoward events such as adequate hydration, postural positioning and daily medications to control blood pressure. Dental treatment recommendations for these patients must be well considered before beginning patient treatment and prevention of physical symptoms of dysautonomia must be strictly followed.

References

- Goldstein DS, Robertson D, Esler M, Straus SE, Eisenhofer G (2002) Dysautonomias: clinical disorders of the autonomic nervous system. *Ann Intern Med* 137(9): 753-763.
- Massin MM, Bourguignon A, Coremans C, Comté L, Lepage P, et al. (2004) Syncope in pediatric patients presenting to an emergency department. *J Pediatr* 145(2): 223-228.
- Matsuura H (1986) Systemic complications concerning dental anesthesia. *J Jpn Dental Assoc* 39: 517-526.
- Yamauchi Y, Kotani J, Urememura A, et al (1992) The survey of the emergency cases of general complication at Osaka Dental University Hospital in 10 years. *J Jpn Dental SocAnesth* 20: 342-348.
- Driscoll DJ, Jacobsen SJ, Porter Q, Wollan PC (1997) Syncope in children and adolescents. *J Am Coll Cardiol* 29(5): 1039-1045.
- Chen-Scarabelli C, Scarabelli TM (2004) Clinical Review: Neurocardiogenic syncope. *BMJ* 329(7461): 336-341.
- Forgoros RN (1999) Practical Cardiac Diagnosis series; Electro physiological Testing. (3rd edn), Blackwell Publishing, Malden, Massachusetts, USA.
- White CM, Tsikouris JP (2000) A review of pathophysiology and therapy of patients with vasovagal syncope. *Pharmacotherapy* 20(2): 158-165.
- Zaqqa M, Massumi A (2000) Neurally mediated syncope. *Tex Heart Inst J* 27(3): 268-272.
- Nair N, Padder FA, Kantharia BK (2003) Pathophysiology and management of neurocardiogenic syncope. *Am J Manag Care* 9(4): 327-334.
- Lewis, DA, Dhaka A (1999) Syncope in the pediatric patient. The cardiologist's perspective. *Pediatr Clin North Am* 46(2): 205-219.
- Linzer M, Pontinen M, Gold DT, Divine GW, Felder A, et al. (1991) Impairment of physical and psychosocial function during recurrent syncope. *J Clin Epidemiol* 44(10): 1037-1043.
- Medow MS, Stewart JM, Sanyal S, Mumtaz A, Sica D, et al. (2008) Pathophysiology, diagnosis, and treatment of orthostatic hypotension and vasovagal syncope. *Cardiol Rev* 16(1): 4-20.
- Nakagawa M, Takahashi N, Yufu K, Fujino T, Ooie T, et al. (2000) Malignant neurocardiogenic vasovagal syncope associated with chronic exaggerated vagal tone. *Pacing Clin Electrophysiol* 23(11 Pt 1): 1695-1697.
- de Jong-de Vos van Steenwijk CC, Wieling W, Johannes JM, Harms MP, Kuis W, et al. (1995) Incidence and hemodynamic characteristics of near-fainting in healthy 6- to 16-year old subjects. *J Am Coll Cardiol* 25(7): 1615-1621.
- Fouad FM, Sitthisook S, Vanerio G, Maloney J, Okabe M, et al. (1993) Sensitivity and specificity of the tilt table test in young patients with unexplained syncope. *Pacing Clin Electrophysiol* 16(3 Pt 1): 394-400.
- Hill L (1895) The influence of the force of gravity on the circulation of the blood. *J Physiol* 18(1-2): 15-53.
- Hellebrandt FA, Franseen EB (1943) Physiologic study of the vertical stance of man. *Physiological Reviews* 23(3): 220-225.
- Gadia C (1998) Syncope. *Int Pediatr* 13: 166-169.
- Grubb BP, Kimmel S (1998) Head-upright tilt table testing: a safe and easy way to assess neurocardiogenic syncope. *Post grad Med* 103(1): 133-138.
- Grubb BP, Kosinski D, Pothoulakis AJ (1995) New and emerging indications for head upright tilt table testing. *Eur J Cardiac Pacing Electrophysiol* 5: 109-112.
- Almquist A, Goldenberg IF, Milstein S, Chen MY, Chen XC, et al. (1989) Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. *N Engl J Med* 320(6): 346-351.
- Raviele A, Menozzi C, Brignole M, Gasparini G, Alboni P, et al. (1995) Value of head-up tilt testing potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. *Am J Cardiol* 76(4): 267-272.
- Waxman MB, Yao L, Cameron DA, Wald RW, Roseman J (1989) Isoproterenol induction of vasodepressor-type reaction in vasodepressor prone persons. *Am J Cardiol* 63(1): 58-65.
- Perennes A, Fatemi M, Borel ML, Lebras Y, L Her C, et al. (2006) Epidemiology, clinical features, and follow up of patients with syncope and a positive adenosine triphosphate test result. *J Am Coll Cardiol* 47(3): 594-597.
- Donato P, Brignole M, Menozzi C, Bottoni N, Alboni P, et al. (2003) Mechanism of syncope in patients with positive adenosine triphosphate tests. *J Am Coll Cardiol* 41(1): 93-98.
- Benditt DG, Ferguson DW, Grubb BP, Kapoor WN, Kugler J, et al. (1996) Tilt table testing for assessing syncope. *American College of Cardiology. J Am Coll Cardiol* 28(1): 263-275.
- Rowe PC, Bou-Holaigah I, Kan JS, Calkins H (1995) Is neurally mediated hypotension an unrecognized cause of chronic fatigue? *Lancet* 345(8950): 623-624.
- Bou-Holaigah I, Rowe PC, Kan J, Calkins H (1995) The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA* 274(12): 961-967.
- LaManca JJ, Peckerman A, Walker J, Kesil W, Cook S, et al. (1999) Cardiovascular response during head-up tilt in chronic fatigue syndrome. *Clin Physiol* 19(2): 111-120.
- Schondorf R, Benoit J, Wein T, Phaneuf D (1998) Orthostatic intolerance in the chronic fatigue syndrome. *J Auton Nerv Syst* 75(2-3): 192-201.
- Occhetta E, Audoglio R (2003) Malignant vasovagal syncope: physiopathology, diagnosis, epidemiology, and medical treatment. *Prog Biomed Res* 8(3): 174-184.
- Milstein S, Buetikofer J, Lesser J, Goldenberg IF, Benditt DG, et al. (1989) Cardiac asystole: a manifestation of neurally mediated hypotension-bradycardia. *J Am CollCardiol* 14(7): 1626-1632.
- Fitzpatrick A, Sutton R (1989) Tilting towards a diagnosis in recurrent unexplained syncope. *Lancet* 1(8639): 658-660.
- Maloney JD, Jaeger FJ, Fouad-Tarazi FM, Morris HH (1988) Malignant vasovagal syncope: prolonged asystole provoked by head-up tilt. Case report and review of diagnosis, pathophysiology, and therapy. *Cleve Clin J Med* 55(6): 542-548.
- Medow MS, Stewart JM (2007) The Postural Tachycardia Syndrome.

- Cardiol Rev 15(2): 67-75.
37. Sra JS (2001) Can we assess the efficacy of therapy in neurocardiogenic syncope? *J Am Coll Cardiol* 37(2): 560-561.
 38. Mustafa HI, Fessel JP, Barwise J, Shannon JR, Raj SR, et al. (2012) Dysautonomia: Perioperative implications. *Anesthesiology* 116(1): 205-215.
 39. Vyas A, Swaminathan PD, Zimmerman MB, Olshansky B (2012) Are treatments for vasovagal syncope effective? A meta-analysis. *Int J Cardiol* 167(5): 1906-1911.
 40. Madrid AH, Ortega J, Rebolla JG, Manzano JG, Segovia JG, et al. (2001) Lack of efficacy of atenolol for the prevention of neutrally mediated syncope in a highly symptomatic population: a prospective, double-blind, randomized and placebo-controlled study. *J Am Coll Cardiol* 37(2): 554-559.
 41. Salim MA, Di Sessa TG (2005) Effectiveness of fludrocortisone and salt in preventing syncope recurrence in children: a double blind, placebo controlled, randomized trial. *J Am Coll Cardiol* 45(4): 484-488.
 42. Connolly SJ, Sheldon R, Roberts RS, Gent M (1999) The North American vasovagal pacemaker study (vps). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. *J Am Coll Cardiol* 33(1): 16-20.
 43. Gregoratos G, Cheitlin MD, Conill A, Epstein AE, Fellows C, et al. (1998) ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices: executive summary-- a report of the American College of Cardiology/American Heart Association task force on practice guidelines. (Committee on Pacemaker Implantation). *Circulation* 97(13): 1325-1335.
 44. Aydin MA, Maas R, Mortensen K, Steinig T, Klemm H, et al. (2009) Predicting recurrence of vasovagal syncope: a simple risk score for the clinical routine. *J Cardiovasc Electrophysiol* 20(4): 416-421.
 45. Ross PJ, Schneider PE, Helpin M (2013) Neurocardiogenic syncope of child dental patient: a case review. *Pediatr Dent* 35(1): 71-73.
 46. Replogle K, Reader A, Nist R, Beck M, Weaver J, et al. (1999) Cardiovascular effects of intravenous injections of 2 percent lidocaine with 1:100,000 epinephrine and 3 percent Mepivacaine. *J Am Dent Assoc* 130(5): 649-657.
 47. Niwa H, Hirota Y, Shibutani T, Matsuura H (1996) Systemic emergencies and their management in dentistry: complications independent of underlying disease. *Anesth Prog* 43(1): 29-35.
 48. Arakeri G, Arali V (2010) A new hypothesis of cause of syncope: trigeminocardiac reflex during extraction of teeth. *Med hypotheses* 74(2): 248-251.