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Minireview

Current aspects of thiamine deficiency on heart function

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ABSTRACT

Beriberi is a disease caused by thiamine deficiency (TD), which may lead to heart problems, including heart failure. Despite the fact that thiamine prevalence is reduced in the industrialized world, it remains a health hazard especially due to chronic alcohol consumption. Diagnosing the presence of TD based on both electrocardiogram and echocardiogram exams is particularly challenging because of its non-specific symptoms. TD diagnosis is unique, which then leads to determination of its severity. If thiamine infusion abrogates its symptomology, only then can the case be definitely diagnosed as TD. Another condition eliciting increased likelihood of developing TD in humans is furosemide administration to heart failure patients. Furosemide administration worsens heart failure due to heightened TD. However, literature data provided are contradictory and require clarification. Up until now, the rat has been the preferred TD animal model. However, the results are even more contradictory than those in humans. It seems that if the rat TD models are separated into two distinct groups, according to animal age, the results appear to be more consistent: younger rats are more prone to develop TD signs similar to those found in humans. Their symptoms stem from changes in cardiac myocyte function that are reversed after thiamine supplementation. However, it remains an open question as to why only younger rats are able to develop human-like symptoms and deserve further investigation.

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Beriberi — discovery of thiamine as an essential nutrient

The first modern description of beriberi was made in the 17th century by a tropical physician, Dutch Jacobus Bontius (Bruyn, 2003). However, the first correlation between beriberi and diet was made by Takaki Kanehiro, M.D., in 1884, a Japanese naval doctor. At that time, he realized that a crew on one of two different ships fed only unpolished rice had a lower incidence of illness than those on another ship also fed only polished rice (Itokawa, 1976). Later, Christiaan Eijkman a Dutch pathologist, using a chicken model, demonstrated, by accident, that polished rice was able to induce beriberi in chicken and he was able to reverse the outcomes feeding them instead of unpolished rice (Raju, 1998). Later, in 1929 Christiaan Eijkman and Frederuck Hopkins shared the Nobel Prize in Physiology or Medicine by showing that some nutrients in rice skin prevent Beriberi. In 1912 Casimir Funk, a Polish biochemist, purified from crude rice straw a substance named “vitamins”, which were later recognized as Vitamin B1 (Piro et al., 2010).

Clinical findings during wet beriberi

A heart disease in humans and related to thiamine deficiency was first reported in 1929. In this report, the authors described the most

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common cardiac manifestation of TD: tachycardia. Interestingly, they described a right and left ventricular hypertrophy, however the right one was more pronounced (Aalsmeer and Wenckebach, 1929). These early findings were confirmed, and in 1945 diagnostic criteria was established for identifying thiamine deficiency (Blankenhorn, 1945): (1) enlarged heart with normal rhythm, (2) dependent edema, (3) elevated venous pressure, (4) peripheral neuritis or pellagra, (5) nonspecific alterations in the electrocardiogram, (6) no other evident cause for heart disease, (7) gross deficiency of diet for 3 months or more, and (8) improvement of symptoms and reduction of heart size after specific vitamin replacement. Later, other symptoms were added including tachycardia (Park et al., 2007; Attas et al., 1978; Yamasaki et al., 2010) (however bradycardia has already been reported (Kawano et al., 2005a)), increased levels of troponin I (Tran, 2006), high-output cardiac failure (Park et al., 2007; Kawano et al., 2005a; McIntyre and Stanley, 1971; Loma-Osorio et al., 2011) and acidosis (Kawano et al., 2005a; Diltoer et al., 2004; Klein et al., 2004; Campbell, 1984). However the main criterion for identifying TD is that all the aforementioned indicators are reversed after 1–2 months of thiamine administration. Wet beriberi is the classical term used for thiamine deficiency with cardiovascular involvement. There has been a long association of rice consumption with beriberi in Asia and other parts of the world including Brazil. A more rapid form of wet beriberi is termed acute fulminant cardiovascular beriberi/Shoshin beriberi, or acute pernicious beriberi. The occurrence of high-output heart failure in classical beriberi is due to excessive vasodilatation in the muscles and a fall in the peripheral vascular resistance with resultant increase in venous return and stroke volume. Either progressive vasodilatation or damage to the myocardium or both may disturb the equilibrium, and a falling blood pressure will signal circulatory breakdown. Direct impairment of myocardial energy production has been proposed as one possible mechanism of the heart failure seen in beriberi as thiamine is required as a cofactor for energy production (Oliveira et al., 2007). In Shoshin beriberi, in addition to falling systemic blood pressure and shock the clinical picture includes vasoconstriction in skin and kidney, which will provoke cyanosis and acute renal shutdown.

There are few reports describing *post-mortem* analysis following thiamine deprivation. In a recent study, autopsy revealed normal heart size and weight. Histologically, the heart presented with focal myocytes necrosis with massive and diffuse polymorphonuclear leukocytes infiltrates with a breakdown of the whole contractile apparatus. This breakdown varied from irregular, pathological and eosinophilic cross-bands consisting of segments of hyper-contracted or coagulated sarcomeres, to a total disruption of myofibrils (Bello et al., 2011).

However, the clinical manifestations of thiamine deficiency are variable making a definitive diagnosis challenging. For example, in a report of beriberi due to excessive alcohol intake, one patient had a high cardiac output index whereas another had a low output cardiac index (McIntyre and Stanley, 1971). In another study, the authors found massive edema and venous hypertension, but with no presence of myocardial failure (Lahey et al., 1953). Another group of patients had increased stroke volume with reduced systemic vascular resistance accompanied by reduced ejection fraction with hypertrophy. Different from other studies, they found in human TD that plasma angiotensin II, aldosterone and cortisol levels were reduced compared to congestive heart failure patients, which indicate a different mechanism involved in hypertrophic activation found in these TD patients (Ikram et al., 1981). In another study, they also reported cardiomegaly (Koike et al., 2006). Considering an electrocardiogram (EKG) alteration, non-specific T-wave changes with tachycardia associated with reduced stroke index and high-output ventricular failure were found (Attas et al., 1978). However in other studies distinct EKG abnormalities were found including ST depression and negative T waves (Park et al., 2007), QT interval prolongation with flat or inverted T wave (Tanphaichitr et al., 1970), and ST-segment elevation (Kawano et al., 2005a). A more complete review about EKG alterations during TD can be found in Jones (1959). Interestingly in most studies the EKG and heart morphology alterations were reversed after thiamine administration, indicating that the heart failure caused by thiamine deficiency is a transient biochemical abnormality (Rowlands and Vilter, 1960).

The lack of long term follow-up studies in TD subjects makes it difficult to validate the view that heart failure is merely a transient effect of thiamine deprivation.

In a short-term follow-up study, where the author evaluated morphometric and EKG parameters this view was challenged. First of all, sinus tachycardia, ST-segment elevation was evident in lead I and ST-segment depression in lead II with reduced left ventricular ejection fraction (44%). All the parameters improved after a single dose of thiamine. About one month after treatment, an endomyocardial biopsy was performed in the left ventricle. In the biopsied myocardium, interstitial fibrosis, variation in size of the myocardial fibers, mild myocyte hypertrophy, and myocyte disorganization were seen. There was mild cell infiltration in the myocardium. The second patient had generalized edema. The EKG showed sinus tachycardia, right bundle branch block, ST-segment depression in leads V2–V4 and inverted T waves in leads III. Additionally a chest X-ray showed cardiomegaly, with reduced left ventricular ejection fraction (51%) accompanied with acidosis. After thiamine treatment, his blood pressure gradually increased, and acidosis improved. One month after treatment, the patient showed interstitial fibrosis, variation in size of the myocardial fibers, mild myocyte disorganization, and mild myocyte vacuolization in the biopsied myocardium. An EKG showed right bundle branch block without ST-segment depression or an inverted T wave and a normal LVEF of 60% (Kawano et al., 2005b).

It is well known that increased interstitial fibrosis and myocyte disorganization could lead to heart dysfunction (Gomez et al., 1997). Also, right bundle branch block is indicative of an increased risk of cardiovascular disease/arrhythmia (Jorge et al., 2003). Thus, it is still an open question whether thiamine administration reverses all of the symptoms indicative of heart failure and therefore deserves further studies. It is important to note that there are other important micronutrients associated with heart failure. At this point the scenario is rather complicated because there are no many studies which actually explore the potential role of various micronutrients in heart failure. Overall, the results are inconsistent due to the large heterogeneity present in the populations investigated (Jorge et al., 2003). For a more comprehensive review about this subject, please refer to McKeag et al. (2012).

Furosemide induces thiamine deprivation: implications to heart failure

Heart failure (HF) is a complex syndrome characterized by impaired heart contractile function leading to low efficiency of blood distribution throughout the vascular system. Etiology of HF has many contributors that include myocarditis, genetic mutations, heart ischemia, volume overload and pressure overload due to hypertension. There are many pharmacological treatments available to treat heart failure including: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, digoxin, beta blockers, aldosterone antagonists and diuretics, one of the diuretics is furosemide (Swedberg et al., 2005).

Furosemide is a loop diuretic increasing urinary output, which helps reduce edema in congestive heart failure (CHF) (Wargo and Banta, 2009). The first report relating furosemide administration to thiamine deprivation dates back to the 1980s (Yui et al., 1980). In a rat model treated with furosemide, liver, heart and kidney thiamine concentration declined whereas urinary thiamine excretion increased. Furthermore, furosemide administration associated with low thiamine intake levels caused left ventricular mass index reduction, indicating a possible pathological association between furosemide and excessive thiamine excretion (da Cunha et al., 2007). Taken all together the authors concluded that administration of furosemide would aggravate thiamine deficiency only in situations associated with insufficient thiamine intake, causing