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Does Riboflavin Transporter Deficiency Syndrome (RTD) Play a Role in the Development of Cardiovascular Disease (CVD)?

Nicholas A Kerna
E-mail: medpublab+drkerna@gmail.com
POB47 Phatphong, Suriwongse Road
Bangkok, Thailand 10500.

Christopher C Ukpong[1] and Nicholas A Kerna[2]*
[1]University of Science, Arts and Technology, BWI
[2]SMC-Medical Research, Thailand

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COLUMN ARTICLE

Abstract

Riboflavin transporter deficiency syndrome (RTD) is a neurodegenerative disorder that is inherited in an autosomal recessive pattern. As a neurodegenerative disorder, its involvement in neuropathy has been discussed. However, RTD's potential effect on organs beyond the nervous system has not been established. Given the physiological interconnection between the nervous system and the cardiovascular system, it is conceivable that a pathological connection may exist between them. If such a connection can be determined in future studies, both conditions may be more effectively diagnosed and treated.

Keywords: Cardiovascular; Nervous System; Riboflavin; Solute Carrier 52A

Abbreviations

BVVLS: Brown Vialetto-Van Laere Syndrome; FAD: Flavin Adenine Dinucleotide; FMN: Flavin Mononucleotide

Introduction

Riboflavin transporter deficiency syndrome (RTD) is a rare neurodegenerative autosomal recessive disorder that generally affects infants and children. However, there have been a few reported cases of RTD in adults. The pathology of RTD is not well understood, but its etiology has been somewhat explained in the medical literature. RTD is referred to as Brown-Vialetto-Van Laere syndrome (BVVLS) and Fazio-Londe disease [1-4].

There are two types of RTD (SLC52A2 and SLC52A3) with overlapping clinical symptoms. Sensorineural deafness, dysphagia, pontobulbar palsy, and dysarthria are the most common symptoms of RTD [5,6].

Genotypically, the mutation of the solute carrier 52A (SLC52A) protein is primarily implicated in RTD. The mutation causes a defective riboflavin transporter, which is unable to function as a biological conduit for riboflavin's entry into the cell. Riboflavin is a precursor of two essential coenzymes, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), that play critical roles in the metabolic pathway for the synthesis of ATP in mitochondria.

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FAD and FMN are vital in specific enzymatic pathways. The tissues of various organs process and utilize FAD and FMN differently, based on their biological needs and their physiologic roles. There is scant research on how the human heart is affected by RTD, especially considering the progressive cellular decline of FAD and FMN and the concomitant impacts thereof.

Research has repeatedly shown that RTD adversely affects the mitochondria, and their oxidative phosphorylation role is disrupted [7,8]. Having a sufficient supply of ATP to an energy-demanding organ such as the heart is critical. Thus, any pathological process that interferes with the production of ATP could be considered a risk factor in developing CVD. The following section considers the role that RTD might play in the development of CVD.

Discussion

RTD is a motor neuron neuropathy (also known as bulbar palsy) that affects the neurons in the brain stem [2]. As such, many vital functions of the body, such as movement, breathing, hearing, speaking, balance, and heart function, deteriorate as the disease progresses [4]. It stands to reason that any pathology in the control center (pontobulba) of these functions could adversely affect innervation. Research has shown that compromised innervation (thus communication) can adversely affect organs and the normal functioning of the human body. However, the research into such adverse affects on cardiac function and physiology is scant compared to the relative importance of the cardiovascular system.

The typical neurological symptoms of RTD (previously mentioned) may appear to justify the exclusion of cardiac involvement in RTD. However, these typical symptoms do not reflect the complete pathological impacts of RTD on various organ systems, particularly in the long term. RTD is a relatively new disorder in medicine, and its systemic impact has not been thoroughly investigated and is not fully understood. Thus, the clinical absence of putative cardiac symptoms in RTD does not necessarily correlate to an absence of potential risks for a pathological connection between the two conditions.

Could RTD-related heart dysfunction occur? The nervous system is in constant physiological communication with the cardiovascular system. Signals from the sympathetic and parasympathetic nervous systems elicit cardiovascular responses [6]. The mutual benefits of this neurological-cardiovascular interaction and interdependence have long been established. For instance, the central and peripheral nervous systems control cardiovascular activities while the cardiovascular system serves as a "sensor" for the nervous system to respond to changes in homeostasis [3,8]. Also, RTD is documented as having a significant pathological effect on neurons; many of these neurons play pivotal roles in cardiovascular function. Thus, it is conceivable that a prolonged neuropathy due to RTD may play a role in the development of CVD and specific disorders of the vascular system.

On a biomolecular level, it is crucial to consider the effect of a decreased level of ATP on the physiology of the heart, since about 95% of the ATP (in normal circumstances) is generated by oxidative phosphorylation in the mitochondrial [7,8]. In the case of RTD, diminished levels of ATP are a result of declines in FAD and FMN, and the concomitant effects on oxidative phosphorylation and ATP production.

Conclusion

Currently, there is insufficient data to include or exclude riboflavin transporter deficiency syndrome as a risk factor in developing cardiovascular disease. However, there is a well-established physiological connection and interdependence between the nervous system and the cardiovascular system, and RTD adversely affects the nervous system. Thus, in theory, RTD could act as a risk factor for CVD or cardiac event. The potential for such a detrimental connection deserves investigation. If such a connection exists, it can be used to treat one or both conditions better.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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