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Better healthcare

The Impact of H63D-Syndrome on Cardiac Function: Evaluating the Risks and Necessity of Regular Heart Monitoring in Affected Individuals

Abstract

H63D-Syndrome, a genetic disorder resulting from the HFE H63D gene mutation, is associated with increased risks of iron overload and subsequent multi-organ damage. Recent evidence suggests that the heart may be particularly susceptible to damage in patients with H63D-Syndrome due to the affinity of non-transferrin bound iron (NTBI) to sodium, potassium, and calcium channels. This paper aims to review the current understanding of H63D-Syndrome, its effects on cardiac function, and the necessity of regular heart monitoring in individuals diagnosed with this condition.

H63D mutation, NTBI formation and the human heart

H63D-Syndrome is are rather genetic disorders caused by the HFE H63D gene mutation, which results in an amino acid substitution in the HFE protein (1). This mutation leads to impaired iron regulation, resulting in iron overload, a condition known as hereditary hemochromatosis (2). The accumulation of iron in various organs can cause multi-organ damage, including liver cirrhosis, diabetes, and heart failure (3). Recent evidence suggests that NTBI, a toxic form of iron, has an affinity to sodium, potassium, and calcium channels, which may increase the risk of cardiac damage in patients with H63D-Syndrome (4). This paper aims to discuss the risks

associated with H63D-Syndrome for the heart and the necessity of regular cardiac monitoring in affected individuals. The HFE H63D gene mutation results in a disruption of the iron regulatory mechanism, leading to iron overload in various organs, including the heart (1). Elevated levels of NTBI, a toxic form of iron, have been found in the plasma of patients with H63D-Syndrome (5).

Whenever transferrin saturation (TFsat) is above >50% NTBI will develop inside the body, invade cells and cause severe damage due to oxidative inflammations. Research indicates that NTBI has also an affinity for sodium, potassium, and calcium channels, which are essential for maintaining the electrical activity and contractility of the heart (4). This interaction can lead to impaired cardiac function and, ultimately, heart failure (6).

In addition to its affinity for ion channels, NTBI can also generate reactive oxygen species (ROS) through the Fenton reaction, causing oxidative stress and damage to cellular components (7). Cardiomyocytes are particularly susceptible to oxidative stress due to their high metabolic rate and limited antioxidant capacity (8). The combination of NTBI accumulation and oxidative stress can result in the development of cardiac fibrosis, arrhythmias, and cardiomyopathy, further compromising cardiac function in patients with H63D-Syndrome (9).

Given the potential for cardiac damage in patients with H63D-Syndrome, it is essential to implement regular cardiac monitoring to identify early signs of dysfunction and initiate appropriate treatment strategies. The American Heart Association recommends the following evaluations for patients with any kind of iron overload, not just for those suffering from hereditary hemochromatosis (10).

NTBI has been shown to have a direct toxic effect on the heart. NTBI has an affinity for sodium channels, which are important for the normal functioning of the heart. Sodium channels are responsible for generating the electrical impulses that control the heartbeat. When NTBI binds to sodium channels, it can interfere with their function, leading to irregular heartbeats and arrhythmias. NTBI can also bind to calcium, sodium and potassium channels, which can further disrupt the electrical activity of the heart.

In addition to its impact all three types of ion channels, NTBI has also been linked to microinflammations in several heart structures. Microinflammations are low-grade, chronic inflammations that can occur in response to various stimuli, including oxidative stress and tissue damage. NTBI type of iron can contribute to microinflammations by promoting the production of reactive oxygen species, which can damage cells and tissues in the heart. Microinflammations in the heart will then lead a variety of heart dysfunctions.

Chronic inflammation can damage the heart muscle and lead to the development of heart failure. In addition, inflammation can contribute to the formation of plaques in the arteries, which can increase the risk of heart attack and stroke. Thus, NTBI has a massive negative impact on the heart. Its affinity for the sodium, natrium, and potassium channels can interfere with the electrical activity (conduction) of the heart, leading to arrhythmias, blocks and other cardiac problems way up to chronic heart failure. Further research is needed to fully understand the mechanisms by which NTBI affects the heart, and to develop new therapies to mitigate its negative effects. An

ultrasound-based imaging is the gold standard in evaluating the cardiac structure, the heart's function, including ventricular dimensions, wall thickness, and contractility. Cardiac magnetic resonance imaging (MRI), a non-invasive imaging technique can also provide detailed information about cardiac structure, function, however, the "live" pictures provided by a high-end state of the art sonography is the better tool in many cases.

Laboratory tests should at least include the measurement of serum ferritin levels and transferrin saturation (TFsat) to monitor iron overload and estimate the cardiotoxic NTBI with the Bartels formula, as well as assessment of biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT), which can indicate early cardiac dysfunction (11). Regular (follow-up) visits with an experienced cardiologist are of help to detect any anomaly in its early stages.

Recommended baseline assessment:

A thorough medical history and physical examination, including an evaluation of cardiovascular risk factors and any signs suggestive of cardiac dysfunction.

Electrocardiogram (ECG):

A non-invasive test that records the electrical activity of the heart and can easily detect all kinds of arrhythmias, conduction abnormalities, and signs of myocardial ischemia or injury.

Sonography:

Heart sonography, also commonly known as echocardiography, is a non-invasive imaging technique that uses high-frequency sound waves to produce images of the heart. The sound waves are emitted from a handheld device called a transducer and are directed towards the heart. When the sound waves encounter the tissues and structures of the heart, they bounce back and are detected by the transducer. The information received by the transducer is then processed by a computer to produce real-time images of the heart. The images produced by heart sonography can provide detailed information about the structure and function of the heart, including the size and shape of the chambers, the thickness of the heart muscle, the functioning of the heart valves, and the movement of blood through the heart. Heart sonography can be performed in different ways, including transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). TTE is the most common type of heart sonography and involves placing the transducer on the chest wall to obtain images of the heart. TEE involves placing a specialized probe into the esophagus to obtain more detailed images of the heart. Heart sonography is a safe and non-invasive procedure that is commonly used to diagnose and monitor various heart conditions, such as heart failure, valve disease, and congenital heart defects. It is also used to guide procedures such as heart surgery and the placement of heart devices like pacemakers.

Conclusion

H63D-Syndrome, resulting from the HFE H63D gene mutation, predisposes affected individuals to iron overload with NTBI and subsequent multi-organ damage, with the heart being particularly vulnerable due to NTBI's affinity for sodium, potassium, and calcium channels. Regular cardiac monitoring is essential for the early detection and management of cardiac dysfunction in patients with H63D-Syndrome. Further research is needed to

elucidate the molecular mechanisms underlying the effects of NTBI on cardiac ion channels and to develop targeted therapies that can mitigate the risk of cardiac complications in this patient population.

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Conflicts of interest

The authors declare no conflicts of interest.

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