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SICK SINUS SYNDROME AND ASSOCIATION WITH MICRO RNA1976 MYH6 AND SCN10A GENE

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Abstract:

Sick sinus syndrome is a leading cause of hospitalization, especially for people over 70 years old. Acute and intensive care nurses play a significant role in supporting patients in cardiac control units with the diagnosis and treatment. The medical care of patients with sick syndrome consists of careful cardiac observation, monitoring of symptoms and correlation of these symptoms with signs of ECG and providing advanced cardiac life support if necessary. Sick sinus syndrome contains anomalies of the sinus node (SAN) and atrial muscle cells resulting in various arrhythmias, such as sinus bradycardia, sinus pauses, sinus arrest, and sinoatrial exit block.

Sick Sinus Syndrome has a strong association with Micro RNA 1976 as it targets the channels Cav1.2 and Cav1.3 Ca2 + that result in sinus node dysfunction .The level of microRNA1976 in the plasma of SSS patients is up-regulated as compared to healthy person. Moreover, the novel MYH6 mutation delE933 causes structural damage to the sarcomere as well as functional impairments which results in the sinus node dysfunction and causes familial SSS. Similarly, the SCN10A gene's genotype AA is associated with a predisposition to the development of Idiopathic Sick Sinus Syndrome. In addition this genotype occurred substantially among men with SSS as compared to the control group.

Keywords: *Sick Sinus Syndrome, Gene, Micro RNA 1976, MYH6, SCN10A, Sinoatrial exit block*

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INTRODUCTION:

The sinus node (SN) is situated in the upper right atrium and is the main pacemaker of the human heart[1].The electrical activity of the SN is regulated directly by the autonomous nervous system, which helps it to adapt the heart rate to the body's needs [2]. The Signs and symptoms of sick sinus syndrome associated with abnormal intrinsic sinus dysfunction (SND) impulse formation and/or propagation. A heterogeneous therapeutic entity involves rhythm disruptions that can result to significant cardiovascular events [3] thrombo-embolism [4] insufficient heart rate reaction to exercise / stress known as chronotropic failure or any other signs involving implantation of a pacemaker. In the United States, the estimated number of new patients of sick sinus disease is expected to rise from 78,000 in 2012 to 172,000 in 2060[5].Sick sinus syndrome is a major indication of pacemaker placement that contributes for about 30 to 50 % of all pacemaker implants in the United States [6-7]. The rate rises with age, it is more common among whites and is the same among men and women.

Other conditions associated with increased incidence of SSS includes elevated body mass index, high blood pressure, hypertension, heart failure and coronary artery disease [8]. Even though SSS is most commonly associated with aging and common diseases in the elderly people, there are cases of SSS in infants and children. Familial SSS is caused by mutations of 1of 3 genes hyperpolarization activated cyclic nucleotide channel 4 (HCN4); sodium channel, voltage-gated, type V, alpha subunit (SCN5A); or myosin, heavy chain 6, heart muscle, alpha (MYH6). The First 2, HCN4 and SCN5A are essential to ion channel development, and a reduction in ion channel production impedes the sinus node's ability to perform normally. .The third gene, MYH6, is responsible for myosin production, a protein in the heart muscle that promotes heart contraction [9].

Clinical Characteristics of Sick Sinus Syndrome:

SSS symptoms include various arrhythmias, including bradycardia Figure 1, tachycardia, sinus arrest, sinus delay,

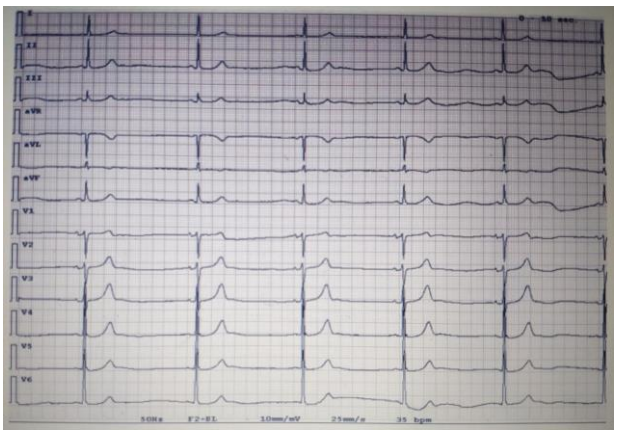

Figure 1. Severe sinus bradycardia with sinus rate 35 beats per min; QRS Complex is normal

Table 1

1. Circumstances Associated with Sinus Node Dysfunction

Primary	Secondary
• Degenerative fibrosis • Chronic ischemia • Sarcoidosis • Atrial tachyarrhythmias • Hemochromatosis • Aging • Calsequestrin, Amyloidosis • Hereditary muscle dystrophies • Hypertension • Heart failure • Myocarditis • Infective Rheumatic fever • Valvular heart disease • Diabetes • Diphtheria • Obesity • Obstructive sleep Apnea • Chagas disease, Ryanodine	• Metabolic disorders like Hypocalcemia, • Hypothermia ,Hyperkalemia • Hypoxia • Acute ischemia • Pharmacologic agents • Antiarrhythmic Medications (class I and III) b-Blockers • Calcium channel blockers (non-dihydropyridine) Cimetidine • Clonidine • Digoxin • Methyldopa • Lithium • Phenothiazine • Amitriptyline • Reserpine • Extra cardiac diseases like Intracranial hypertension and Hypothyroidism

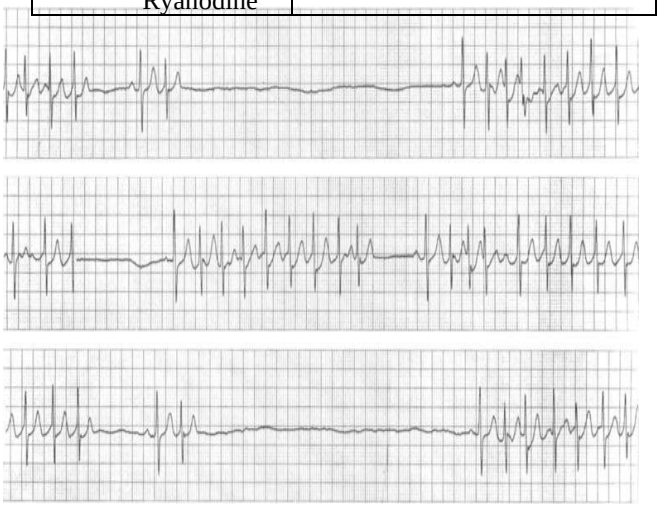

Figure 2. Electrocardiogram that demonstrates alternating patterns of bradycardia and tachycardia seen in patients with sick sinus syndrome.

sinus node exit block with intermittent atrial bradyarrhythmia and tachyarrhythmia as in figure 2, which may lead to significant cardiovascular events such as thromboembolism, syncope, sudden cardiac death or chronotropic incompetence10].It may be difficult to diagnose SSS, but finally it can be achieved by electrocardiographic detection of signs of arrhythmia or end-organ hypoperfusion [11].

Diagnosis of Sinus Node Dysfunction:

SND diagnosis may be obvious if there is a clear correlation between ECG abnormalities and symptoms such as dizziness Figure 3, syncope, heart failure, fatigue, and intolerance to exercise. Nevertheless, if SND occurs intermittently and the association between electrocardiographic anomalies and medical diagnosis is difficult to evaluate, further investigations may be required.

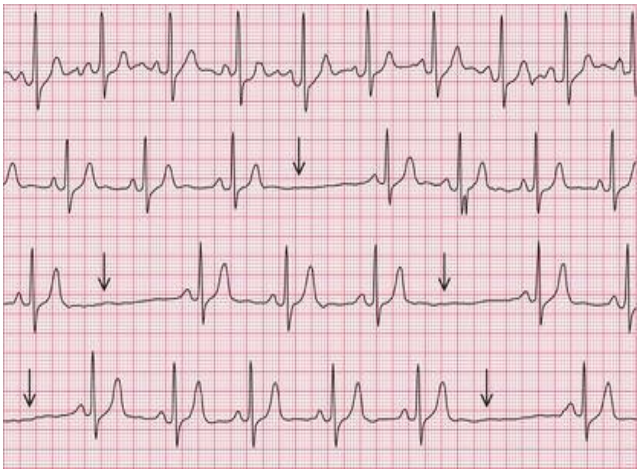

Figure 3. Ambulatory record from a young woman who complained of short-lived attacks of dizziness. When she had these, the ECG showed sinus pauses.

Holter monitoring may be helpful when SND occurs transiently, but with an expected reoccurrence frequently sufficient to allow documentation during monitoring, Usually, a 24-hour or 72-hour ECG examination can be used to assess the correlation between ECG abnormalities and symptoms, as well as other medical arrhythmias, such as Atrial fibrillation in bradycardia tachycardia syndrome. If Holter monitoring is unreliable and SND is strongly suspected which is based on clinical diagnosis, in selected cases an implantable loop recorder may be recommended for longer surveillance (up to 24 months), particularly when patients receive syncope medical attention. Exercise stress tests are useful in distinguishing an inherent form of SND from the bradycardia due to a vagal hypertonia which may be responsible for electrocardiographic aspects like those induced by SND. In the former case, chronotropic failure with inadequate increases in heart rate during exercise is evident, resulting in functional weakness, while in the latter, the ability to perform a peak exercise stress test is found with a normal and gradual rise in sinus frequency. Such discrimination is necessary in order to make appropriate therapeutic choices. Head-up tilt tests are used to classify disorders in which bradycardia is caused by irregular nervous system causes, which may be responsible for neuromodulated syncope. Eventually, in chosen cases in which other diagnostic tools have been insufficient in the diagnosis of SND, an electrophysiological analysis can also be performed and the recovery period of the SN as well as the conduction time of the sinoatrial can be calculated using various pacing maneuvers.

Epidemiology:

The study of epidemiology of sinus node dysfunction is difficult due to the variable disease manifestations and ECG findings because of the variable manifestations of disease and findings of ECG.

However, according to a pooled analysis from two extensive studies that included 20,572 patients with a 59-year-old average age, 43% were males, followed by researchers for an average of 17 years. Sinus node dysfunction prevalence was 0.8 per 1000 person-years. Age has shown the greatest importance as a risk factor for sinus node dysfunction [12].

Sick Sinus Syndrome association with MicroRNA1976, And MHY6, SCN10A Genes:

The sick sinus Syndrome includes a variety of signs and heart rhythm changes consistent with irregular sinus impulses and/or distribution Fig 4.This disorder has multiple electrocardiographic

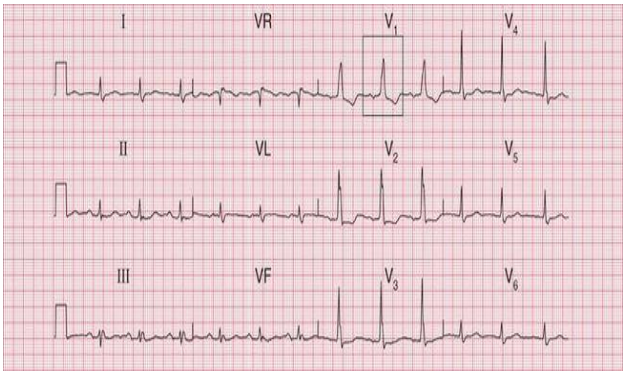

Figure 4. Shows the ECG from a patient who, when asymptomatic, showed first degree block and right bundle branch block. He complained of fainting attacks, and an ambulatory recording showed that this was due to sinus arrest with a very slow AV nodal escape rhythm, giving a ventricular rate of 15/min .It is an example of the combination of sick sinus syndrome and conduction system disease.

manifestations, such as bradycardia, sinus arrest, sinoatrial block and intermittent bradycardia and tachycardia episodes. SSS have a strong association with Micro RNA 1976 as it targets the Cav1.2 and Cav1.3 Ca2+ channels which results in SND. In the plasma of SSS patients the level of micoRNA1976 is up-regulated as compared to healthy person [17]. Furthermore The novel MYH6 mutation delE933 induces structural damage to the sarcomere as well as functional impairments causing dysfunction of the sinus node and inducing familial SSS[18].Similarly the SCN10A gene's genotype AA is associated with a predisposition to the development of Idiopathic Sick Sinus Syndrome[18].

MicroRNA 1976:

The first miRNA, lin-4, was discovered at C elegans in 1993. Lin-4 regulates the formation of C elegans by attaching the Lin-14 mRNA to suppress the expression of LIN-14 proteins [6-7]. MicroRNAs (miRNAs) are small, endogenous, non-coding RNAs that mediate post-transcription gene silencing by annealing to inaccurately complementary sequences of protein-coding genes in the 3'-untranslated regions (UTRs) of the target mRNAs [19-20].It is estimated that the human genome may contain around 1000 miRNAs. More than 100 of them were found in sera from healthy subjects and are known as circulating miRNAs. Most of the circulating miRNAs are derived from blood cells with certain from various tissues such as the heart, liver, lung and kidney. Evidence has emerged to indicate the crucial role that miRNAs perform in regulating the expression of cardiac ion channel genes following post transcription Muscle-specific miR-1 has been shown to regulate cardiac arrhythmogenic potentials by post-transcription modification of the GJA1 and KCNJ2 ion channel genes in myocardial infarction (MI) and inhibition of miR-1 activity with antisense oligoribonucleotides has been found to normalize GJA1 and KCNJ2 expression and decrease arhythmia after MI.[21].Accumulating evidence suggests that circulating miRNAs can be used potentially as diagnostic tools, as they provide specific disease knowledge under pathological conditions[22].

The study showed that the upregulated miR-1976 suppresses the expression of Cav1.2 and Cav1.3 proteins, which reflect the post-translation process underlying SAN dysfunction during aging.

Apparently, miRNAs are remarkably stable in plasma and resistant to freezing cycles and long-term storage [23]. Importantly, miRNAs can be rapidly, effectively and reproductively quantified by RT-PCR or microarrays to provide more detailed and specific information [24]. In comparison, plasma is much easier to collect than tissues for diagnostic study; therefore, plasma miRNAs provide very useful biomarkers in clinical practice for the diagnosis and prognosis of SSS.

MYH6:

Myosin is an essential component of the sarcomere, the building block of the contractile heart muscle system. Myosin is a cellular motor protein ATPase composed of two heavy chains and two light chains. The two heavy chains are alpha heavy chains aMHC and beta myosin (bMHC) coded with MYH6 and MYH7, respectively. Both aMHC and bMHC are expressed throughout the heart in embryonic cardio genesis, and bMHC continues to do so in the adult heart, while aMHC activity is limited to atrium [25].

The MYH6 gene gives instructions for making a protein known as the heavy cardiac alpha (α)-myosin chain. This protein is located in the muscle cells of the heart (cardiac) where it forms part of a larger protein called myosin type II.

Type II myosin tends to generate the mechanical force needed to contract the heart muscle and enables the heart to pump blood to the rest of the body. Genetic variations of the alpha myosin heavy chain gene (MYH6; a-MHC) are significantly enriched with congenital heart disease (CHD) anatomically and clinically severe form of Hypoplastic Left Heart Syndrome (HLHS).HLHS is characterized by atresia and stenosis of aortic and mitral valves and severe hypoplasia of the aorta and left ventricle. In a multi-generational family afflicted by HLHS and other types of CHD, a novel mutation resulting in an arginine to proline shift (R443P) in the MYH6 head domain was shown to segregate with disease.

A-MHC is an essential contractile protein in developing muscle. Upon development, a-MHC is predominantly in the atria whereas the beta isoform (b-MHC), encoded by the MYH7 gene, is mainly in the ventricles. Variations in both isoforms were previously linked to hypertrophic and dilated cardiomyopathy, a major cause of sudden cardiac death in children and adults, as well as CHD. [26]

On the contrary, recent genome-wide interaction studies have shown that a specific non-synonymous variant A1101V in MYH6 is associated with an increased heart rate at rest; [27-29].Whereas another rare non-synonymous form (R721W) was associated with an elevated risk of SSS [30]

When expressed in cardiomyocytes, delE933-MYH6 impeded the potential propagation of the atrial action and disrupted sarcoma integrity in accordance with R721W-MYH6.Among Icelanders, high-risk genetic predisposition to SSS was shown.

SCN10A:

The gene SCN10A belongs to a gene family which provides instructions for making sodium channels. Such pathways, which carry positively charged sodium atoms (sodium ions) through cells, play an important role in producing and transmitting electrical signals from a cell.

The gene SCN10A provides instructions to make one component of a sodium channel called NaV1.8 (the alpha subunit).NaV1.8 sodium channels are found in nerve cells or nociceptors that send out pain signals,

Nociceptors are a part of the peripheral nervous system that links the brain and spinal cord to cells that sense stimuli such as touch, smell, and pain. Nociceptors are mainly involved in transmitting pain signals. The centers of nociceptors, known as the cell bodies, form part of the spinal cord called the dorsal root ganglion. The fibers called axons spread across the body from the cell bodies and reach the sensory information.

Besides nociceptors, NaV1.8 sodium channels were also located in heart muscle cells where they are likely to play a role in sustaining a normal heart rhythm by controlling the flow of sodium ions.

The SCN10A gene is located on the 3p22.2 chromosome. Gene SCN10A encodes one of the sodium subunits channels. Associations of this gene have been identified with several cardiovascular diseases (CVD).So a group of Japanese researchers in 2015 demonstrated the link between the SCN10A gene's rs6795970 polymorphism and cardiac conduction in patients with hypertrophic cardiomyopathy[31].

Group pf Japanese researchers in 2015 also studied various mutations in the SCN10A gene in patients with Brugada syndrome. A positive association has been proven the mutations in this gene are related to the development of Brugada syndrome [32]. In addition, Genotype AA of SCN10A gene associated with a predisposition to the development of idiopathic SSS. Predisposition to the development of sinus node syndrome in men is associated with the carrier of the AA genotype of the SCN10A gene, whereas in women none of the genotypes affects the risk of this syndrome. Homozygous GG genotype of the SCN10A gene associated with increased risk of developing version of sinus node weakness syndrome

Treatment of Sick Sinus Syndrome:

Pacemaker implantation may reduce symptoms of SND in the sick sinus syndrome. Managing the condition of bradycardia-tachycardia can be more complicated since antiarrhythmic medications used to treat atrial arrhythmias exacerbate the SND, Ultimately, combined therapy is often needed. In this particular clinical setting, the pacing modality should be carefully considered when a pacemaker is implanted, because it may influence the progression of the coexisting atrial arrhythmias. Dual chamber pacing with precise algorithms to reduce the ventricular rhythm and reduce and manage atrial tachyarrhythmias is superior to the standard double chamber pacing in cardiovascular mortality and hospitalization [13-14].And this gain is motivated by the reduction in long-term and irreversible AF improvement. Improvement of AF with the application of specialized algorithms. An alternative to pacemaker implantation in patients with bradycardia-tachycardia syndrome, catheter ablation of AF is considered reasonable by an expert consensus report recently published.(class Ilia, level of evidence B, non-randomized[15].Even though complex (such as atypical atrial flutter or atrial tachycardia in patients with congenital heart disease), catheter ablation can treat more organized atrial arrhythmias[16].The efficacy of avoiding recurrence of AF in bradycardia-tachycardia syndrome should be carefully observed for potential recurrence of arrhythmia and the need to maintain antiarrhythmic treatment during follow-up.

CONCLUSION:

There is evidence of posttranscription processes that demonstrate the upregulation of miR-1976 in SSS patient plasma and animal SAN tissue, and that miR-1976 caused SAN degeneration by targeting Cav1.2 and Cav1.3, resulting in age-related SSS. Plasma miR-1976 can therefore be considered a non-invasive biomarker of diagnosis and a therapeutic target for SSS related to ageing. Accumulating data suggests that circulating miRNAs can be used theoretically as diagnostic tools, since they bear precise disease information under pathological conditions. Furthermore, the novel MYH6 mutation delE933 triggers all sarcomere structural damage as well as functional impairments on propagation of atrial activity. The report demonstrates the importance of MYH6 to the function of the sinus node and identifies a novel pathophysiology that underlies familial sick sinus syndrome

The evidence illustrates the importance of the role of the MYH6 sinus node and indicates that sarcomere structural disruption on potential atrial action propagation may be underpinned by family SSS with MYH6 mutations.

In addition, the distribution type of the SCN10A gene in a group of men with Sick Sinus Syndrome .Genotype AA of SCN10A gene associated with a predisposition to the development of idiopathic SSS.

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