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Image in Congenital Cardiac Disease

Sick sinus syndrome: a family study

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Abstract A case of related individuals affected by sick sinus syndrome is presented in this study. The clinical and electrocardiographic signs of sinus node dysfunction and the most common causes of this disease are presented. Subsequently, the article includes descriptions of sinus node disease in three related children as well as details of the disease in their relatives. A literature review of the genetics of familial sinus node dysfunction concludes the study.

keywords: Sick sinus syndrome; children; congenital arrhythmia

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Electrocardiographic signs and symptoms of sick sinus syndrome.

SINUS NODE DYSFUNCTION, KNOWN AS SICK SINUS syndrome, is a disease that usually occurs in the elderly but is occasionally seen in children. The incidence of this disease in children without congenital heart disease is rare and should always arouse suspicion of a congenital predisposition to arrhythmia.

Electrocardiograph changes suggest that the diagnosis of sinus node dysfunction includes sinus bradycardia; low atrial rhythm; junctional rhythm; sinus arrhythmia with PP intervals above 160 ms, which as opposed to a vagal tone does not persist after breath holding; and tachycardia–bradycardia syndrome, which is the alternating occurrence of sinus bradycardia and atrial tachyarrhythmias. It can also manifest as a lack of accelerating cardiac function during maximal exercise, defined as a failure to achieve the 85% pulse limit for the patient's age.[1,2]

The clinical manifestation of sinus node dysfunction includes a number of non-specific symptoms; however, this disease can also be asymptomatic, and at times its visible symptoms may comprise only one of the aforementioned changes in electrocardiogram. Patients with sinus node dysfunction may experience dizziness, syncope, reduced exercise capacity, and increased fatigue.

Experts point out that the occurrence of clinical symptom-associated bradycardia, and not just the number of heart beats per minute, should be taken into account while confirming patients for pacemaker implantation. No symptoms, even in the presence of electrocardiographic changes, raise doubts on the relevance of cardiac electrotherapy, except for a extremely low heart rate.[3,4]

Description of a family with sinus node dysfunction

We present the case of a family in which nine closely related individuals, belonging to two generations (Fig 1), have symptoms and electrocardiographic evidence of sinus node dysfunction; six of them have a pacemaker implanted and one of them (II-9) died of natural causes. Having these many individuals affected by the disease in a family is a clear indication of its genetic predisposition. One boy, A.H. IV 4-H, is still under the observation of our Pediatric Cardiology Clinic.

The proband A.H. IV 4-H was referred to the Cardiology Clinic of Memorial Health Institute at the age of 9 years because of a very low heart rate

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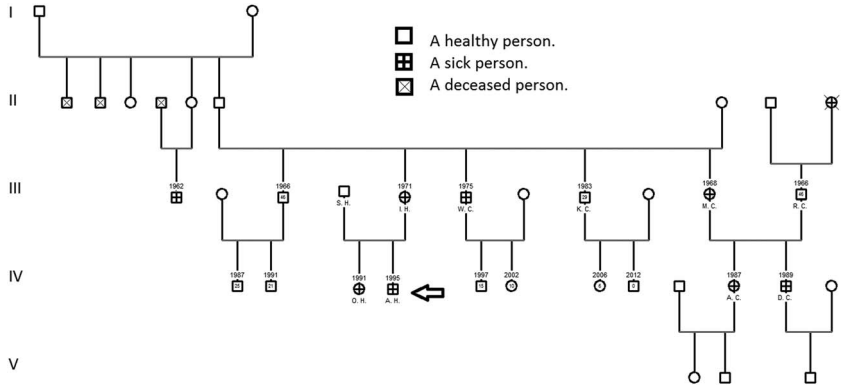

Figure 1.
The family tree. The proband is indicated by an arrow.

and episodes of fainting with a frequency of once per week. The boy also suffered from headaches daily, which were accompanied by cardiac palpitations. Echocardiography revealed no morphological and haemodynamic cardiac abnormalities. Holter electrocardiograph revealed a sinus bradycardia and a nodal bradycardia, with a mean heart rate of 56/minute (range of 35–139/minute), a periodical wandering pacemaker, and a severe cardiac irregularity. An asystole lasting 7.9 s in the mechanism of sinus rhythm inhibition with junctional escape rhythm was also observed (Fig 2). During the asystole, the boy who was earlier in a sitting position fainted. It was then decided to implant a transvenous dual-chamber pacemaker. The boy weighed 29.3 kg and was 134.5 cm tall. The procedure was uneventful. The symptoms resolved after the operation.

The boy's older sister, O.H. IV-3, was referred to the Cardiology Clinic of Memorial Children's Health Institute at the age of 16 years because of a single fainting episode preceded by non-specific chest pain. Echocardiography excluded any cardiac defects. In Holter electrocardiograph, a wandering pacemaker, that is, alternating sinus/atrial rhythm/junction rhythms, was observed; the average heart rate was 54/minute (range 32–116/minute). During theophylline intake at night (dose of 5 mg for 1 kg body mass), there was a minimal increase in the heart rate. To date, there have been no clear indications for pacemaker implantation, and an episode of fainting has never recurred.

A cousin of the siblings also suffers from sick sinus syndrome. The patient, A.C. IV-10, now a 26-year-old woman, was referred to the Cardiology Clinic of Memorial Children's Health Institute in the fourth year of life because of a bradycardia detected by a paediatrician during a routine examination. In her childhood, she had a decreased heart rate of 40 beats/minute, an irregular heartbeat, and a quiet systolic murmur along the left sternal border. On the basis of two-dimensional echocardiographic examinations, a cardiac defect was excluded. After analysis of the Holter electrocardiographic records, the paediatrician recommended a tablet of 0.25 mg atropini sulphas (Bellapan).

In the eighth year of life, the girl experienced tremors of the whole body after exercise without loss of consciousness, without an urinating. Neurological testing was performed and revealed no evidence of epilepsy. An exercise test on a treadmill according to the Bruce protocol was performed. During exercise and recovery, no alarming symptoms were reported; on maximal effort, the heart rate reached only 134 beats/minute, which was 64% of the limit for her age at the time. During the atropine test – 1 mg of atropine administered intravenously – the heart rate accelerated to up to only 100 beats/minute. The girl was recommended therapy with ipratropium bromide (Itrop – 10 mg tablets three times per day) and showed a good tolerance. The psychological consultation revealed ADHD features, which could be associated with the tremors.

In the ninth year of life, the girl experienced a complete loss of consciousness during a school day. After this incident, she was admitted to the Department of Cardiology for urgent heart pacemaker implantation. The girl weighed 32 kg and was 138 cm tall, and it was decided to use a transvenous pacing system. Because of the difficulty in an atrial lead assumption, during the surgery, dual-chamber stimulation was abandoned. In Holter electrocardiograph were seen ventricular beats conducted retrogradely after paced one. Propranolol therapy was initiated and resulted in a reduction in pacemaker-mediated arrythmias.

Since the implantation of a pacemaker, the girl has had a normal development, and no alarming symptoms of the cardiovascular system have occurred.

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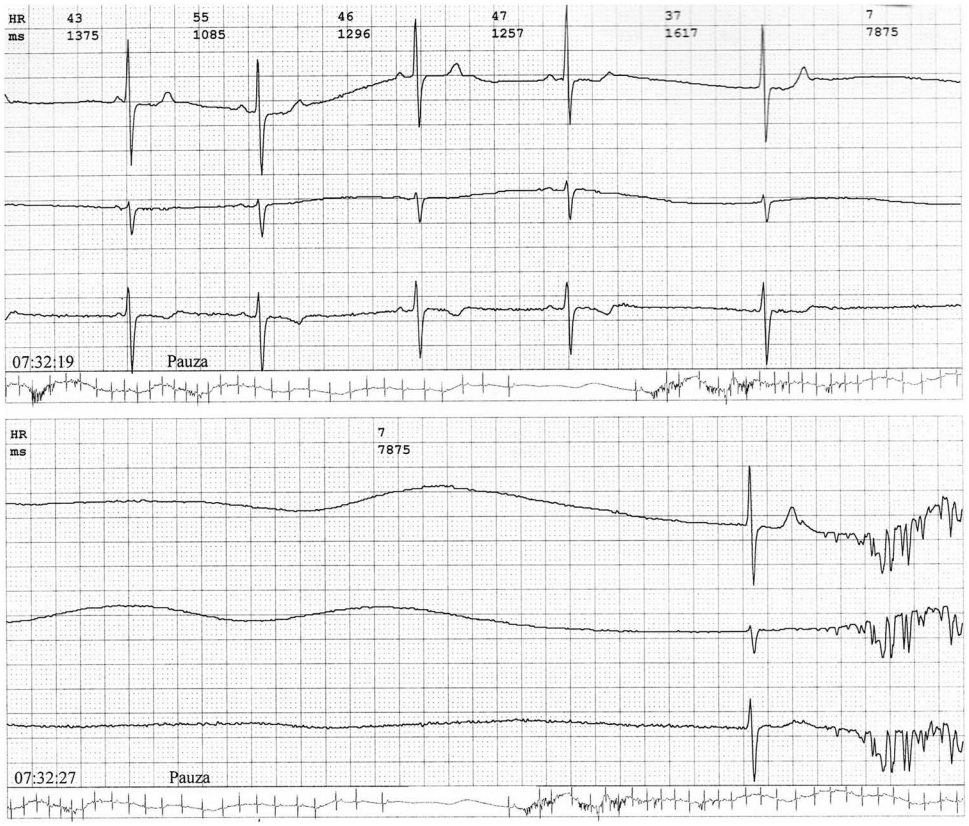

Figure 2.
The Holter electrocardiograph record. An asystole in the mechanism of sinus rhythm inhibition with junctional escape rhythm can be seen.

However, at the age of 15 years, 6 years after implantation of the pacemaker, battery depletion was reported. It was decided to replace the cardiac pacing systems and a double-chamber intravenousus pacemaker was implanted. The girl was under the care of our Pediatric Cadiology Clinic until 2005, and until then she did not demonstrate any clinical symptoms.

The girl's brother, D.C. IV-11, also had a low resting heart rate but did not require any intervention in his childhood. It is known that he had a fainting episode on a military range, which led to his dismissal from military services. To date, he has not had a pacemaker implanted.

In the third generation of the family, three of the five siblings suffer from sinus node dysfunction. Further, their cousin also has a pacemaker implanted.

The representative of the third generation, the patient W.C. III-6, was diagnosed with myocarditis at the age of 12 years. During his childhood, he had a very low cardiac rhythm, headaches, palpitations, and frequent episodes of fainting. At the age of 22 years, he experienced a stroke and has been disabled since then. Despite obvious indications for pacemaker implantation, he refuses the proposed treatment.

Sinus node dysfunction was also present in the mothers of all sick children from generation IV. The course of the disease in the sisters, M.C. III-5 and I.H. III-10, was very similar. Both women since childhood have had a low resting heart rate, have complained of severe headaches in the forehead, and have had an accompanying feeling of a rapid heartbeat resolving spontaneously. During a similar stage of life – M.C. III-5 at the age of 34 years and I.H. III-10 at the age of 30 years – both women experienced fainting under various circumstances, which occurred with a frequency of ~1 episode per month. In Holter electrocardiograph, a rhythm below 40/minute was recorded. Both women had a pacemaker implanted and thus were completely relieved of the symptoms of their disease.

Discussion

Attempts to demonstrate the cause and effect relationship between cardiac arrhythmias and a single causative gene in families for many arrhythmias are the subject of ongoing investigations.

Current knowledge on the hereditary factors of sinus node dysfunction has helped identify three syndromes with a similar clinical profile and

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electrocardiographic manifestations but a different mode of inheritance.

The first family sick sinus syndrome (FSSS1 – Familial Sick Sinus Syndrome 1) is associated with mutations in the sodium channel *SCN5A*. The disease is inherited as an autosomal recessive trait.[5,6] FSSS2 is associated with the presence of an abnormal *HCN4* gene, encoding a protein regulating the sodium–potassium channel, and demonstrates an autosomal dominant mode of inheritance.[7] It was also found that a mutation in the gene *MYH6*, which encodes a cardiac myosin heavy chain, is associated not only with cardiomyopathy, but also with various kinds of conduction abnormalities. The presence of the variant *MYH6–R721W* causes an increased risk of developing sick sinus syndrome (FSSS3) throughout life.[8]

Sick sinus syndrome was also observed in patients with mutations in genes CX40 and ANK2, as well as many others. However, the role of these genes has not been clearly documented.[8,9]

The genealogical tree (Fig 1) and distribution of the disease in the presented family suggests a diagnosis of familial sick sinus syndrome and an autosomal dominant inheritance pattern. We could not perform any molecular genetic tests to identify the genes responsible for sick sinus syndrome; however, none of these results would have changed the treatment.

The European Society of Cardiology, in its Guidelines on the management, that is, diagnosis and treatment, of syncope, 2009, reported stimulation of the heart as a highly effective treatment resolving the symptoms in patients with a proven relationship between bradyarrhythmia and syncope. According to experts, cardiac pacing in such individuals may not have an impact on the overall survival. The patient W.C. II-5, despite obvious indications for permanent cardiac pacing, continues to refuse a pacemaker implantation. There are disadvantages of having a foreign device, such as a pacemaker, implanted in the body; however, taking into consideration the frequency of his symptoms and the benefits of proposed electrotherapy, the question on how such a decision affects the quality of his life remains unanswered.

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