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Original article

Heparan sulfate storage in the cardiac conduction system triggers atrioventricular block

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Abstract

Objective: To elucidate the novel biological functions of heparan sulfate (HS) by clinic-pathologically studying a patient with paroxysmal atrioventricular (AV) block.

Patient: A long-surviving male patient with Sanfilippo syndrome type A presented with paroxysmal AV block at age 33 years. He then survived another 2.5 years after the onset of paroxysmal AV block and pacemaker implantation.

Methods and results: His cardiac histopathological examination at autopsy showed HS storage in the cardiac conduction system (CCS), especially in the atrioventricular node (AVN)-His bundle branches.

Conclusion: HS storage in the CCS might trigger AV block, arising from below the AVN-His bundle branches. This is the first description to indicate that HS might be an essential constituent of life-long CCS plasticity and that its storage in the CCS results in AV block.

Keywords: Sanfilippo syndrome; Long-surviving patient; Heparan sulfate; Cardiac conduction system; Atrioventricular block

1. Introduction

Sanfilippo syndrome is characterized by severe central nervous system degeneration, resulting in deficits such as behavior problems, psychomotor retardation, epileptic seizures and somatic dysmorphism, but the cardiovascular system is generally not severely affected. Studies of the heart and cardiac conduction system (CCS), focusing on pathophysiological features, have been limited [1–4].

Herein, we evaluated a potentially novel biological role of HS based on clinicopathological findings in a long-surviving Sanfilippo syndrome type A patient who was autopsied 2.5 years after developing AV block and undergoing pacemaker implantation in the final stage of his disease course.

1.1. Clinical findings

The patient was a 36-year old male, the first product of non-consanguineous healthy Japanese parents

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(No. 0019-997-8). He was born uneventfully at term, weighing 3220 g. His developmental milestones had been mildly delayed since infancy. He began to walk at age 1 year and 3 months. At age 1 year and 8 months, he spoke only a few words and his vocabulary never increased beyond this level. He presented with motor impersistence, panic and aggressive behaviors at the age of 2 years. Sanfilippo syndrome type A was diagnosed based on increased urinary excretion of HS and defective activity of heparan-N-sulfatase in peripheral leukocytes, with a value of ⩽0.1 nmole/mg protein/h (normal range: 18.8–58.1), at the age of 6 years. Symptomatic fronto-temporal lobe epilepsy manifested at age 7 years, associated with multifocal epileptic spikes in the right-posterior temporal, frontal and occipital regions. He was able to walk with support at age 15 years, and had become bedridden by age 24 years. At 33 years 11 months of age, regular electroencephalography (EEG) showed diffuse low voltage activity, with no epileptic discharges, but an electrocardiogram (ECG) at the bottom of this EEG recording showed arrhythmia and bradycardia (Fig. 1). Another ECG showed second degree AV block (Mobitz type II) (Fig. 2), and Holter ECG monitoring revealed sporadic advanced and paroxysmal AV block with long pauses, especially during sleep (Fig. 3A and B). A chest roentgenogram showed a normal cardio-thoracic ratio, 0.50, without pulmonary congestion. B-type natriuretic peptide (BNP) was elevated, at 86.4 pg/ml (<18.4). Echocardiography revealed moderate mitral and aortic regurgitation, but the left ventricular volume was normal and the ejection fraction was 69.9%. Conservative management failed to ameliorate the abnormalities. Pacemaker implantation was performed at age 34 years 4 months. The heart rate normalized to 60–70 bpm. ^{99}Tc-pyrophosphate myocardial scintigraphy showed neither abnormal accumulation nor any defects. He died of sudden cardiac arrest at age 36 years and 5 months, 2 years 1 month after pacemaker implantation. At the time of death, he had no signs of pulmonary infection, carditis, or pericarditis and aortic and mitral valves are normal macroscopically. Furthermore, there were no problems with the pacemaker or its battery. His parents gave permission for a full autopsy to be performed.

1.2. Autopsy and pathological findings

The patient was 143 cm in height and weighed 38.8 kg. The heart weighed 260 g (average value for a normal adult Japanese male: 280 g). The brain weighed 720 g (1360 g) and showed severe atrophy of both cerebral hemispheres. The liver and spleen weighed 1370 g (1190 g) and 210 g (100 g), respectively, and were free of congestion, but showed slight enlargement and induration.

1.3. Histological study

The autopsy specimens were fixed with 20% buffered formalin and embedded in paraffin. Histological examinations were performed using hematoxylin and eosin (HE) stained sections 5 μm in thickness. HS was stained with toluidine blue using pH 7.0 buffer. The paraffin-embedded sections were also immunostained by the streptavidin method with diaminobenzidine as the

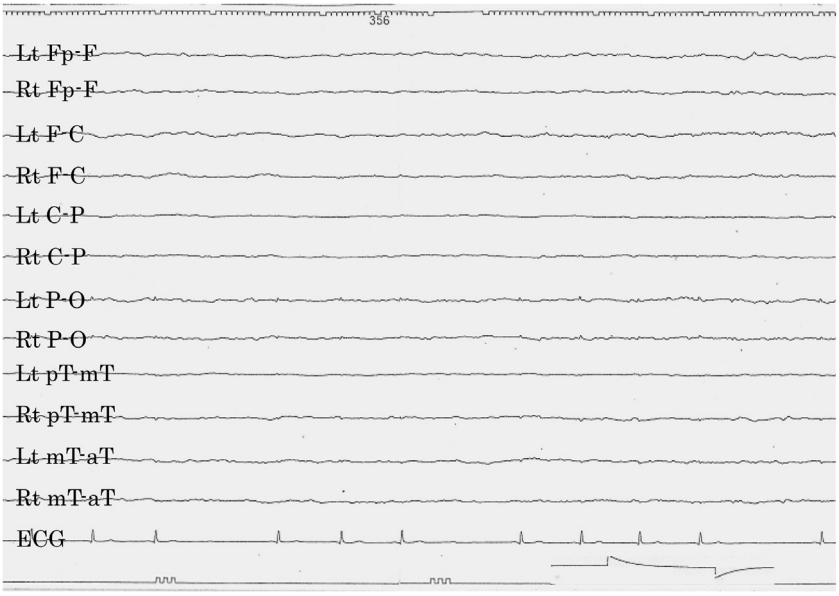

Fig. 1. EEG at age 33 years and 11 months shows diffuse low voltage activity, with a flat pattern but no epileptic discharges. ECG at the bottom of this EEG recording shows arrhythmia and bradycardia. Scale bars show 2 s on the abscissa and 50 μV on the ordinate.