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CASE REPORT

A Case of Complete Atrioventricular Block Associated with Pathogenic Variants in the SCN5A and GATA4 Genes

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Summary

A 27-year-old male patient undergoing regular hemodialysis three times per week did not miss any dialysis sessions during the week of referral. He presented with dizziness and was found to have complete atrioventricular (AV) block on electrocardiography. The patient was admitted to the intensive care unit, where a temporary pacemaker was implanted. Subsequently, a dual-chamber permanent pacemaker was implanted. No electrolyte imbalance was detected. Because of suspected congenital anomalies, the patient underwent a thorough evaluation, which revealed pathogenic variants in the SCN5A and GATA4 genes.

Keywords: Atrioventricular Block; GATA4 Gene; SCN5A Gene

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Introduction

Atrioventricular (AV) block is a delay or interruption in the transmission of electrical impulses from the atria to the ventricles. AV block may be congenital or acquired and can result from medications such as beta-blockers, calcium channel blockers, or digoxin; myocardial infarction; myocarditis; electrolyte imbalances such as hyperkalemia; transcatheter aortic valve implantation; cardiac surgery; infectious diseases such as Lyme disease; rheumatologic conditions such as Wegener's granulomatosis; inflammatory diseases such as sarcoidosis; or exposure to toxic substances, including mad honey.[1-4]

In addition to the well-established causes, certain gene mutations have been rarely identified as causes of AV block. Here, we present a case of complete AV block associated with a genetic mutation.

Case Report

A 27-year-old patient undergoing routine hemodialysis three times per week presented to the emergency department with dizziness. Electrocardiography revealed atrioventricular dissociation, with no relationship between P waves and QRS complexes. A ventricular escape rhythm at a rate of 37 beats/min was observed (Figure 1). The corrected QT interval (QTc), calculated using the Fridericia formula, was 417 ms, and the JT corrected interval (JTc) was 278 ms. These findings were consistent with complete AV block.

Transthoracic echocardiography revealed no congenital heart disease or segmental wall motion abnormalities. The left ventricular ejection fraction was 60%. Because the patient had missed a scheduled dialysis session, hyperkalemia-related complete AV block was initially suspected; however, laboratory evaluation revealed no electrolyte imbalance. A temporary pacemaker was implanted via the right femoral vein.

The patient continued routine hemodialysis, reached his dry weight, and was not receiving any antiarrhythmic medications; however, complete atrioventricular block persisted at 72 hours. Consequently, a dual-chamber permanent pacemaker was implanted.

A detailed medical history revealed that the patient had congenital bilateral hearing loss. He was found to have multiple congenital anomalies, including a rectourethral fistula, urethral duplication, right renal atrophy, hypospadias, and a congenital extravesical

anomaly. The patient had undergone urethral dilatation and hypospadias repair during childhood. Because of these congenital abnormalities, the patient was referred to the department of genetic disorders. Genetic testing revealed pathogenic variants in the SCN5A and GATA4 genes. The SCN5A variant was identified as a heterozygous missense mutation located in exon 28 (NM_000335.5), c.5189C>A, resulting in the amino acid substitution p.Thr1730Asn. The GATA4 variant was also a heterozygous missense mutation located in exon 2 (NM_001308093.3), c.487C>T, resulting in the amino acid substitution p.Pro163Ser. The patient's family was referred for genetic counseling.

Discussion

In patients with chronic renal failure who present with AV block, electrolyte imbalance and medication use are the primary considerations. However, in the absence of these factors, as in our patient, further investigation of the underlying etiology is warranted. In this case, pathogenic variants in the SCN5A and GATA4 genes were identified.

A detailed review of the ClinVar database revealed no previously reported information regarding the SCN5A NM_000335.5 nucleotide variant detected in our patient. In contrast, the GATA4 NM_001308093.3 nucleotide variant identified in this case has been reported to be associated with AV septal defects.

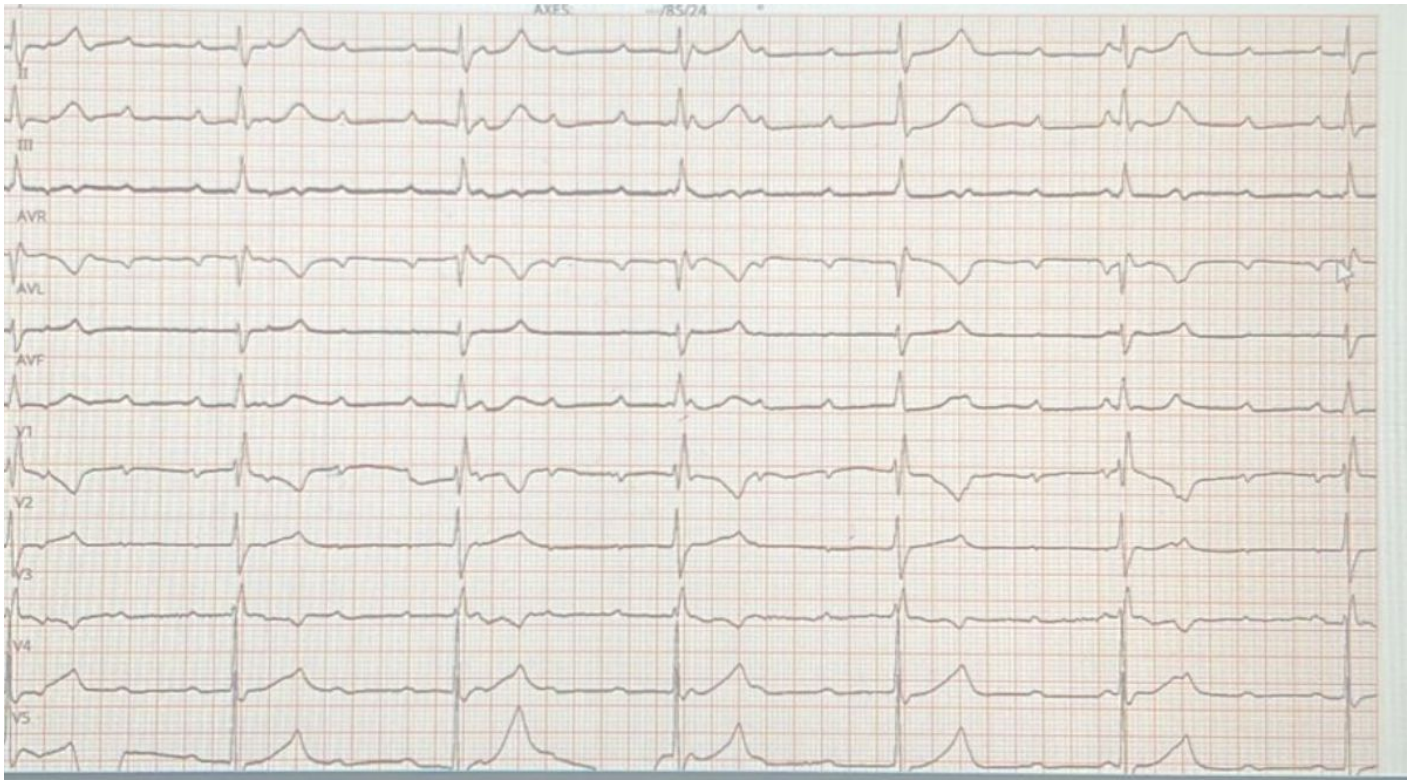

Figure 1. Electrocardiographic recording demonstrating complete AV block.

The SCN5A gene plays a critical role in regulating sodium ion flow through voltage-gated ion channels in cardiac myocytes.[5] Mutations in SCN5A are most commonly associated with Brugada syndrome and long QT syndrome.[6,7] However, SCN5A variants have also been linked to isolated cardiac conduction disorders, atrial fibrillation, sick sinus syndrome, and complete AV block.[6,8]

Mutations in the GATA4 gene have been shown to be associated with disorders of testicular development and also have significant cardiac effects.[9] The GATA4 gene plays a critical role in cardiac morphogenesis and coronary artery development, and its variants have been implicated in acute myocardial infarction.[10] Additionally, GATA4 mutations have been associated with congenital heart diseases, particularly atrial septal defects (ASD) and ventricular septal defects (VSD).[11,12]

Given that GATA4 gene mutations are frequently associated with structural and coronary abnormalities, whereas SCN5A gene mutations are primarily linked to cardiac conduction system disorders, these findings initially suggest that SCN5A may be the principal contributor to the development of complete AV block. However, closer examination of the literature reveals evidence of functional interactions between GATA4 and SCN5A.

Tarradas et al. demonstrated that GATA4 binds to the first intronic region of SCN5A in the left ventricle and regulates its expression, underscoring the importance of GATA4 in SCN5A transcriptional control.[13] Furthermore, animal studies investigating AV conduction have shown that both Tbx5 and GATA4 influence AV conduction, with GATA4 playing a role in maintaining normal AV delay.[14]

In light of these findings, it is more appropriate to attribute the complete AV block in our patient to the combined effects of SCN5A and GATA4 mutations, rather than to SCN5A alone.

A dual-chamber pacemaker was implanted because we lacked sufficient experience with left bundle branch area pacing at the time of implantation and the patient was pacemaker-dependent. With our current experience and technical capabilities, left bundle branch area pacing would have been the preferred approach.

Given that SCN5A gene mutations are associated with ventricular arrhythmias, the patient will be closely monitored during follow-up. If ventricular arrhythmias develop, placement of a defibrillator shock lead and device upgrade will be considered.

In conclusion, as demonstrated in our case, young patients presenting with complete AV block should undergo a thorough etiological evaluation. When appropriate and cost-effective, targeted screening for common genetic mutations known to affect ECG parameters—including the P wave, PR interval, QRS complex, and QT interval—should be considered.

In patients with AV block in whom common etiologies are excluded, or in those with congenital anomalies suggestive of an underlying genetic disorder, genetic counseling is essential for both the patient and their family. In such cases, clinicians should avoid proceeding directly to pacemaker implantation and discharge, and instead perform a comprehensive and detailed diagnostic evaluation.

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Informed consent

Written informed consent was obtained from the patient for the publication of the manuscript.

Conflict of Interests

None

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