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CASE REPORT

Neonatal Ventricular Tachycardia Linked to CACNA1C Variant: A Rare Presentation of Brugada Syndrome Type 3

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Abstract

Brugada syndrome (BrS) is a rare inherited cardiac channelopathy disorder. It is known for its distinctive electrocardiogram (ECG) patterns and often manifests with unexplained syncope or sudden cardiac arrest. The genetic basis of BrS is diverse, involving mutations in genes that encode cardiac ion channel subunits, including calcium, sodium and potassium, alongside genes governing their transport regulation. Although BrS is well-documented in adults and older children, its presentation during the neonatal period is uncommon and poorly described. We present a case of a full-term newborn, delivered at 40 weeks of gestation, who experienced multiple episodes of ventricular tachycardia. These episodes began on the fourth day of life during neonatal intensive care unit (NICU) admission for transient tachypnoea of the newborn and tachycardia. An extensive evaluation was conducted, including genetic testing for channelopathies, which identified a heterozygous mutation (AD) in the CACNA1C gene that encodes the alpha-1C subunit of the L-type voltage-gated calcium channel located on chromosome 12p13, thus confirming the diagnosis of BrS type 3.

Keywords: Ventricular Tachycardia, Neonate, Calcium Channelopathy, Brugada Syndrome

Introduction

Brugada syndrome (BrS) is an inherited cardiac channelopathy that predisposes to fatal arrhythmias and may end up with sudden, unexplained cardiac arrest.[1] It is distinguished by characteristic patterns on electrocardiographic (ECG) that include right bundle branch block and ST-segment elevation in the right precordial leads (V1-V3).[2] Although BrS typically manifests in healthy young adults with no evidence of structural heart diseases, researchers have identified minor structural defects in the right ventricle (RV) and the right ventricular outflow tract (RVOT) that could contribute to the arrhythmogenic event.[3,4]BrS typically presents after adolescence and

is infrequently detected in children unless triggered by specific precipitating factors.[5]

Genetic mutations affecting cardiac ion channels, specifically those for calcium, sodium, and potassium, are associated with Brugada syndrome (BrS). The genes included are CACNA1C, CACNB2B, GPD1-L, HCN4, KCNE3, SCN5A, SCN1B, and SCN3B.[6] These genes interfere with the natural functioning of ion channels that influence cardiac electrical impulses, restricting sodium/calcium inward currents or augmenting potassium outward currents; this distorts the ionic current equilibrium from its physiological state during the initial stages of the electrical activity, leading to BrS pro-arrhythmia.[6] Among genetic mutations contributing to BrS, approximately 20% of cases with an established family history are linked to the SCN5A gene, while other genetic variants have a less significant correlation.[7] At first, identifying SCN5A mutations provided significant insight into BrS; however, it has been recognized as a multifactorial disorder affected by various genetic loci and environmental factors, complicating the established autosomal dominant inheritance model.[6] The number of reports describing BrS in the pediatric literature remains limited.[8] Here, we report a male infant at 40 weeks gestational age with Brugada syndrome type 3 who had incessant infant ventricular tachycardia within the first week of life.

Case Presentation

A male neonate, delivered at 40 weeks of gestation via an elective cesarean section, had a birth weight of 3,430 grams and APGAR scores of 9 and 10 at 1 and 5 minutes, respectively. He was born to consanguineous parents. The mother was a 29-year-old gravida 3, para 2, abortion 1 (G3P2A1); she was diagnosed with hypothyroidism and was on thyroxin medication. There is no family history of arrhythmias or sudden death. The patient has two healthy siblings.

The physical examination revealed normal findings except for tachypnoea and tachycardia. He was admitted to the neonatal intensive care unit (NICU) with transient tachypnoea of the newborn and suspected neonatal sepsis. He required non-invasive respiratory assistance via nasal cannula intermittently until the 6th day of life and received empirical antibiotics (Ampicillin and Gentamycin). However, blood culture showed no growth.

During his NICU admission, he initially developed recurrent episodes of sinus tachycardia that progressed to junctional tachycardia, which was detected on a cardiac monitor and confirmed with a repeated electrocardiogram (ECG). His basic hematological and biochemical parameters, including serum calcium and thyroid function tests, were normal. He was referred to a pediatric cardiologist, and his ECG showed wide complex tachycardia with ventricular rates reaching up to 200 beats per minute with left axis deviation consistent with right ventricular outflow tract (RVOT) ventricular tachycardia (Figure 1).

He was treated with an intravenous amiodarone infusion due to recurrent wide QRS arrhythmia of ventricular origin, which was later switched to oral amiodarone. Although he remained asymptomatic, he experienced intermittent transient episodes that were detected on a continuous cardiac monitor.

A 24-hour Holter monitor recording was obtained later while the patient was on oral amiodarone, and no arrhythmia was reported. An electrocardiogram was normal as well (Figure 2). The infant was discharged on the 19th day of life. A genetic test using next generation sequencing (NGS) for a cardiac channelopathy panel detected a heterozygous missense variant in the CACNA1C gene, which encodes the α-1C subunit of the L-type voltage-dependent calcium channel (CACNA1C; 114205) on chromosome 12p13, which is compatible with Brugada syndrome type 3.[9] (Table 1). Genetic testing was not conducted on the parents.

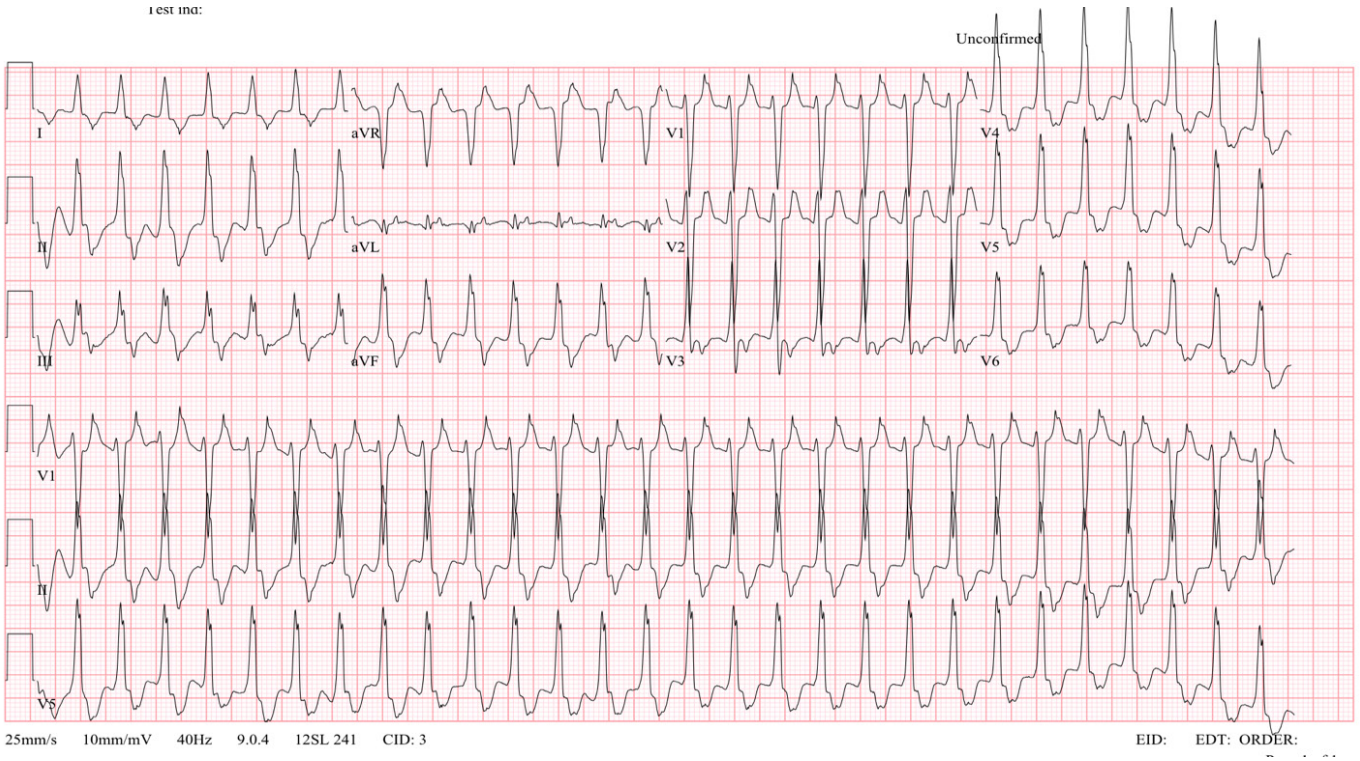

Figure 1: Wide complex tachycardia, with left axis deviation consistent with right ventricular outflow tract ventricular tachycardia noted on 12-lead electrocardiogram.

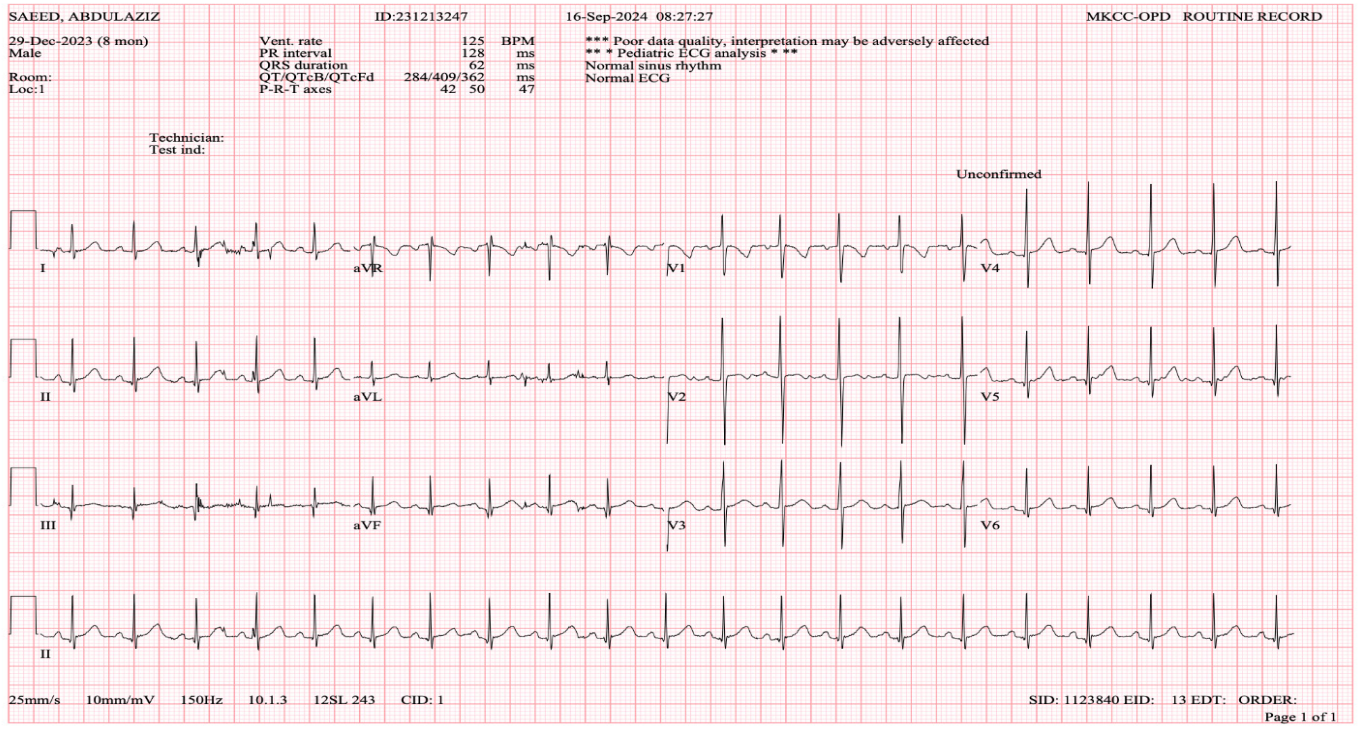

Figure 2: 12-lead electrocardiogram showing normal sinus rhythm at a rate of 125 beats per minute.

Table 1: The next-generation sequencing results of the cardiac channelopathies panel show a heterozygous missense variant of uncertain significance in the CACNA1C gene, suggesting Brugada Syndrome 3.

GENE/ REFSEQ	COORDINATE (GRCh38)	VARIANT* (32x)	EXON/ INTRON	VARIANT TYPE	ZYGOSITY/ INHERITANCE	OMIM/ PHENOTYPE	CLASSIFICATION* ACMG/AMP
CACNA1C / NM_000719.7	chr12:2605754	c.3124A>C p.Met1042Leu	Exon 24	Missense	Heterozygous/ AD	Brugada syndrome-3 (OMIM#611875)	Variant of uncertain significance

Discussion

Brugada syndrome (BrS) was first documented in the pediatric population in 1992.[10] The global prevalence of BrS has increased over the years, particularly due to mutations in the genes encoding cardiac sodium and calcium channels. The overall prevalence of BrS is estimated to be 1 in 2,000 to 1 in 5,000 individuals worldwide, although it is more common in the Southeast Asian population.[10] The prevalence of BrS is generally higher and more severe among males.[12] Indeed, BrS was identified in only 1 out of 10,235 children (0.0098%) in a study of Japanese children.[11]

There is limited data on the prevalence of Brugada syndrome (BrS) in neonates, particularly those with calcium channel mutations. Our patient displayed one of the rarest mutations linked to BrS, specifically type 3.

BrS 3 is an autosomal dominant inherited disease. It affects the CACNA1C (Calcium Voltage-Gated Channel Subunit Alpha1 C) protein-coding gene. This protein is found in various organs, including the heart, lungs, brain, and smooth muscle. Mutations in the CACNA1C gene have been identified as responsible for approximately 6.6% of confirmed BrS cases.[13] Subsequently, mutations in the CACNA1C gene have been linked to a range of phenotypic manifestations, including long QT syndrome type 8, neurodevelopment disorder, and Timothy syndrome.[14]

The clinical presentation of neonates diagnosed with BrS can include life-threatening symptoms such as syncope, arrhythmia, and even sudden infant death. However, most of these patients are asymptomatic, thus diagnosing BrS in this age group is particularly challenging. J.R. Skinner et al. and Britten S. Sutphin reported cases of a neonate and a child presenting with life-threatening arrhythmias, with genetic testing confirming Brugada syndrome due to mutations in sodium and calcium channels, respectively.[15]

The characteristic ECG patterns of BrS type 3 include a less pronounced ST elevation compared to types 1 and 2, a J point elevation of less than 1 mm, and a normal T wave.[16] Furthermore, these changes can be transient or concealed, making the diagnosis of BrS challenging. Our patient initially presented with simple tachycardia that progressed to junctional tachycardia. For this reason, a high index of suspicion is necessary, particularly in families with a history of the same condition.

Emiliana Franco and many others reported certain triggers, such as fever, hyperkalemia and hypercalcemia, and the use of certain medications, such as sodium channel blockers, that can influence patients' susceptibility to arrhythmic events.[17] Vincent Proust et al., reported that fever is the most common trigger among children.[18] Similarly, neonatal sepsis unmasked the typical ECG pattern in our patient.

The optimal management of BrS continues to be challenging due to the highly dynamic nature of the BrS ECG pattern and clinical presentation. Risk stratification for sudden cardiac death may facilitate treatment guidance. The current standard treatment of BrS includes recognition and management of any febrile illness, pharmacological therapy aimed at rebalancing and restoring electrical homogeneity, and non-pharmacological interventions that primarily involves the use of an implantable cardioverter-defibrillator (ICD).[13]

Conclusion

In summary, Brugada Syndrome is a disorder that can manifest as unexpected cardiac death. Although it usually occurs in older individuals, our patient

presented in the neonatal period, the rarest age of presentation. Pediatricians should be able to recognize BrS in this age group to ensure timely and appropriate management.

Ethical approval

Not required.

Consent

Following the policies of King Hamad University Hospital, informed consent for admission includes obtaining permission to use patient data for research and publication in all formats. This consent is documented in the patient's electronic medical record and signed by the parents since the patient is under 18.

Conflict of Interest

The authors state that they have no conflicts of interest related to this publication.

Acknowledgments

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