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Simultaneous presence of Brugada and overgrowth syndromes

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Abstract

In the present article, we describe the case of a 21-year-old male presenting to the emergency department following a syncopal episode. Physical examination revealed a distinctive facial appearance in the context of an overgrowth syndrome. Also, an ajmaline test was performed because of the evidence of an incomplete right bundle branch block with ST-T segment elevation in the right precordial derivations, revealing a type-1 Brugada electrocardiographic pattern. Considering the high cardiovascular risk phenotype, the patient underwent subcutaneous cardiac defibrillator implantation. The subsequent comprehensive genomic testing analysis led to the diagnosis of a variant of uncertain significance of the nuclear receptor binding SET domain protein 1 (*NSD1*) gene and a heterozygous mutation of the calsequestrin 2 (*CASQ2*) gene. *NSD1* gene alterations are usually responsible for the Sotos syndrome, characterized by distinctive facial appearance, learning disability, and overgrowth, in addition to cardiac anomalies ranging from single self-limiting alterations to more severe, complex cardiac abnormalities. On the contrary, a compound heterozygous or homozygous alteration of the *CASQ2* gene is usually associated with catecholaminergic polymorphic ventricular tachycardia; however, the significance of a merely heterozygous alteration in the *CASQ2* gene, as in the present case report, is not yet clear. In conclusion, to the best of our knowledge, this is the first description of the coexisting presence of Brugada and overgrowth syndromes in a single patient.

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Introduction

Brugada syndrome was first described in 1992 by Josep and Pedro Brugada, two Catalan cardiologists brothers, in eight patients with recurrent episodes of aborted sudden death [1]. It is an inherited primary arrhythmogenic disorder in a structurally normal heart [1-3]. The diagnosis is based on a typical electrocardiographic (ECG) pattern observed spontaneously or during a Na^+-channel blocker test [1-3]. Potential complications of Brugada syndrome include syncopal episodes, ventricular arrhythmias, and sudden cardiac death (SCD) [1-3]. Brugada syndrome can also be associated with cardiac and extra-cardiac abnormalities [4].

The Sotos syndrome was first described in 1964 in children affected by excessively rapid overgrowth, typical craniofacial gestalt, and nonprogressive learning disabilities [5,6]. It is inherited in an autosomal dominant manner and is estimated to occur in ~1:15,000 to 1:20,000 live births [6]. The Sotos syndrome is known to be caused by an alteration of the nuclear receptor binding SET domain protein 1 (*NSD1*) gene, located at chromosome region 5q35 [7]. In particular, the *NSD1* gene encodes a histone methyltransferase involved in chromatin regulation mechanisms [7]. In the published literature, several cardiac anomalies have been documented in patients with Sotos syndrome, including iso-

lated or complex cardiac pathologies [8]. However, the simultaneous description of a Brugada syndrome with an overgrowth syndrome in a single patient has never been previously reported.

In the present article, we report the contemporaneous observation of a pharmacologically induced type-1 Brugada ECG pattern and an *NSD1* alteration at genetic testing in a young subject.

Case Report

A 21-year-old male arrived by ambulance at the Emergency Department following a syncopal episode without prodromes that lasted a few seconds, and that was associated with head trauma to the ground, as documented by the family bystander (brother). The patient only reported a history of myoclonus and tics in childhood, limited to involuntary eye movements. In the past, he required treatment with valproic acid; however, in the last period, he was not taking any drugs because of the absence of symptoms. At hospital admission, he was in good general condition and asymptomatic for chest pain; his blood pressure was 110/70 mmHg, his heart rate was 107 bpm, and his oxygen saturation was 97% at room air. Physical examination revealed no heart alterations; however, he was noted to have scoliosis and peculiar physical tracts, including an elongated face, a long linear body habitus, remarkable thinness, and arachnodactyly (Figure 1). Also, a neurological examination revealed repetitive, stereotyped ocular movements indicative of tics without other alterations responsible for the syncopal episode.

The admission electrocardiogram showed sinus tachycardia, normal atrioventricular conduction, and an incomplete right bundle branch block with ST-T segment elevation in the right precordial derivations (Figure 2). Routine blood samples displayed mild neutrophilic leukocytosis, while the high-sensitivity troponin was normal. Also, a computed tomography scan excluded the presence of acute brain diseases. The trans-thoracic echocardiogram revealed regular chamber dimensions, preserved biventricular functions, and no valve alterations or pericardial effusion. Therefore, considering ECG alterations and no neurological disease explaining the clinical picture, it was decided to hospitalize the patient in the cardiology ward for further assessment.

In suspicion of Brugada syndrome, we performed pharmacological testing by intravenous ajmaline infusion. Within a few minutes, a type-1 Brugada ECG pattern appeared, characterized by the morphological alterations of the QRS in V1-V2, with an elevation of the J point and an ST-segment elevation with a negative T wave (Figure 3).

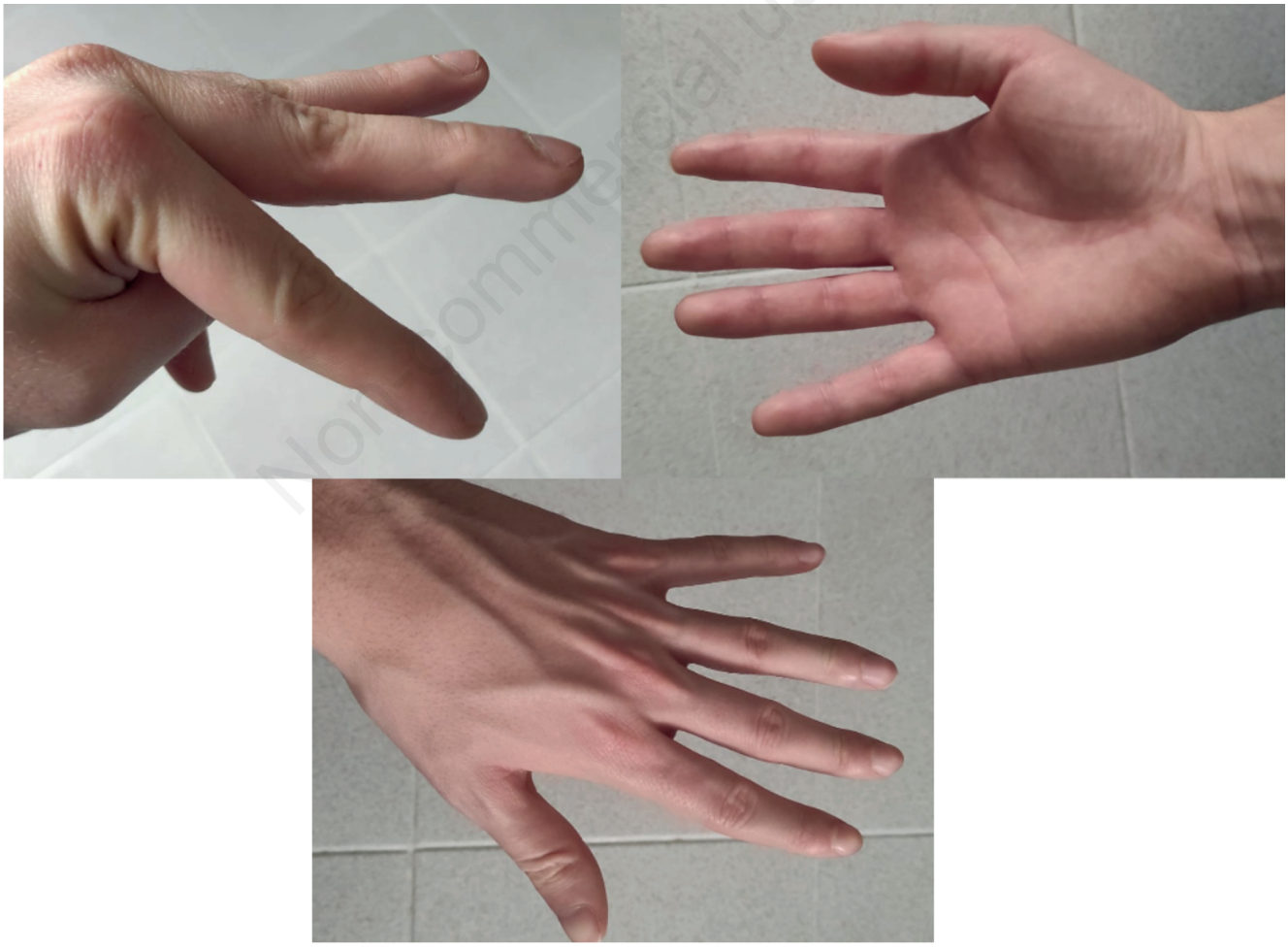

Figure 1. Arachnodactyly: fingers abnormally thin, long, and slender. The fingers have a "spider-like" aspect. Because of the asymptomatic character, the patient was unaware of the abnormal appearance of his fingers.

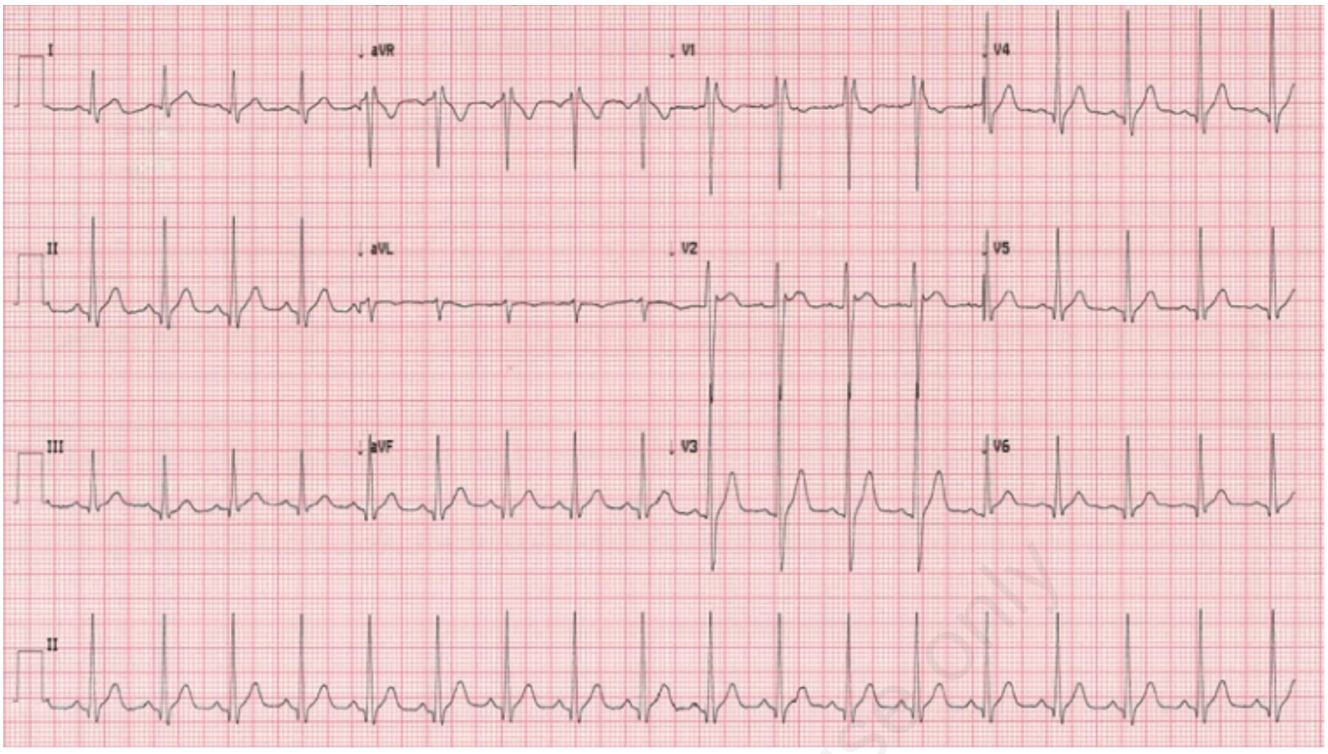

Figure 2. Admission electrocardiogram showing sinus tachycardia (107 bpm), normal atrioventricular conduction, incomplete right bundle branch block, and ST-T segment elevation in V1-V2 derivations.

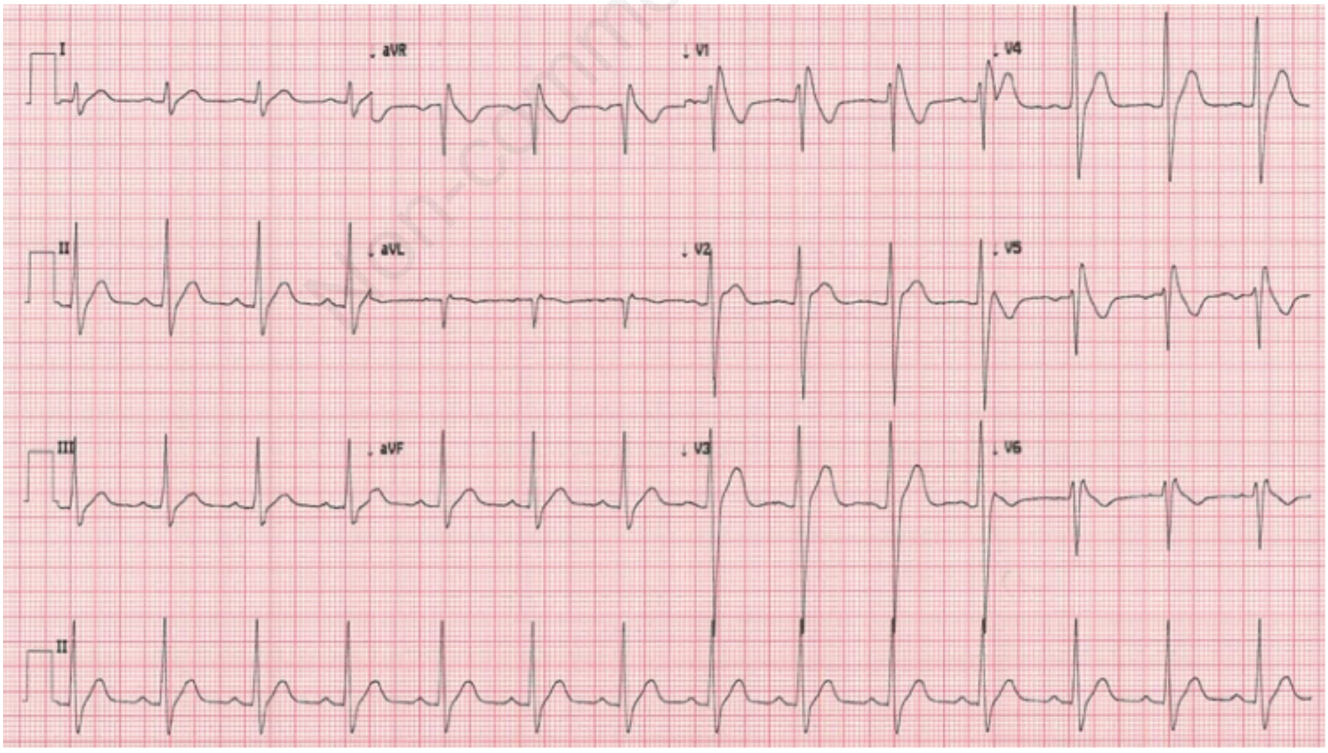

Figure 3. Intravenous ajmaline infusion: within a few minutes, a type-1 Brugada electrocardiographic pattern appeared, characterized by the morphological alterations of the QRS in V1-V2, with an elevation of the J point and an ST-segment elevation with a negative T wave. V1 and V2 are positioned in the second intercostal space.

Considering that syncope had features compatible with an arrhythmic origin and was associated with head trauma, in the context of a type-1 induced Brugada ECG pattern, we decided to proceed with the implantation of a subcutaneous cardiac defibrillator for primary prevention of arrhythmias, as recommended by the 2022 European Society of Cardiology (ESC) guidelines [9].

The subsequent genetic testing revealed a heterozygous mutation of the *NSD1* gene, *i.e.*, c.737G>T (p.Gly246Val), and a heterozygous mutation of the calsequestrin 2 (*CASQ2*) gene, *i.e.*, c.482T>C (p.Ile161Thr).

At last, the familial screening indicated that the patient's brother was also diagnosed with a pharmacologically induced type-1 Brugada ECG pattern, but no signs of overgrowth syndrome were identified.

Discussion

In the presented case report, a type-1 pharmacologically induced Brugada ECG pattern was concurrently observed with a variant of uncertain significance (VUS) in *NSD1*, the causative gene for Sotos syndrome. To the best of our knowledge, this is the first report of an association between Brugada syndrome and overgrowth syndrome in a single patient. Indeed, the simultaneous diagnosis of two rare diseases requires some consideration.

Dominant *NSD1* mutations (*i.e.*, heterozygous) are known to be associated with Sotos syndrome. However, in the present case, the *NSD1* alteration was not present in the Genome Aggregation Database (https://gnomad.broadinstitute.org/) and in ClinVar Database (https://www.ncbi.nlm.nih.gov/clinvar/) and therefore is to be indicated as a VUS.

The estimated prevalence of Sotos syndrome is ~1:15,000 to 1:20,000 live births per individual [6]. About 98% of patients diagnosed with Sotos syndrome have a *de novo* pathogenic variant, while the remaining have an affected parent [7]. Usually, clinicians may suspect Sotos syndrome in cases of specific facial and body alterations and confirm the diagnosis by molecular genetic testing encompassing a heterozygous pathogenic variant or a deletion of the *NSD1* gene [6,7].

The *NSD1* protein is essential in multiple aspects of embryonic development because it is implicated in cell growth and differentiation [10]. In particular, this gene encodes a histone methyltransferase involved in transcriptional regulation *via* chromatin remodeling [10]. Indeed, *NSD1* binds various promoter elements; it catalyzes the transfer of methyl groups to lysine residues of histone tails, more specifically, lysine residue 36 of histone H3 (H3K36) and, less frequently, lysine residue 20 of histone H4 (H4K20) [10]. More than 90% of cases of Sotos syndrome are caused by an intragenic mutation of the *NSD1* gene or 5q35 microdeletions encompassing *NSD1* [10]. Cardinal features of Sotos syndrome include characteristic facial appearance (prominent forehead with a receding hairline, downward slanting palpebral fissures, and pointed chin), learning disability, and overgrowth, mainly in height and head circumference [6,7]. Also, several other possible features are bone alterations, including scoliosis, arachnodactyly, and neurological findings [6,7]. The latest include tonic-clonic, myoclonic, absence, and complex partial seizures [6,7]. *NSD1* can also be genetically or epigenetically deregulated (inactivated or overexpressed) in several cancer types. However, tumors occur in <1% of patients with Sotos syndrome [6].

Because Sotos syndrome has distinctive facial features, it is most easily recognized in early childhood. However, sometimes the diagnosis is made in adulthood [11], as it seems in the present case report. Indeed, the syndrome displays a broad spectrum of intellectual ability and clinical manifestation, sometimes with atypical phenotypic features. Also, facial appearance sometimes changes with time, and the typical gestalt may become less evident [6]. In addition, sometimes bone abnormalities have an asymptomatic character, and patients may be unaware of the abnormal appearance of their bones.

Several cardiac anomalies may be encountered in ~20% of patients with Sotos syndrome, ranging in severity from single self-limiting anomalies to more severe, complex cardiac abnormalities [7,8]. The reported cardiac diseases include patent ductus arteriosus, atrial septal defect, ventricular septal defect, aortic dilatation, aortic coarctation, aortopulmonary window, increased aortic compliance, hypertrophic cardiomyopathy, malformation of aortic and mitral valves, ventricular pre-excitation, and left ventricular noncompaction [7,8,12,13]. In addition, arrhythmias like Wolff-Parkinson-White syndrome and atrial flutter have also been reported, even if uncommon [6]. Further, an association with the right bundle branch block has been described in the literature [14].

To explain the association between these cardiac abnormalities and Sotos syndrome, we must consider that the *NSD1* gene maps to chromosome 5q35. In particular, haploinsufficiency of the 5q31-qter region is associated with a high frequency of congenital heart defects [12,13]. For example, the NK2 homeobox-5 (*NKX2-5*) gene is localized in the same chromosome (*i.e.*, 5q35); it maps very close to the *NSD1* gene (the one involved in Sotos syndrome development). It is known that *NKX2-5* mutations are associated with congenital heart defects, cardiomyopathies (*e.g.*, left ventricle noncompaction), and atrioventricular conduction defects. Therefore, a wide microdeletion may concomitantly encompass the *NSD1* and *NKX2-5* genes, leading to heart defects in a picture of Sotos syndrome [12,13]. However, none of the genes reported in the published literature known to cause the Brugada syndrome are localized at the 5q chromosome [15].

The Brugada syndrome is an inherited disorder characterized by a specific ECG pattern associated with symptoms. It is associated with an increased risk of ventricular arrhythmias and SCD in a morphologically normal heart [1-3]. The patient described in the present case report has a high cardiovascular risk phenotype (maybe further corroborated by the genetic alteration in the *CASQ2* gene). Indeed, also considering that syncope likely had an arrhythmic origin, according to ESC guidelines [9], we decided to implant a subcutaneous cardiac defibrillator.

The worldwide prevalence of Brugada syndrome is estimated to be 1 in 2,000 subjects [3]. The diagnosis is based on an ECG pattern represented by coved type ST-segment elevation ≥2 mm followed by a negative T-wave in ≥1 of the right precordial leads in V1 or V2 positioned in the second, third, or fourth intercostal space. The pattern can occur spontaneously or during a provocative drug test with intravenous administration of Na^+-channel blockers (such as ajmaline, flecainide, procainamide, or pilsicainide) [1-3]. Most Brugada syndrome patients have a structurally normal heart; however, several clinical studies have described the presence of minor structural alterations in both ventricles [2].

Brugada syndrome shows an autosomal dominant transmission pattern. Mutations in the Na^+ voltage-gated channel alpha subunit 5 (*SCN5A*) gene, have been causally related to most cases of Brugada syndrome (*i.e.*, about 20% of cases) [1-3]. However, the disease could be sporadic in up to 60% of patients. Indeed, more than 350 pathogenic mutations in several genes encoding for subunits of cardiac Na^+, K^+, and Ca^{2+} have been linked to the disease [2, 3].

Many people with Brugada syndrome are unaware of the disease, as they can live without symptoms for decades or even their whole life. However, the first manifestation of the syndrome can be

unexpected SCD due to polymorphic ventricular tachycardia or ventricular fibrillation, and genetic testing cannot always identify those at risk. Also, these arrhythmias can cause clinical manifestations like syncope, seizures, nocturnal agonal breathing, and, when sustained, cardiac arrest or SCD [1-3].

The Brugada ECG pattern has been associated with other cardiac and extra-cardiac pathologies like neural, digestive, and metabolic. This association can be explained by similar ion channel expressions shared by the heart and different tissue types [4]. For example, *SCN5A* is expressed nearly throughout the body [4]. However, no previous evidence of an association between Brugada and Sotos syndrome is reported in the published literature.

As previously claimed, in Sotos syndrome, histone modifications are secondary to genetic alterations. In eukaryotes, the chromatin state, *i.e.*, the packaging of DNA with histone proteins, contributes to the control of gene expression [16,17]. Therefore, histone methylation is an essential epigenetic mechanism that affects transcriptional levels depending on the position and degree of lysine and arginine methylation on histone tails [16,17]. Accordingly, this epigenetic mechanism dictates biological processes in the context of development and cellular responses by activating and repressing gene transcription [16,17]. In particular, histone methylation is involved in maintaining cardiac homeostasis and hypertrophy. Not surprisingly, chromatin dysregulation can result in pathological cardiac gene expression and developmental cardiac diseases [18]. Interestingly, these epigenetic modifications are involved both in the pathogenesis of Sotos syndrome and in the onset and progression of arrhythmias in cardiomyopathies [16]. For example, histone modification has been linked to the dysregulation of repolarizing K+ currents and depolarizing Ca^{2+} current [19].

Another consideration concerns the possible, independent, specific role of the *NSD1* gene in genomic transcription and cardiac embryogenesis, as confirmed by the finding of congenital cardiac abnormalities in about 20% of Sotos patients.

Also, the association in the present overgrowth syndrome case with a Brugada pattern may be explained by the heterozygous alteration in the *CASQ2* gene revealed by the multigene panel. This gene is mapped in the short arm of chromosome 1 and encodes calsequestrin, an intra-sarcoplasmic reticulum protein involved in Ca^{2+} regulation [15]. Recessive mutations (composed heterozygous or homozygous) of the *CASQ2* gene are known to cause inappropriate Ca^{2+} release from the sarcoplasmic reticulum and to underlie catecholaminergic polymorphic ventricular tachycardia syndrome, *i.e.*, a catecholamine-induced bidirectional ventricular tachycardia and polymorphic ventricular tachycardia in the absence of structural heart disease or ischemia [9]. However, as in the present case report, the significance of a merely heterozygous mutation (*i.e.*, not compound) of the *CASQ2* gene is unknown. Recently, a heterozygous mutation of the *CASQ2* gene has been described as a VUS in a patient with Brugada syndrome [20]; however, the significance of this association has yet to be entirely determined.

In any case, in the present case report, multigene panel analysis did not identify the most commonly mutated gene in Brugada syndrome, *i.e.*, the *SCN5A* gene, nor another gene alteration known to be involved in Brugada syndrome [15].

Therefore, we cannot establish whether the combination of Brugada syndrome and Sotos syndrome in our patient is casual or due to a common underlying genetic etiology. Indeed, we must consider the possibility that the simultaneous presence of the two syndromes was merely incidental. Sotos syndrome is inherited as an autosomal dominant disorder, and in molecularly confirmed patients, ~98% of individuals have a *de novo* pathogenic variant [6]. However, a small number of familial cases have been reported [6]. A type-1 induced Brugada ECG pattern was also observed in the patient's brother; however, no signs of overgrowth syndrome were identified.

Anyhow, it is still being determined if patients with overgrowth syndrome require proper Brugada syndrome screening. In any case, the found association will help consider further investigation on this topic. In the meantime, we suggest that cardiologists consider Brugada syndrome as a possible associated cardiac anomaly in patients affected by overgrowth syndrome.

Conclusions

Brugada syndrome and overgrowth syndromes have been associated with other cardiac and extra-cardiac diseases. However, the present is the first description of the association between Brugada syndrome and an overgrowth syndrome characterized by a VUS genetic alteration in *NSD1*. Similar signaling pathways may be present in both conditions; however, we cannot exclude a merely casual simultaneous occurrence of the diseases in the same patient. Therefore, further observations will clarify the possible association between these two conditions and whether patients affected by a genetic alteration in *NSD1* need proper screening for Brugada syndrome.

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