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Original Article

Sudden unexpected intrapartum death and left ventricular noncompaction involving the right ventricle

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ABSTRACT

Left ventricular noncompaction (LVNC), involving mainly the right ventricle, is a rare form of congenital heart disorder characterized by a developmental arrest in myocardial compaction, resulting in a spongy appearance of the myocardium, mainly of the right ventricle, rarely detected in fetuses. We report the case of a female fetus with a gestational age of 41^{+4} weeks who came to our attention for intrapartum sudden unexpected death, resulting in stillbirth. The ventricular walls, particularly the right ventricular wall, appeared thick, hypertrabeculated and spongy, leading to the diagnosis of LVNC involving mainly the right ventricle. The atrioventricular node and His bundle presented areas of fetal dispersion and resorptive degeneration; islands of conduction tissue were detected in the central fibrous body. Arcuate nucleus of the brainstem showed bilateral severe hypoplasia. The right bundle branch was hypoplastic. The final cause of death was an electrical conduction disfunction in an LVNC involving mainly the right ventricle. To the best of our knowledge, the herein described case is the first reported observation of sudden intrapartum death from LVNC involving mainly the right ventricle well documented post-mortem with cardiac conduction and brainstem studies. Our findings confirm the need of an accurate post-mortem examination including the study of the cardiac conduction system on serial section in every case of sudden unexpected fetal death, although there are no universally recognized guidelines.

1. Introduction

Left ventricular noncompaction (LVNC) involving mainly or exclusively the right ventricle, also known as right ventricular noncompaction (RVNC) is a rare cardiomyopathy in which the noncompaction myocardium of the right ventricle can be concomitant with that of the left ventricle, or present in the right ventricle as a unique anatomic area [1]. LVNC is a cardiomyopathy marked by controversies and unresolved questions. The lack of a universally accepted definition, the overlap with other cardiomyopathies, the genetic complexity, uncertain prognostic factors, and varying management strategies all contribute to the ongoing debates surrounding LVNC. Little is known about RVNC, which is surrounded by considerable gaps in its understanding.

RVNC, akin to its left ventricular counterpart, presents a distinct and uncommon congenital disorder characterized by impaired myocardial compaction during embryonic development. The result is a prominent trabeculated appearance of the right ventricular myocardium, a cardiomyopathy infrequently observed and rarely documented in literature, mainly as case reports [2–10]. Ventricular noncompaction is a rare form of congenital cardiomyopathy characterized by an arrest in the normal process of prenatal myocardial compaction, resulting in a spongy appearance of the myocardium, particularly the left ventricle [11,12]. Currently, even the classification of (LVNC) remains controversial as it has been classified into the group of genetic cardiomyopathy by the American Heart Association (AHA) [13] and into the group of unclassified cardiomyopathies by the European Society of Cardiology (ESC) [14]. Arbustini et al. [1] questioned whether LVNC is a distinct cardiomyopathy rather than a morphologic trait that can be observed in healthy subjects with normal left ventricular size and function, and can be shared by different cardiomyopathies.

The LVNC prevalence in the general population seems to be 0.014%–1.3% [11], but its true prevalence remains hard to define. The prevalence of RVNC is unknown. RVNC has been reported mostly in adults [4–8,15], rarely in children [3] and newborns [9,16], but its detection in fetuses [2,10] is exceedingly rare, making it a challenging diagnostic entity to encounter. Clinically, RVNC can present with heart failure [3,15], pulmonary embolism [4,6], pulmonary hypertension [3], ventricular tachycardia [4], right bundle block [4], and sudden cardiac death [7]. RVNC has been associated with hypoplastic left heart syndrome [9], atrial and ventricular septal defects [7], tetralogy of Fal-

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lot [7], Williams syndrome [17], and pulmonary artery sling [10,18,19]. Currently, there are no literature reports of intrapartum unexpected death from RVNC.

We report the case of a female fetus with a gestational age of 41^{+4} weeks who came to our attention for intrapartum sudden unexpected death, resulting in stillbirth. The post-mortem investigations disclosed the presence of LVNC affecting mainly the right ventricle accompanied by cardiac conduction system and brainstem anomalies.

2. Case presentation

We report the case of a female 41^{+4} gestational weeks fetus who came to our attention for intrapartum sudden unexpected death, resulting in stillbirth. The mother, a 34-year-old gravida 2 para 0 (G2 P0) woman, had a previous spontaneous abortion at week 6th, and no otherwise relevant medical history. Pregnancy had a regular course, with no evidence of any maternal, placental or fetal pathologies. Prenatal genetic test showed low risk profile for chromosomal aneuploidy and extra copy of chromosome 21.

Prenatal ultrasonography did not detect any congenital malformation. At a gestational age of 41^{+4} weeks, the fetal ultrasound showed a single fetus in cephalic presentation, with a normal pattern of fetal growth consistent with the 40th percentile and regular cardiac activity; anteriorly normal-inserted placenta, and regular amniotic fluid. The umbilical artery Doppler velocimetry was within normal limits.

The mother, when hospitalized for induction of labor, was in good condition and she was not on any significant medication. As labor commenced, the fetal heart rate, as detected at fetal cardiotocography, suddenly significantly decelerated, indicating deep bradycardia. Consequently, an emergency cesarean section was promptly performed. However, upon delivery, no fetal heartbeat was detected, culminating in the tragic outcome of stillbirth.

3. Pathological findings

An autopsy was requested with a clinical suspect of sudden unexplained intrauterine death syndrome (SIUDS). After the general autopsy, the cause of death was unknown and the case was submitted to the Lino Rossi Research Center, Università degli Studi di Milano where a more in-depth examination was performed, including in particular the study of the cardiac conduction system and brainstem on serial sections [20,21].

The stillborn was described as a well-developed, well-nourished white female fetus, with a body weight of 3,720 grams (g), a crown-rump length of 35.5 centimeters (cm), a crown-heel length of 50 cm, head circumference of 33 cm, chest circumference of 34 cm, and an abdominal circumference of 33.5 cm. Morphometric measurements were appropriate for the gestational age. External examination did not show any facial or body dysmorphism.

Internal examination revealed correctly developed and located organs. Few *petechiae* were found on the back side of lungs; adrenals and kidneys were congested.

The fetal adnexa showed normal developmental morphology with normal location and dimensions. The gross examination of the placenta failed in determining significant macroscopic abnormalities. Microscopically, no meconial free deposits (nor incorporated in histocytes) were evident on membranes surface. Finally, no histological features of chorioamnionitis were spotted.

The heart, including the initial tracts of the great vessels, weighed 22 g; the cardiac diameters were: longitudinal 5 cm, transverse 3.5 cm, antero-posterior 2.5 cm. Grossly, the heart showed a smooth and shiny valvular and parietal endocardium; patent *foramen ovale*. The ventricular free walls and the interventricular septum appeared thick, hypertrabeculated, and spongy with deep intertrabecular spaces. The left ventricle was 6 millimeters (mm) thick, the right ventricle was 6 mm thick, and the interventricular septum was 7 mm thick. The noncompaction was observed in both ventricles, indicating biventricular involvement. The histopathologic analysis of the myocardium showed a thin compacted (N) layer and a thick noncompacted (NC) layer characterized by an increase in trabeculae and intertrabecular recesses depth, with a NC/C ratio > 2 diagnostic of a left ventricular noncompaction, particularly involving the right ventricle (Fig. 1). The right ventricular myocardium showed a NC/C ratio $> 75\%$ leading to the diagnosis of LVNC involving mainly the right ventricle (Fig. 1). Our assessment was in adherence to the histologic criterion proposed by Burke et al. [22], which describes the right ventricular involvement of LVNC if the NC/C ratio in the right ventricle is greater than 75%. Mild hemorrhagic suffusions of the myocardium were noted.

The atrioventricular node and the his bundle presented areas of fetal dispersion and areas of loose connective tissue, also extending to the central fibrous body, attributable to resorptive degeneration. Islands of conduction tissue were detected in the central fibrous body (Fig. 2). The right bundle branch was hypoplastic.

The lungs showed normal anatomic lobes bilaterally, with red-brown discoloration. Several hemorrhagic petechiae were present, mainly on the posterior lungs surface. The hydrostatic test showed sinking of all the fragments bilaterally. Histologically diffuse masses of meconium were spotted to varying degrees in intra-bronchial and intra-

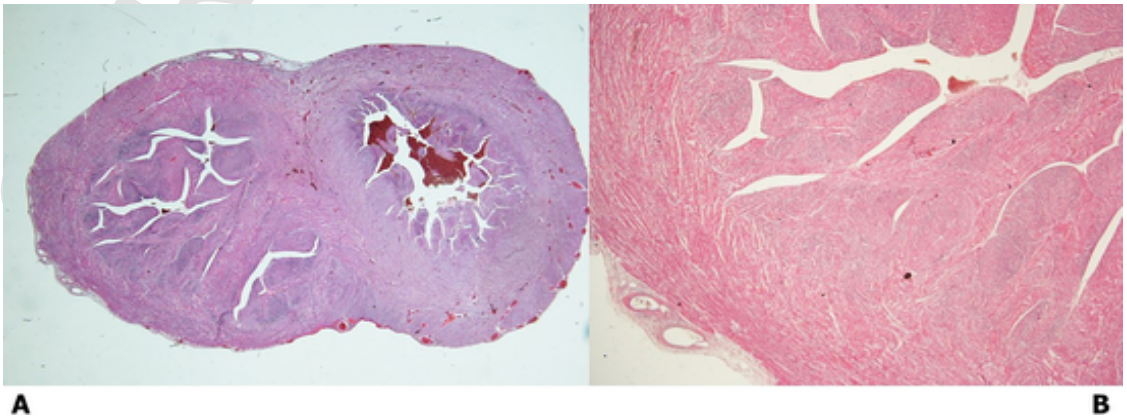

Fig. 1. (A) Biventricular para-apical section. Increased depth of trabeculae and intertrabecular recesses with a noncompacted myocardium-to-compacted myocardium ratio $> 75\%$, leading to the diagnosis of left ventricular noncompaction (LVNC) involving the right ventricle. (B) Right ventricular wall at higher magnification. Stain: Hematoxylin-Eosin; original magnifications: (A) 5x; (B) 25x.

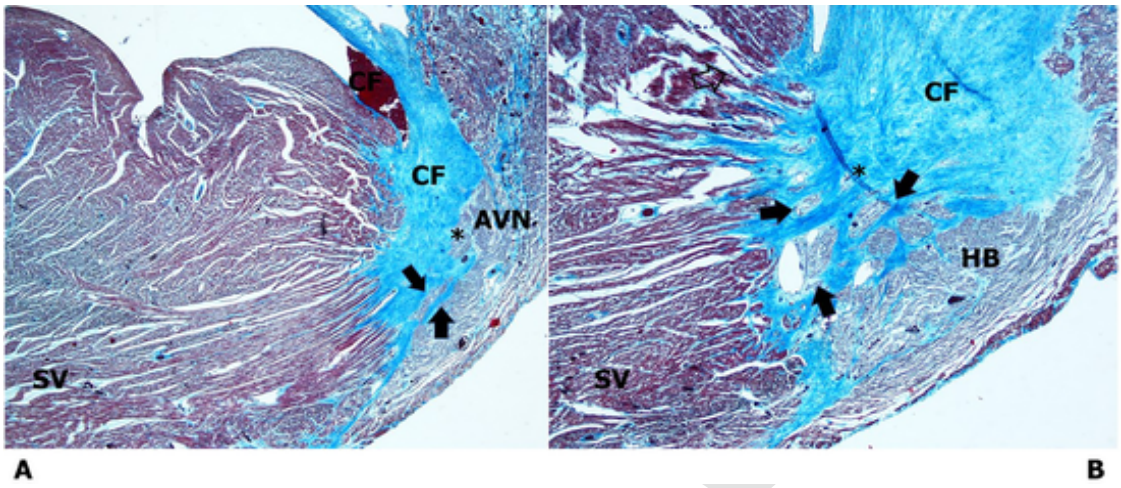

Fig. 2. Serial sections of the atrioventricular junctional tissue. (A) Both the atrioventricular node (AVN) (B) and the His bundle (HB) exhibit areas of fetal dispersion (arrows) and areas of resorptive degeneration (*) in the central fibrous body (CF). IVS = Interventricular Septum. Stain: Trichromic Heidenhain (Azan); original magnifications: (A) 20x; (B) 40x.

alveolar spaces, together with intra-alveolar squamous cells. No pulmonary artery wall thickness and formation of hyaline membrane were observed.

The examination of the brainstem on serial sections disclosed a severe bilateral hypoplasia of the arcuate nucleus in the medulla oblongata (Fig. 3).

4. Discussion

The pathophysiology of LVNC involves impaired myocardial compaction during embryonic development, leading to a dysfunctional myocardial architecture. The arrest of the normal process of trabecular remodeling during embryonic development causes a two-layered ventricular wall: a thinner compact layer and a spongy noncompacted layer predominantly involving the apical portion of the left ventricle, with prominent intertrabecular recesses (sinusoids) in communication with the ventricular cavity [23,24].

The etiology of LVNC is not fully understood, but it is believed to have a genetic basis [2,3]. LVNC can present mutations in genes encoding sarcomeric proteins, such as the genes *MYH7, MYBPC3*, and *JUP* [25]. Genes encoding cytoskeletal, sodium channel, and nuclear- membrane proteins have been causally related to LVNC [23]. Little is known about the genetic bases of RVNC. In one reported case of RVNC in fetal death, the whole exome sequencing showed a likely pathogenic variant in the *MYH7* gene [2], in a case of RVNC death of a child the whole exon gene assay indicated a mutation of the *ACVRL1* gene [3], while in an adult patient of RVNC a mutation of the *TTN* gene was detected [15]. In the present case, prenatal genetic testing showed a low risk profile for chromosomal aneuploidy and extra copy of chromosome 21, but a limitation of the present study is that no whole exome sequencing (WES) investigation has been yet carried out, which would provide valuable insights into the underlying etiology of the observed cardiac abnormalities.

Clinically, the diagnosis of LVNC involving the right ventricle is made using two-dimensional echocardiography, which reveals the presence in the myocardium of a thin outer compact layer and a much thicker non-compacted inner layer formed by the trabecular meshwork with deep endocardial spaces. While for LVNC, a ratio > 2 of non-compacted to compacted myocardium (non-compaction index) at systole is a characteristic feature [26], for LVNC involving the right ventricle, or RVNC, no specific diagnostic criteria have been defined. Since in normal individuals the right ventricle is coarsely trabecular with an irregular endocardial surface, the noncompaction should be higher than

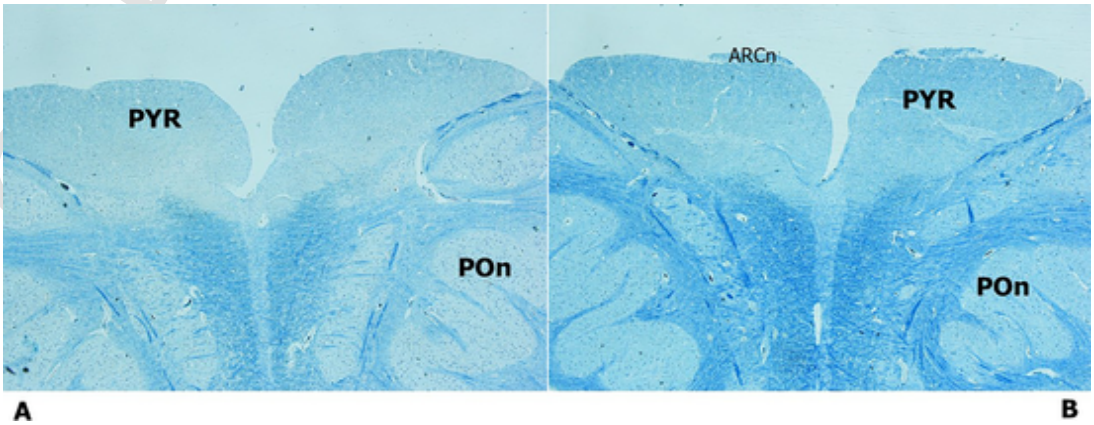

Fig. 3. Serial transversal sections of the medulla oblongata show severe bilateral severe hypoplasia of arcuate nucleus. (A) The arcuate nucleus (ARCn) is bilaterally absent; (B) The ARCn is hypoplastic. POn; Principal inferior olivary nucleus; PYR; Pyramid; VMS. Stain: Klüver-Barrera; original magnification: 20x.

2. Cardiac computed tomography angiography and MRI are also being used for a more accurate diagnosis of RVNC [5,8].

Histopathologically, there are no established criteria to diagnose LVNC involving the right ventricle, or RVNC. Burke et al. [22] proposed as histologic criterion for the right ventricular involvement of LVNC the transmural thickness of the noncompacted right ventricle greater than 75%. In our case, at autopsy, the pathological finding included an increase in trabeculae and intertrabecular recesses depth and a thick, hypertrabeculated and spongy right ventricular wall with a NC/C ratio > 75% that lead to the diagnosis of LVNC involving in particular the right ventricle (Fig. 1). Indeed, it is essential to highlight that the right ventricle and the right side of the ventricular septum typically exhibit a highly trabeculated appearance, contrasting with the smoothness typically observed on the left ventricle and the left side of the ventricular septum [27]. Furthermore, it should be kept in mind that in fetuses the right and left ventricles are more similar in size, while in adults the left ventricle leads in terms of size and function. These physiological anatomical features underscore the importance of discerning between normal trabeculations and pathological features, such as those seen in conditions like LVNC involving the right ventricle.

In the present case, the atrioventricular node, the central fibrous body and the his bundle presented areas of fetal dispersion and resorptive degeneration; islands of conduction tissue were detected in the central fibrous body (Fig. 2); the right bundle branch was hypoplastic. These findings in the conducting tissue could have led to fatal cardiac arrhythmias. However, the fetal dispersion, the resorptive degeneration and the islands of conducting tissue in the central fibrous body could underline a physiological state of cardiac electrical instability in fetuses, rather than a pathological condition, having been detected also in fetuses who succumbed from known causes of death [31]. The right bundle branch was hypoplastic, as detected in the current case, was not reported in control cases [28,29,31]; it could be part of the LVNC involvement of the right ventricle and right side of the ventricular septum, and could be the morphologic basis for lethal arrhythmias in the present case.

In our case, a severe bilateral hypoplasia of the arcuate nucleus in the medulla oblongata was the only alteration detected in the brainstem (Fig. 3). The arcuate nucleus hypoplasia has been described in cases of sudden intrauterine unexplained death [28,29] and could have played a role in determining the unexpected death of the herein presented case. However, further studies are needed on control group to accurately assess the significance of the arcuate hypoplasia findings. The study of the brainstem, which houses the cardio-respiratory and arousal pacemaker, holds significance in cases of sudden infant death syndrome (SIDS), where infants are found deceased in their cribs, often due to respiratory arrest. However, in cases of SIUDS, where the fetus's life is independent of breathing, the study of the conduction system and brainstem is not generally carried out, especially due to the absence of international guidelines [28,29].

The cardiac conduction and brainstem anomalies detected in the present case have been described in cases of sudden intrauterine unexplained death syndrome (SIUDS) [28,29]. A wide control group would enable researchers to distinguish between pathological changes and benign variations in the arcuate nucleus and other “vital” cardio-respiratory and arousal nuclei of the brainstem, as well as of the cardiac conduction system, thereby providing a more nuanced understanding of the observed findings in the context of sudden intrauterine death.

RVNC has been described only in two other cases of fetal deaths [2,10], one of which presented with pulmonary artery sling [10]. Management of RVNC in newborns have been described in four cases [9,16] and involves a multidisciplinary approach, including medical therapy for heart failure symptoms and surgical interventions, if necessary. The prognosis of LVNC involving the right ventricle varies depending on the severity of cardiac involvement and the presence of associated anomalies. Long-term follow-up is essential to monitor for complications and optimize management strategies.

The pathological findings of our case underscore the potential interplay between various pathological processes contributing to the sudden death associated with biventricular LVNC, predominantly involving the right ventricle. Specifically, our observations suggest that concurrent abnormalities affecting both the cardiac conduction system and the brainstem may have played a pivotal role in precipitating the fetal sudden unexpected death. Considering that the right ventricle serves as the systemic ventricle during fetal life [30], it is plausible that the mechanism of death in this case was primarily arrhythmic rather than mechanical with congestive heart failure. The presence of a biventricular LVNC involving predominantly the right ventricle likely contributed to electrical conduction abnormalities, potentially leading to arrhythmias such as ventricular tachycardia or ventricular fibrillation, resulting in bradycardia and sudden cardiac arrest and subsequent fetal demise. Additionally, the involvement of the cardiac conduction system and the brainstem, as indicated in the case, further supports the hypothesis of an arrhythmic mechanism of death. Abnormalities in these regions can disrupt the normal regulation of cardiac rhythm and may predispose the fetus to life-threatening arrhythmias.

It is to be acknowledged that a comprehensive post-mortem evaluation, including detailed examination of cardiac function and histopathological analysis, like in this case, is necessary to ascertain the exact mechanism of death in this particular case. However, the suggestion to routinely examine the conduction system, even without prenatal clinical indications of fetal cardiac electrical abnormalities, is questionable, particularly in the absence of universally recognized guidelines from scientific societies worldwide.

It is conceivable that the identified findings within the cardiac conduction system and brainstem instigated a cascade of events leading to fetal distress and intrauterine hypoxia. This distress may have subsequently triggered the prenatal passage of meconium into the amniotic fluid and initiated fetal gasping. Notably, the absence of histological evidence of chorioamnionitis and meconial deposits on the placental fetal surface suggests an acute and abrupt sequence of events precipitating the fatal event.

There are no other reports of well documented post-mortem investigations of LVNC involving the right ventricle, or of RVNC, including the study of the cardiac conduction system and the brainstem. In this case, an electrical conduction disfunction, in a predominantly right located LVNC, could have been the final cause of death.

Further research is warranted to elucidate the precise mechanisms linking cardiac abnormalities, brainstem dysfunction, and adverse perinatal outcomes. Such insights are crucial for enhancing our understanding of LVNC-related complications and informing strategies for risk assessment and management in affected pregnancies.

5. Conclusions

LVNC involving the right ventricle is a rare form of congenital heart disease that can present intrapartum like in the present cases. This report documents the first reported case of sudden unexpected intrapartum death attributed to LVNC involving the right ventricle, or RVNC, supported by a comprehensive post-mortem assessment, including meticulous evaluation of the cardiac conduction system and of the brainstem. The insights derived from this case underscore the critical importance of carrying out accurate and thorough post-mortem examinations, incorporating the study of the cardiac conduction system through serial sections, in all cases of sudden, unanticipated fetal demise. These findings not only contribute to our understanding of RVNC, but also underscore the necessity of enhanced post-mortem investigations for elucidating the multifaceted factors underlying sudden unexpected fetal deaths.

CRediT authorship contribution statement

Giulia Ottaviani: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Tobia Tomasello:** Data curation, Investigation. **Francesca Boggio:** Data curation, Formal analysis, Investigation, Methodology. **Letterio Runza:** Investigation, Methodology. **Alessandro Del Gobbo:** Formal analysis. **L. Maximilian Buja:** Supervision.

Declaration of competing interest

All authors do not have any financial or personal relationships with people or organizations that could inappropriately influence their work.

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