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Late prenatal diagnosis of complete pentalogy of Cantrell

Pozdní prenatální diagnostika kompletní pentalogie Cantrella

M. E. M. Albrecht, R. Sevillano Filho, E. Araujo Júnior

Department of Obstetrics, Paulista School of Medicine – Federal University of São Paulo (EPM-UNIFESP), São Paulo-SP, Brazil

Summary: Cantrell's pentalogy is a rare syndrome associated with a midline embryological defect involving a series of malformations: anomalies of the lower sternum, anterior diaphragm, heart, and anterior abdominal wall. It can be classified as complete, probable or partial, but the most important thing is to describe and understand the anomalies involved. We describe a case of a late diagnosis of Cantrell's pentalogy at 35 weeks and 5 days of pregnancy in a woman from the interior of Pará state, an Amazon Brazilian region. Fetal echocardiography confirmed the diagnosis of Cantrell's pentalogy with tetralogy of Fallot and ultrasound examination showing a bilateral clubfoot. Cesarean section was performed at 36 weeks because of pre-eclampsia superimposed on chronic arterial hypertension with signs of severity. The male newborn was delivered weighting 2,320 grams. Postnatal echocardiography confirmed the diagnosis of Cantrell's pentalogy and karyotype was normal (46, XY). Infant was discharged at 47 days of age with good weight gain, artificial breastfeeding, and outpatient follow-up by the cardiology and cardiac surgery specialists.

Key words: pentalogy of Cantrell – prenatal diagnosis – tetralogy of Fallot – fetal echocardiography

Souhrn: Cantrellova pentalogie je vzácný syndrom spojený s embryologickou vadou střední linie zahrnující řadu malformací: anomálie dolní části hrudní kosti, přední části bránice, srdce a přední části břišní stěny. Lze jej klasifikovat jako úplný, pravděpodobný nebo částečný, ale nejdůležitější je popsat a pochopit příslušné anomálie. Popisujeme případ pozdní diagnózy Cantrellovy pentalogie v 35. týdnu a 5 dnech těhotenství u ženy z vnitrozemí státu Pará v brazilské Amazonii. Fetální echokardiografie potvrdila diagnózu Cantrellovy pentalogie s Fallotovou tetralogií a ultrazvukové vyšetření ukázalo oboustranný talipes. Císařský řez byl proveden ve 36. týdnu z důvodu preeklampsie superponované na chronickou arteriální hypertenzi se známkami závažného průběhu. Novorozenec mužského pohlaví se narodil s hmotností 2 320 g. Postnatální echokardiografie potvrdila diagnózu Cantrellovy pentalogie a karyotyp byl normální (46, XY). Novorozenec byl propuštěn ve 47 dnech věku s dobrým hmotnostním přírůstkem, umělým kojením a ambulantním sledováním kardiologem a kardiochirurgem.

Klíčová slova: Cantrellova pentalogie – prenatální diagnostika – Fallotova tetralogie – fetální echokardiografie

Introduction

Cantrell's pentalogy is a rare congenital syndrome first described by Cantrell et al. [1] in 1958. It is a midline embryonic condition characterized by a complex combination of anomalies of the lower sternum, anterior diaphragm, heart, and anterior abdominal wall [2]. All of these findings are necessary to make a complete diagnosis, but there are incomplete cases with only some of these findings, called variants or partial cases. Estimates of the prevalence of Cantrell's pentalogy vary widely, with reported incidences ranging from 1 in 65,000 to 200,000 live births [3–5]. Due to the paucity of cases described in the literature, the etiology is not fully understood [6].

Clinical presentation of Cantrell's pentalogy is highly variable, ranging from severe, life-threatening forms to milder manifestations that can be surgically corrected. Diagnosis can be made in the prenatal period using imaging techniques such as ultrasound, and more recently, magnetic resonance imaging. Postnatal confirmation of Cantrell's pentalogy involves detailed clinical examination and complementary imaging studies such as echocardiography and computed tomography to assess the extent of the anomalies and guide the therapeutic approach.

This case report describes a late prenatal diagnosis of Cantrell's pentalogy aiming to discuss and review aspects related to this syndrome such as classification, clinical features, differential diagnosis, and therapeutic strategies.

Case report

A pregnant woman, 39-years-old, terciparous, with two previous cesarean

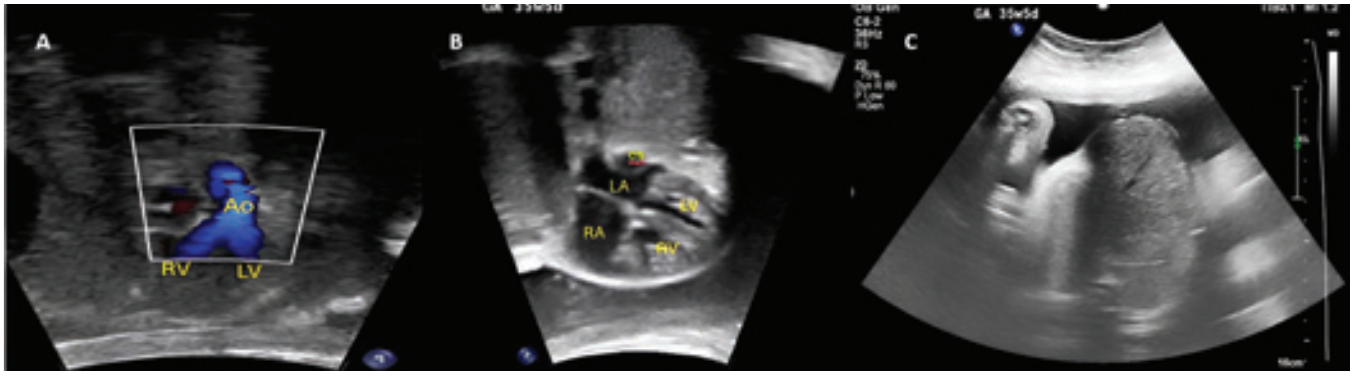

Fig. 1. Fetal echocardiogram showing ventricular septal defect type malaligned with overriding aorta 50% of interventricular septum using color Doppler (A) and normal four-chamber view with dilated coronary sinus and ectopia cordis (B). Axial section of the upper abdomen showing an omphalocele by ultrasound (C).
Obr. 1. Fetální echokardiogram zobrazující defekt komorového septa typu špatného spojení s přečnívající aortou o 50 % nad interventrikulárním septem pomocí barevného doppleru (A) a normální čtyřkomorový pohled s dilatovaným koronárním sinem a ektopií srdce (B). Axiální řez horní částí břicha zobrazující omfalokélu pomocí ultrazvuku (C).

AO – aorta, CS – coronary sinus/koronární sinus, LA – left atrium/levá síň, LV – left ventricle/levá komora, RA – right atrium/pravá síň, RV – right ventricle/pravá komora

sections, who was from a city in the interior of the state of Pará in the Brazilian Amazon region where she had 16 prenatal consultations at a primary health care unit. Her personal history was of grade I obesity (pre-gestational body mass index – BMI of 31.5 kg/m^2), chronic hypertension (irregular use of methyldopa and nifedipine), untreated gestational diabetes mellitus, and two previous hospitalizations due to uncontrolled blood pressure.

The first ultrasound scan at 13 weeks and 3 days of pregnancy showed a thoracic malformation, an abdominal hernia, and bilateral club feet. No further ultrasounds were performed. At 34 weeks of gestation, due to the complexity of the fetal malformations, they migrated to the city of São Paulo in search of a referral service for diagnostic confirmation, delivery, and postnatal care.

The patient was admitted to our emergency department at 35 weeks and 5 days of gestation for uncontrolled blood pressure and complaints of headache, scotoma, and epigastralgia. An obstetric ultrasound showed a thoracic-abdominal closure defect with ectopia cordis, omphalocele, and tetralogy of Fallot, suggesting a diagnosis of Cantrell's pentalogy, and bilateral club feet with a fetal estimated weight of 2,142 grams. Because of impending eclampsia, intravenous magnesium sulfate was started. Fetal echocardiography was performed showing ectopia cordis, normal systemic and pulmonary venous drainage with persistent left superior vena cava, atrioventricular and arterial ventricular concordance, normofunctional foramen ovale, ventricular septal defect measuring 7 mm malaligned type with overriding aorta 50% of the interventricular septum, moderate right ventricular hypertrophy, dilated aortic valve, anterosuperior deviation of the infundibular septum causing mild stenosis of the right ventricular outflow tract, and pulmonary artery hypoplasia measuring 3.2 mm (Z-score of –7.12) with anterograde flow with slight acceleration (Fig. 1). Prenatal karyotype was not indicated because of the late gestational age (35 weeks) when she arrived in our service. Magnetic resonance imaging for better assessment of fetal malformations was planned before delivery, but was not possible due to the maternal emergency (impending eclampsia). Similarly, the termination of pregnancy was not requested due to the advanced gestational age, as Brazilian law requires a judicial decision in cases of severe fetal malformations.

Cesarean section was indicated at 36 weeks due to pre-eclampsia superimposed on chronic arterial hypertension with signs of severity, associated with two previous cesarean sections and transverse fetal presentation. The newborn had a loud cry, adequate tone, and no complications. He was male, weighed 2,320 grams, and had an Apgar score of 8 in the 1st min and 9 in the 5th min (Fig. 2).

The newborn was admitted to the neonatal intensive care unit, where he remained on room air for 3 days, requiring an oxygen catheter after oscillating oxygen saturation. An echocardiogram was performed on the first day of life and confirmed tetralogy of Fallot and persistence of the left superior vena cava draining into a dilated coronary sinus, patent foramen ovale measuring 3 mm with left-right flow, ventricular septal defect measuring 5.4 mm with 50% of aorta overriding the interventricular septum, bicuspid pulmonary valve, and pulmonary infundibulo-valvar stenosis with a maximum systolic gradient of 23 mmHg. Pulmonary ring measured

4.8 mm (Z-score –2.39). Pulmonary artery trunk measured 6.3 mm (Z-score –0.91). Due to worsening tachypnea and hypoxemic crises, it was decided to start propranolol at a dose of 0.5 mg/kg/dose every 8 hours. Karyotype was normal (46, XY).

Fasting was maintained until 4 days after birth, when he was started on enteral feeds with breast milk, and after transition to oral feeds, he was able to suspend the gastric tube at 12 days of age. Additional diagnoses were as follows: right optic nerve hypoplasia, convergent strabismus with enophthalmos, right choroid plexus cyst, congenital clubfoot, and congenital hip dysplasia. Infant was discharged at 47 days of age with good weight gain, artificial breastfeeding and outpatient follow-up by the involved specialists mainly in pediatric cardiology and surgery, where a surgical program will be performed to correct the chest/abdominal wall defect.

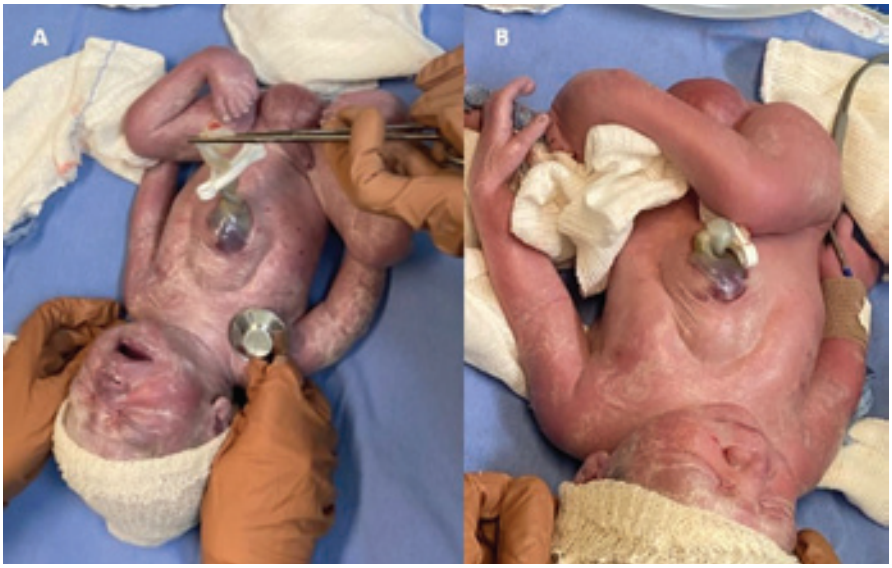

Fig. 2. Newborn showing a pulsatile mass in the lower chest region covered by skin with extension to the anterior wall of the supraumbilical abdomen, associated with bilateral congenital clubfoot (A, B).
Obr. 2. Novorozenec vykazující pulzující útvar v dolní části hrudníku krytý kůží s rozšířením na přední stěnu nadbřišku, spojený s oboustranným vrozeným talipem (A, B).

Discussion

Cantrell's pentalogy was first described as a combination of five defects involving the midline abdominal wall, inferior sternum, anterior diaphragm, diaphragmatic pericardium, and some form of intracardiac defect [1,2]. The majority of documented cases have occurred in the United States and Europe (72%) and the incidence is approximately 1 in 65,000 to 200,000 live births with a male predominance of 1.35 : 1 [5,7,8]. At the end of the 20th century, the mortality rate for Cantrell's pentalogy was estimated to be 52% [3]. In 2014, Zhang et al. [5] reported a mortality rate of 61%, but this mortality rate is closely related to the severity of the associated defect and can vary widely depending on the management of each case.

Embryologically, the ectoderm differentiates into the surface ectoderm and neuroectoderm, giving rise to the future epidermis and neural tube. The mesoderm differentiates into paraxial, intermediate, and lateral plate mesoderm, which will give rise to the peritoneal and pleural membranes, as well as bone, cartilage, tissue, muscle, blood and vascular, reproductive, excretory, and urogenital tissues. Finally, the endoderm differentiates to form the endocrine glands, respiratory system, and intestines [5]. Cantrell et al. [1] believed that a defect in the development of the transverse septum associated with the somatic and splanchnic mesoderm, as well as the non-migration of the primordial sternum with complete fusion and fixation of the anterior abdominal musculature, could explain this series of malformations, which occurred between 14 and 18 days of embryonic life. Cantrell et al. [1] also divided the classical defects into two categories:

1. Defects resulting from disruption of normal development of the mesoderm, causing pericardial, anterior diaphragmatic, and intracardiac defects.
2. Defects resulting from disruption of normal development of primordial mesenchymal structures, causing sternal and abdominal wall defects.

One or both categories of defects may be observed in any patient. Contrary to what Cantrell et al. [1] postulated, Chandran and Ari [9] found that the developmental defect could occur a little earlier, but the basic principles would remain the same.

In the first reports of Cantrell's pentalogy, it was thought that there was no associated genetic mutation, but it could have a strong association with some chromosomal disorders: trisomy 21, trisomy 18, or Turner syndrome. In addition to these associations, there were reports of Gotz-Gorlin syndrome [9]. In 2022, Fazea et al. [8] described a mutation in the BMP2 gene (bone morphogenetic protein 2) as the main etiology of Cantrell's pentalogy, since these genes are responsible for the normal development of the midline structure. The aldehyde dehydrogenase 1 A2 (ALDH1A2) family member on chromosome 15 has recently been implicated in the progression of Cantrell's pentalogy. ALDH1A2 encodes the enzyme retinaldehyde dehydrogenase type 2, which is required for the conversion of vitamin A to

Tab. 1. Classification of Cantrell's pentalogy according to Toyama [3].
Tab. 1. Klasifikace Cantrellovy pentalogie podle Toyamy [3].

Class I	Class II	Class III
complete	**probable**	**incomplete**
5 defects	4 defects (2 of which must always be included)	< 4 defects (one of which must always be included)
diaphragmatic pericardial defect	congenital intracardiac anomalies	lower sternal defect
anterior diaphragm defect	supraumbilical abdominal wall defects	
congenital intracardiac anomalies		
supraumbilical abdominal wall defects		
lower sternal defect		

trans-retinoic acid. Retinoic acid is an essential morphogen for embryogenesis as it is required for the formation of the pleuroperitoneal diaphragm [8].

Due to the many descriptions of cases with a wide variety of defects, Toyama [3] developed a classification system in 1972 to better define Cantrell's pentalogy. He divided patients into three groups: complete (Class I), probable (Class II), or incomplete (Class III) pentalogy of Cantrell. Patients were considered complete if they had all five defects, probable if they had four defects, including an intracardiac abnormality and a ventral wall defect, and incomplete if they did not have the intracardiac defect or one or more of the remaining defects that prevented classification as certain or probable (Tab. 1).

Recent studies have shown that the classification of Cantrell's pentalogy is not as important as a good description and understanding of the anomalies involved [10]. Kubba et al. [11] described Cantrell's hexalogy, which includes the complete pentalogy plus the presence of a single umbilical artery. The presence of an omphalocele is immediately apparent after birth of Cantrell's pentalogy. The complete combination of defects gives the appearance of a pulsating mass visible and palpable under the skin, in the lower chest and upper abdomen upon physical examination [12]. Gastroschisis, absent umbilicus, and diastasis of the rectum have also been reported, but their incidence has not been quantified due to the paucity of described cases [5].

Postnatal echocardiography is essential to confirm the prenatal diagnosis. Cardiac malformations are common in Cantrell's pentalogy with the most common being: ventricular septal defect, atrial septal defect, left ventricular diverticulum, pulmonary stenosis or atresia, tetralogy of Fallot (20%), dextrocardia, patent ductus arteriosus, hypoplastic left heart syndrome, and transposition of the great arteries and left superior vena cava [1,13–15]. Ectopia cordis is a particularly characteristic and dramatic finding in which the heart is totally or partially outside the chest cavity due to a defect of the lower sternum [8,14]. Ectopia cordis is classified into four subtypes based on the anatomical location of the heart:

- thoracic (60%);
- abdominal (30%);
- thoracoabdominal (7%);
- cervical (3%) [16].

Cantrell's pentalogy can manifest in a variety of forms depending on the defect. Some authors postulate that the degree of pulmonary hypoplasia is more indicative of poor prognosis than any specific classification system used [5,10]. Additional anomalies are present in up to 28% of affected individuals, with associations described as: cleft lip, cleft palate, encephalocele, hydrocephalus, pulmonary hypoplasia, adrenal hypoplasia, gallbladder agenesis, renal agenesis, polysplenia, colonic malrotation, intestinal herniation into the pericardium and limb defects including clubfoot, absence of tibia and radius, and hypodactyly [8,16–18]. Differential diagnoses for Cantrell's pentalogy include isolated ectopia cordis, isolated abdominal wall defects (omphalocele), amniotic band syndrome, limb-body wall complex, and isolated thoracic ectopia [19,20].

Conclusion

In summary, the aim of this case report was to review the literature and raise awareness of the early diagnosis of Cantrell's pentalogy so that pregnant women can be supported, guided, and referred to referral services from the beginning of pregnancy. In addition, early diagnosis helps to define the birth plan, obstetric and neonatal management, and to program surgical correction.

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ORCID of authors

M. E. M. Albrecht 0009-0002-6859-7213
R. Sevillano Filho 0009-0005-5211-9729
E. Araujo Júnior 0000-0002-6145-2532

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Prof. Edward Araujo Júnior, MD, PhD
Rua Belchior de Azevedo
156 apto. 111 Torre Vitoria
Vila Leopoldina
CEP 05089-030
São Paulo-SP, Brazil
araujojred@terra.com.br

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