Pentalogy of Cantrell in the human foetuses: A rare congenital malformation

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Abstract

Introduction

Pentalogy of Cantrell consists of the following five congenital major malformations: (a) a defect in the anterior diaphragm, (b) a midline supraumbilical anterior abdominal wall defect, (c) a defect in the diaphragmatic pericardium, (d) various congenital cardiovascular malformations and (e) a defect in the lower part of the sternum typically with ectopia cordis. Moreover, additional features may exist to a various extent. The pathogenesis of pentalogy of Cantrell remains uncertain and most of the cases are thought to be sporadic. Genetic and environmental factors or disrupted defects of the vessels have also been implicated. Prenatal diagnosis of pentalogy of Cantrell is easily obtained when malformations such as ectopia cordis with omphalocele or other midline abdominal wall defects are visible during the foetal ultrasound scans. The diagnosis of pentalogy of Cantrell with ultrasonography is made after the 12th week of gestation, because of the normal bowel herniation outside the abdomen before that time and offers the option of termination of the pregnancy in cases with complexity of the cardiac defects and serious associated malformations. With the Color and Power Doppler ultrasound scans the heart is easily recognized protruding outside the thorax.

Also, MRI enhances the visualization of the defects, confirms the diagnosis and guides the surgical decisions. In patients choosing to continue the pregnancy the best treatment approach includes a multispecialty medical team and the surgical corrections should be attempted at the same time soon after delivery. The aim of this review is to remind in Obstetricians Gynaecologist the rare entity of pentalogy of Cantrell.

Conclusion

The pentalogy of Cantrell is an extremely rare entity with a generally poor prognosis. The treatment of all the congenital heart defects found in this entity is very important for the long-term prognosis of children.

Introduction

Pentalogy of Cantrell is a high mortality congenital anomaly first described by Cantrell and colleagues in 1958, who reported 5 neonates with this anomaly.¹ Other synonyms of the syndrome include: Cantrell - Haller - Rawitch syndrome, pentalogy syndrome, thoraco-abdominal ectopia cordis and peritoneopericardial diaphragmatic hernia.²³ The prevalence of Pentalogy of Cantrell ranges from 1:65 000 to 1:200 000 births with a 2:1 male predominance and less than 200 cases reported in the medical literature around the world.⁴⁵

Pentalogy of Cantrell consists of the following five major features, although additional features may exist to a various extent: (a) a defect in the anterior diaphragm, (b) a midline supraumbilical anterior abdominal wall defect, (c) a defect in the diaphragmatic pericardium, (d) various congenital cardiovascular malformations and (e) a defect in the lower part of the sternum typically with ectopia cordis. Ectopia cordis is the displacement or evagination of the heart through the abdominal - thoracic wall defect and outside the body and is divided into cervical, cervico - thoracic, thoraco - abdominal and abdominal types depending on the location of the displaced or eventrated heart.⁶⁷ When foetal ectopia cordis is detected then the physicians should look for the other features of Pentalogy of Cantrell.⁶

A classification of three classes has been suggested by Toyama with a review of 61 cases: in Class 1 the patient has all five defects (definite diagnosis), in Class 2 the patient has 4 defects, including intracardiac and midline anterior abdominal wall abnormalities (probable diagnosis), while in the Class 3 the patient shows various combinations of defects with a defect of the lower part of the sternum always present (incomplete diagnosis).⁸

Associated intracardiac anomalies described in Pentalogy of Cantrell are atrial septum defects (ASD), ventricular septum defects (VSD), single atrium, Ebstein’s anomaly, tricuspid atresia, tetralogy of Fallot, left ventricle diverticulum, pulmonary stenosis and cyanotic tricuspid atresia.⁹¹⁰¹¹¹² Defects of the sternum include a cleft sternum and absence of the entire sternum.¹⁰

The main abdominal wall malformations include epigastric hernia, umbilical hernia, diastasis recti and omphalocele which is most commonly found.¹⁰¹² Other possible extracardiac anomalies include craniofacial anomalies (e.g. cleft lip, cleft palate), central nervous system anomalies (e.g. hydrocephalus, meningomyelocele, anencephalia, encephalocele, exencephaly, spina bifida and crianaorachischisis), thoracic malformations (e.g. lung hypoplasia), abdominal organ abnormalities (e.g.
polysplenia, galbladder agenesis, malrotation of the colon, hernia of the bowel into the pericardial cavity, adrenal aplasia, renal dysplasia or agenesis, pyelectasia), skeletal malformations (e.g. arthrogryposis, club foot, absence of tibia or radius, hypodactyly), genitalia abnormalities (e.g. undescended testicle) and cystic hygroma. The aim of this review is to make Obstetricians Gynaecologists familiar with the rare entity of pentalogy of Cantrell.

Discussion

Embryology

The pathogenesis of pentalogy of Cantrell remains uncertain, whereas genetic and environmental factors or disrupted defects of the vessels have been implicated with most of the cases thought to be sporadic. The condition is believed to be caused by a failure of the lateral folds of the mesoderm to migrate and fuse in the medial line of the thoracic and abdominal region properly during the 14th to 18th day of the embryonic development, resulting in defect of the thoraco - abdominal wall. Also a failure of the development of the lateral mesodermal segment during the same period causes failure of the development of the transverse septum of the diaphragm resulting in diaphragmatic defect. Chorionic or yolk sac rupture is a possibility for the pathogenesis of pentalogy of Cantrell. The variability of the defects found in the three Classes of pentalogy of Cantrell could be explained by the differences of the time they occur. It has been suggested that the complete pentalogy of Cantrell results when the mesodermal failures occur before the differentiation of the mesoderm into splanchnic and somatic layers, while the heart is not involved when the mesodermal failures occur after this differentiation.

Regarding the genetic pathogenesis of pentalogy of Cantrell, alterations in the genes involved in the normal development of midline structures such as in SHH, BAPX1, BMP2 (Bone morphogenetic protein-2), MID1 and MID2 genes might be responsible for this entity. HOX genes are other candidate-genes for the pathogenesis of pentalogy of Cantrell as they are responsible for the neural cell crest migration during the fourth week of gestation, the formation of the endocardial cushion and the fusion of bilateral septal folds. Also alterations in TAS gene, which is mapped on the Xq25-q26.1 area, seem to have some roles in the defects reported in pentalogy of Cantrell. Alterations in the genes NKX2.5 and TBX5, which are involved in the normal development of the conductive tissue of the heart and the cardiac septa respectively play important role for the pathogenesis of this entity. In addition, X-linked or autosomal recessive inheritance has been suggested. For the gene alterations found in pentalogy of Cantrell, environmental and chemical mutagens seem to be responsible. Chromosomal abnormalities, trisomies such as trisomy 13, 18, 21 and the Turner syndrome are also involved in the formation of pentalogy of Cantrell in some cases.

Prenatal Diagnosis

Ultrasoundography is helpful for the diagnosis of pentalogy of Cantrell when malformations such as ectopia cordis with omphalocele or other midline abdominal wall defects are visible. In this case, the additional features of the syndrome should be looked into. Figure 1 shows the ventration of the foetal abdominal contents outside the body with ectopia cordis at a second trimester ultrasound scan. With the Color and Power Doppler ultrasound scans the heart is easily recognized protruding outside the thorax and there is no doubt about the diagnosis of the ectopia cordis. Figures 2 and 3 demonstrate a complete ectopic foetal heart with Color and Power Doppler sonograms in a second trimester foetus (14-15 weeks of gestation). The diagnosis of pentalogy of Cantrell is made after the 12th week of gestation, because of the normal bowel herniation outside the abdomen before that time. The early diagnosis of the syndrome offers the option of early termination of the pregnancy. Small defects are difficult for ultrasonographic diagnosis when they are located in the sternum, pericardium or diaphragm and without any evident herniation of the heart. The 3D obstetric ultrasonography can be used for confirmation of the malformation during the second and third trimesters of pregnancy. With the foetal echocardiography the complexity of the cardiac defects is well evaluated.

Also, MRI enhances the visualization of the defects, confirms the diagnosis and guides the surgical decisions. The differential diagnosis of pentalogy of Cantrell includes isolated ectopia cordis due to a sternal or a pericardial defect, the syndrome of amniotic bands and the foetal abdominal wall defects such as omphalocele and gastrochisis.

In pentalogy of Cantrell the location of the heart in the thorax is normal, while in the isolated ectopia cordis the location of the heart is ectopic without any diaphragmatic, pericardial or abdominal wall defects. Pleural and pericardial effusions are considered as indirect markers for the pathology of Cantrell because these findings are common in this malformation. In pentalogy of Cantrell the abdominal wall defects are periumbilical, while in the syndrome of amniotic bands the defects are present in the extremities with adhering bands.
Management
Termination of pregnancy is considered when prenatal diagnosis suggests complexity of the cardiac defects, serious associated malformations and poor prognosis. In patients choosing to continue the pregnancy the best treatment approach of pentalogy of Cantrell includes a multispeciality medical team of obstetrician-gynaecologists, neonatologists, paediatric cardiologists and cardiac, paediatric and plastic surgeons. The strategies for the preferable treatment of pentalogy of Cantrell depend on the location and extent of the defects and consist of cardiovascular surgery for the congenital heart malformations and the proper surgery for the diaphragmatic, abdominal and associated defects, which surgery should be attempted at the same time soon after delivery.

Conclusion
Pentalogy of Cantrell is an extremely rare entity with a generally poor prognosis, which is incompatible with life for the most cases.

In patients choosing to continue the pregnancy with this entity, soon after delivery the surgical corrections of all the congenital heart defects found are very important for the survival of the infants after treatment and for the long-term prognosis of children.

References