

SWISS SOCIETY OF NEONATOLOGY

Pentalogy of Cantrell

December 2015



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Title figure: Human embryo 6-7 weeks
(source: www.animal-kids.com)

This was the first pregnancy of a 21-year-old G1/P1. Prenatal ultrasound examination at 14 weeks revealed a large anterior abdominal wall defect with protruding bowel, liver, as well as an ectopic heart, consistent with pentalogy of Cantrell. The case was discussed in a multidisciplinary team consisting of gynecologists, pediatric surgeons and neonatologists before counseling the parents.

Given the poor prognosis, the parents opted for termination of pregnancy. At 16 0/7 weeks, RU-486 and misoprostol were administered to induce labor and delivery. A male fetus was delivered within 48 hours. At birth, despite complete lack of any respiratory effort, the heart continued to beat for more than 30 minutes. No other signs of life were detected.

On clinical examination, there was a large abdominal wall defect: liver, spleen, stomach, small and large bowel were displaced from the abdominal cavity (Fig. 1–3). None of these organs were covered by a membrane. At the thoracic level, the entire heart protruded through a sternal and pericardial defect, which allowed identification of the atria and ventricles as well as the inferior and superior venae cavae (Fig. 1, 2).

The parents requested that no autopsy be performed. Therefore, it was not possible to determine if additional malformations, particularly cardiac defects, might have been present.



Fig. 1

Postmortem view of the thoracoabdominal wall defect (liver positioned to the right)



Legend

1 liver, 2 heart, 3 stomach, 4 small and large bowel



Postmortem view of the thoracoabdominal wall defect (liver positioned to the left)



Legend

1 liver, 2 heart, 3 small and large bowel

Fig. 2



Fig. 3

Postmortem view of the thoracoabdominal wall defect (liver positioned to the right)



Legend

1 liver, 2 heart, 3 stomach, 4 spleen, 5 small and large bowel

Pentalogy of Cantrell (PC) (OMIM 313850), or Cantrell-Haller-Ravitsch syndrome, was first described in 1958 and has an estimated incidence of 1 per 65'000 to 1 per 180'000 live births (1–3). In these patients, differentiation of somatic and splanchnic mesoderm, which takes place on day 14–18 of embryonic life, is disturbed. Failure of the transverse septum (arising from the mesoderm) to partially or entirely complete the process of flexion or ventral folding is believed to cause the ventral diaphragmatic defects. Disrupted mesoderm development involving failure of ventral migration can cause sternal and abdominal wall defects (1, 4).

The full spectrum of PC consists of the following five anomalies: a deficiency of the anterior diaphragm, a midline supraumbilical abdominal wall defect (omphalocele, gastroschisis, absent umbilicus), a defect of the lower sternum (cleft or absent sternum), a defect in the diaphragmatic pericardium (ectopia cordis (EC), communication between pericardial and peritoneal cavities), as well as various congenital intracardiac abnormalities such as VSD, ASD, tetralogy of Fallot, or ventricular diverticulum. Diagnosis is possible antenatally (2). Ultrasonography can reveal EC in the first trimester of pregnancy; more challenging is the detection of smaller defects. It is crucial to determine the severity of the disorder in detail in order to discuss the adequate therapeutic steps. In severe cases, early termination of pregnancy or a postnatal palliative approach may have to be considered.

A minority of cases with PC present with these five classical findings. In 1972, Toyama sub-classified PC into three groups, based on the expression of symptoms: class I presents with all five defects and is a definite diagnosis; class II presents with four of the five defects including ventral wall and intracardiac abnormalities, and is a probable diagnosis; and class III presents with varying combinations of defects and is considered an incomplete expression (5).

Prognosis of patients with PC depends on the size of the abdominal wall defect, the type of EC, and the associated anomalies (6). In 2008 van Hoorn et al. reviewed case reports of 58 infants with PC, of which 33 were complete and 23 were incomplete forms. Two patients were incompletely defined (3). Fourteen infants had EC with a structurally normal heart, 16 had a normal cardiac situs with intracardiac defects and 23 infants had both. Twenty-nine infants had further anomalies. Thirty-seven of 58 (64%) patients died within days of birth, including these fetuses in which cases the pregnancy was terminated early as a consequence of the diagnosis of PC. Mortality was higher in infants with the complete form of PC and associated extra-cardiac anomalies, such as cleft lip with or without cleft palate together with encephalocele or patients with trisomy 18. Intracardiac abnormalities itself do not seem to influence prognosis (3).

Most cases so far described were sporadic, but in some families an X-linked pathway has been suggested and in some cases alterations in the region Xq25-q26.1 were found. However, there is still no conclusive data available on the etiology and pathogenesis of PC. In 1990, the thoracoabdominal syndrome (THAS, cytogenetic location Xq25-q26.1) was described for the first time (8). It is characterized by X-linked midline defects including PC, with diaphragmatic and ventral hernias, hypoplastic lung as well as cardiac anomalies (transposition of the great vessels, patent ductus arteriosus). Diaphragmatic and lung anomalies were mostly seen in males, and in the majority of cases the outcome was fatal. There is an association with limb defects in both PC and THAS. This implies that an alteration of genes responsible for limb morphogenesis and fusion of the sternum is likely (9).

Goltz-Gorlin syndrome, also referred to as focal dermal hypoplasia, is another rare congenital multisystem disorder with a vast variety of symptoms due to alterations of ecto- and mesodermal-derived tissue origin. It is an X-linked dominantly inherited disorder with mutations in the *PORCN* gene (codes for a member of the Porcupine protein family which are membrane-bound endoplasmic reticulum proteins). PC can be associated with a mutation within *PORCN*. Smigielski et al. stated uncertainty on whether there are further genetic alterations present in these patients or whether the findings are due to environmental and /or epigenetic factors (8, 10).

In conclusion, pentalogy of Cantrell is a rare, complex disorder including an anterior abdominal wall defect with EC, with poor prognosis, especially in patients with the complete form presenting all five clinical findings and with associated, extracardiac anomalies. A timely antenatal multidisciplinary approach is essential to define the best possible approach for the patient and the family.

For another case report of PC, see COTM October 2004 (*Cantrell's pentalogy: an unusual midline defect*).

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