Heterotaxy syndrome with intestinal malrotation, polysplenia and azygos continuity

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Abstract

Heterotaxy syndrome is a situs anomaly that comprises a large spectrum of cardiac and extracardiac malformations. Its association with intestinal malrotation is frequent. This later might be asymptomatic or manifest by signs of abdominal discomfort or of intestinal obstruction. We report on the case of a full term, small for gestational age neonate in whom heterotaxy syndrome with partial situs inversus abdominalis, intestinal malrotation, polysplenia and vena azygos continuity was diagnosed at prenatal echography. Due to the high risk of volvulus carried by the malrotation, Ladd's procedure was performed at the age of two months. Follow-up examination at the age of four years shows excellent post-operative result and normal development of the child.

Introduction

Heterotaxy is defined as the lateralization defect of normally lateralized thoraco-abdominal organs such as the heart, the liver or the stomach, or as the asymmetry inversion of normally bilateral asymmetric organs such as the lungs. In contrast to the complete inversion (*situs inversus totalis*) where thoraco-abdominal organs are in mirror image arrangement of the normal anatomy, heterotaxy is characterized by partial organ inversion with random distribution (*partial situs inversus or situs inversus ambiguus*).[1] Heterotaxy is rare with an estimated prevalence of 1/10,000.[2]

Multiple congenital malformations are usually associated, in particular heart defects that condition patient outcome.[3] Extra-cardiac anomalies comprise among others rotation defects of the middle intestine that takes place in the 10th week of embryonic development, and that can be complicated by a volvulus.[4]

Case Report

We report the case of a neonate in whom prenatal diagnosis of *situs ambiguus* was done at 31 weeks of gestation.

The pregnancy begun under oral contraceptives and was discovered at 27 weeks of gestation. Gestational diabetes was well controlled by diet.

Prenatal echography showed absent inferior vena cava with azygos continuity, levocardia and normal intracardiac structures (Figure 1). Stomach was visualized on the right side, the gale bladder was in median position with slight leftward deviation. The small intestine was deviated on the left- and the colon on the right side.

Genetic testing on amniotic fluid was normal.

The baby was born after spontaneous delivery. Apgar score was 7 at 1 min and 9 at 5 min.

Birth weight was 2.210 g (<3th percentile), high 46.5 cm (<3th percentile) and head circumference 31 cm (<3th percentile).

Clinical examination was normal.

Abdominal echography and barium transit confirmed the diagnosis of *situs ambiguus* involving stomach, duodenum and small intestine with inversion of the colic arch, persistence of the fetal cecum position in the left hypochondrium as well as an intestinal malrotation with volvulus risk (Figure 2). The liver was in median position, there was a right sided polysplenia.

Additionally, the examination showed frequent gastro-esophageal reflux.

Echocardiography confirmed absent inferior vena cava with azygos continuity, and showed the presence of a slight mitral valve prolapse with mitral regurgitation grade I/IV.

The patient was asymptomatic during the first week of life. She developed afterwards frequent regurgitations and increasing abdominal discomfort that, due to the known intestinal malrotation with volvulus risk, justified surgery. Laparoscopic Ladd's procedure was performed at the age of 2 months. First, anatomical verification showed the right-sided stomach, the median-sided and butterfly-shaped liver, the infra-hepatic right-sided polysplenia (5 spleens), a pre-duodenal portal vein, and incomplete common mesentery with narrow base and contracted Ladd's bands between the epigastric cecum, the mesentery and the ligament of Treitz (Figure 3). The procedure itself consisted of Ladd's bands lysis that permitted to mobilize the ileo-cecal region, to enlarge the mesentery base, to perform appendicectomy and to place the intestine in a situation of complete common mesentery with all the small intestine on the left- and the colon on the right side. The post-operative course was uneventful. The child is well and without any complaint at the age of 4 years.

Discussion

Heterotaxy and intestinal malrotation: embryology

Mechanisms regulating organ lateralization are complex and yet not fully understood. They involve initial molecular lateralization present as early as during the 2nd gestational week. In vertebrates, 5 steps have been identified to establish normal asymmetry: i) signaling upstream of the primitive node, (the node is a transient embryonic organizer that contains monociliated cells with central motile- and peripheral sensory cilia); ii) signaling at the node; iii) generation by the motile cilia of a nodal leftward flow of a fluid that transports morphogenic proteins; iv) asymmetric gene expression transferred from the node to the lateral plate mesoderm; v) signaling from this latter to the organs.

Multiple genes are required for normal ciliogenesis and cilia function that in turn condition normal lateralization. Conversely, abnormal ciliogenesis causes random thora-

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co-abdominal organ distribution, congenital heart defects, and ciliary dysfunction as it is seen in the Kartagener syndrome.[1,5]

Malrotation of the intestine is an example of random distribution of an abdominal organ. The consequences of primary intestinal loop malrotation are duodenal fixation on the right side of the abdominal cavity and cecum fixation below the pylorus. This may cause duodenal compression by thickened peritoneal bands, the so-called Ladd's bands. In addition, duodeno-jejunal junction and cecum are located in the superior and median part of the abdominal cavity, creating a narrow based mesentery. This in turn favors volvulus around the superior mesenteric artery, carrying a high risk of mesenteric ischemia.[6]

Why heterotaxy and intestinal malrotation should be diagnosed before birth

In the absence of severe cardiac defect heterotaxy and intestinal malrotation usually manifest by non-specific symptoms in neonates and infants such as cry and vomiting. For that reason, the diagnosis may be delayed until patient present with intestinal obstruction.[7] If congenital heart defect is present, birth and post-natal care must be planed in order to provide immediate specialized treatment.[8] The prenatal diagnosis of heterotaxy in presence of a cardiac defect must lead to the assessment of the abdominal situs. Genetic counseling is recommended.

Genetics of heterotaxy

Over hundred genes have been identified to play an important role in left-right asymmetry in animals. In human, most cases of heterotaxy are sporadic. Familiar forms exist however, with autosomal recessive inheritance as it is the case for primary cilia dyskinesia. More rarely, there is autosomal dominant inheritance of gene mutation in the Nodal signal transduction pathway or X-linked inheritance of a mutation of ZIC3, a transcription factor that acts upstream of Nodal signaling.[1,5,9]

Last, complex inheritance involves mutations with reduced penetrance and variable expression that suggest the role of environmental factors such as pre-gestational diabetes, exposition to retinoic acid or maternal cocaïn consumption.[1]

Complications due to intestinal malrotation and prevention

In the large majority of cases (90%), volvulus complicating intestinal malrotation occurs in the first year of life, even in the first months (66-80%), respectively.[10] This is the reason why some authors propose a prophylactic Ladd's procedure consisting in the lysis of the Ladd's bands, enlarging the mesenteric base and repositioning of the intestine.[11] While the procedure is commonly accepted in the context of acute volvulus treatment, its indication as a prophylactic procedure in asymptomatic patients is highly controversial. Indeed, a recent study suggests higher morbidity and mortality at subsequent admission in operated patients.[10,12]

In our case, operation indication was guided by the clinical complaints of the infant.

Malformations associated with heterotaxy

Congenital heart defects are part of heterotaxy syndrome in 5-10% of the cases. Their relative frequencies depend on whether heterotaxy is related to asplenia or polysplenia.[13] The spectrum of severity varies from severe defects such as hypoplasic left heart syndrome to less severe such as common atria or even defects without any hemodynamic significance such as bilateral superior vena cava or absent inferior vena cava.[13] This latter anomaly present in our patient is the consequence of early developmental defect of the cardinal system characterized by the failure of connection of the right sub-cardinal vein with the intrahepatic segment of the inferior vena cava.[14]

Other malformations such as polysple-

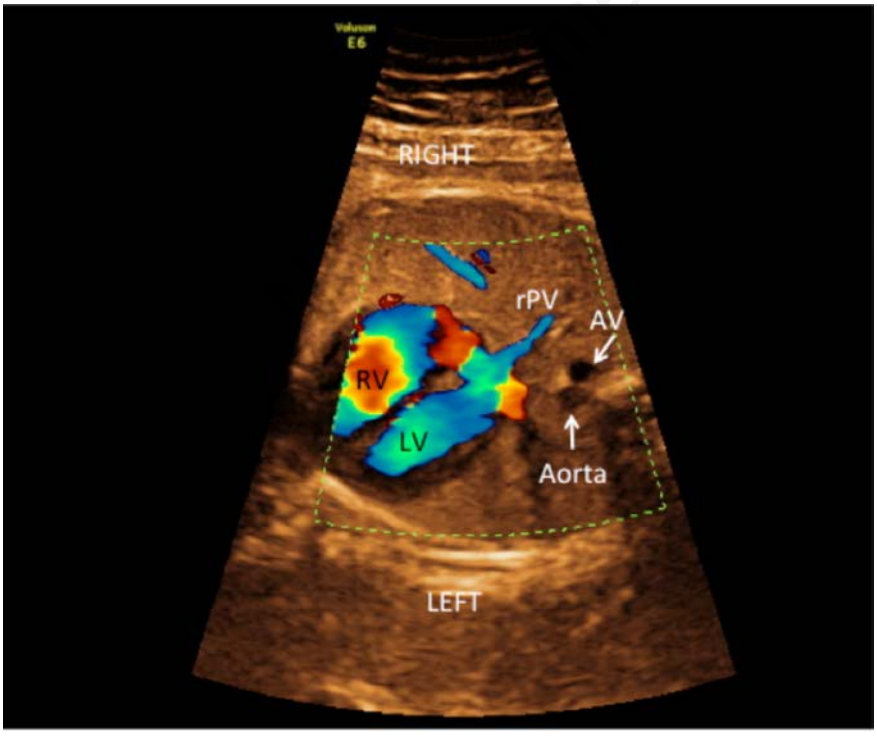

Figure 1. Fetal echocardiography performed at 35 weeks of gestation. The vena azygos (AV) is positioned on the right side of the aorta (Ao). Intracardiac structures are normal. rPV, right pulmonary vein; LV, left ventricle; RV, right ventricle.

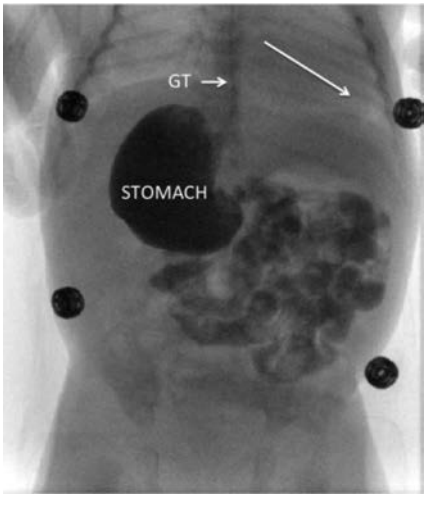

Figure 2. Barium transit showing dextroposition of the stomach. The heart is in normal position (cardiac axis depicted by the arrow). GT, gastric tube showed in the esophagus.

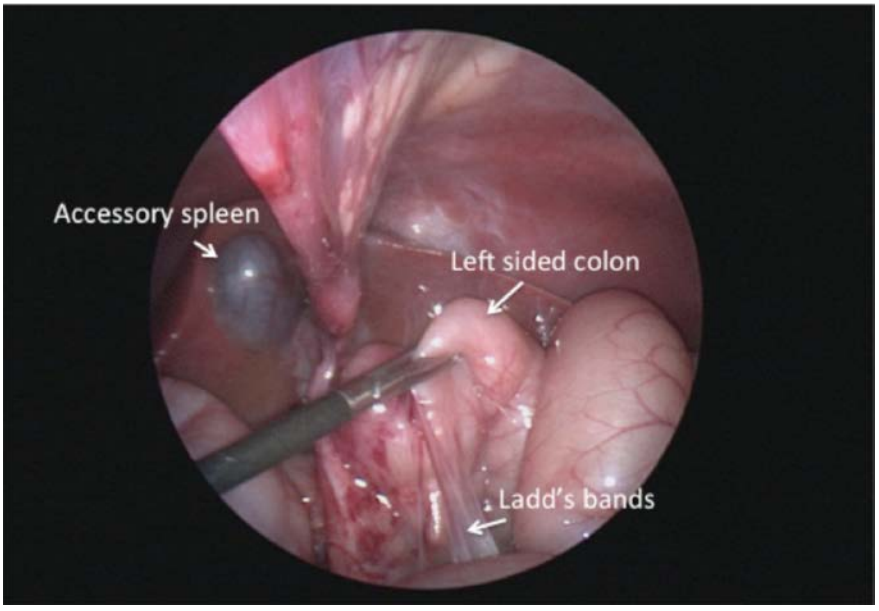

Figure 3. Intraoperative laparoscopic examination showing one of the 5 right-sided spleens, the left-sided colon and Ladd's bands.

nia, asplenia, biliary- or duodenal atresia, polycystic kidney disease, abnormal lung lobe number or anomaly of the median line are also associated.[13,15,16]

It is therefore recommended to perform a complete evaluation of patients with heterotaxy syndrome by chest X-ray, echocardiography, abdominal echography and abdominal resonance magnetic imaging.

Besides structural anomalies, heterotaxy is also related to functional disorders such as ciliary dysfunction. This latter is the hallmark of primary ciliary dyskinesia observed among others in patients with Kartagener syndrome.[17]

Conclusions

Heterotaxy is a rare genetic disorder. The presence of a congenital heart defect conditions overall patient outcome. Prenatal- or early post-natal diagnosis is necessary to optimize patient care. Heterotaxy is frequently associated with intestinal malrotation. If this later has a high risk for volvulus or is symptomatic, Ladd's procedure is generally performed.

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