Heterotaxy syndrome with intestinal malrotation, polysplenia andazygos continuity

Stéphanie Cupers,1 Christine Van Linhout,2 Brigitte Desprechins,2 Léon Rausin,4 Martine Demarche,6 Marie-Christine Seghaye1
1Department of Pediatrics, University Hospital Liège; 2Department of Gynecology and Obstetrics, University Hospital Liège; 3Medical Imaging, University Hospital Liège; 4Department of Medical Imaging, Regional Hospital Center La Citadelle; 5Department of Surgery, Regional Hospital Center La Citadelle, Liège, Belgium

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 azigos 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 ambiguous).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 azigos 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. Appgar score was 7 at 1 min and 9 at 5 min.

Birth weight was 2.210 g (<3rd percentile), high 46.5 cm (<3rd percentile) and head circumference 31 cm (<3rd 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 azigos continuity, and showed the presence of a slight mitral valve prolapse with mitral regurgitation grade 1/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 laterization 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-
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.8

**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 planned in order to provide immediate specialized treatment.9 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

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 cocaine consumption.7

**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 hypoplastic 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-
nia, asplenia, biliary- or duodenal atresia, polycystic kidney disease, abnormal lung lobe number or anomaly of the median line are also associated.\textsuperscript{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.\textsuperscript{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.

References

1. Sutherland MJ, Ware SM. Disorders of left-right asymmetry: heterotaxy and situs inversus. Am J Med Genet Part C Semin Med Genet 2009;151C:307-17.
2. Lin AE, Ticho BS, Houde K, et al. Heterotaxy: associated conditions and hospital-based prevalence in newborns. Genet Med 2000;2:157-72.
3. Patel A, Costello JM, Backer CL, et al. Prevalence of noncardiac and genetic abnormalities in neonates undergoing cardiac operations: analysis of the society of thoracic surgeons congenital heart surgery database. Ann Thorac Surg 2016;102:1607-14.
4. Gottschalk I, Stressig R, Ritgen J, et al. Extracardiac anomalies in prenatally diagnosed heterotaxy syndrome. Ultrasound Obstet Gynecol 2016;47:443-9.
5. Tena TC, Burkhalter MD, Philipp M. Left-right asymmetry in the light of TOR: an update on what we know so far. Biol Cell 2015;107:306-18.
6. Morris G, Kennedy A Jr, Cochran W. Small bowel congenital anomalies: a review and update. Curr Gastroenterol Rep 2016;18:16.
7. Stephens LR, Donoghue V, Gillick J. Radiological versus clinical evidence of malrotation, a tortuous tale - 10-year review. Eur J Pediatr Surg 2012;22:238-42.
8. Seghaye MC. Management of children with congenital heart defect: state of the art and future prospects. Future Cardiol 2017;13:65-79.
9. Sutherland MJ, Wang S, Quinn ME, et al. Zic3 is required in the migrating primitive streak for node morphogenesis and left-right patterning. Hum Mol Genet 2013;22:1913-23.
10. Salavitabar A, Anderson BR, Aspelund G, et al. Heterotaxy syndrome and intestinal rotational anomalies: impact of the Ladd procedure. J Pediatr Surg 2015;50:1695-700.
11. Torres AM, Ziegler MM. Malrotation of the intestine. World J Surg 1993;17:326-31.
12. Lampl B, Levin TL, Berdon WE, et al. Malrotation and midgut volvulus: a historical review and current controversies in diagnosis and management. Pediatr Radiol 2009;39:359-66.
13. Degenhardt K, Rychik J. Fetal situs, isomerism, heterotaxy syndrome: diagnostic evaluation and implication for postnatal management. Curr Treat Options Cardiol Med 2016;18:77.
14. Malaki M, Willis AP, Jones RG. Congenital anomalies of the inferior vena cava. Clin Radiol 2012;67:165-71.
15. Tawfik AM, Batouty NM, Zaky MM, et al. Polysplenia syndrome: a review of the relationship with viscera-atrial situs and the spectrum of extra-cardiac anomalies. Surg Radiol Anat 2013;35:647-53.
16. Ware SM, Gunay-Aygun M, Hildebrandt F. Spectrum of clinical diseases caused by disorders of primary cilia. Proc Am Thorac Soc 2011;8:444-50.
17. Narasimhan V, Roy S. Cilia: organelles at the heart of heart disease. Curr Biol 2015;25:R549-68.

Case Report

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