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Is every innocent murmur innocent?

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Rüegger C, Malär R, Schraner T, Weber R, Arlettaz Mieth R, Clinic of Neonatology (RC, AMR), University Women's Hospital Zurich, Switzerland, Division of Hematology (MR), Department of Radiology (ST) and Division of Cardiology (WR), Department of Pediatrics, University Children's Hospital Zurich, Switzerland

We present the case of a female neonate born to a 32 year-old G2/P2 at 40 weeks of gestation. With the exception of a non-detectable stomach bubble, prenatal ultrasound scans (including amniotic fluid volumes) had always been normal. An elective primary caesarean section was performed due to transverse presentation and suspected cephalopelvic disproportion. The neonatologist was present during delivery in order to exclude oesophageal atresia suspected on fetal ultrasound scan. Postnatal adaption was uneventful with Apgar scores of 8, 9, 9 at 1, 5, and 10 minutes, respectively. By introducing a feeding tube into the stomach, an oesophageal atresia could be ruled out easily. The length was 54.5 cm (P 75-90), but both, the birth weight (4800 g) and the head circumference (38.5 cm) exceeded the 97. Percentile.

Routine physical examination on day two was inconspicuous except for a systolic murmur, which was unchanged one day later. Although the murmur was clinically considered to be innocent, echocardiography was performed to reassure the mother. The heart was functionally and anatomically normal except for a persistent ductus arteriosus (PDA) and a patent foramen ovale (PFO), both with left-to-right-shunting and without hemodynamic relevance. A subcostal view, however, revealed an abdominal situs ambiguous with absence of the vena cava inferior, vena azygos continuity and a left sided aorta. Consecutive abdominal

ultrasound confirmed both a right-sided stomach and a midline liver (Fig. 1). No spleen could be detected.

On a blood smear, there were Howell-Jolly (Fig. 2) as well as Heinz bodies (Fig. 3) consistent with anatomical or functional asplenia. Together with the sonographic findings, a laterality sequence, particularly "isomerism of the atrial appendages" or "atrial isomerism" with functional asplenia was assumed and antibiotic prophylaxis with amoxicillin was initiated. To test splenic reticuloendothelial function, Howell-Jolly body and pocked (pitted or vacuolated) erythrocyte count were performed (Tab. 1).

The pocked erythrocyte count in the first blood sample at 2 weeks of age was normal. In the second sample, however, an increase in pocked red cell count as well as persistent Howell Jolly bodies were observed. These findings were consistent with an inadequate function of the spleen. By the age of 19 weeks, laboratory findings had normalized, indicating sufficient splenic function, and the amoxicillin prophylaxis was stopped.

For accurate assessment of the laterality sequence, echocardiography was repeated, confirming previously suspected interrupted inferior vena cava with azygos continuity, leading into the venous angle. The superior vena cava emptied into a right-sided left atrial appendage (Fig. 4, 5). The PDA as well as the PFO could still be detected but continued to be hemody-

namically irrelevant. Electrocardiography showed an atrial rhythm with a rate of 126 bpm. A chest X-ray was normal except for suspected presence of two left-sided bronchi (Fig. 6).

With thoracic bilateral left-sidedness and an abdominal situs ambiguous, with multiple ectopic spleens initially correlating to a functional asplenia, the diagnosis of a left isomerism was suspected.

Abdominal ultrasound: right-sided stomach (S), midline liver (L) and descending aorta (arrowhead).

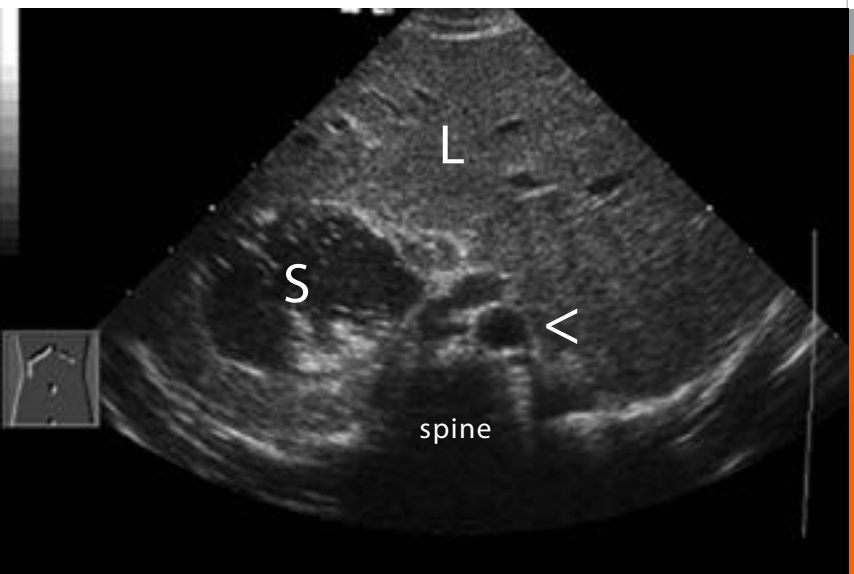

Fig. 1

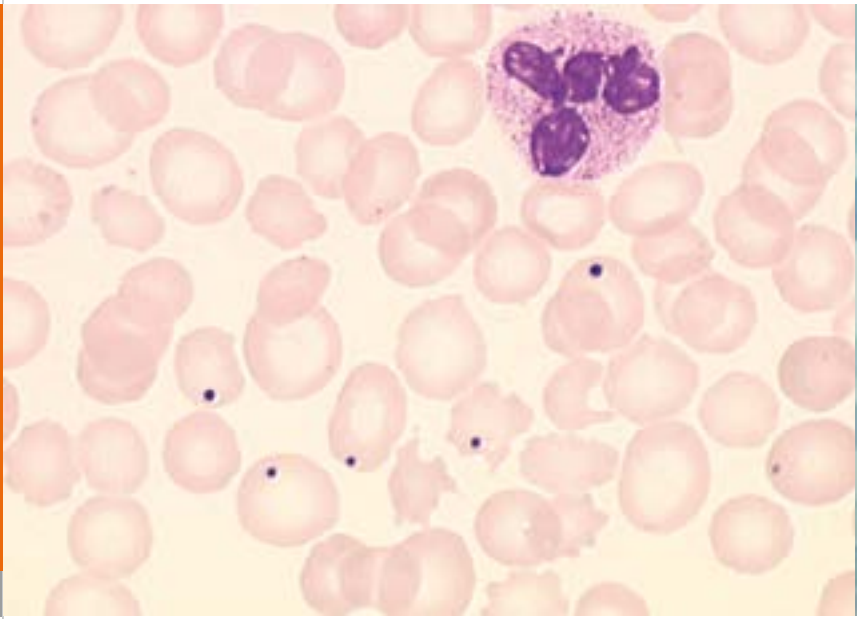

Fig.2

Blood smear with Howell-Jolly bodies (May-Grünwald-Giemsa stain).

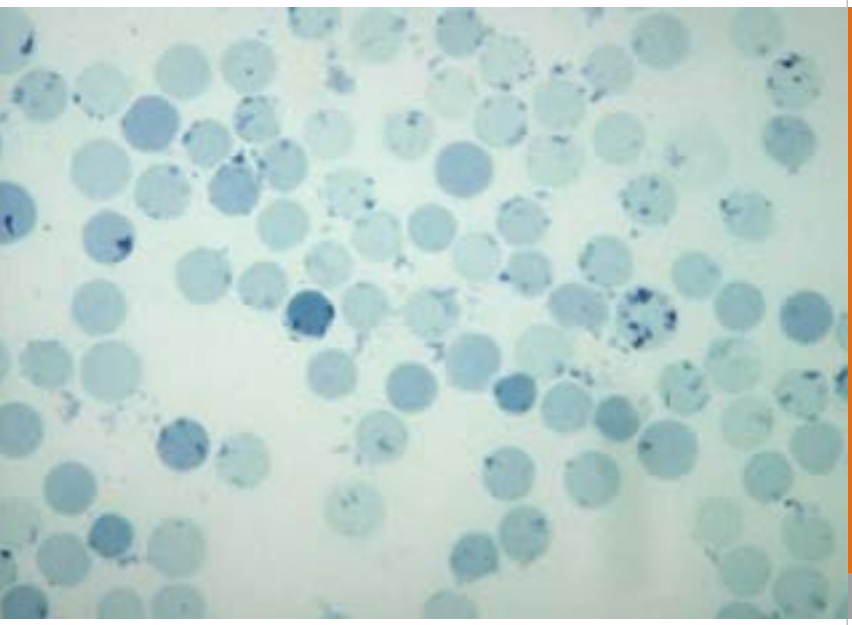

Fig.3

Blood smear with Heinz bodies (supravital stain).

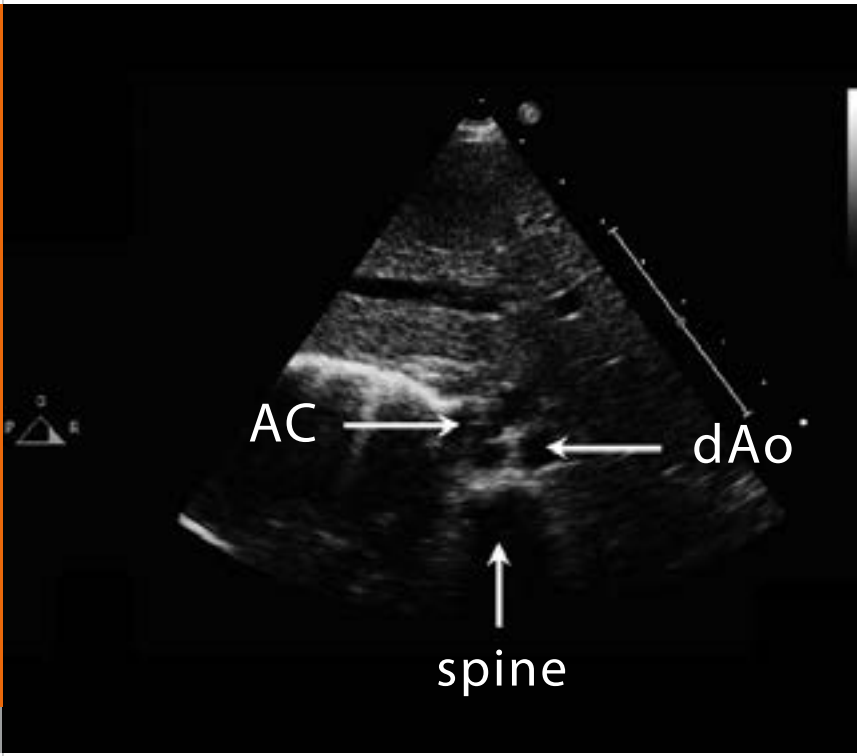

Fig. 4

Echocardiographic transverse abdominal view showing the left descending aorta (dAo) and azygos continuity (AC). No intrahepatic part of the vena cava inferior can be visualized at their typical right sided position.

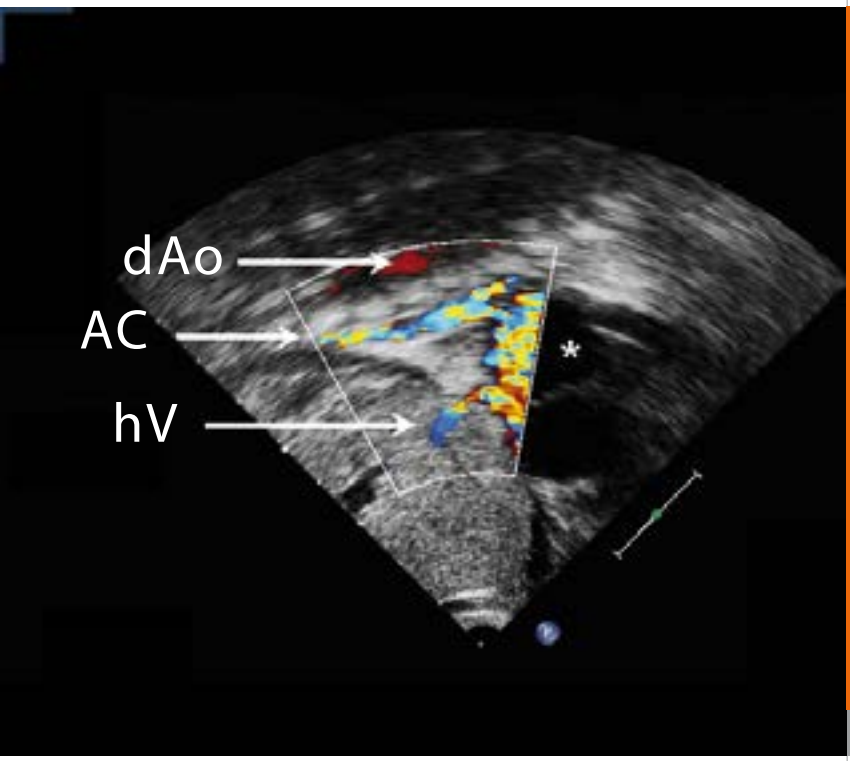

Fig. 5

Echocardiographic sagital abdominal view showing the left descending aorta (dAo) and azygos continuity (AC). Hepatic veins (hV) are joining directly the right atrium (asterisk) instead of entering the vena cava inferior.

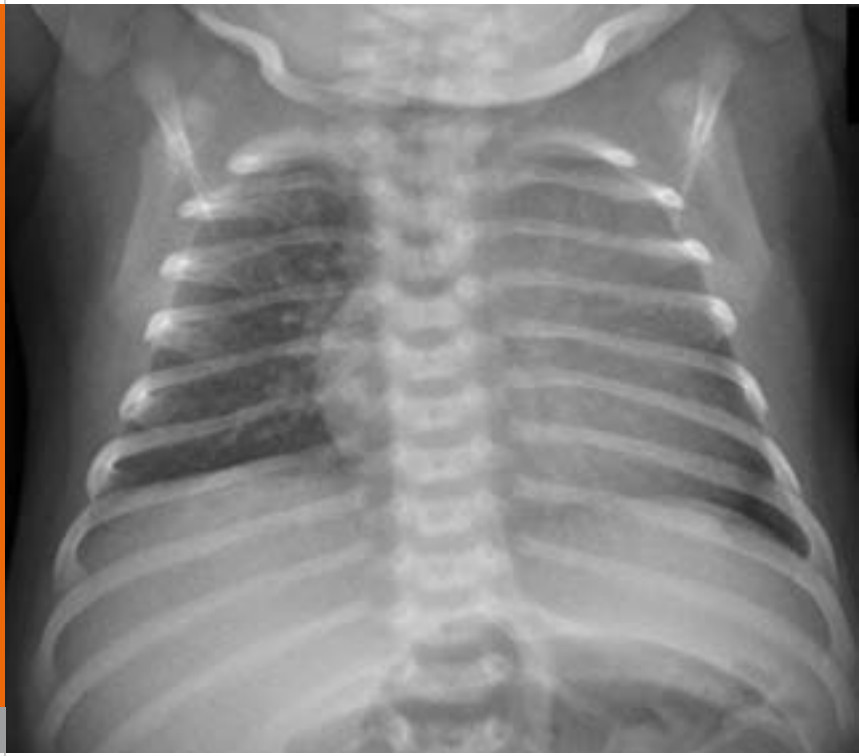

Fig. 6

Chest X-ray.

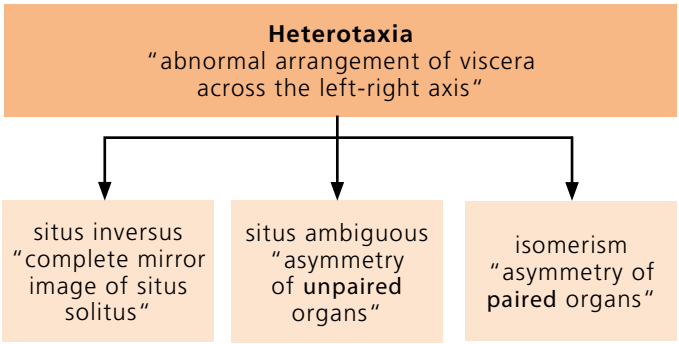

Fig. 7

Overview of laterality disturbances.

Interference phase contrast microscopy showing pocked (pitted or vacuolated) red blood cells (arrows).

Fig. 8

Table 1

Age (weeks)	2	5	19
Howell-Jolly bodies (%, normal 0%	0.4	0.2	0.1
Pocket red blood cells (%, normal <3%)	0.7	3.4	0.3

Howell-Jolly bodies and pocked red blood cell counts.

Table 2

Incidence of various cardiovascular abnormalities in patients with left isomerism.

Cardiovascular abnormality	Incidence (%)
Interrupted inferior vena cava	88
Atrioventricular septal defect	68
Complete heart block	38
Viscerocardiac heterotaxy	54
Right ventricular outflow tract obstruction	35
Right ventricular outflow tract obstruction	21
Double outlet right ventricle	23
Total anomalous pulmonary venous drainage	5

The failure to generate left-right asymmetry or normal situs results in a spectrum of laterality disturbances. Heterotaxia, which means abnormal arrangement of viscera across the left-right axis, is a common term used for all laterality disturbances within this spectrum. Three types of anatomical derangements can be recognized, each corresponding to defects in situs orientation, asymmetry of unpaired organs or asymmetry of paired organs (Fig. 7) (1).

Heterotaxia, which mainly occurs sporadic and non-syndromic, is genetically highly heterogeneous with monogenic, polygenic or multifactorial causes. In less than 5%, familial cases with autosomal dominant, recessive or X-linked inheritance have been described and present either as an isolated malformation or in the context of a disorder with additional congenital anomalies (2).

Clinically, laterality disorders are frequently linked with organ malformations and/or functional disorders. Situs ambiguous can be associated with complex cardiovascular malformations as well as anomalies of the spleen and the gastrointestinal system (3). Over 80% of children with situs ambiguous present with complex congenital heart disease compared to only 3-9% in children with situs inversus totalis. However, the risk of congenital heart defects in situs inversus totalis is still higher than in situs solitus (0.6%) (4).

Isomerism refers to a defect in asymmetry of paired organs that usually have distinct right and left forms, but in this condition, are mirror images. Left atrial isomerism is also known as bilateral left-sidedness sequence or polysplenia syndrome. Right atrial isomerism, also known as bilateral right-sidedness sequence, asplenia syndrome or Ivemark syndrome is almost invariably related to complex cardiac anomalies and other organ malformations.

Left atrial isomerism is associated with paired left-sided viscera, while right-sided structures may be absent. Bilateral morphologically left atrial appendages, bilateral morphologically left (bilobed) lungs, multiple splenules (accessory spleens), a malpositioned stomach, malrotation of the intestines and a midline liver are typical features of left isomerism. The echocardiographic findings are varied. Interruption of the inferior vena cava with azygos continuity is almost pathognomonic. The incidence of cardiovascular abnormalities in fetuses with left isomerism described in the literature are listed in table 2 (5, 6).

The absence of a true right atrium and, therefore, the sinus node in left isomerism often leads to rhythm disturbances. Three types of cardiac arrhythmias may occur: sinus node dysfunction, atrioventricular block and dual atrioventricular nodal pathways. Slow atrial rates associated with junctional escape are common and do not alter the prognosis. Nevertheless,

implantation of a pacemaker can be necessary in some cases (7, 8).

Multiple spleens along the greater curvature of the stomach are a typical feature in left atrial isomerism. Although splenic activity in the polysplenic state is generally expected to be normal, functional asplenia can occur. In our case, characteristic morphological abnormalities of the red blood cells such as Howell-Jolly bodies and pocked red cells allowed the diagnosis of functional asplenia initially, but together with the growth of all other organs splenic activity improved. Looking for erythrocytes with Howell-Jolly bodies (round, purple staining nuclear fragments of DNA resulting from incomplete nuclear expulsion) in a peripheral blood smear is a simple screening test for asplenia but is less sensitive in hyposplenia. The pocked red cell count (pit count) is a more sensitive test for splenic clearance. The test identifies the percentage of erythrocytes with autophagic vacuoles adjacent to the cell membranes (senescent erythrocytes) which should be cleared to values below 1.5% in the presence of a functional spleen (Fig. 8).

People with a lack of functional splenic tissue are at high risk for infections caused by encapsulated organisms such as Streptococcus pneumoniae, Haemophilus influenzae type b and Neisseria meningitidis. Overwhelming postsplenectomy sepsis (OPSS) remains a significant concern in the asplenic patient (mortality

rate of nearly 50%). Especially children less than 2 years of age are at high risk to develop OPSS. Therefore, antibiotic prophylaxis with amoxicillin or penicillin V is strongly recommended for children < 5 years of age. Furthermore, pneumococcal and Neisseria meningitidis group C vaccination is indicated for all children with congenital asplenia, hyposplenism or post-splenectomy state (9).

Left atrial isomerism should be accurately diagnosed in the prenatal period in order to allow appropriate counselling of parents and to plan delivery and neonatal management. At the routine anomaly scan, the condition can be identified as a result of complex combinations of structural cardiac malformations or visceroatrial heterotaxy. Discontinuity of the inferior vena cava for example represents an excellent marker of left isomerism. Additionally, left atrial isomerism appears to be associated with an increased nuchal translucency and can present with rhythm disturbance or even hydrops in the first trimester of pregnancy. Morbidity and mortality in the neonatal period are mainly determined by the cardiac defects whereas the visceral anomalies affect the long-term outcome of these patients. Varying degrees of malrotation and malfixation of the bowel, preduodenal portal vein, gastric volvulus, oesophageal hiatus hernia and annular pancreas are common in left atrial isomerism.

REFERENCES

1. Peeters H, Devriendt K. Human laterality disorders. Eur J Med Genet 2006;49:349-362

2. Nora JJ, Berg K, Nora AH. Cardiovascular diseases. Genetics, epi demiology and prevention. Oxford monographs on medical genetics n. 22, Oxford University Press, New York, 1991

3. Kosaki K, Casey B. Genetics of human left-right axis malformations. Semin Cell Dev Biol 1998;9:89-99

4. Merklin RJ, Varano NR. Situs inversus and cardiac defects. A study of 111 cases of reversed asymmetry. J Thorac Cardiovasc Surg 1963;45:334-342

5. Pepes S, Zidere V, Allan LD. Prenatal diagnosis of left atrial isomerism. Heart 2009;95:1974-1977

6. Lim J, McCrindle B, Smallhorn JF, et al. Clinical Features. Management and outcome of children with fetal and postnatal diagnoses of isomerism syndrome. Circulation 2005; 112:2454-2461

7. Hassem Sobrinho S, Moscardini AC, et al. Sinus node dysfunction in a patient with left atrial isomerism. Arq Bras Cardiol 2006;87:e122-123

8. Wren C, Macartney FJ, Deanfield JE. Cardiac rhythm in atrial isomerism. Am J Cardiol 1987;59:1156-1158

9. Engelhardt M, Haas PS. Prävention von Infektionen. Dtsch Med Wochenzeitschrift 2009;134:897-902

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CONTACT

Swiss Society of Neonatology
www.neonet.ch
webmaster@neonet.ch