CASE REPORT

Right Heterotaxy With Hirschsprung’s Disease—
A New Association

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A baby girl with prenatal diagnosis of complex cardiac anomalies and diaphragmatic hernia was born at 36 weeks of gestation. At 4 hr of life, the baby developed respiratory distress and was intubated. She was found to have right heterotaxy with total anomalous pulmonary venous drainage into the portal vein, five hepatic veins draining the liver and intrathoracic herniation of the stomach. The child also developed abdominal distension on the second day of life with passage of scanty meconium. The diagnosis of Hirschsprung’s disease (HD) was confirmed by histology. HD in association with right heterotaxy has not been reported earlier. The association of heterotaxy with HD in our patient raises a possible genetic link between the two anomalies that needs further research. Clin. Anat. 00:000–000, 2010.

Key words: heterotaxy; asplenia; Hirschsprung’s disease; intrathoracic stomach

INTRODUCTION

The position of the heart and viscera relative to midline of the body is referred to as “situs.” The normal position of the heart and abdominal viscera, with the cardiac apex, spleen, stomach, and aorta located on the left and the liver and inferior vena cava (IVC) located on the right is termed as situs solitus. In situs inversus, the arrangement is mirror image of situs solitus. Situs ambiguous, also known as heterotaxy or isomerism represents a spectrum of abnormalities characterized by symmetrical arrangement of the organs, which are normally asymmetrical (Applegate et al., 1999; Fulcher and Turner, 2002).

In classical right heterotaxy, bilateral right sidedness occurs. The right and left lungs have three lobes each and the main bronchus runs above the main pulmonary artery on both sides. The liver extends across the midline to the left side of the abdomen and the spleen is absent. Hence, right heterotaxy is also referred to as right isomerism with asplenia. Most patients with asplenia have a common single atrium (Applegate et al., 1999; Fulcher and Turner, 2002). In classical left heterotaxy, bilateral left sidedness occurs; the lungs on both sides have two lobes and the main pulmonary artery arches over the main bronchus on both sides. Spleen occupies both right and left quadrants and hence left heterotaxy is also referred to as left isomerism with polysplenia. Polysplenia is often associated with abnormal pulmonary vein entry to IVC and either absent or anomalous termination of IVC into azygos veins (Applegate et al., 1999).

However, such classical combinations of anomalies may not be present in all patients and frequently there is an overlap of multisystem anomalies in patients with asplenia and polysplenia syndromes. Hence, it is proposed that positional abnormalities of the abdominal and thoracic viscera (other than situs inversus) be grouped under the common term heterotaxy with detailed description of the anatomy in parentheses e.g. right heterotaxy (bilateral trilobed lungs, asplenia, malrotation). Such a terminology emphasizes the clinical importance of all the components of the heterotaxy syndrome (such as asplenia that renders the patient immune deficient and malrotation which is prone for volvulus) even to those who are not familiar with these anomalies (Applegate et al., 1999).

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CASE REPORT

A baby girl with prenatal diagnosis of complex cardiac anomalies and diaphragmatic hernia was born at 36 weeks of gestation by vaginal delivery. At 4 hrs of life, the baby developed respiratory distress and was intubated. The following anomalies in the thorax and abdomen were demonstrable: both lungs were trilobed, and the upper lobe bronchus was epiaresetal on both sides. There was dextrocardia with a single atrium. The right and left innominate veins in the thorax formed the superior vena cava that opened on the left side of the single atrium. The suprahepatic IVC drained into the atrium on its left side. The right ventricle was located anteriorly and the left ventricle posteriorly. The aorta arose from the left ventricle and curved towards the left as in normal anatomy. The liver bridged across the upper abdomen to the left and the spleen was absent (Fig. 1). At least five main hepatic veins were present that drained into the IVC (Fig. 2).

The right renal vein crossed to the left behind the aorta to drain into the infrahepatic IVC, while the left renal vein drained into the IVC at a higher level than right. The right renal, left renal, and superior mesenteric arteries arose from a common trunk off the aorta. The superior mesenteric vein drained into a large main portal vein that further divided into the left and right portal veins. There were four pulmonary veins in the thorax, two on each side and all four drained into a large vessel outside the pericardium. This vessel coursed down into the abdomen to open into the portal vein which was larger than normal (Figs. 3A–3C).

In the lower thorax and abdomen, the aorta descended in midline with the infrahepatic IVC to the left of spine (Fig. 1). Kidneys and the urinary bladder were normal. Barium meal revealed a centrally located stomach, loss of C-configuration and inferior location of third part of duodenum with the duodenojejunal flexure closer to midline at the third lumbar vertebra. The gastro-esophageal junction, fundus, and proximal half of body of the stomach were located above the diaphragm, consistent with sliding type of hiatus hernia. There was significant esophageal reflux till the cervical esophagus. The child developed abdominal distension on the second day of life with passage of scanty meconium. Initial lower contrast study did not reveal any transition zone. However, axial CT abdominal scan done in third week after birth showed the dilated upper sigmoid with transition zone and narrow lower sigmoid.

The small bowel was seen centrally with peripheral location of the large bowel. The patient required repeated rectal wash out to clear the bowel. Suction rectal biopsy showed absence of ganglion cells and the presence of hypertrophic nerve bundles in the submucosa, confirming the diagnosis of Hirschsprung’s disease (HD).

The child developed recurrent aspiration pneumonia with cardiac failure and died in the fifth week of life.

DISCUSSION

Patients with right heterotaxy tend to have complex cardiac lesions more frequently than those with left heterotaxy (Lee et al., 2006). The cardiac anomalies and abnormal immune status due to asplenia are linked to the mortality of nearly 80% in the first year of life (Applegate et al., 1999). Ipsilateral location of the aorta and IVC relative to the spine is said to be a consistent finding in asplenia (Fulcher and Turner, 2002). The cardiac apex often is contralateral or discordant relative to the position of stomach (Applegate et al., 1999). Total anomalous pulmonary venous drainage (TAPVD) may be associated with the heterotaxic syndromes, especially right heterotaxy (Hideki et al., 1995). Early in fetal life, the common pulmonary vein develops as an endothelial out sprouting from the left atrium and grows towards the lung buds which are supplied by splanchnic circulation. The common pulmonary vein of the left atrium then connects with the pulmonary venous plexus, while connections between the pulmonary and splanchnic plexuses involute. If the common pulmonary vein fails to connect with the pulmonary venous plexus, connections between the pulmonary and splanchnic plexuses fail to involute. The pulmonary plexus then may drain into a common channel that pierces the diaphragm to communicate with the portal system (Kaiser et al., 2007).

The analysis of human fetal development has been considerably aided by Streeter's concept of dividing the fetal age based on the identifiable features of major internal organs. On the basis of this concept, the developmental stages of human embryo are subdivided into 23 age groups or developmental “horizons” with an interval of 2–3 days between successive horizons (Chi and Kyung, 1986) Most abnormalities in asplenia are linked to horizon XIII at which time the embryo has a gestational age of approximately 28 days and has 28 somites. The primitive heart and venous connections form at about 20–30 days of gestation. Embryologic defects that occur at this time lead to incomplete septation of cardiac chambers with the preponderance of common atrium, abnormal pulmonary venous connections, and conotruncal anomalies frequently associated with heterotaxy syndrome (Applegate et al., 1999).

In our patient, the right heterotaxy was associated with HD and such an association has not been reported before. The diagnosis in our patient would be better described as heterotaxy syndrome (bilateral trilobed lungs, dextrocardia, asplenia, intrathoracic stomach, and HD) so as to stress the clinical importance of all the anomalies in the patient (Applegate et al., 1999). The gastrointestinal anomalies that have been frequently reported with right heterotaxy include malrotation, right sided or midline stomach and intrathoracic herniation of the stomach (Lee et al., 2006). Their occurrence may be explained by the positional abnormalities characteristic of heterotaxy.

Genetic mutation involving ZIC gene has been reported in association with heterotaxy (Merzdorf, 2007). ZIC gene has been implicated in many developmental processes of the mesoderm and neural development including neurogenesis, myogenesis,
**Fig. 1.** Axial CT of the upper abdomen showing five hepatic veins (black arrows) that drain into the left sided IVC (white arrow).

**Fig. 2.** Axial CT abdomen demonstrates centrally located liver with asplenia. The feeding tube (black arrow) in the stomach is on the right side of abdomen and the gallbladder (white arrow) is seen near the midline. The aorta (A) is seen in the midline in front of the vertebra and the IVC is seen to the left and front of aorta.
Fig. 3. (A) Coronal reconstruction image of CT thorax and upper abdomen showing anomalous pulmonary venous drainage. The right (P1) and left (P2) pulmonary veins drain into a large common venous channel behind and inferior to the heart instead of the left atrium (PV, portal vein). (Figs. 3A–3C sequentially show the downward course of the anomalous pulmonary vein into the portal vein.) (B) Coronal reconstruction image of CT thorax and upper abdomen showing the large common venous channel (CVC) into which the right and left pulmonary veins drain. (C) Coronal reconstruction CT image showing the large PV into which the common venous channel from thorax drained.
skeletal patterning, and neuroectodermal differentiation (Merzdorf, 2007). ZIC proteins act as transcriptional cofactors to modulate the hedgehog-signaling pathway (Aruga, 2004). Hedgehog pathway has been implicated in HD (Santos et al., 2000). The association of heterotaxy with HD in our patient may provide a clue on the possible genetic link between heterotaxy and HD that needs further research.

REFERENCES


AQ1: Kindly provide the article title for reference “Hideki et al., 1955.”