REVIEW ARTICLE

Non-cardiac issues in patients with heterotaxy syndrome

Shyam S Kothari
Department of Cardiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

ABSTRACT

Management of complex congenital heart disease in patients with Heterotaxy syndrome (HS) has steadily improved. However, there is an insufficient appreciation of various non-cardiac issues that might impact the overall status of these patients. This article briefly reviews the implications of gastrointestinal, immunologic, genitourinary, respiratory, and central nervous system involvement in HS patients with a view to aid in their comprehensive clinical management.

Keywords: Asplenia, congenital heart disease, heterotaxy syndrome, polysplenia

INTRODUCTION

Visceral heterotaxy or heterotaxy syndrome (HS) is a birth defect resulting in abnormal left right axis patterning of the organs of the body.[1] Heart being the most important asymmetric organ suffers the most, although HS may occur without any congenital heart disease (CHD). By convention, complete mirror image of normal (or situs inversus totalis) is not considered heterotaxy;[2] and it is intriguing that complete left right axis inversion as in situs inversus totalis results in little or no cardiac or other organ abnormalities, whereas profound organ disturbances occur in other situations of left right axis disturbances or HS. The precise terminology of HS and the nosologic relationships of various disorders within HS are debated, but generally it is classified as having bilateral right-sidedness (usually with Asplenia syndrome), or bilateral left sidedness(usually with polysplenia syndrome), even though there are overlap and uncertainties.[2,3] The status of spleen does not always correlate with the presumed right or left sidedness, and right or left isomerism might be preferable terms, but in this article asplenia and polysplenia are used to mean right isomerism and left isomerism respectively. The term situs ambiguous may be considered practically synonymous with HS by some,[2] although this might not be universally acceptable. The constellation of typical cardiac findings in subgroups of patients with HS are well-described in the cardiology literature. Patients with Asplenia characteristically have total anomalous pulmonary venous connection, unbalanced atrioventricularseptal defect, double outlet right ventricle, pulmonary atresia or stenosis, absent coronary sinus and bilateral 'right atrial like' appendages.[4-6] Patients with polysplenia typical have inferior venacava (IVC) interruption with azygous or hemiazygous continuation, atrioventricular septal defect(with more often balanced ventricles), less severe heart defects, and bilateral "left atrial like" appendages.[5-7] The poor prognosis of HS patients, despite surgical management, is well-recognized.[8] With operation, the 5-year survival rate of asplenia patients of 35%,[9] and that for polysplenia of 61% were reported.[10] More recent reports have shown improvements in these results with better techniques.[11] The nature of cardiac disease is the most important determinant of survival, but there are multiple other system involvement influencing the lives of these patients. Since the parents of these children with CHD usually consult the treating cardiologist for clinical problems and decisions, a general appreciation of various system involvement in HS is warranted.

Systemic involvement in HS is the rule. Previous autopsy studies have shown various system involvement in 40-70% of patients with HS.[4,5,12] Numerous structural deviations are reported, although individual lesions are uncommon. Most defects are common to asplenia and polysplenia both, although some lesions like biliary atresia and extra hepatic porto-systemic anastomosis almost always occur in polysplenia only.

Access this article online

Quick Response Code:

Website: www.annalspc.com

DOI: 10.4103/0974-2069.140834

Address for correspondence: Dr. Shyam S Kothari, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India.
E-mail: kothariss100@gmail.com

A brief description of clinically important malformations follows:

A) **Gastrointestinal System:** Intestinal malrotation and biliary atresia might have major clinical effects although midline liver and gall bladder, annular pancreas, duodenal atresia, agenesis of dorsal pancreas, preduodenal portal vein are reported in HS. Rarely, anal atresia (only in asplenia) and trachea-oesophageal fistula are found.

Some degree of intestinal malrotation is seen in about 70 % of HS patients although most patients are asymptomatic.[13,14] Intestinal malrotation may cause midgut volvulus in neonates and infants resulting in bilious vomiting, bloody diarrhoea and acute abdominal emergency. Abdominal ultrasound can be diagnostic with abnormal superior mesenteric artery and vein position, or with a wrap up of mesentry on the superior mesenteric artery (whirl pool sign).[15] But sometimes, abdominal CT or laparoscopy may be required. In view of high prevalence of malrotation, and fear of midgut volvulus resulting in catastrophic intestinal necrosis, some have advocated prophylactic pre-emptive surgery (LADD operation).[16] Others have not found it useful in the asymptomatic patients.[13,17] In general, elective intervention for malrotation is preferably done after the cardiac intervention, if required.

These structural gastrointestinal defects might also be responsible for feeding difficulties, failure to thrive, recurrent aspirations, atypical abdominal pain and other symptoms. A higher interstage mortality in HS patients awaiting a Fontan operation might be contributed indirectly by some of these factors.[18] An awareness of these symptoms might direct appropriate investigation and therapy. A high index of suspicion and appropriate investigations are required in these patients, although routine investigations for gastrointestinal abnormalities are not mandated.[14]

Biliary atresia in neonates with polysplenia is a serious disease that profoundly affects the prognosis.[19,20] It may occur in 10% of neonates with polysplenia.[21] Features of obstructive jaundice in a neonate with polysplenia should immediately raise the suspicion of biliary atresia. Polysplenia related biliary atresia accountsfor only for 7-10% of patients with biliary atresia and presents earlier after birth.[22,23] Antenatal diagnosis of biliary atresia may be difficult, and is suggested by cystic malformation in biliary tract, or by absent, smaller, or indistinct gall bladder in mid trimester fetal echo.[24] Some of these neonates do not have severe heart disease.[25] Thus the possibility of biliary atresia should be kept in mind for counselling purpose in any antenatal echo suggestive of polysplenia in view of it's poor prognosis with or without heart defects. Kasai operation or liver transplant might be required depending on detailed anatomic evaluation. The outcomes with treatment in this subset is similar to those without HS, with 10 year survival rates approaching 72% in one report.[22]

Propensity for gall stones, pancreatitis, diabetes mellitus (from dorsal agenesis of pancreas?), or intestinal obstruction might occur from other structural abnormalities. Rare case reports like preportal duodenal vein causing obstructive jaundice,[26] or appendicitis resulting in epigastric or right hypochondrial pain because of undescended appendix emphasise the importance of awareness of gastrointestinal system involvement in HS.[27,28] Similarly, confusing imaging patterns in dealing with acquired diseases,[28] or unexpected findings on the operation table might be encountered by the unwary in HS.

B) **Immunologic System:** It is well-known that absence or hypofunction of spleen (despite polysplenia) in patients with HS render them susceptible to infection especially with encapsulated organisms.[29,30] However, there is a surprising lack of adequate data regarding this issue in HS and it's management. The recommendations are based on extrapolations from acquired asplenic patients and might not be directly comparable. Early studies suggested that in asplenia patients, the risks of dying from infections were higher than those from the heart disease and recommended lifelong antibiotics prophylaxis for them.[31] Subsequent follow-up studies in operated patients have either not commented on infection as a major risk factor for death, or found it in a smaller number of patients.[8-11,32] More recent retrospective studies have found sepsis in nearly 20% of patients over 2 years,[33,34] and this is nearly twice the rates of infection in children with comparable heart disease but without HS.[35] A higher risks of nosocomial sepsis was found in one,[33] but not in another study.[34]

From a practical standpoint following issues are important:

- The risks of infections relate to the quality and quantity of spleen available. Thus, the risks in polysplenia patients might be lower, although fatal sepsis occurs in them as well.
  - Presence of Howell Jolly bodies perhaps indicate the susceptibility to infection. Pocked Erythrocyte test (PIT test) by interference microscopy is more sensitive. A PIT count of >3.8 % indicate splenic hypofunction (<2% is normal).[29]
  - The risk of overwhelming sepsis is highest in the young infants and perhaps decrease with age, though systematic data are not available.

- The fatality rates of overwhelming sepsis are high (40-50%) despite the use of antibiotics, and some of the reported patients were receiving prophylactic antibiotics as well. This probably suggests that sepsis should be recognized earlier, and underscores the need for patient education.
- Infants less than 6 months of age seem more susceptible to gram negative organisms, and older children might be susceptible to unusual organisms like Babesia, Capnocytophaga, in addition to the known capsular microbes. Infection with Capnocytophaga can result from Dog or cat bites or scratches, and patients should be appropriately advised. Whether Malaria in hyposplenic patient is any more severe than in normals has not been confirmed.[29]

Prophylactic antibiotics and vaccination[29,30]: It is recommended to treat asplenic patients with daily prophylactic Penicillin (or erythromycin, or amoxicillin). Neonates and infants might be given trimethoprim-sulfamethoxazole upto 6 months of age. The recommended duration of antibiotics prophylaxis have varied from upto 5 years, 16 years of age, or lifelong.[29,30] Though attractive in theory, the utility of antibiotics in this setting has not been rigorously tested. It appears reasonable to give prophylactic antibiotics till 5 years of age. Patient education, early institution of antibiotics for treatment at any sign of sepsis, and vaccination may be more important in preventing overwhelming sepsis than lifelong antibiotics.

Vaccination: Routine vaccination protocol as for other newborns is followed for HS patients. In addition, 23 valent Pneumococcal polysaccharide vaccine (PPV-23) is administered beyond 2 years of age. The antibody response in children under 2 years of age is not good with this vaccine, but a heptavalent conjugate vaccine (PPV7) may be given in the first 2 years. A repeat dose once after 3 years in children <10 years, or after 5 years in older children is advised. The repeated booster dosages are not recommended beyond that. One dose of H influenza B vaccine is given at 2 months. Seasonal influenza, varicella, Salmonella vaccines, and Meningococcus vaccines might be considered as per local schedule in consultation with paediatrician. Whether vaccine schedules should be any different in tropical countries is not clear.

C) **Genitourinary System:** A high prevalence of genitourinary system abnormalities (26%) were reported in an autopsy study of HS.[12] Horse shoe kidney, hypoplastic, dysplastic, or absent kidney, and ureteral obnormalities were seen. These abnormalities might predispose them to urinary tract infections, pelviureteral obstruction, or nephrolithiasis. The unilateral hypoplastic kidney might cause hypertension, or decrease renal function in future.[36] The impact of these genitourinary system abnormalities might become more apparent with longer survival of patients. Bilateral cryptorchidism is another clinically important problem in HS.[5]

D) **Respiratory System:** Sinopulmonary infections, bronchiectasis are well-recognized in Kartagener syndrome that is due to Primary Ciliary Dyskinesia or the motile cilia dysfunction. Similarly, ciliary dysfunction resulting in postoperative lung complications in patients with HS is recognized recently.[37,38] Unrecognized ciliary dysfunction might contribute to poor secretion clearance, atelectasis and recurrent chest infections in HS patients. Patients with such dysfunction perhaps need vigorous physiotherapy, and might improve with B agonists.[38] Unrecognized ciliary dysfunction might be the cause for respiratory distress in some neonates with undiagnosed HS.

It is conjectural whether the presence of bilateral right sided, or bilateral left sided lungs alter the conventional propensity of aspiration to the right bronchus, or predilection of collapse in the left bronchus.

E) **Central Nervous System:** The presence of lateralisation in central nervous system is not intuitively obvious, but seem to exist as seen in people with situs inversuss.[39] CNS abnormalities are also noted in HS including hydrocephalus, absent corpus callosum, holonprosencephaly, meningomyelocoele etc. The clinical implications of brain anomalies in HS is not clear. On follow up after operation, the functional status of patients with HS is similar to that of other patients,[40] perhaps suggesting similar brain functioning, however specific data in this regard are lacking. It may be relevant that higher prevalence of dyslexia is reported in people with primary ciliary dyskinesia.[41] Similar situation might exist in HS, but this needs to be studied.

F) **Thromboembolism:** Thromboembolism complicates 3-20% of patients with Fontan operation.[42] Whether thromboembolism is commoner in patients with HS has not been systematically studied. It is strange that despite clear evidence of hypofunction of spleen in HS, platelet counts or functions have not been studied in these patients until recently.[43] One study noted higher platelet counts and higher chances of thromboembolism in HS patients (28%) compared to non-HS patients (10%).[43] Stronger antiplatelet therapy or anticoagulation might be desirable in these patients, but further studies are warranted.

G) **Venous Anomalies:** Patients with polysplenia are known to have higher chances of extra hepatic portocaval communications (Abernethy malformations) that might be responsible for idiopathic pulmonary arterial hypertension, or

diffuse pulmonary arteriovenous fistula causing cyanosis.[44-46] In a study of 58 patients with Abernethy malformations, 9% had polysplenia.[44] Most of these patients did not have significant heart disease. The possibilities of extra hepatic portocaval shunts should always be considered in a patient with interrupted IVC and cyanosis from pulmonary fistulae or pulmonary arterial hypertension. Closure of the shunt often results in resolution of cyanosis or pulmonary hypertension.[46] The importance of a hepatic factor in the genesis of PAVF is well-recognized, and the occurrence of cyanosis in the follow up of Kawashima procedure (univentricular repair with interrupted IVC that exclude hepatic veins blood to lungs) is well-known.[47] The presence of extra hepatic portocaval shunts in these patients can be a real trap, and the cyanosis might be attributed only to lack of hepatic venous inclusion in the circuit.[45] Incorporation of hepatic veins in the fontan circuit (or Kawashima circuit) should be routine in view of high prevalence of PAVF in these patients.[48] Sometimes the anomalies of hepatic veins might make this technically difficult. PAVF might also occur in post operative Fontan patients due to streaming of hepatic blood only to one lung and this is less well-recognized;[49] such a situation might be more likely in HS patients due to hepatic venous anomalies, although may occur in others due to technical reasons.

Interrupted IVC with azygous (or hemiazygous continuation) might occasionally confuse the unwary in the cath lab, or might cause unexpected errors in the operation theatre.[50] Sometimes, interrupted IVC may be the only manifestation of HS and polysplenia (and rarely asplenia) and not accompanied by other heart disease.

Whether it results in any hemodynamic disadvantage is not clear, but in some circumstances it might be causing venous stasis as the reports of deep venous thrombosis in a few patients with interrupted IVC and no other predisposing factors suggest.[51] This possibility should be excluded in young patients with venous thrombosis. The hemodynamic disadvantage might contribute to poorer results of Kawashima operation, in addition to PAVF in these patients, but this has not been formally studied.

H) **Ciliary Dysfunction:** There are very significant advances in the understanding of the pathogenesis of HS from genetic and animal experimental studies.[52] There appears to be a large genetic component in etiogenesis of HS, and autosomal dominant, autosomal recessive, and X-linked transmissions are described though most occurrence are sporadic. The involved genes are responsible for the functions of cilia in the embryogenesis, thus HS might be considered a form of ciliopathy. Therefore it is not surprising that 5.6% of patients with Primary Ciliary Dyskinesia had features of HS.[53] The ciliary dysfunction during embryogenesis is likely the cause of severe congenital heart malformations. The best characterised genes in the pathogenesis of HS include ZIC3 in X linked HS, nodal, LEFTY, PITX2 and other TGF-B family genes in the nodal signalling cascade. Clinical Genetic testing is available for some of these genes for counselling of recurrence. In general, the recurrence rates in HS are higher than generally seen with other congenital heart disease. It is tempting to speculate that ciliary dysfunction might have a role in the ill understood hepatic fibrosis seen in postoperative Fontan patients,[54] as congenital hepatic fibrosis is one manifestation of ciliopathy.[55] Whether ciliary related CNS dysfunction, or subfertility occurs in HS remains to be studied.

In conclusion, widespread alterations in form and function occur in different organs in HS. A better appreciation of the various systems involvement in HS and their implications is required for comprehensive clinical management of patients with complex congenital heart disease and HS.

REFERENCES

1. Casey B. Two rights make a wrong: Human left-right malformations. Hum Mol Genet 1998;7:1565-71.
2. Jacobs JP, Anderson RH, Weinberg PM, Walters HL 3rd, Tchervenkov CI, Del Duca D, *et al.* The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. Cardiol Young 2007;17 (Suppl 2):1-28.
3. Cohen MS, Anderson RH, Cohen MI, Atz AM, Fogel M, Gruber PJ, *et al.* Controversies, genetics, diagnostic assessment, and outcomes relating to the heterotaxy syndrome. Cardiol Young 2007;17 (Suppl 2):29-43.
4. Phoon CK, Neill CA. Asplenia syndrome: Insight into embryology through an analysis of cardiac and extracardiac anomalies. Am J Cardiol 1994;73:581-7.
5. Van Praagh S. Cardiac malpositions and the heterotaxy syndrome. In: Keany JF, Lock JE, Fyler DC, editors. Nadas's Pediatric Cardiology. 2nd ed. Philadelphia: Saunders Elsevier; 2006. p. 589-608.
6. Uemura H, Ho SY, Devine WA, Anderson RH. Analysis of visceral heterotaxy according to splenic status, appendage morphology, or both. Am J Cardiol 1995;76:846-9.
7. Peoples WM, Moller JH, Edwards JE. Polysplenia: A review of 146 cases. Pediatr Cardiol 1983;4:129-37.
8. Bartz PJ, Driscoll DJ, Dearani JA, Puga FJ, Danielson GK, O'Leary PW, *et al.* Early and late results of the modified fontan operation for heterotaxy syndrome 30 years of experience in 142 patients. J Am Coll Cardiol 2006;48:2301-5.

9. Hashmi A, Abu-Sulaiman R, McCrindle BW, Smallhorn JF, Williams WG, Freedom RM. Management and outcomes of right atrial isomerism: A 26-year experience. J Am Coll Cardiol 1998;31:1120-6.
10. Gilljam T, McCrindle BW, Smallhorn JF, Williams WG, Freedom RM. Outcomes of left atrial isomerism over a 28-year period at a single institution. J Am Coll Cardiol 2000;36:908-16.
11. Jonas RA. Surgical management of the neonate with heterotaxy and long-term outcomes of heterotaxy. World J Pediatr Congenit Heart Surg 2011;2:264-74.
12. Ticho BS, Goldstein AM, Van Praagh R. Extracardiac anomalies in the heterotaxy syndromes with focus on anomalies of midline-associated structures. Am J Cardiol 2000;85:729-34.
13. Borenstein SH, Langer JC. Heterotaxia syndromes and their abdominal manifestations. Curr Opin Pediatr 2006;18:294-7.
14. Choi M, Borenstein SH, Hornberger L, Langer JC. Heterotaxia syndrome: The role of screening for intestinal rotation abnormalities. Arch Dis Child 2005;90:813-5.
15. Orzech N, Navarro OM, Langer JC. Is ultrasonography a good screening test for intestinal malrotation? J Pediatr Surg 2006;41:1005-9.
16. Tashjian DB, Weeks B, Brueckner M, Touloukian RJ. Outcomes after a Ladd procedure for intestinal malrotation with heterotaxia. J Pediatr Surg 2007;42:528-31.
17. Papillon S, Goodhue CJ, Zmora O, Sharma SS, Wells WJ, Ford HR, *et al*. Congenital heart disease and heterotaxy: Upper gastrointestinal fluoroscopy can be misleading and surgery in an asymptomatic patient is not beneficial. J Pediatr Surg 2013;48:164-9.
18. Song J, Kang IS, Huh J, Lee OJ, Kim G, Jun TG, *et al*. Interstage mortality for functional single ventricle with heterotaxy syndrome: A retrospective study of the clinical experience of a single tertiary center. J Cardiothorac Surg 2013;8:93.
19. Davenport M, Tizzard SA, Underhill J, Mieli-Vergani G, Portmann B, Hadzić N. The biliary atresia splenic malformation syndrome: A 28-year single-center retrospective study. J Pediatr 2006;149:393-400.
20. Silveira TR, Salzano FM, Howard ER, Mowat AP. Congenital structural abnormalities in biliary atresia: Evidence for etiopathogenic heterogeneity and therapeutic implications. Acta Paediatr Scand 1991;80:1192-9.
21. Lim JS, McCrindle BW, Smallhorn JF, Golding F, Caldarone CA, Taketazu M, *et al*. Clinical features, management, and outcome of children with fetal and postnatal diagnoses of isomerism syndromes. Circulation 2005;112:2454-61.
22. Varela-Fascinetto G, Castaldo P, Fox IJ, Sudan D, Heffron TG, Shaw BW, *et al*. Biliary atresia-polysplenia syndrome: Surgical and clinical relevance in liver transplantation. Ann Surg 1998;227:583-9.
23. Karrer FM, Hall RJ, Lilly JR. Biliary atresia and the polysplenia syndrome. J Pediatr Surg 1991;26:524-7.
24. Dreux S, Boughanim M, Lepinard C, Guichet A, Rival JM, de Becdelievre A, *et al*. Relationship of non-visualization of the fetal gallbladder and amniotic fluid digestive enzymes analysis to outcome. Prenat Diagn 2012;32:423-6.
25. Pepes S, Zidere V, Allan LD. Prenatal diagnosis of left atrial isomerism. Heart 2009;95:1974-7.
26. Low JP, Williams D, Chaganti JR. Polysplenia syndrome with agenesis of the dorsal pancreas and preduodenal portal vein presenting with obstructive jaundice: A case report and literature review. Br J Radiol 2011;84:e217-20.
27. Odabasi M, Arslan C, Abuoglu H, Gunay E, Yildiz MK, Eris C, *et al*. An unusual presentation of perforated appendicitis in epigastric region. Int J Surg Case Rep 2014;5:76-8.
28. Ben Ely A, Gorelik N, Cohen-Sivan Y, Zissin R, Carpineta L, Osadchy A, *et al*. Appendicitis in adults with incidental midgut malrotation: CT findings. Clin Radiol 2013;68:1212-9.
29. Melles DC, de Marie S. Prevention of infections in hyposplenic and asplenic patients: An update. Neth J Med 2004;62:45-52.
30. Price VE, Blanchette VS, Ford-Jones EL. The prevention and management of infections in children with asplenia or hyposplenia. Infect Dis Clin North Am 2007;21:697-710.
31. Waldman JD, Rosenthal A, Smith AL, Shurin S, Nadas AS. Sepsis and congenital asplenia. J Pediatr 1977;90:555-9.
32. Jacobs ML. Complications associated with heterotaxy syndrome in Fontan patients. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2002;5:25-35.
33. Prendiville TW, Barton LL, Thompson WR, Fink DL, Holmes KW. Heterotaxy syndrome: Defining contemporary disease trends. Pediatr Cardiol 2010;31:1052-8.
34. Chiu SN, Shao PL, Wang JK, Chen HC, Lin MT, Chang LY, *et al*. Severe bacterial infection in patients with heterotaxy syndrome. J Pediatr 2014;164:99-104.
35. Barker GM, O'Brien SM, Welke KF, Jacobs ML, Jacobs JP, Benjamin DK Jr, *et al*. Major infection after pediatric cardiac surgery: A risk estimation model. Ann Thorac Surg 2010;89:843-50.
36. Westland R, Schreuder MF, van Goudoever JB, Sanna-Cherchi S, van Wijk JA. Clinical implications of the solitary functioning kidney. Clin J Am Soc Nephrol 2014;9:978-86.
37. Nakhleh N, Francis R, Giese RA, Tian X, Li Y, Zariwala MA, *et al*. High prevalence of respiratory ciliary dysfunction in congenital heart disease patients with heterotaxy. Circulation 2012;125:2232-42.
38. Harden B, Tian X, Giese R, Nakhleh N, Kureshi S, Francis R, *et al*. Increased postoperative respiratory complications in heterotaxy congenital heart disease patients with respiratory ciliary dysfunction. J Thorac Cardiovasc Surg 2014;147:1291-8.
39. Kennedy DN, O'Craven KM, Ticho BS, Goldstein AM, Makris N, Henson JW. Structural and functional brain asymmetries in human situs inversus totalis. Neurology 1999;53:1260-5.

40. Atz AM, Cohen MS, Sleeper LA, McCrindle BW, Lu M, Prakash A, *et al;* Investigators of the Pediatric Heart Network. Functional state of patients with heterotaxy syndrome following the Fontan operation. Cardiol Young 2007;17(Suppl 2):44-53.

41. Brandler WM, Paracchini S. The genetic relationship between handedness and neurodevelopmental disorders. Trends Mol Med 2014;20:83-90.

42. Firdouse M, Agarwal A, Chan AK, Mondal T. Thrombosis and thromboembolic complications in Fontan patients: A literature review. Clin Appl Thromb Hemost 2014;20:484-92.

43. Yamamura K, Joo K, Ohga S, Nagata H, Ikeda K, Muneuchi J, *et al.* Thrombocytosis in asplenia syndrome with congenital heart disease: A previously unrecognized risk factor for thromboembolism. Int J Cardiol 2013;167:2259-63.

44. Murray CP, Yoo SJ, Babyn PS. Congenital extrahepatic portosystemic shunts. Pediatr Radiol 2003;33:614-20.

45. McElhinney DB, Marx GR, Newburger JW. Congenital portosystemic venous connections and other abdominal venous abnormalities in patients with polysplenia and functionally univentricular heart disease: A case series and literature review. Congenit Heart Dis 2011;6:28-40.

46. Newman B, Feinstein JA, Cohen RA, Feingold B, Kreutzer J, Patel H, *et al.* Congenital extrahepatic portosystemic shunt associated with heterotaxy and polysplenia. Pediatr Radiol 2010;40:1222-30.

47. Srivastava D, Preminger T, Lock JE, Mandell V, Keane JF, Mayer JE Jr, *et al.* Hepatic venous blood and the development of pulmonary arteriovenous malformations in congenital heart disease. Circulation 1995;92:1217-22.

48. Burstein DS, Mavroudis C, Puchalski MD, Stewart RD, Blanco CJ, Jacobs ML. Pulmonary arteriovenous malformations in heterotaxy syndrome: The case for early, direct hepatic vein-to-azygos vein connection. World J Pediatr Congenit Heart Surg 2011;2:119-28.

49. McElhinney DB, Marx GR, Marshall AC, Mayer JE, Del Nido PJ. Cavopulmonary pathway modification in patients with heterotaxy and newly diagnosed or persistent pulmonary arteriovenous malformations after a modified Fontan operation. J Thorac Cardiovasc Surg 2011;141:1362-70.

50. Pillai JB, Kpodonu J, Yu C, Borger MA. Heterotaxy syndrome with azygous continuation-causing pseudo Budd-Chiari syndrome after cardiopulmonary bypass. Ann Thorac Surg 2006;81:1890-2.

51. Lambert M, Marboeuf P, Midulla M, Trillot N, Beregi JP, Mounier-Vehier C, *et al.* Inferior vena cava agenesis and deep vein thrombosis: 10 patients and review of the literature. Vasc Med 2010;15:451-9.

52. Shiraishi I, Ichikawa H. Human heterotaxy syndrome — from molecular genetics to clinical features, management, and prognosis. Circ J 2012;76:2066-75.

53. Kennedy MP, Omran H, Leigh MW, Dell S, Morgan L, Molina PL, *et al.* Congenital heart disease and other heterotaxic defects in a large cohort of patients with primary ciliary dyskinesia. Circulation 2007;115:2814-21.

54. Johnson JA, Cetta F, Graham RP, Smyrk TC, Driscoll DJ, Phillips SD, *et al.* Identifying predictors of hepatic disease in patients after the Fontan operation: A postmortem analysis. J Thorac Cardiovasc Surg 2013;146:140-5.

55. Ware SM, Aygun MG, Hildebrandt F. Spectrum of clinical diseases caused by disorders of primary cilia. Proc Am Thorac Soc 2011;8:444-50.

How to cite this article: Kothari SS. Non-cardiac issues in patients with heterotaxy syndrome. Ann Pediatr Card 2014;7:187-92.
Source of Support: Nil, **Conflict of Interest:** None declared