Prenatal diagnosis of Shone's syndrome: ultrasonographic features and differential diagnosis with coarctation of the aorta

Zhuoyan Li
Shanghai Jiaotong University School of Medicine Xinhua Hospital
Liqing Zhao
Shanghai Jiaotong University School of Medicine Xinhua Hospital
Yurong Wu
Shanghai Jiaotong University School of Medicine Xinhua Hospital
Sun Chen (chensun@xinhuamed.com.cn)
Shanghai Jiaotong University School of Medicine Xinhua Hospital

Research

Keywords: fetal echocardiography, prenatal diagnosis, Shone's syndrome, coarctation of the aorta

Posted Date: September 1st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-21277/v2

Abstract

Objective: To improve the prenatal diagnosis of Shone's syndrome and identify the mitral valve obstruction associated with the anomaly by comparing the fetal echocardiographic features between Shone's syndrome and coarctation of the aorta (CoA).

Method: Between January 2015 to December 2019, 17 fetuses were diagnosed with Shone's syndrome prenatally and 8 were analyzed in our final study, their data were compared to normal controls and CoA cases. The main points of identification were summarized.

Results: By comparing data between three groups, elevated PA/AO ratio and RV/LV ratio were detected in both Shone's syndrome and CoA cases. However, TVC/MVC ratios was only increased in Shone's syndrome. Analysis revealed that the TVC/MVC ratio had the best capability in predicting Shone's syndrome. Ultrasonographic features of mitral valve obstruction in Shone's syndrome were unique which help clinicians to distinguish the anomaly from CoA, including (1) morphologic changes in short-axis view: restrictive opening of the mitral valve with diastolic deformity, thickened leaflets, echo-enhancement of chordae tendineae and mitral valve, single papillary muscle or dominant papillary muscle; (5) in color Doppler image: decreased antegrade flow and abnormal flow pattern of mitral valve.

Conclusion: There are two key points of prenatal diagnosis of Shone's syndrome which could help fetal cardiologist to distinguish Shone's syndrome from CoA in clinical practice, including (1) echocardiographic measurements: the elevated TVC/MVC ratio; (2) morphologic changes of mitral valve indicating left ventricle inflow obstruction in two-dimension short-axis section view.

Background

Shone's syndrome is a constellation of congenital abnormalities characterized by four lesions including parachute mitral valve, supravalvular mitral ring, subaortic stenosis and coarctation of aorta. It was first described in 1963 by Dr JD Shone[1]. Incomplete Shone's syndrome, which consists of at least 1 left ventricular inflow tract lesion and at least 1 left ventricular outflow tract (LVOT) lesion, is more common than complete Shone's syndrome in clinical practice[2]. Shone's syndrome is compromising approximately 0.6% of all cases of congenital cardiac abnormalities[3]. The clinical setting is characterized by a congenital mitral valve anomaly resulting in stenosis, with resultant downstream underdevelopment of left heart outflow tract[4].

Shone's syndrome is a rare complex with few data published on its prenatal diagnosis[5] which could provide less help for fetal cardiologist to clinical determination. Shone et al.[1]noted that mitral valve obstruction appeared to be the most critical problem associated with the anomaly. The severity of mitral valve obstruction correlates with poor long-term outcomes[5,6]. However, mitral stenosis is difficult to be accurately diagnosed and may go unnoticed in the fetus with coarctation of the aorta (CoA). Several Shone's syndrome cases were misdiagnosed with CoA and found mitral valve obstruction lesions not

until adult[7,8]. So, evaluation of mitral valve is important in prenatal diagnosis of Shone's syndrome, especially in its differential diagnosis with isolated coarctation.

This study was conducted to improve the prenatal diagnosis of Shone's syndrome, and the main points of identification in mitral valve obstruction associated with the anomaly were summarized by comparing the fetal echocardiographic features between Shone's syndrome and CoA.

Methods

This was a single-center retrospective study conducted by Pediatric Cardiology Department of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine between January 2015 to December 2019. Ethical approval was obtained from the Institutional Review Board of the Xinhua Hospital affiliated to the Shanghai Jiao Tong University School of Medicine (No. XHEC-C-2016-105). Informed consent was obtained from each patient.

Between January 2015 and December 2019, a total of 1500 fetuses were examined in our center and 17 fetuses were diagnosed with Shone's syndrome prenatally. A detailed fetal echocardiography was performed by at least 2 trained pediatric cardiology physicians with at least 3 years of experience in accordance with the 2013 guidelines of the American Institute of Ultrasound in Medicine[9]. All fetal echocardiographic examinations were performed on GE Voluson E8 with a 4 to 8-MHz transabdominal probe. The following cardiac views were examined in each fetus: the abdominal view, the four chamber view, the left and right ventricular outflow tract view, the three vessel trachea view, the short-axis view of the great vessels, the short-axis view of the mitral valve, the vena cava view, and the long axis view of the aortic arch and the ductal arch. The following measurements were assessed:

- Inflow tracts: tricuspid valve circle (TVC) dimension, mitral valve circle (MVC) dimension and Z score
- Outflow tracts: aortic valve dimension and z score, ascending aorta diameter and z score, aortic isthmus (in sagittal) diameter and Z score, transverse aortic arch diameter, pulmonary valve dimension, main pulmonary artery diameter, arterial duct diameter
- Ratios: Right ventricular diameter/left ventricular diameter (RV/LV), TVC/MVC, pulmonary valve dimension/aortic valve dimension (PA/AO)
- Doppler signs: mitral velocity (MV), aortic velocity (AoV), aortic isthmus peak systolic velocity, reversed or mixed flow at the aortic arch

RV and LV diameters were measured in the apical four-chamber view at end-diastole. TVC and MVC diameters were measured in diastole in the four-chamber view. We assigned z-scores for valve dimensions based on fetal biometry[10].

Statistical analysis

All statistical analyses were performed with SPSS21.0 software, and p-values under 0.05 following two-tailed t test, and one-way ANOVA were considered as statistically significant. Receiver-operating characteristic (ROC) curve were used to detect the predictors of Shone's syndrome.

Results

General information

Among seventeen cases who were diagnosed with Shone's syndrome prenatally in our center, eight were contained in our final study including three confirmed with the anomaly by postmortem autopsy, five confirmed with the anomaly by postnatal echocardiography **Fig.1**. Clinical information and echocardiographic data of these Shone's syndrome cases were summarized at **Table 1**. Of these eight fetuses, five were diagnosed with mitral stenosis and CoA, two with mitral stenosis, CoA and aortic valve stenosis, one with mitral stenosis, CoA and bicuspid aortic valve (BAV). In five cases genetic tests were performed, one had KMT2D mutation, one had 12q14.1del and three were with normal results. Results of postmortem autopsy showed smaller mitral annulus and parachute mitral valve in case B and D **Fig. 2a, b**.

In five cases who were delivered at term, four underwent operations within few months and one died shortly after birth. The median age at operation was 2 months (1 month to 3 month). The median postnatal follow-up time was 2 years (1year to 4 years). Except for one patient, who declared growth retardation after surgery, all patients remained asymptomatic following their operation.

Comparing and analyzing of echocardiographic measurements

The data were compared between normal controls (N=30), Shone's syndrome (N=8) and CoA (N=10) and several shared features between Shone's syndrome and CoA were detected, including (1) LVOT obstructions, with no significance in Z scores of ascending aorta (P=0.7333) or aortic isthmus (P=0.8894) between two groups **Fig. 3a;** (2) great vessel disproportion and ventricular disproportion, with elevated PA/AO ratio and RV/LV ratio in both diseases **Table 3**, which were in accord with other centers' results[11,12]. However, Shone's syndrome cases exhibited more evident signs of great vessel and ventricular disproportion than CoA cases. The fetuses with Shone's syndrome had higher PA/AO ratio and RV/LV ratio than those with CoA **Fig. 3b**. The TVC/MVC ratio was increased in Shone's syndrome cases (P< 0.0001) but not CoA cases. The Shone's syndrome cases also seemed to get higher MV than control groups, although no statistical significance was detected (P= 0.250). ROC curve indicated that the fetuses with TVC/MVC ratio over 1.260 were more likely to have Shone's syndrome rather than CoA with a sensitivity of 100% and a specificity of 87.5%. Analysis of ROC curve for the TVC/MVC ratio revealed an area under the curve of 0.953 **Fig. 3c**.

Unique echocardiographic features of mitral valve obstruction in Shone's syndrome

Shone's syndrome fetuses had unique sonographic features indicating mitral valve obstruction in two-dimension short-axis section view which hadn't been detected in normal controls or CoA cases, including (1) restrictive opening of the mitral valve with diastolic deformity were detected in three cases **Video 1**; (2) thickened leaflets were detected in two cases **Video 1**; (3) echo-enhancement of chordae tendineae and mitral valve were detected in two cases **Video 2**; (4) single papillary muscle or dominant papillary muscle were detected in two cases **Video 3** and (5) decreased antegrade flow and abnormal flow pattern of mitral valve in color Doppler image were detected in one case **Fig 4**. In CoA cases, on the contrast, developments of mitral valve and papillary muscle were normal **Video 4**.

Discussion

Shone's syndrome is a rare and under-recognized diagnostic entity[13]. The obstructive lesions in Shone's complex have a tendency to worsen over time as compared to other congenital heart defects[14]. The antenatal recognition of Shone's syndrome, which remains infrequent in the literature[15], is still challenging, the complex hemodynamic interactions between multiple levels of left-side obstructions challenge the clinical determination of prognoses[16] and sometimes the diagnosis at mid-gestation is misleading, as both steady state and worsening by the end point are possible[5].

A key point in diagnosis of Shone's syndrome is a comprehensive evaluation of the number, position, morphology, and severity of left-sided obstructions. The LVOT is not difficult to be detected during clinical practice while mitral stenosis is hard to be accurately diagnosed. In our study, we found out that the TVC/MVC ratio seemed to have the best capability in predicting Shone's syndrome which provide a clue of mitral stenosis. Besides, morphologic changes of mitral valve are unique and can be used to distinguish the anomaly from CoA. These findings could provide some information for fetal cardiologist to determine those with Shone's syndrome from those with just an isolated coarctation to help better counsel the family.

However, misdiagnosis and missed diagnosis are inevitable in prenatal diagnosis[17]. The incidence of Shone's syndrome in our center is about 0.53%, which is lower than the reported 0.67%. A lower incidence means missed diagnosis during our clinical practice. In this study, there were 5 patients diagnosed with Shone's syndrome prenatally and opted termination of pregnancy but refused to have autopsy thus remained it unclear the exact diagnosis of fetuses. In addition, another two cases in our center who were not enrolled in this study, had been diagnosed with isolated CoA prenatally but found to be combined with mitral stenosis after birth. Thus, the sensitivity and specificity of prenatal diagnosis of Shone's syndrome still need to be improved.

Mitral stenosis is a progressive process which could be missed occasionally if obstruction is mild in early stage of pregnancy or overlapped by signs of severe LVOT obstruction. In these patients, prenatal echocardiography diagnosis is less satisfactory and serial assessment after initial diagnosis is needed for evaluating progress of the obstructions. The leaflet morphology, papillary muscle morphology and chordal length of left heart should be observed. Fetal echocardiograms may be performed every 4 weeks

based on the gestational age at the time of initial suspicion. In addition, prenatal echocardiography diagnosis relies on the quality of image extremely[18].Sometimes suboptimal imaging of fetal heart could interfere the clinical determination by physicians.

Referring to a Fetal Medicine Unit is required in order to obtain a better monitor and management for Shone's syndrome patients after birth, especially for those who may require special intervention at birth or within the first days of life. The patient outcome of Shone's syndrome is widely variable because of the diversity and complex nature of cardiac anomalies itself [4]. It is reported that operative outcome is excellent in Shone's syndrome patients[19] and surgical intervention is recommended to be undertaken early before the onset of pulmonary hypertension[20].

Limitations

This is a retrospective study with its inherent limitations. In addition, our study population was limited to fetuses who were suspected with congenital heart defects and referred to our hospital for further diagnosis and treatment. Our results reflected a single center's experience. Larger sample sizes are needed to validate the result we got from this study.

Conclusion

There are two key points of prenatal diagnosis of Shone's syndrome by fetal echocardiography which could provide important clues for fetal cardiologist to distinguish the anomaly from CoA, including (1) echocardiographic measurements: the elevated TVC/MVC ratio has the best capability in predicting Shone's syndrome; (2) morphologic changes of mitral valve in two-dimension short-axis section view: restrictive opening of the mitral valve with diastolic deformity, thickened leaflets, echo-enhancement of chordae tendineae and mitral valve, single papillary muscle or dominant papillary muscle, decreased antegrade flow and abnormal flow pattern of mitral valve.

References

1 Shone JD, Sellers RD, Anderson RC et al. The developmental complex of "parachute mitral valve," supravalvular ring of left atrium, subaortic stenosis, and coarctation of aorta. Am J Cardiol. 1963; 11714-725.

2 Opotowsky AR & Webb GD. Evolving Understanding of Shone Complex Through the Lifespan: What's in an Eponym? Can J Cardiol. 2017; 33(2): 214-215.

3 True A, Baidya M, Lui C et al. Computed tomography imaging characteristics of shone syndrome. Radiol Case Rep. 2019; 14(2): 164-167.

4 Nicholson GT, Kelleman MS, De la Uz CM et al. Late outcomes in children with Shone's complex: a single-centre, 20-year experience. Cardiol Young. 2017; 27(4): 697-705.

5 Zucker N, Levitas A & Zalzstein E. Prenatal diagnosis of Shone's syndrome: parental counseling and clinical outcome. Ultrasound Obstet Gynecol. 2004; 24(6): 629-632.

6 Popescu BA, Jurcut R, Serban M et al. Shone's syndrome diagnosed with echocardiography and confirmed at pathology. Eur J Echocardiogr. 2008; 9(6): 865-867.

7 Grimaldi A, Vermi AC, Maisano F et al. Echocardiographic patterns of incomplete Shone's syndrome in adults. J Heart Valve Dis. 2011; 20(5): 552-556.

8 Vivas MF, Politi MT, Riznyk LM et al. Shone's syndrome: Insights from three-dimensional echocardiography. Echocardiography. 2018; 35(3): 417-419.

9 AIUM Practice Guideline for Documentation of an Ultrasound Examination. J Ultrasound Med. 2014; 33(12): 2219-2224.

10 Schneider C, McCrindle BW, Carvalho JS et al. Development of Z-scores for fetal cardiac dimensions from echocardiography. Ultrasound Obstet Gynecol. 2005; 26(6): 599-605.

11 Familiari A, Morlando M, Khalil A et al. Risk Factors for Coarctation of the Aorta on Prenatal Ultrasound: A Systematic Review and Meta-Analysis. Circulation. 2017; 135(8): 772-785.

12 Edwards LA, Arunamata A, Maskatia SA et al. Fetal Echocardiographic Parameters and Surgical Outcomes in Congenital Left-Sided Cardiac Lesions. Pediatr Cardiol. 2019; 40(6): 1304-1313.

13 Aslam S, Khairy P, Shohoudi A et al. Shone Complex: An Under-recognized Congenital Heart Disease With Substantial Morbidity in Adulthood. Can J Cardiol. 2017; 33(2): 253-259.

14 Ganju NK, Kandoria A, Thakur S et al. A Constellation of Cardiac Anomalies: Beyond Shone's Complex. Heart Views. 2016; 17(1): 23-26.

15 Ma XJ, Huang GY, Liang XC et al. Atypical Shone's complex diagnosed by echocardiography. Pediatr Cardiol. 2011; 32(4): 442-448.

16 Ikemba CM, Eidem BW, Fraley JK et al. Mitral valve morphology and morbidity/mortality in Shone's complex. Am J Cardiol. 2005; 95(4): 541-543.

17 Wang Y, Zhang J, Feng W et al. Description of misdiagnosis and missed diagnosis of fetal complex heart malformations by prenatal echocardiography combined with postnatal cardiovascular casting. Prenatal diagnosis. 2020.

18 Maulik D, Nanda NC, Maulik D et al. A brief history of fetal echocardiography and its impact on the management of congenital heart disease. Echocardiography. 2017; 34(12): 1760-1767.

19 Kumar A, Bhat IH, Kumar B et al. Role of perioperative echocardiography in repair of incomplete shone complex: A case series. Ann Card Anaesth. 2019; 22(4): 444-448.

20 Bolling SF, Iannettoni MD, Dick M, 2nd et al. Shone's anomaly: operative results and late outcome. Ann Thorac Surg. 1990; 49(6): 887-893.

Declarations

Competing interests: The authors declare that they have no competing interests.

Ethical approval and Informed consents: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the Xinhua Hospital affiliated to the Shanghai Jiao Tong University School of Medicine and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consents were obtained from all individual participants included in the study.

Availability of data and materials: All data generated or analyzed during this study were included in this published article and its supplementary information files.

Funding: This work was supported by the National Key R&D Program of China (No. 2018YFC1002400).

Authors' contributions: Zhuoyan Li drafted the manuscript and was responsible for collecting and analyzing patient data. Yurong Wu was in charge of informed consents of patients. Sun Chen designed this study. All authors read and approved the final manuscript.

Tables

Table 1

Clinical information of ten prenatally diagnosed Shone's syndrome cases.

Patient	Gestational Age	Age	Prenatal echocardiographic diagnosis	Extracardiac malformation
A	21 + 3	26	Mitral stenosis, aortic valve stenosis, COA, VSD	none
B	27 + 4	30	Mitral stenosis, COA, VSD	none
C	24 + 2	34	Mitral stenosis, aortic valve stenosis	none
D	35 + 2	35	mitral stenosis, COA	none
E	25 + 1	29	Mitral stenosis, aortic valve stenosis, COA	none
F	30 + 3	30	Mitral stenosis, COA	none
G	25 + 2	26	Mitral stenosis, aortic valve stenosis	none
H	26	21	Mitral stenosis, COA	none
I	23 + 5	25	Mitral stenosis, aortic valve stenosis	none
J	25 + 6	22	Mitral stenosis, COA	none

Table 2

Echocardiographic measurements of ten prenatally diagnosed Shone's syndrome cases.

Patient	RV/LV	TVC/MVC	PA/AO	MV (m/s)	Z score of MVC	Aortic valve diameter Z score	Ascending aorta diameter Z score	Aortic isthmus diameter Z scores (in sagittal)
A	1.71	1.54	2.33	0.7	-0.97	-3.22	-3.7	-2.77
B	1.37	2.44	1.63	0.8	-6.51	-1.5	-1.41	-1.96
C	1.8	2.1	2.0	0.41	-5.38	-3.09	/*	/*
D	1.02	1.33	1.07	0.9	-2.33	0.19	-1.97	-1.82
E	1.5	1.63	2.11	0.6	-4.12	-3.13	-2.89	-2.74
F	1.7	1.5	1.58	0.52	-2.12	-1.08	-3.12	-3.33
G	0.93	3.59	2.63	0.42	-7.71	-4.48	-4.94	-1.93
H	1.51	1.5	1.66	0.42	-2.15	-1.14	-0.5	-3.26
I	1.39	1.55	1.7	1	-2.93	-1.43	-1.39	-0.81
J	1.24	1.37	1.55	0.57	-1.23	-0.04	-1.18	-3.56

**The lost data were showed as /.*

Table 3

Measurements were compared between three groups.

Measurements	Normal controls N = 30	Shone's syndrome N = 10	CoA N = 10	P value
PA/AO	1.069 ± 0.05	1.796 ± 0.47	1.471 ± 0.14	.000*
RV/LV	1.029 ± 0.05	1.391 ± 0.30	1.159 ± 0.16	.000*
TVC/MVC	1.070 ± 0.06	1.855 ± 0.70	1.160 ± 0.11	.000*
MV	0.554 ± 0.09	0.634 ± 0.21	0.506 ± 0.10	.071

Table 4

Binary logistic regression analysis showed predictors of Shone's syndrome.

Variables	OR	95% CI	P Value
PA/AO	0.900	0.732–1.107	.640
RV/LV	1.750	0.740–4.139	.371
TVC/MVC	5.000	1.448–17.271	.000*

Table 5

Main points of identifying mitral valve obstruction in Shone's syndrome.

Features	Shone's syndrome	CoA	P value
	N (n%)	N (n%)	
Left ventricle short-axis section			
restrictive opening of the mitral valve	5 (50%)	0	.0098*
thickened leaflets	2 (20%)	0	.1360
echo-enhancement of chordae tendineae	1 (10%)	0	.3049
single papillary muscle	4 (40%)	0	.0253*
Color Doppler Image		0	
decreased antegrade flow	1 (10%)	0	.3049
abnormal flow pattern	1 (10%)	0	.3049

Figures

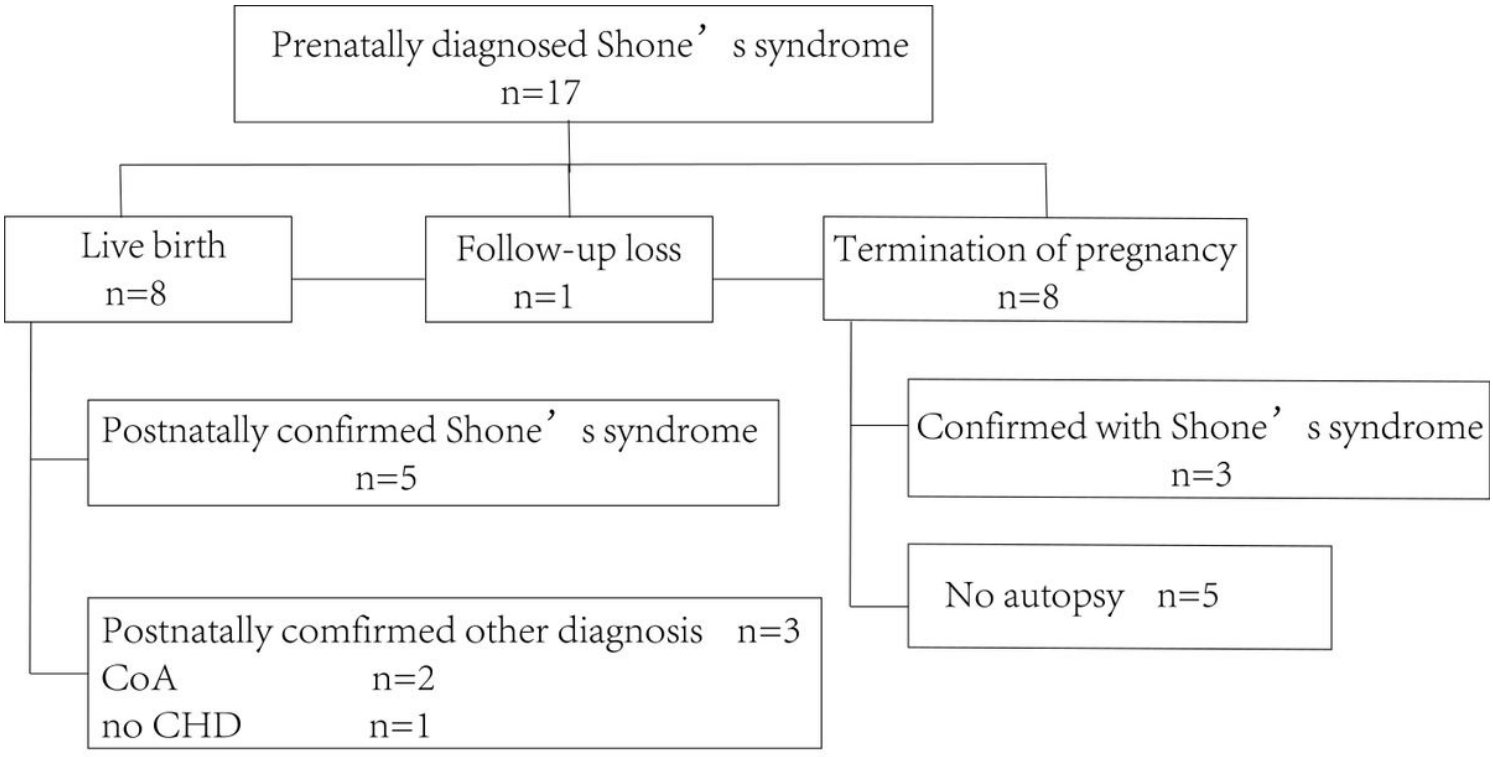

Figure 1

Figure 1. Flow chart of 17 patients diagnosed with Shone's syndrome prenatally. Among all the seventeen patients, eight patients were confirmed with Shone's syndrome by postnatal echocardiography or postmortem autopsy. Five patients opted termination of pregnancy without autopsy and three were confirmed other diagnosis by postnatal echocardiography.

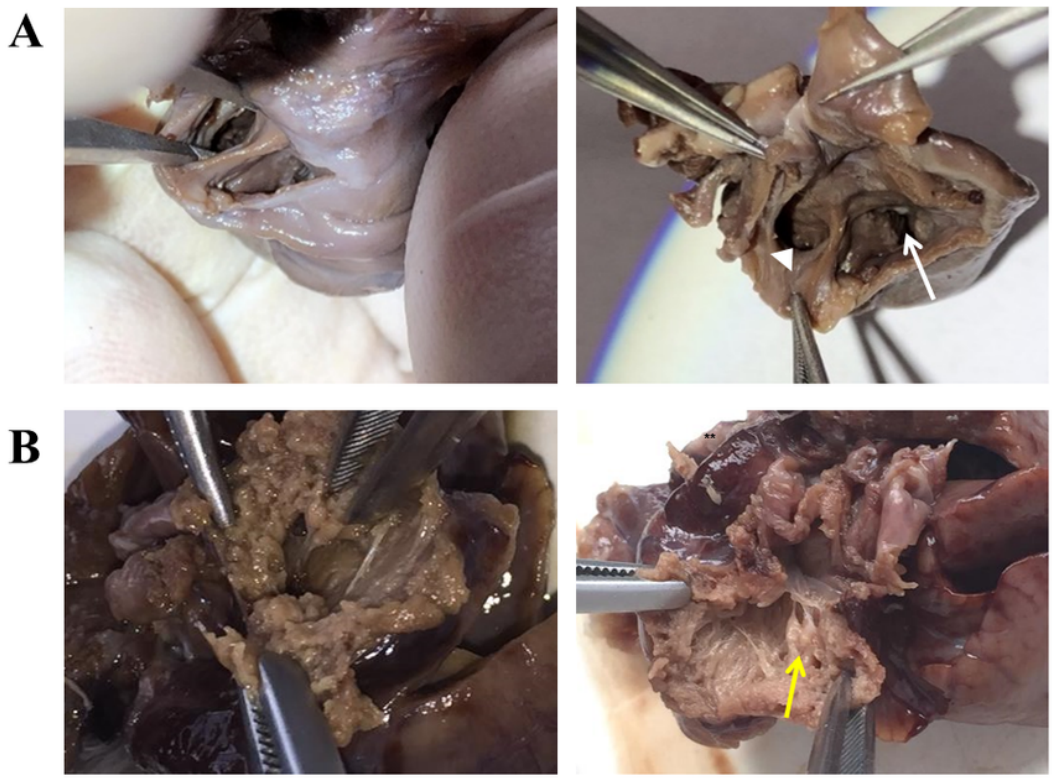

Figure 2

Figure 2. Postmortem autopsy of two Shone's syndrome cases. (a) Autopsy showed smaller mitral annulus in case B and (b) parachute mitral valve in case D. White arrowhead indicated mitral valve, white arrow indicated tricuspid valve, yellow arrow indicated parachute mitral valve.

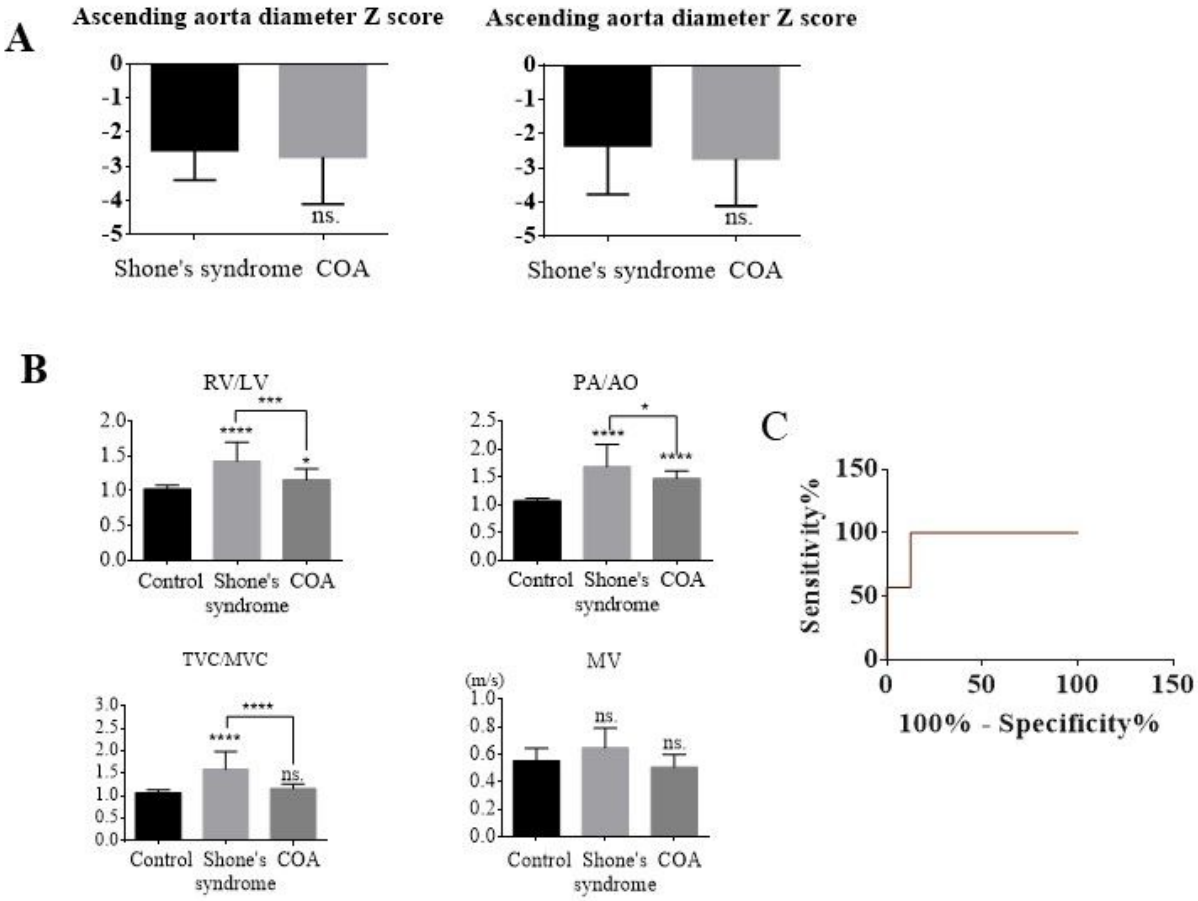

Figure 3

Figure 3. Comparison of echocardiographic features between three groups. (a) Z scores of ascending aorta (P=0.7333) and aortic isthmus (P=0.8894) showed no difference between Shone's syndrome and CoA. (b) Compared to normal controls, the ratios of PA/AO and RV/LV were increased in both Shone's syndrome (P<0.0001, P<0.0001) and CoA (P<0.0001, P= 0.034). However, fetuses with Shone's syndrome had higher PA/AO ratio and RV/LV ratio than those with CoA (P=0.035, P<0.0001). But TVC/MVC ratio

was increased only in Shone's syndrome cases (P<0.0001). (c) Receiver-operating characteristic curve of TVC/MVC ratio for the predictor of Shone's syndrome.

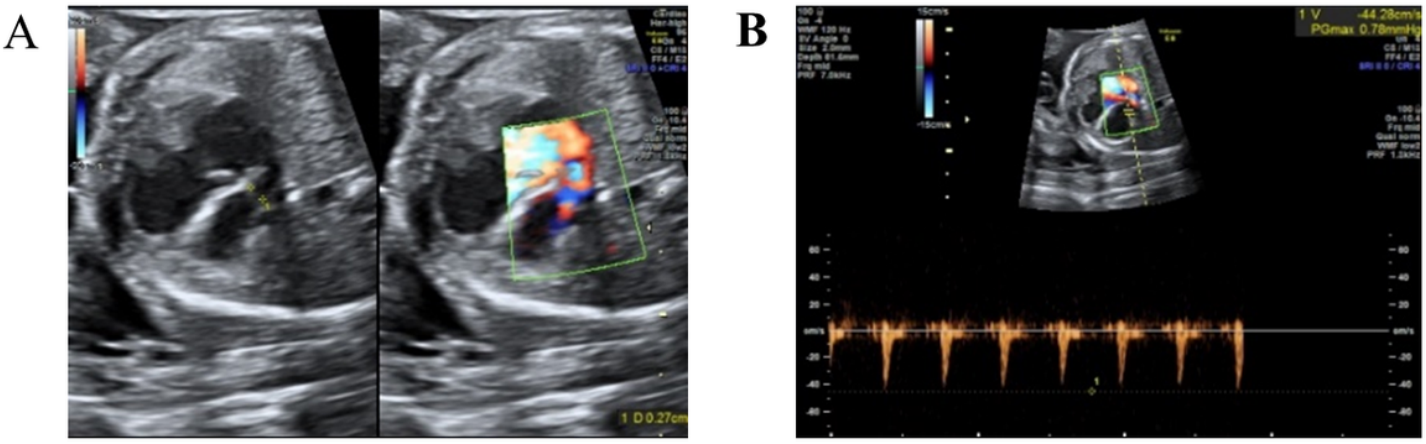

Figure 4

Figure 4. Unique sonographic features of mitral valve obstruction in Shone's syndrome cases. (a) Decreased antegrade flow and (b) abnormal mitral flow pattern (single peak) of a Shone's syndrome case.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- video1.rar
- video2.rar
- video3.rar
- video4.rar
- supplementary.docx