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Single left superior vena cava antenatal diagnosis, associations and outcomes

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Contribution

What are the novel findings of this work?

This is the largest series of single LSVC diagnosed antenatally. In most cases, this was an isolated finding. No major cardiac abnormalities were seen. Significant extracardiac or genetic findings were seen in ~6%. Most fetuses were identified after introduction of 3VV and 3VT to routine screening despite the 4-chamber view also being abnormal.

What are the clinical implications of this work?

More fetuses with single LSVC are likely to be detected as antenatal screening improves. Differently from those with bilateral SVC, significant associated abnormalities are uncommon. However, it is still important to perform a thorough investigation for possible associated abnormalities and consider genetic disorders, despite an expected low yield.

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Abstract

Objectives: To describe the associated cardiac and extracardiac findings and estimate the prevalence of single left superior vena cava (LSVC) among fetuses referred for fetal echocardiography.

Methods: This is a retrospective case series study of fetuses diagnosed with situs solitus and single LSVC at the Brompton Centre for Fetal Cardiology, from October 2006 to December 2020. Prenatal and postnatal outcome data were collected. Prenatal diagnosis was based on abnormal vessel alignment at the 3-vessel view (3VV) and/or 3-vessel and trachea view (3VT), showing a vessel to the left of the pulmonary artery, the LSVC, and absence of the usual vessel to the right of the ascending aorta, the right superior vena cava (RSVC), and further visualisation of the LSVC draining to the coronary sinus.

Results: Amongst 19,968 fetal echocardiograms, 34 cases were identified (prevalence 0.17%). There were 32 livebirths, 1 lost to follow up and one fetal demise. Single LSVC was isolated in most cases. No major CHD was identified. One fetus showed mild isthmus hypoplasia, with no aortic coarctation postnatally. Two fetuses had umbilical vessel abnormalities. Genetic abnormality was found in one case.

Conclusions: Antenatal diagnosis of single LSVC in situs solitus is usually a benign isolated finding. Nevertheless, investigation of other cardiac, extracardiac and genetic disorders should be considered.

Introduction

Anomalies of the venous system are common. With the offer of prenatal screening for malformations, more cases of venous anomalies have been diagnosed antenatally. During embryogenesis, the systemic venous system includes the right and left anterior cardinal veins, which evolves to form the right superior vena cava (RSVC) and the bridging innominate vein, while the left anterior cardinal vein regresses. Sporadically, the left anterior cardinal vein fails to regress and a persistent left superior vena cava (LSVC) is formed, which usually drains into an enlarged coronary sinus. The majority of individuals with LSVC have an intact RSVC, namely, bilateral superior vena cava (BSVC). This is the most common systemic venous anomaly with a reported incidence of 0.2-0.5% in low-risk fetal population[1-3], reaching 9% in fetuses with congenital heart disease (CHD)[2].

In rare circumstances, the right anterior cardinal vein regresses, resulting in absence of the RSVC and a persistent LSVC, namely, single LSVC. Therefore, the entire upper body venous drainage is through the single LSVC usually draining to the enlarged coronary sinus. This diagnosis is usually reported as an incidental finding during invasive procedures or autopsy series, with reported incidence of 0.05%[4-6]. There are only a few, isolated cases of antenatal diagnosis of single LSVC reported to date[7-12].

Herein we present a series of 34 consecutive cases of single LSVC diagnosed prenatally, describing the associated cardiac and extracardiac findings and estimating its prevalence in a selected population of fetuses referred for fetal echocardiography.

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Methods

This is a retrospective study of a cohort of fetuses diagnosed with single LSVC at tertiary centres. The aim was to describe features and frequency of antenatal diagnosis, associated anomalies and outcomes to help with prenatal counseling. The study was registered as a clinical audit (004398) and no ethical approval was required in accordance with local governance. Cases were identified from our fetal echocardiography database at the Brompton Centre for Fetal Cardiology, London, United Kingdom, since our first diagnosis in October 2006 until December 2020.

Inclusion criteria was presence of a single LSVC in the setting of situs solitus. Cases associated with isomerism were excluded since absence of the RSVC is a common feature of heterotaxy syndrome. In this paper the term single LSVC implies the presence of situs solitus. Pre- and postnatal data were retrieved from medical charts and hospital clinical databases. Antenatal data included maternal age, reason for referral, gestational age at diagnosis, cardiac and extracardiac findings and karyotype or other genetic studies. Postnatal cardiac, paediatric and genetic follow-up data were systematically collected, including data from outreach clinics if the child was followed up elsewhere.

Fetal echocardiography comprised a comprehensive cardiovascular examination by experienced fetal cardiologists using various ultrasound systems (Aloka Alpha 10, Aloka Medical, Ltd., Tokyo, Japan; Aplio i800, Canon Medical Systems Inc., Tokyo, Japan; GE Healthcare, Zipf, Austria) with curvilinear transducers of appropriate frequency for the patient and gestational age. The cardiac scans were carried out in a segmental approach, combining two-dimensional imaging, M-mode and colour/pulsed wave Doppler imaging. Systemic, pulmonary and umbilical venous return and great arteries are systematically evaluated in all fetal echocardiograms in our units. Information is routinely entered in the appropriate computer database at the time of scanning. When required, additional information was retrieved from recorded videoclips and stored images.

Prenatal diagnosis of single LSVC was made on the basis of an abnormal 3-vessel view (3VV) and/or 3-vessel and trachea view (3VT) at the upper mediastinum, showing the presence of a vessel to the left of the pulmonary artery, the LSVC, together with the absence of the usual vessel to the right of the ascending aorta, the RSVC (Figure 1). In addition, on colour Doppler, the presence of reversed flow direction at the innominate vein, from right to left, should raise the suspicion of single LSVC. The diagnosis was then confirmed in the long-axis view, demonstrating the site of drainage of the LSVC into the dilated coronary sinus and the absence

of the RSVC in the bicaval view (Figure 2). At the four-chamber view, the coronary sinus was dilated.

All parents received detailed counseling after the fetal cardiac scan. Extracardiac structures were evaluated by experienced practitioners or fetal medicine specialists. Invasive genetic prenatal diagnosis, i.e. karyotype/microarray based comparative genomic hybridization (array-CGH), or non-invasive prenatal testing (NIPT) were not systematically offered. Follow-up scans were arranged, usually one further scan during the 3rd trimester to document normal growth of cardiac structures and review the aortic arch, and a perinatal management plan established accordingly. It is our policy to organize postnatal follow up for any cardiac abnormality detected antenatally. This is to confirm normal transition from fetal to postnatal circulation (closure of the foramen ovale and arterial duct), verify coronary artery anatomy and to reassess for minor defects that can potentially be overlooked prenatally. Additionally, in the absence of formal genetic investigations, postnatal follow up allows confirmation of phenotype.

Descriptive statistics are reported as median (range or interquartile range) or percentage for qualitative variables. Statistical analyses were performed on Microsoft Excel, version 16.42.

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Results

Out of 19,968 new fetal echocardiograms performed from October 2006 to December 2020, a total of 34 fetuses (0.17%) were diagnosed with single LSVC. The median gestational age at diagnosis was 23^{+4} weeks (range: 17^{+6} to 33^{+5} weeks). Maternal age varied from 17 to 46 years (median 32, IQR 7).

In four cases (11.8%), the presence of a single LSVC was not appreciated on the first fetal echocardiogram, only on subsequent scans. Postnatal follow up and confirmation of the diagnosis was available for 30 / 34 cases. One was lost to follow-up and there are two livebirths pending postnatal review. There was one spontaneous intrauterine death and no terminations of pregnancy. The survival rate was 97.0%. Single LSVC was isolated in the majority (79.4%) of fetuses.

Cardiac findings

There was no major structural CHD identified prenatally but two fetuses showed a small muscular ventricular septal defect (VSD). Postnatally, there were additional minor echocardiographic findings in two children. Each had small bronchial collaterals, one of whom also had a small coronary fistula to the pulmonary artery. These were of no haemodynamic significance and required no treatment (Table 1). One fetus had cardiomegaly related to an extracardiac abnormality. The aortic arch was normal in all, with no evidence of discrete coarctation. One fetus showed mild isthmal hypoplasia but normal aorta postnatally.

Extracardiac/ genetic findings

Extracardiac findings were present in two fetuses (5.9%). One had a single umbilical artery, normal NIPT and normal phenotype. One growth restricted fetus, who presented with cardiomegaly, had a large umbilical vein varix, mild cerebral ventriculomegaly and normal array-CGH. This fetus died in utero at 32 weeks of gestation, likely due to heart failure secondary to large umbilical vein varix.

Genetic investigation was carried out in approximately ¼ of the cases (26.5%). PCR and array-CGH were performed in five fetuses and one child (17.6%) and cell-free DNA test in three cases (8.8%). Results were normal in all but one, in which a 15q24.1-q24.2 deletion, which overlaps 15q24 deletion syndrome, was identified postnatally as part of investigations for mild neurodevelopmental delay.

The main reason for referral was suspected cardiac abnormality at the routine anomaly scan, accounting for approximately 85%, followed by increased nuchal translucency (Table 1). The frequency distribution of these referrals over the study period is shown in Figure 3.

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Discussion

We describe a cohort of 34 fetuses with single LSVC and show this to be an isolated condition in the majority. Only two fetuses (5.8%) had abnormalities with clinical impact, one extracardiac and one genetic. No major CHD was present. Minor cardiac findings were identified in four cases (11.8%). The aortic arch was normal in all. This is the largest reported collection of single LSVC diagnosed antenatally.

Only 13 cases of single LSVC have been previously reported in fetuses, being isolated in all[7-10, 12] but in one case, which was associated with VACTERL[11]. However, in postnatal series there is a stronger association with CHD (46 to 100%)[4-6], some of which also had rhythm (25%) or chromosomal abnormalities, including trisomy 21 and trisomy 18 (7%)[5]. The postnatal diagnosis of isolated single LSVC is usually an incidental finding at autopsy or invasive procedures[5,6].

The rate of single LSVC in fetuses referred for fetal echocardiography in this study (0.17%) is about three times that reported in general postmortem series (0.05%)[4] and twice that seen in series of CHD[5]. Our estimated prevalence is presumably closer to that of the general population, since single LSVC can be suspected during routine screening that incorporates the 3VV and 3VT. Although all cases we describe had fetal echocardiography, ~ 85% were low-risk families. . However, the true prevalence may be even higher, as it is still possible that not all cases will be picked up by screening.

In the United Kingdom, The Fetal Anomaly Screening Programme (FASP)[13] is part of the National Health Service wider screening programme. It includes a detailed fetal structural investigation, usually performed by trained sonographers. A national cardiac protocol was introduced in 2010 which included the 3VV and in 2015, the 3VT was added[14]. These screening cardiac views are in agreement with international guidelines[15]. Of interest, in our study, only one case was diagnosed prior to 2010 and the majority (64.7%) was detected after 2015 (Figure 3). Our data point to a clear increase in detection of single LSVC along with the incorporation of 3VV and 3VT to routine screening protocols. In these views, three vessels will be present, but 'abnormally' arranged, as shown in Figure 1 and 2.

An abnormal 3VV and/or 3VT on routine screening was the main reason for referral when an abnormality was suspected (24 of 29 cases), followed by an abnormal 4-chamber view (5 of 29 cases). It is interesting that although the 4-chamber view is abnormal due to a dilated coronary sinus, as it receives the entire upper body blood return, this was not the main reason for referral.

It has been postulated that dilatation of the coronary sinus could lead to restriction of left ventricular inflow, contributing to the development of left heart obstructive disease[16]. However, a recent meta-analysis concluded that BSVC, a condition associated with dilated coronary sinus, did not carry an increased risk for coarctation[17]. In this series, no coarctation or left heart obstruction was present.

BSVC is a relatively frequent antenatal finding, therefore, when a persistent LSVC is identified during a fetal heart scan, the RSVC will be present in the vast majority of cases. However, one should not assume this is the case, as it is necessary to visualize both superior vena cavas. In four of our cases, the absence of the RSVC was not appreciated on the first scan. Care should be taken correctly to identify the upper mediastinal structures and not to misinterpret the trachea as being the RSVC (Figure 4). The trachea is more posterior and has a hyperechogenic ring. In addition, in BSVC the bridging innominate vein is usually absent, whereas it is present in single LSVC, but flow direction is right to left, the opposite to normal.

LSVC draining into the coronary sinus, single or bilateral, is a venous abnormality with no haemodynamic significance but with different clinical implications. BSVC is most frequently associated with cardiac or extracardiac findings[18-20-20] (Table 2), when a genetic concern is present in up to 45% of cases[19]. When strictly isolated, a genetic anomaly is usually absent. Conversely, single LSVC is usually an isolated antenatal finding[7-10,12] as seen in this series. Genetic abnormalities are rarely reported[11] and was seen in only one of our cases. The association between single LSVC and cardiac, extracardiac and genetic disorders seem to be low, but not absent (Table 2).

It is now commonly accepted that in fetuses with an increased nuchal translucency, irrespective of the karyotype, the prevalence of major CHD is higher than in the general population, although the mechanism underlying this relationship is still poorly understood. Increased nuchal translucency has been reported in 29% of fetuses with BSVC[2], whereas in this series it was increased in about 15% of cases.

This study, despite being retrospective, reports the largest series of single LSVC diagnosed antenatally. The use of a standardized protocol for fetal heart screening in our network, with systematic referral for fetal echocardiography in the presence of abnormal cardiac views is one of the strengths of our study. Similarly, our unit's strict protocol for postnatal follow up of any cardiac abnormality detected antenatally, allowed us to have good postnatal outcome data. Although the number of genetic studies performed is relatively low, we were able to confirm normal phenotype in the vast majority of cases.

In conclusion, single LSVC when diagnosed antenatally, is usually a benign isolated finding. Nevertheless, it is important that these cases be thoroughly investigated to exclude associated cardiac, extracardiac and genetic disorders, even if the risk seems to be small. With the offer of prenatal screening for malformations and improvement in screening standards more cases of single LSVC are likely to be detected prenatally.

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Figure legends

Figure 1. Schemes and ultrasound cross sections of the three-vessel view: (a and b) normal arrangement of the vessels, from left to right, pulmonar artery (PA), aorta (Ao) and right superior vena cava (SVC). Abnormal arrangment of the vessels in the setting of single left superior vena cava, from left to right, left superior vena cava (SVC), pulmonary artery (PA) and aorta (Ao). DAo, descending aorta; T, trachea.

Figure 2. (a) Apical cross-section of the four-chamber view in a slightly caudal plane demonstrating the dilated coronary sinus (star). (b) Sagittal-oblique view of the left superior vena cava (LSVC) showing drainage into the coronary sinus (star). (c) Bicaval view demonstrating the inferior vena cava (IVC) draining normally into the right atrium (RA) and absent right superior vena cava (arrow). RV, right ventricle; L, left; R, right; I, inferior; S, superior.

Figure 3. Frequency distribution of single LSVC diagnosed over the study period. The two dotted lines indicate the year of introduction of the 3VV (2010) and 3VT (2015) to the cardiac screening protocol in England.

Figure 4. Cross-sectional images at the level of the 3VT: (a) Case with single LSVC and (b) an example of bilateral SVCs for comparison. Note that in (a) the fluid-filled space to the right of the aorta corresponds to the trachea (T), which should not be mistaken to be the RSVC. The trachea shows an echogenic ring and occupies a more posterior position than that expected by the absent RSVC, indicated by the circle. L, left; R, right.

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Table 1 - Antenatal and postnatal data in 34 fetuses with single left superior vena cava

	n/N (%)
Reason for referral	
Abnormal 3VV /3VT	24/34 (70.6%)
Abnormal 4-chamber view	5 /34 (14.7%)
Increased nuchal translucency	5 /34 (14.7%)
Other fetal cardiac findings	
Small muscular ventricular septal defect	2 /34 (5.9%)
Normal aorta	33/34 (97.1%)
Isthmal hypoplasia	1/34 (2.9%)
Other postnatal cardiac findings*	
Small coronary fistula & bronchial collaterals	1/30 (3.3%)
Isolated bronchial collaterals	1/30 (3.3%)
Extracardiac findings	
Single umbilical artery	1/34 (2.9%)
Umbilical vein varix, growth restriction, ventriculomegaly	1/34 (2.9%)
Genetic Findings†	
15q24 deletion syndrome	1/32 (3.1%)
Outcome	
Intrauterine death	1/34 (2.9%)
Lost to follow up	1/34 (2.9%)
Pending postnatal review	2/34 (5.8%)

3VV = three-vessel view, 3VT = three-vessel and trachea view

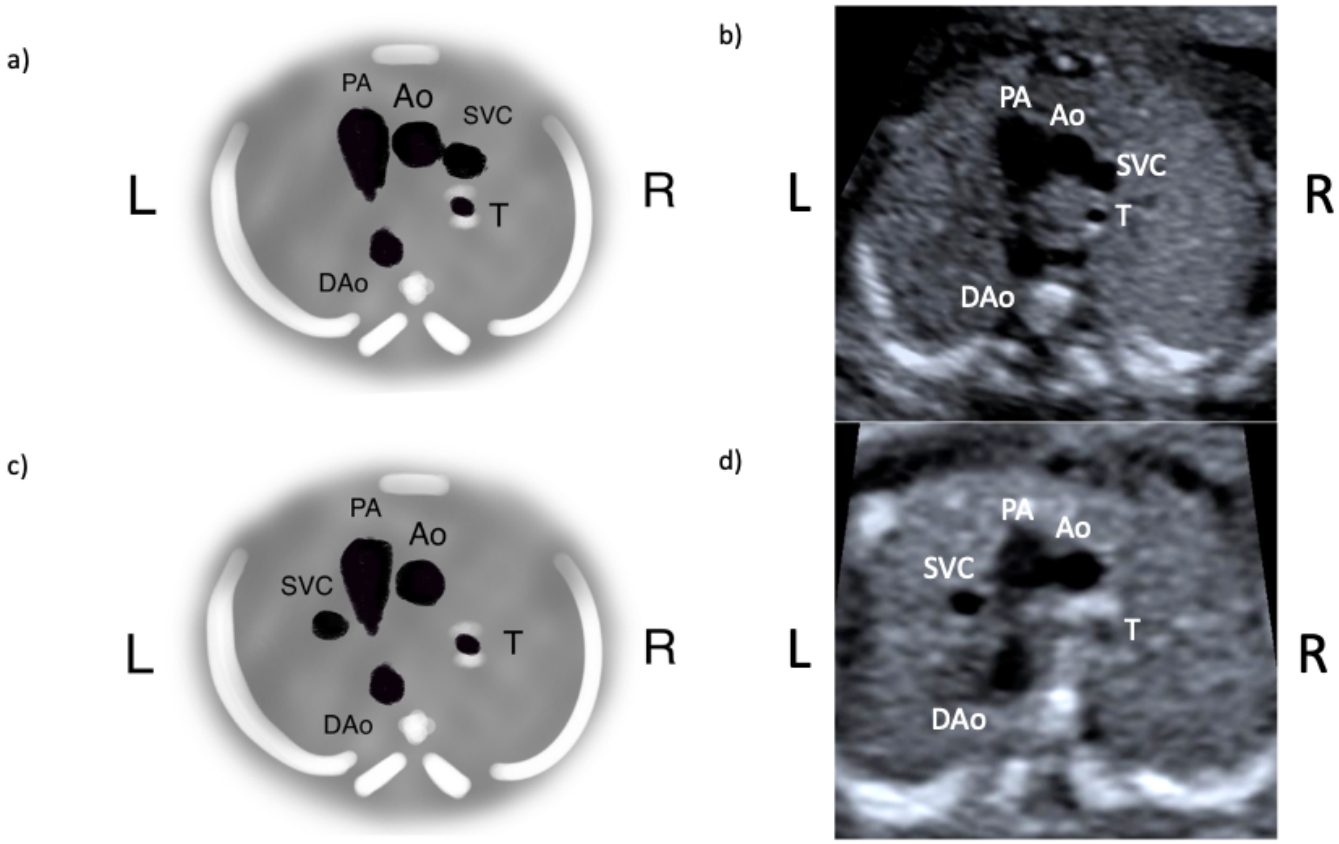
* Includes only those with known outcome data.

† Includes only those tested and/or with known phenotype.

Table 2 - Largest antenatal series of left superior vena cava

	Single LSVC	**Bilateral SVC**		
	This series	Minsart 2019	Gustapane 2016	Du 2014
n	34	229	501	164
Prevalence	0.17%	1%	-	0.7%
Isolated	79.4%	17%	17.4%	26.8%
Associated cardiovascular abnormality	11.6%	31%	56.6%	46.9%
Associated extracardiac abnormality	5.8%	51%	37.8%	45%
Associated genetic abnormality	2.9%	22%	12.5%	15.4%

SVC = superior vena cava



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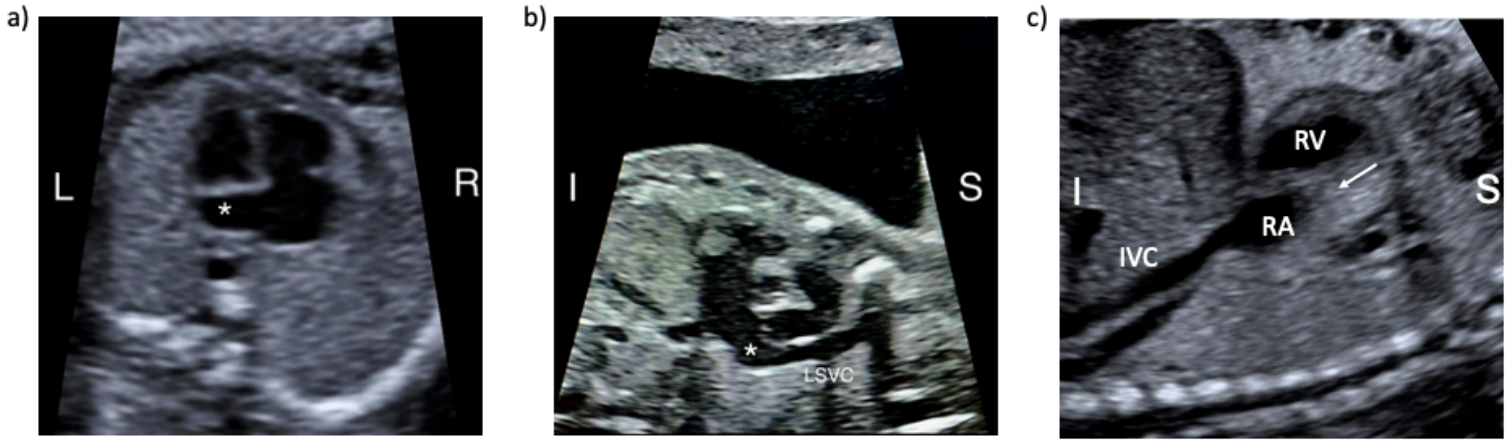

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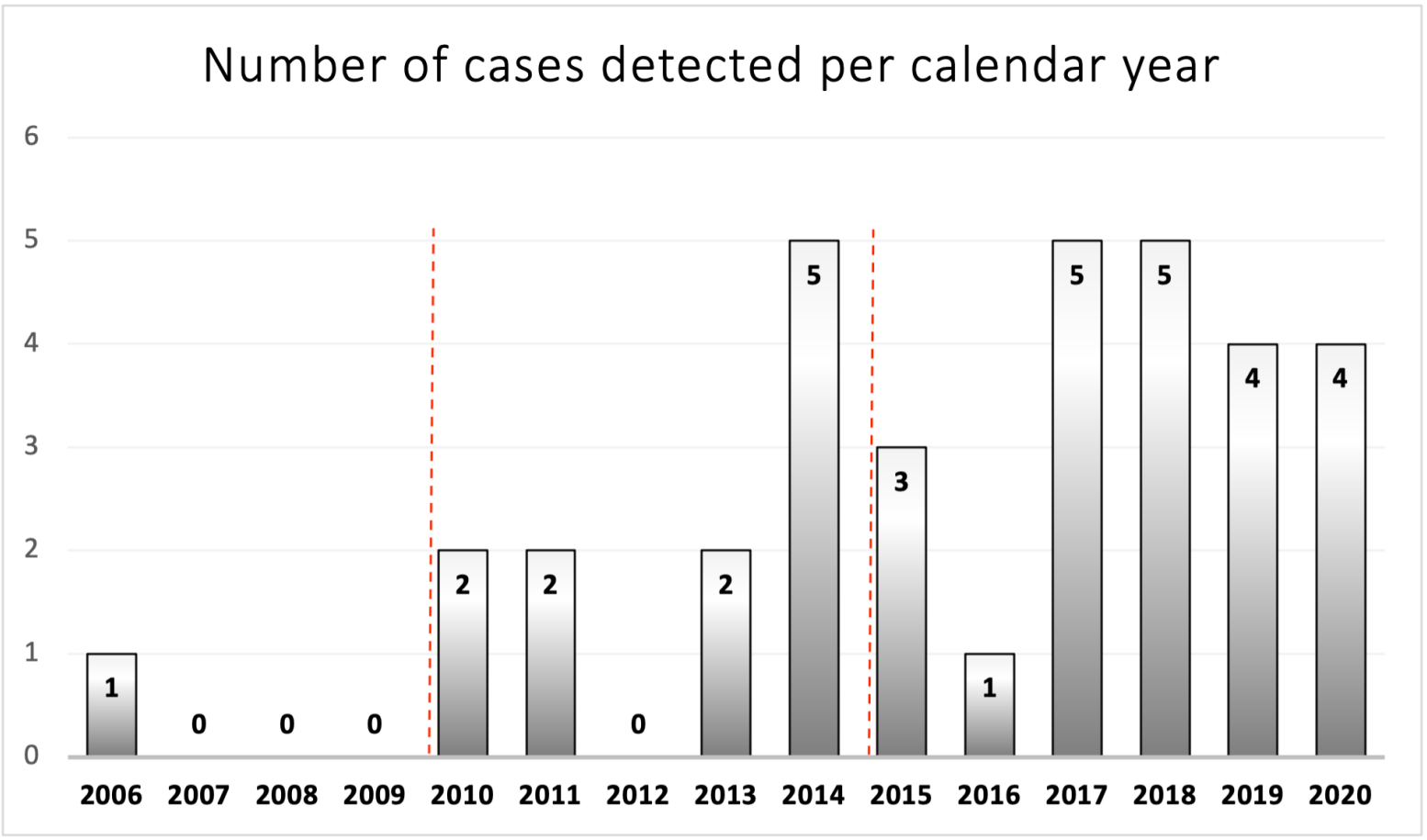

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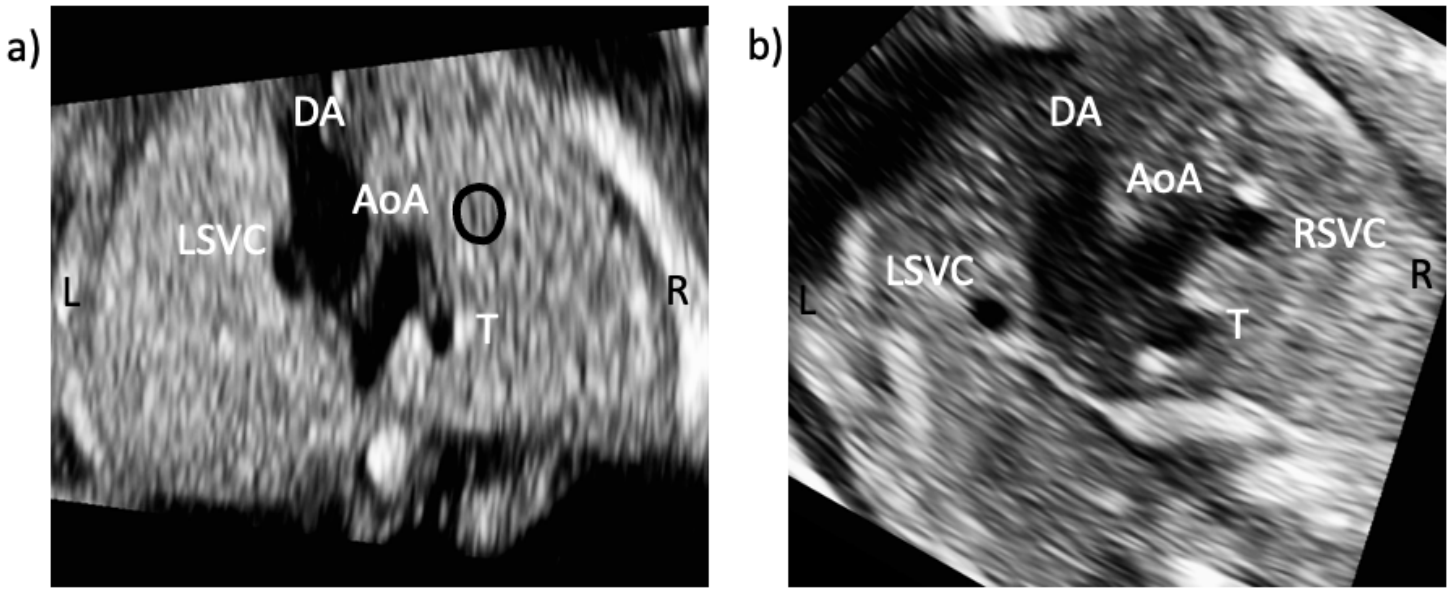

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