



CASE REPORT

# Pierre Robin sequence and double aortic arch: a case report<sup>☆</sup>

Edward T. Waters<sup>a,\*</sup>, James P. Oberman<sup>b</sup>, Abhik K. Biswas<sup>c</sup>

<sup>a</sup>Department of Pediatrics, Naval Hospital Beaufort, One Pinckney Blvd., Beaufort, SC 29902, USA

<sup>b</sup>Department of Otolaryngology, Naval Medical Center Portsmouth, Portsmouth, VA 23708, USA

<sup>c</sup>Pediatric Critical Care Medicine, Naval Medical Center Portsmouth, Portsmouth, VA 23708, USA

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**Summary** We present an 8-day-old female with two admissions for respiratory failure. On the first admission, the diagnosis of Pierre Robin sequence (PRS) and laryngomalacia was made after assessment with chest radiography, echocardiography, and flexible fiberoptic laryngoscopy. Four days after discharge, the child presented with stridor and respiratory distress, and a new cardiac murmur was noted after admission. Repeat echocardiography, with confirmatory direct laryngobronchoscopy, revealed a double aortic arch (DAA) with distal tracheal compression. This case illustrates the necessity of a complete otolaryngic evaluation, including direct laryngobronchoscopy, to search for a synchronous airway lesion in any neonate with severe respiratory distress associated with stridor.

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## 1. Introduction

Pierre Robin sequence (PRS) and double aortic arch (DAA) are two conditions that are known causes of

respiratory distress in the newborn period. We describe an infant whose diagnosis of DAA was delayed as a result of the concomitant presence of PRS and laryngomalacia. This case highlights the need for diagnostic persistence when one is faced with confounding clinical data that incompletely explains the patient's symptoms. It also identifies DAA as another congenital cardiovascular defect associated with PRS.

## 2. Case presentation

An 8-day-old infant female, born at 36 weeks estimated gestational age, presented to the Emergency Department (ED) with the chief complaint of 4 days of nasal congestion and "difficulty breathing".

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\* Corresponding author. Tel.: +1 843 228 2218;  
fax: +1 843 228 5165.

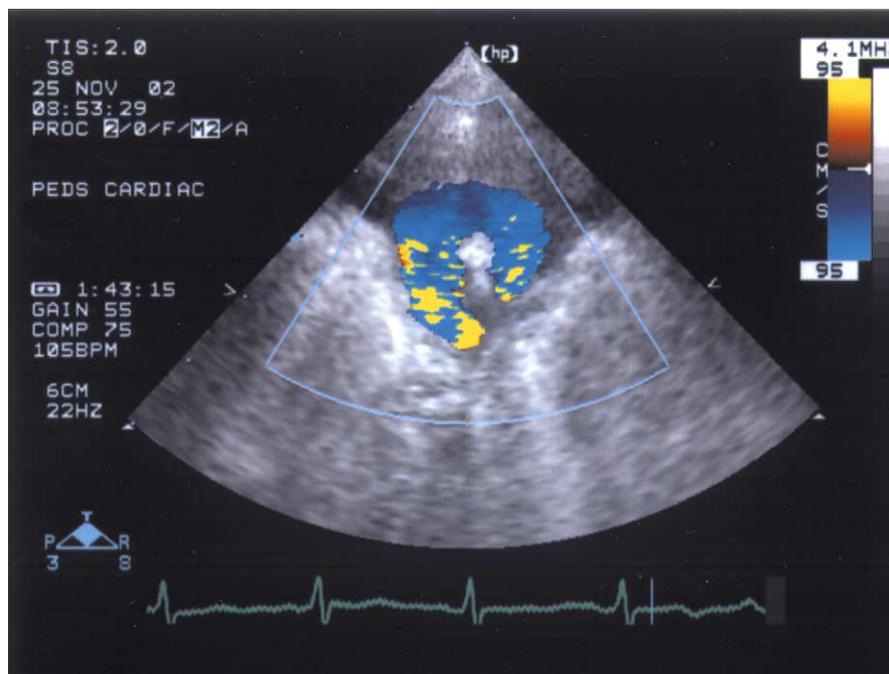
E-mail address: taguas@pol.net (E.T. Waters).

There was no report from the parents of any antecedent trauma, feeding intolerance, hoarseness or change in the quality of her cry. The parents did report “noisy breathing” since birth, which varied with position and was mostly associated with inspiration. In the ED, the patient received nebulized albuterol for wheezing and two normal saline boluses for poor perfusion. She remained tachypneic and mottled, so she was screened for sepsis with a complete blood count, and blood, urine and cerebral spinal fluid cultures. During the lumbar puncture, while being held in the side-lying and flexed position, the baby became apneic and cyanotic. She was resuscitated quickly, and was electively intubated prior to her transfer to the Pediatric Intensive Care Unit (PICU) due to persistent respiratory distress. Upon close physical assessment after her admission and stabilization, it was noted that she had features consistent with PRS, i.e. glossoptosis, micrognathia, high-arched palate, and monophasic inspiratory stridor, which was noted prior to intubation. No cardiac murmurs were appreciated on initial and follow-up exams during this admission. A detailed family history was notable for a deceased brother with Cornelia de Lange syndrome (CDLS). Our patient had no findings suggestive of CDLS aside from her micrognathia.

Admission venous blood gas while intubated on an  $\text{FiO}_2$  of 0.80 revealed the pH was 7.21;  $\text{PaCO}_2$ , 75 mmHg;  $\text{PaO}_2$ , 47 mmHg; and  $\text{SaO}_2$ , 100%. Her serum bicarbonate was 30 mmol/L. She was

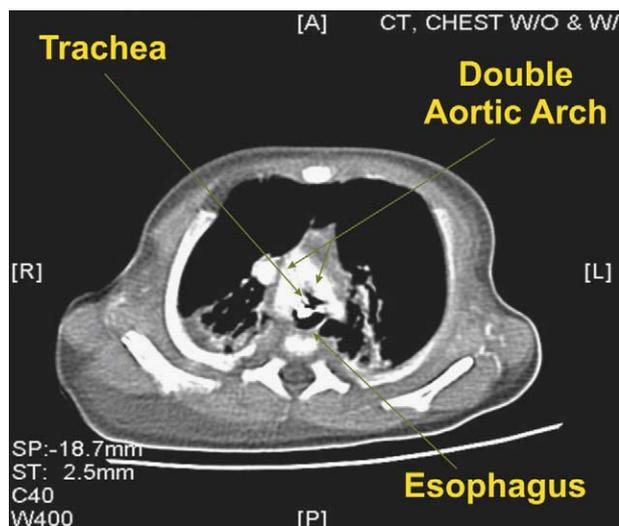
assessed for other syndromic features, specifically Stickler syndrome and Velo-cardio-facial syndrome (VCFS), and none were found. Her renal ultrasound, head ultrasound, chest X-rays and echocardiogram were read as normal and chromosomal studies were sent. She weaned quickly off the ventilator to nasal cannula by hospital day # 2. After extubation, persistent positional inspiratory stridor was noted, particularly while lying supine. The otolaryngology (ENT) service performed flexible fiberoptic laryngoscopy (FFL) which showed mild laryngomalacia and peri-arytenoid edema and erythema. The subglottis and trachea were not visualized due to the limitations of bedside FFL. These findings were felt to be consistent with laryngopharyngeal reflux. She remained hemodynamically stable throughout this hospitalization and never required inotropic support. Her respiratory syncytial virus washing and viral and bacterial cultures all returned negative. Upon discharge on hospital day # 6, she was noted to have mild residual stridor that was associated with supine positioning and inspiratory in nature. She was feeding well and discharge was arranged. Her parents were given instructions for prone positioning, close parental monitoring, and empiric gastroesophageal reflux treatment with an H2 blocker, and she was expected to progressively improve as she grew.

Four days after her discharge from the PICU, she presented again to the ED with tachypnea, inspiratory stridor, retractions, and evidence of poor per-

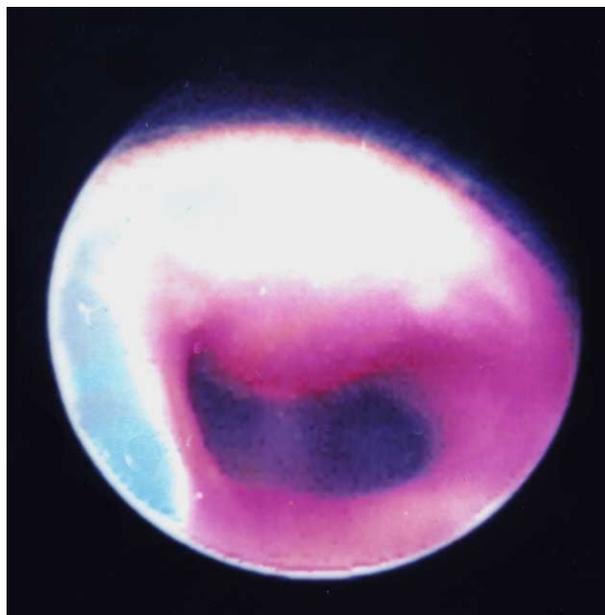


**Fig. 1** Color doppler image of great vessels via echocardiogram in our patient with double aortic arch. Vascular ring is clearly demonstrated surrounding the trachea.

fusion. The parents noted the sudden onset of respiratory difficulty without prodromal upper respiratory infection symptoms. The baby had been evaluated by her pediatrician 1 day prior and was noted to be well appearing except for mild tachypnea and isolated retractions. She was again intubated in the ED for respiratory distress and transferred to the PICU for treatment of respiratory failure and hemodynamic lability. She was placed on mechanical ventilation and required inotropic support to maintain perfusion and blood pressure. Her arterial blood gas in the ED on an  $\text{FiO}_2$  of 1.00 showed her pH was 6.8;  $\text{PaCO}_2$ , 195 mmHg;  $\text{PaO}_2$ , 467 mmHg, and  $\text{SaO}_2$ , 99%. Her serum bicarbonate was 30 mmol/L. After stabilization, discussion with the ENT service focused on her PRS. Alternative causes of respiratory failure in the newborn period, specifically vascular rings, were considered unlikely, primarily because of her normal echocardiogram 1 week prior to this admission. Therefore, reassessment with an echocardiogram was not initially performed. On PICU day # 3, the patient developed hypotension, weak distal pulses and decreased urine output. Evaluation revealed a new grade II/VI systolic murmur and repeat echocardiography showed a vascular ring suggestive of a DAA (Fig. 1). Thoracic computed tomography with angiography followed by direct laryngobronchoscopy (DLB) confirmed this diagnosis, demonstrating external compression of the distal right and anterior trachea (Figs. 2 and 3). She was referred to another center, where her left aortic arch was ligated without complication (Fig. 4). Currently, at 18 months of age, she is thriving, with excellent growth and achievement of all developmental milestones.



**Fig. 2** Chest CT with contrast demonstrating double aortic arch compressing the trachea anteriorly and the esophagus laterally.

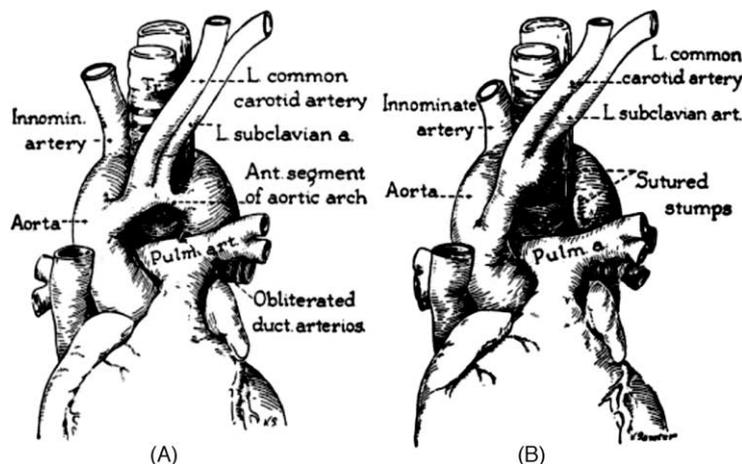


**Fig. 3** Direct laryngobronchoscopy (DLB) demonstrating distal tracheal compression, with “fish-mouthing” of trachea proximal to the carina.

### 3. Discussion

To our knowledge, this is the first description in the medical literature of a patient with PRS and DAA. PRS was first described in 1923 as micrognathia, glossoptosis, and respiratory distress [1], but reference to this constellation of findings can be found in publications dating back to 1846 [2,3]. Robin revised the definition in 1934 to include cleft palate [4], however, debate persists regarding the precise definition of PRS. Some authors allow for cleft palate as a variable finding [5–8]. Our patient, with micrognathia, glossoptosis, high arched palate without clefting, and obvious respiratory distress, meets most accepted definitions of PRS, and certainly falls in line with Robin’s initial description of the condition.

Vascular rings occur infrequently, estimated at <1% of all cases of CHD. DAA is the most common form of symptomatic vascular ring, accounting for up to 40% of complete rings, and commonly occurs in isolation [9]. Normal embryologic cardiovascular development proceeds from initially paired mediastinal vessels connected by branchial arches. Normal cardiovascular relationships are formed through a series of branchial arch and aortic root regressions [10]. Vascular anomalies can result from regression of vessels that normally persist, or nonregression of vessels that should regress. In DAA, failure of vessels to regress creates a redundant ring and compression



**Fig. 4** Artist's rendering depicting double aortic arch before and after surgical ligation of the non-dominant arch. Taken from Behrman: *Nelson's Textbook of Pediatrics*, 17th ed., 2004, p. 1546, Fig. 425.2-1.

around the trachea and esophagus which can cause respiratory distress and dysphagia. The embryologic events that cause DAA occur weeks before palate formation [11]. It is possible that DAA and PRS in this patient are not embryologically related, however, the literature does support an association between PRS and congenital heart disease (CHD).

We reviewed the PRS and CHD literature looking broadly for an association between these two conditions, and specifically for any previously described cases of PRS and DAA. A 4-year retrospective review of patients with CHD demonstrated that 395/1566 (25.5%) had other congenital anomalies; five had PRS and none had DAA [12]. In a review of the association of CHD with PRS [7], it was estimated that one of every five patients with PRS has CHD. The review asserted that only 37 cases of documented CHD with PRS existed in the medical literature. This study delineated the types of CHD associated with PRS, with ventricular septal defect, patent ductus arteriosus, and atrial septal defect occurring most commonly. DAA was not a finding in this review. A retrospective necropsy review combined with a prospective cross-sectional study of patients in a large cleft lip and palate clinic revealed 21 of the 32 deaths had concomitant CHD, and only one of those had PRS (coarctation of the aorta) [11]. The prospective arm of this study showed that 15 of 150 patients with cleft palate (10%) were diagnosed with PRS, none of whom had CHD. In another study of 201 children born with PRS [13], comparison of birth and death certificates showed 59 deaths and 10 of those who died had CHD. This study demonstrated higher mortality rates among PRS children with CHD than among those with cleft lip and palate who had no CHD. However, no information was provided about the type of CHD in these children. One more study demonstrated a 13.6% prevalence rate of CHD in PRS

patients, and none of these had DAA [14]. Velocardio-facial syndrome (VCFS), a congenital malformation syndrome linked to chromosome 22, can have both PRS and CHD [15–17]. In a series of 39 patients with VCFS, 84% had CHD and 11% had PRS [17]. Twelve (30%) patients in this series had right-sided aorta and one had “third aortic arch syndrome”. No data was provided to determine how many of those with CHD had PRS. Of note, our patient had a normal fluorescent in situ hybridization (FISH) study of chromosome 22.

Our patient presented with symptoms explained logically and physiologically by her physical findings of both PRS and laryngopharyngeal reflux (LPR) with laryngomalacia. Her relatively rapid recovery in the intensive care setting on first admission was consistent with the expected hospital course of a patient experiencing respiratory compromise secondary to mild PRS anatomy, exacerbated by concomitant laryngomalacia and LPR. This supposition is reasonable, as it has been suggested that laryngomalacia alone may be a cause for early apnea of infancy [18]. Laryngomalacia has been mentioned as a possible cause for apnea and bradycardia of infancy, and even for sudden death, by numerous theoretical mechanisms, to include laryngeal spasm; reflex apnea exacerbated by LPR; and laryngomalacic upper airway obstruction causing sleep disturbances with sleep fragmentation, acting to hinder arousal response to respiratory stimuli [18]. When our patient presented again 4 days after discharge in respiratory distress, the PICU team approached her as a known entity, and did not immediately return to the original differential diagnosis for stridor and respiratory failure in a newborn. The findings of PRS in this child, combined with the false negative echocardiogram, delayed the diagnosis of DAA. Furthermore, although it is

often debated within the Pediatric Otolaryngology community, a fastidious search by the otolaryngology consultants for a synchronous airway lesion (SAL) by performing a DLB during the first admission may have expedited identifying the correct diagnosis. Because of the documented association of laryngomalacia with SALs [19–21], some authors have suggested that rigid endoscopic evaluation be performed in all cases of documented laryngomalacia for the sole purpose of ruling out SALs [19,22]. However, since the clinical significance of a given SAL is unknown, and because most infants with laryngomalacia followed over time improve without intervention, Mancuso et al. suggest that formal rigid aerodigestive endoscopy is not necessarily essential or cost effective [23,24]. They suggest that it should be reserved for stridor uncharacteristic of laryngomalacia; inconsistent findings observed with FFL; abnormal high-kilovolt anteroposterior and lateral airway radiographic films; and a high degree of clinical suspicion, such as a documented history of cyanosis. This approach is supported by Friedman et al. [20], who demonstrated in their retrospective review that 45% of infants presenting with cyanosis had one or more SALs. Furthermore, in a separate retrospective review of all neonates presenting over an 8-year period with either cyanosis, stridor, or feeding difficulty, 77.4% of cases had more than one diagnosis or finding on formal aerodigestive endoscopy, emphasizing the need for a thorough examination of the entire aerodigestive tract, especially in the neonate [25]. Other clinical features which should prompt formal endoscopy (DLB) include history of apnea and failure to thrive [26]. A retrospective review by McMurray and Holinger [27] looked at their institution's diagnoses of infants presenting with an apparent life-threatening event (ALTE) and found that 50% of their series who underwent DLB actually had some anatomic abnormality of the aerodigestive tract demonstrated. Furthermore, in a retrospective review by Gormley et al., who looked at a series of 16 neonates diagnosed with a congenital vascular anomaly causing tracheobronchial compression, the exact etiology of a neonate's stridor and ALTE was misdiagnosed without DLB in 44% of cases [28]. In their review, DLB was diagnostic of a vascular anomaly with a sensitivity of 100% and is, therefore, their investigation of choice.

This case highlights the need for a broad differential diagnostic approach to the recently-discharged patient returning unexpectedly with identical symptomatology, and it emphasizes the need to suspect a second airway lesion in any child with severe airway compromise which is poorly explained by a primary lesion. In addition, it is also

possible that DAA is another, previously unreported, cardiovascular malformation associated with PRS, and should be considered in the differential diagnosis of a PRS patient presenting with respiratory or cardiovascular compromise.

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