

Genetics Corner: A Term Infant with a Bilateral Cleft Lip and Palate and Coarctation of the Aorta

Robin Dawn Clark, MD

Case Summary:

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This baby was born AGA at 40 weeks 0 days gestation by NSVD in the vertex presentation through meconium-stained fluid with aspiration to a 27-year-old primigravida mother. Apgar scores were 1st, 5th, and 8th. A bilateral cleft lip and palate (complete L cleft lip, incomplete R cleft lip) was appreciated at birth. He had poor tone and no respiratory effort; he did not cry spontaneously at birth. He required positive pressure bag and mask ventilation, but his heart rate remained in the 80s. He was intubated at 2 minutes of life after three attempts. A large quantity of particulate meconium was suctioned from the ET tube. His respiratory effort improved by 10 minutes of life. He was extubated at 12 minutes and brought to the NICU after delivery.

Cord blood gas pH 7.17/BE -4.6. BW 2890 g (16th %ile), BL 50.8 cm (68th %ile), HC 32.5 cm (6th %ile). He was reintubated for 48 hours for meconium aspiration and extubated on the third day of life to a high-flow nasal cannula via Vapotherm at FiO₂ 30%. He could not be weaned off nasal cannula. He received one dose of Curosurf. A respiratory virus panel was negative. He received total parenteral nutrition for five days and was on full feeds by gavage only due to concern for aspiration. An echocardiogram on the day of birth showed a small ASD, PDA, dilated right atrium, right ventricle, and main pulmonary artery. The repeat echocardiogram on the second day of life was unchanged. Blood culture was negative. He received seven days of ampicillin and gentamicin. A chromosome microarray was negative. He was transferred at 16 days of life for further evaluation of poor feeding and concern

for aspiration. Breath sounds were equal and clear. There was no cardiac murmur.

After transport to this NICU, a swallow study was normal at 17 days. An abdominal ultrasound showed minimal central calyceal dilation of both kidneys (UTD P1). The head ultrasound was normal. He had persistent desaturations and could not be weaned off supplemental oxygen, requiring 1L of 23–30% FiO₂. Upon admission at 16 days of age, mean arterial pressure was elevated at 59/42 mmHg, and it remained elevated subsequently: 86/65 at 17 days, 65/27 at 18 days, 69/39 at 19 days, and 65/40 at 20 days.

At 22 days of age, an echocardiogram showed a discrete coarctation of the aorta with narrowing of the isthmus, ~2.8 mm, and a peak gradient of ~29 mmHg in the descending aorta. There was a moderate patent foramen ovale with a left to right shunting, mean gradient ~8 mmHg, persistent left superior vena cava draining to the coronary sinus, and a small apical muscular VSD. The mitral valve was borderline hypoplastic, 7.8 mm (Boston Z-score -2.1), with mild stenosis, mean gradient ~4 mm Hg. The cardiologist noted diminished lower extremity pulses with good capillary refill, warm extremities, and no murmur. He was started on prostaglandin (PGE) infusion, and his ductus arteriosus opened overnight with increased flow across the isthmus compared to the day before PGE began. Peak lactate level was within expected limits at 1.5 mMol/L.

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At 25 days of age, he had an urgent surgical repair with isthmus excision, end-to-end repair of the coarctation, and ligation of a small patent ductus arteriosus. Post-operatively, the patient tolerated room air without apnea, bradycardia, or desaturation. He was advanced to breastmilk fortified to 24 calories/oz by nipple gavage, taking 5–15 mL by mouth using a Dr. Brown's Ultra Preemie nipple at discharge. He passed the newborn hearing screen. A gene panel for cardiac anomalies was pending at the time of discharge at 33 days of age.

The pregnancy history was noncontributory except for maternal obesity (prepregnancy BMI 30.7). The family history was negative for oral clefts or congenital cardiac anomalies. The parents denied consanguinity. The physical exam after surgery was pertinent for an irritable, vigorous infant with a lusty cry who calmed after the exam. He had hypertelorism, long transverse ear crus bilaterally, and bilateral cleft lip (complete on the left, incomplete on the right) and palate.

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Discussion:

This term, AGA infant had a bilateral cleft lip with a cleft palate complicated by meconium aspiration and neonatal depression. His initial echocardiograms and normal chromosome microarray did not explain his poor feeding and continuing need for supplemental oxygen. After a normal swallow study, a diagnostic echocardiogram at just over three weeks of age identified a coarctation of the aorta.

These two congenital anomalies, oral clefts, and cardiac defects, frequently occur together.

Cleft lip with or without cleft palate (CL+/-P) occurs in about 1 in 1000 liveborn infants in the United States, with an excess of males. Coarctation of the aorta (CoA), an anomaly in the left-sided obstruction lesion (LSOL) group of disorders, makes up about 7% of all congenital heart defects. CoA has a prevalence of approximately 4 per 10,000 births, and, like cleft lip, it is more common in males.

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The initial evaluation of a child with an oral cleft should include a careful evaluation for other anomalies, the most common of which is a congenital cardiac defect. In their study of 200 patients with cleft lip and palate, Kasatwar and colleagues (1) found that 30 patients (15%) had a congenital cardiac anomaly, of which the most common defect was ventricular septal defect. Sun et al. (2) reported that among 2180 patients with orofacial clefts, 657 (30.1%) had other congenital abnormalities. These associated anomalies were significantly more common in the cleft palate group (47.9%; 329/687) than in the cleft lip group (10.6%; 80/755) but still quite substantial in the cleft lip and palate group (33.6%; 248/738) ($p < 0.01$). A congenital heart defect accounted for 45.1% (296/657) of all associated malformations. The most common heart defect was an atrial septal defect, representing 39.7% (118/296) of all congenital heart defects. These studies justify the recommendation that every child with an oral cleft should have a detailed cardiac evaluation, with an echocardiogram, before discharge.

The fact that neither of the baby's congenital anomalies was diagnosed prenatally may not be such a rare event. Although about 70% of cleft lip is diagnosed prenatally, this baby's mother was obese, which is an important factor. The quality of second-trimester scans is reduced in obese women, which could also reduce the detection rate of fetal congenital anomalies in this group. In a prospective study, Fuchs et al. (3) compared the quality of 20–24 weeks scans in 223 pregnant women with a prepregnancy body mass of $>30 \text{ kg/m}^2$ with a control group of 60 pregnant women with normal BMI (20–24.9 kg/m^2). Anatomical quality scores were significantly lower in the obese group (22.3 vs. 27.2; $p = 0.001$). The authors concluded that “image quality and global anatomical scores are significantly lower among obese than normal-weight women.”

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Around 60% of coarctation of the aorta is not detected prenatally. Zwanenburg et al. (4) reviewed prenatal detection of aortic coarctation from 2012–2021 in Holland. Only 49/116 (42.2%) were detected prenatally. The authors illustrated the importance of prenatal detection by showing the medical cost of lack of detection: undetected cases presented with acute circulatory shock in 20.9% and were more likely to have severe lactic acidosis ($p=0.02$) and impaired cardiac function ($p<0.001$) before surgery.

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Between 2015 and 2016, van Nisselrooij et al. (5) found that half of severe cardiac defects were not diagnosed prenatally with standard second-trimester anatomy scans in the Netherlands. They analyzed the factors that contributed to the lack of prenatal diagnosis of severe congenital heart defects (CHD). A total of 114 cases of isolated severe CHD at birth were analyzed. Of these, 58 (50.9%) were missed, and 56 (49.1%) were detected on the standard anatomy scan. The defects comprised transposition of the great arteries (17%), aortic coarctation (16%), tetralogy of Fallot (10%), atrioventricular septal defect (6%), aortic valve stenosis (5%), ventricular septal defect (18%) and other defects (28%). Although more cases were missed among obese mothers, this failed to reach statistical significance. In 49% of missed cases, the lack of detection was due to poor adaptational skills, resulting in inadequate images in which the CHD was not clearly visible. In 20%, the cardiac planes had been obtained properly but showed normal anatomy. In 31%, the images showed an abnormality, mainly septal defects and aortic arch anomalies, which had not been recognized at the time of the scan, a factor that can be attributed to variable operator education, training, and experience.

Artificial intelligence (AI) may improve the prenatal diagnosis of CoA by reducing operator variability, standardizing the ultrasound planes for cardiac imaging, and improving the accuracy of cardiac measurements. Researchers in Denmark (6) examined prenatal images from individuals subsequently diagnosed with coarctation of the aorta within a ten-year study period. They found that fetuses postnatally diagnosed with CoA displayed significant deviations from healthy controls in their cardiac structures, but

the quality of prenatal CoA images varied considerably, and that variability potentially impacted the accuracy of measurements. They developed an AI algorithm to recognize cardiac planes and perform automatic biometric measurements during the 18–22-week anatomy scan to ensure a standard approach. In their study, AI measurements on routine screening images yielded 20–40% better results than current detection rates, comparable to specialized echocardiography settings. By improving prenatal diagnosis, AI algorithms may also improve outcomes in the NICU.

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Until his aortic coarctation was detected, this baby's oral clefts and a possible associated swallowing defect were suspected to be the cause of his poor feeding. Was this a reasonable assumption? Are babies with oral clefts generally poor feeders? Most term newborns with oral clefts do not have feeding problems. Reid et al. (7) identified a feeding problem in about one-third of 2-week-old infants with oral clefts. In their review of feeding abilities in 62 Australian infants with oral clefts, these authors noted that “at two weeks of age, babies with [a] syndrome or Pierre-Robin sequence were *15 times more likely* to have poor feeding skills than their nonsyndromic counterparts” (*italics mine*). My default position is that term infants with an isolated cleft lip and/or palate are capable oral feeders, and those who do not feed well are likely to have other contributing factors beyond the cleft. My motto: Poor feeding is the baby's way of telling us to look beyond the cleft.

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This infant had no record of pulse oximetry screening at the birth hospital prior to transfer, but it may not have made a difference in terms of a timely diagnosis of his aortic coarctation had it been done. Geggel (8) reviewed 200 consecutive cases of aortic coarctation in 2006–2011 and 2015–2019, before and after pulse oximetry screening, respectively. Pulse oximetry was abnormal in only 8/47 patients. Coarctation was diagnosed by fetal echocardiography more often, 30.5%, in the 2015–2019 cohort compared with 20.5% in the earlier group ($p < 0.03$). Despite these modest improvements in detection, many children with CoA were still undiagnosed. He noted that about 50% of patients in both groups were diagnosed in the first five days, and in each group, about 25% were diagnosed after one year. In both cohorts, decreased femoral pulses or systemic hypertension were infrequently documented by referring physicians. He concluded that “although fetal echocardiography and neonatal pulse oximetry contribute to the diagnosis of coarctation, physical examination has an important complementary role. Evaluation of peripheral pulses on initial and early follow-up neonatal examinations and consideration of coarctation in any patient with hypertension are needed to improve timely detection.” This adds to the importance of the careful physical examination of all newborns.

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In 1978, Graham et al. (9) documented the first use of prostaglandin infusion as emergency palliation in a one-day-old with symptomatic aortic coarctation. It significantly increased lower body perfusion by dilating the ductus arteriosus. Although the patient described above was over three weeks old at the time, prostaglandin therapy was still successful in increasing perfusion by opening the PDA prior to surgery.

Nonsyndromic left-sided heart defects are often observed in multiple family members and are associated with high sibling recurrence risk (10). From a genetic point of view, I recommend parental echocardiograms after the birth of all children with a left-sided obstructive heart defect, but perhaps this recommendation should be limited to the families of infants with isolated heart defects.

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This baby benefited from a repeat echocardiogram, timely prostaglandin therapy, and surgery. At discharge, however, he was still not taking full oral feedings, so there may be more to learn about his condition. Given his low initial Apgar scores and meconium aspiration, he might benefit from a brain MRI. His cardiac gene panel test results are still pending. His genetic evaluation is ongoing, but a whole exome sequencing test may be worth considering if the gene panel test is negative. In one study, exome testing identified a diagnosis in 9.6% of individuals with isolated cleft lip +/-P and 16.7% of patients with syndromic CL +/-P (11). Several monogenic disorders can cause cleft lip and cardiac anomalies; not all responsible genes are included in gene panels. The differential diagnosis includes the more common CHARGE syndrome (OMIM #214800) and the much rarer *HYAL2* deficiency (12), an autosomal recessive syndrome of cleft lip, myopia, hearing loss, and cor triatriatum sinister.

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Practical Applications:

1. Do not rely on a normal prenatal anatomy scan as a confirmation that a baby does not have other congenital anomalies.
 - a. Understand that many factors limit the quality of prenatal ultrasound anatomy scans, including operator variability and maternal obesity, which may result in poor image quality and reduced detection rates.
2. Recall that coarctation of the aorta is not reliably detected by prenatal anatomy scan or by neonatal pulse oximetry screening.
 - a. Watch for incorporating AI-associated algorithms that may increase the prenatal detection rate for CoA.
 - b. Recognize that a newborn echocardiogram performed prior to closure of the PDA *does not* rule out CoA.
 - c. Because most patients with CoA are diagnosed after delivery, examine infants carefully for signs of CoA, such as decreased femoral pulses and hypertension.
3. Examine all infants with oral clefts for other associated congenital anomalies, of which cardiac anomalies are the most common.

4. Realize that most infants with isolated oral clefts are capable oral feeders.
 - a. Recognize that poor feeding in an infant with an oral cleft indicates a syndrome. Remember to look beyond the cleft.
5. Understand that there is an increased recurrence risk for siblings of nonsyndromic left-sided obstructive cardiac defects, including CoA.
6. Consider a whole exome sequencing test in infants with isolated or syndromic oral clefts.
9. Graham TP, Atwood GF, Boucek RJ. Use of prostaglandin E1 for emergency palliation of symptomatic coarctation of the aorta. *Cathet Cardiovasc Diagn.* 1978;4(1):97–102. doi: 10.1002/ccd.1810040114. PMID: 77192.
10. Parker LE, Landstrom AP. Genetic Etiology of Left-Sided Obstructive Heart Lesions: A Story in Development. *J Am Heart Assoc.* 2021 Jan 19;10(2):e019006. doi: 10.1161/JAHA.120.019006. Epub 2021 Jan 12. PMID: 33432820; PMCID: PMC7955312.
11. Yan S, Fu F, Li R, Yu Q, Li F, Zhou H, Wang Y, Huang R, Ma C, Guo F, Wang D, Yang X, Han J, Lei T, Li D, Liao C. Exome sequencing improves genetic diagnosis of congenital orofacial clefts. *Front Genet.* 2023 Sep 7;14:1252823. doi: 10.3389/fgene.2023.1252823. PMID: 37745857; PMCID: PMC10512413.
12. Muggenthaler MM, Chowdhury B, Hasan SN, Cross HE, Mark B, Harlalka GV, Patton MA, Ishida M, Behr ER, Sharma S, Zahka K, Faghih E, Blakley B, Jackson M, Lees M, Dolinsky V, Cross L, Stanier P, Salter C, Baple EL, Alkuraya FS, Crosby AH, Triggs-Raine B, Chioza BA. Mutations in *HYAL2*, Encoding Hyaluronidase 2, Cause a Syndrome of Orofacial Clefting and Cor Triatriatum Sinister in Humans and Mice. *PLoS Genet.* 2017 Jan 12;13(1):e1006470. doi: 10.1371/journal.pgen.1006470. PMID: 28081210; PMCID: PMC5230738.

References:

1. Kasatwar A, Borle R, Bhola N, K R, Prasad GSV, Jadhav A. Prevalence of congenital cardiac anomalies in patients with cleft lip and palate - Its implications in surgical management. *J Oral Biol Craniofac Res.* 2018 Sep–Dec;8(3):241–244. doi: 10.1016/j.jobcr.2017.09.009. Epub 2017 Oct 3. PMID: 30191117; PMCID: PMC6107920.
2. Sun T, Tian H, Wang C, Yin P, Zhu Y, Chen X, Tang Z. A survey of congenital heart disease and other organic malformations associated with different types of orofacial clefts in Eastern China. *PLoS One.* 2013;8(1):e54726. doi: 10.1371/journal.pone.0054726. Epub 2013 Jan 21. PMID: 23349958; PMCID: PMC3549991.
3. Fuchs F, Houllier M, Voulgaropoulos A, Levallant JM, Colmant C, Bouyer J, Senat MV. Factors affecting feasibility and quality of second-trimester ultrasound scans in obese pregnant women. *Ultrasound Obstet Gynecol.* 2013 Jan;41(1):40–6. doi: 10.1002/uog.12311. PMID: 23023941.
4. Zwanenburg F, Ten Harkel ADJ, Snoep MC, Bet BB, Linskens IH, Knobbe I, Pajkrt E, Blom NA, Clur SB, Haak MC. Prenatal detection of aortic coarctation in a well-organized screening setting: Are we there yet? *Prenat Diagn.* 2023 May;43(5):620–628. doi: 10.1002/pd.6291. Epub 2023 Jan 5. PMID: 36549919.
5. van Nisselrooij AEL, Teunissen AKK, Clur SA, Rozendaal L, Pajkrt E, Linskens IH, Rammeloo L, van Lith JMM, Blom NA, Haak MC. Why are congenital heart defects being missed? *Ultrasound Obstet Gynecol.* 2020 Jun;55(6):747–757. doi: 10.1002/uog.20358. PMID: 31131945; PMCID: PMC7317409.
6. Taksoee-Vester CA, Mikolaj K, Petersen OBB, Vejlstrop NG, Christensen AN, Feragen A, Nielsen M, Svendsen MBS, Tolsgaard MG. Role of AI-assisted automated cardiac biometrics in screening for fetal coarctation of aorta. *Ultrasound Obstet Gynecol.* 2024 Feb 9. doi: 10.1002/uog.27608. Epub ahead of print. PMID: 38339776.
7. Reid J, Kilpatrick N, Reilly S. A prospective, longitudinal study of feeding skills in a cohort of babies with cleft conditions. *Cleft Palate Craniofac J.* 2006 Nov;43(6):702–9. doi: 10.1597/05-172. PMID: 17105331.
8. Geggel RL. Coarctation of the Aorta: Delay in Diagnosis and Referral Basis from Infancy to Adulthood. *J Pediatr.* 2022 Mar;242:57–62. doi: 10.1016/j.jpeds.2021.11.066. Epub 2021 Dec 1. PMID: 34863817.

Disclosure: The author has no conflicts of interests to disclose.

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Corresponding Author



Robin Clark, MD
Professor, Pediatrics
Loma Linda University School of Medicine
Division of Genetics
Department of Pediatrics
E-mail: rclark@llu.edu