Genetics Corner: Alveolar Simplification and Down Syndrome

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A Case History:

A 7 month-old Hispanic male with translocation Down syndrome was referred to the genetics clinic for an initial evaluation. His prenatal history was complicated by an abnormal maternal serum screening test that revealed an increased risk for Down syndrome, and there was pylectasis on fetal ultrasound. He was born at 39 1/7 weeks to a 35-year old G3P2->3 mother by C-section at a community hospital. Birth weight was appropriate at 3.880 kg. He was transferred to a tertiary care facility 2 hours away for a higher level of care because of bilateral hydronephrosis, microphalus, and right undescended testis. Chromosome analysis there revealed Down syndrome with a translocation between two chromosomes 21: 46,XY,+21,der(21;21)(q10;q10). Parental testing has not been completed.

He remained in the NICU for two months due to respiratory distress attributed to alveolar simplification. An initial echocardiogram demonstrated a patent foramen ovale (PFO) and tiny patent ductus arteriosus (PDA) with no pulmonary hypertension. Since discharge, he has been followed by multiple specialists at the tertiary facility. He is followed by Pulmonology for hypoxemia. He was treated with supplemental oxygen, day and night, during his first six months, but for the last month, he has only been using oxygen at night when his oxygen levels drop to lower than 80%. Both PFO and PDA have resolved, and his cardiologist at the tertiary care facility plans on discharging from further follow up once he is completely off oxygen.

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He was breastfed until he was six months and is now on formula. His mother is concerned that he is not interested in feeding, but his growth is adequate according to growth charts for Down syndrome. His phallus was of adequate size but appeared small because it was buried in perineal fat. The right testicle was undescended. He was seen by a nutritionist and a urologist at the tertiary care facility.

Developmental History:

He was able to lift his head at two months and started babbling at 4-5 months. He was rolling over at seven months. He is not receiving early infant intervention services because the mother has not initiated the referral.

Discussion:

In the 1980s, early in my genetics fellowship, my mentor, Dr. Michael Kaback, sat all of us trainees around a table and asked us to recite a fact about Down syndrome (DS) that had not yet been mentioned. We were confident for the first few turns around the table, but soon, our answers did not come as quickly, and then, embarrassed, we collectively ran out of facts. Instead of dwelling on our ignorance, he suggested that we try to learn something new about DS each time we saw a patient with the condition. I thought it was good advice then, and I still do. Responding to Dr. Kaback these many years later, I tasked myself to learn more about DS from this patient. I have more questions than I can address here (including why would such devoted parents decide to stop breastfeeding and why would they fail to initiate early intervention services and could all that driving and all those appointments so far from home have contributed to those decisions?). I will not discuss the nature of translocation Down syndrome now either (although I recommended chromosome analysis for both parents). This discussion will focus on only 2 of the many questions that could be asked: 1. How often are full-term babies with DS who do not have congenital anomalies admitted to the NICU, and why? And 2. How common is alveolar simplification in newborns with DS, and what are its effects?

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A study from Dublin, Ireland, by Martin et al. (2018) addressed my first question. These authors found that 87% of all infants with DS in their sample required NICU admission prior to discharge. Among their cohort of 121 infants with DS, 54 (45%) were initially admitted to the well newborn nursery, but 38 of these (70%) were later admitted to the NICU. A low oxygen saturation profile was the most common cause for the initial and subsequent admission to the NICU.

McAndrew et al. (2018) reviewed the databases of 277 Pediatrix NICUs from 2005-2012 to identify 4623 infants with DS and 606,770 infants without DS. They found that 36% of infants with DS who were admitted to the NICU were full-term and without a major anomaly, surprisingly similar to the proportion in the euploid group (37%). The term infants with DS were admitted for reasons that could not be anticipated prior to delivery. Many diagnoses were only slightly, but still significantly, more common among the term DS group compared to the term group without DS: rule out sepsis (80% vs. 77%), hyperbilirubinemia (65% vs. 42%) and respiratory distress (58% vs. 50%). However, term infants with DS had strikingly and significantly more frequent diagnoses of throm-

bocytopenia (38% vs. 5%), PDA (37% vs. 3%), feeding problems (34% vs. 15%), persistent pulmonary hypertension of the newborn (27% vs. 3%), polycythemia (12% vs. 0.8%), VSD (25% vs. 1.4%) and ASD (15% vs. 0.8%). There was no difference in the need for mechanical ventilation between the two groups, but significantly only 28% of the term infants with DS remained in room air, compared to 56% of the term infants without DS. Term infants with DS had significantly longer stays in the NICU compared to term infants without DS: 10 days vs. five days. At discharge, term infants with DS had significantly higher needs for home oxygen (8.3% vs. 0.7%) and tube feeding at home (5.2% vs. 0.4%). (All significant differences had p values<0.001).

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Moving to the second question, alveolar simplification (fewer and larger alveoli), which is probably better known as the predominant pathologic finding associated with prematurity, is also a common and even typical feature of DS. The lung architecture of DS, enlarged airspaces, and fewer and more dilated alveoli, appears to reflect poor postnatal alveolarization rather than primary lung hypoplasia. Bush et al. (2017) reported abnormal lung histology in a retrospective review of autopsies in 13 children with Down syndrome, ages 0-8 years, most of whom died of cardiac-related deaths, and four age-matched controls with congenital heart defects but without DS. They found alveolar simplification, a persistent double capillary network, and intrapulmonary bronchopulmonary anastomoses in all cases of DS, implicating impaired alveolar and pulmonary vascular development in Down syndrome. Several anti-angiogenic peptides, such as endostatin, are encoded on chromosome 21 and may contribute to the reduced total arterial surface area in DS. Both the reduced alveolar surface area and the diminished vascular bed are likely to contribute to the increased requirements for supplemental oxygen in infants with DS, who lack other reasons for an increased oxygen requirement, such as prematurity, congenital heart defects or pulmonary hypertension.

These differences may help explain why DS infants are at increased risk for lower respiratory tract infections in general and the respiratory syncytial virus (RSV) in particular. This relationship was supported by the meta-analysis performed by Mitra et al. (2018), who found that children with DS have a significantly increased risk for RSV infection, RSV-related hospitalization (RR 6.06; 95% CI, 4.93-7.45), hospital length of stay (mean difference 2.11 days) and need for assisted ventilation (RR 5.82; 95% CI, 1.81-18.69). Children with DS without congenital heart disease also had a significantly increased risk of RSV-related hospitalization (RR 6.31; 95% CI, 4.83-8.23).

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Infants with prematurity and those with DS share common lung histology and an increased risk for RSV infection, but current AAP guidelines do not yet recommend prophylactic palivizumab for children with DS as they do for premature infants. However, data from Japan and elsewhere have demonstrated a beneficial effect for prophylactic palivizumab in infants with DS. Yi and colleagues (2014) compared hospitalization rates for RSV infection among 532 Canadian children with DS who prospectively received palivizumab and an untreated group of 233 Dutch children with DS. In total, 31 RSV-related hospitalizations were documented: 23 untreated and eight treated. Their results suggest that palivizumab is associated with a 3.6-fold reduction in the incidence rate ratio for RSV-related hospitalization in children with DS during the first two years of life (95% CI, 1.52–8.67). A randomized prospective trial may be needed to eventually settle the question.

Practical applications:

1. Expect that term infants with Down syndrome who lack major congenital anomalies may require NICU admission.
2. Anticipate that infants with DS have alveolar simplification and be ready for the pulmonary sequelae. Be prepared to offer more respiratory support than might be expected for an infant of similar gestational age or cardiac status but without DS.
3. Consider infants with Down syndrome at increased risk for RSV infection and advise parents about risk reduction strategies. Expect evolving recommendations regarding palivizumab prophylaxis in DS infants.
4. Encourage parents to prioritize breastfeeding and early infant stimulation programs to optimize outcome in infants with DS.
5. Make recommendations that support the health of the child. Recognize the unintended consequences (opportunity costs) associated with referrals to distant health care facilities (especially when they bypass closer facilities) including time away from home and work, cost and stress of traffic, separation, and stress to other family members, early termination of breastfeeding, lack of time for other supportive

services.

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The authors have no relevant disclosures.

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