Peer Reviewed

Genetics Corner: Sleep-Disordered Breathing in a Term Newborn with Achondroplasia

Robin Dawn Clark, MD

"A 39-week-gestation female infant with suspected skeletal dysplasia was born to a 32-year-old G6P4SAb2 mother of average stature by repeat C-section."

Case Summary:

A 39-week-gestation female infant with suspected skeletal dysplasia was born to a 32-year-old G6P4SAb2 mother of average stature by repeat C-section. BW was 3.42 kg, BL was 37.3 cm, and HC was 37.3 cm. She was treated with blow by O_2 at 4 minutes of life with fluctuating saturations at 39-76% and weaned to room air by 8 minutes without grunting or retractions. A nasal cannula was applied with a flow of 1LPM at 21% FiO_2 x 1 hour. Saturation in room air was normal, 96% and respiratory rate was 41. Initial glucose was 51. Apgar scores were 7 and 9. The baby was admitted to the regular nursery to room in with her mother.

Radiographs showed classic features of achondroplasia: macrocephaly, small chest, short ribs, narrow thorax, anterior vertebral beaking, lack of the normal progression of interpedicular distance from the upper thoracic to the lumbar vertebrae, flat acetabular roof, squared iliac wings, narrow sacrosciatic notch. The metacarpals and long bones were short, especially the humeri, tibiae, and femurs. Metaphyses were flared and irregular, especially proximal femoral metaphyses. There was mild bowing of the tibiae and fibulae.

The infant had typical features of achondroplasia on physical examination. When sleeping, there was no respiratory distress. She had macrocephaly with frontal bossing and hypoplastic midface. Her thorax was narrow and short without cyanosis, tachypnea, or retractions, although there was paradoxical breathing: the chest sunk, and the abdomen rose with inspiration. There was a mild lumbar gibbus. She had disproportionate short stature with rhizomelic shortening of the extremities and trident-shaped hands with a distal gap between the middle and ring fingers. She had generalized joint hypermobility and hypotonia. Hip abduction was limited to 145 degrees.

The family history was not contributory. The father was 36 years of age.

"A polysomnogram on day of life 5 was abnormal, with significant central and obstructive sleep apnea and short (< 20 seconds) central apneas associated with significant desaturations. A pulmonology consultant recommended a repeat sleep study with supplemental O2. There was a substantial improvement in the sleep study performed on day of life 8 with 0.5LPM of supplemental O2 by nasal cannula."

When the mother was ready for discharge, the baby had not yet had a sleep study that had been ordered shortly after delivery. The family lived an hour from the hospital in a rural area, so the infant was transferred to the NICU to complete the recommended workup before discharge. A polysomnogram on day of life 5 was abnormal, with significant central and obstructive sleep apnea and short (< 20 seconds) central apneas associated with significant desaturations. A pulmonology consultant recommended a repeat sleep study with supplemental O_2. There was a substantial improvement in the sleep study performed on day of life 8 with 0.5LPM of supplemental O_2 by nasal cannula.

"A brain and cervical spine MRI showed no cord impingement at the level of the foramen magnum as the CSF space around the cranio-medullary junction was maintained."

	Central Apneas (Index: #events /hr)	Obstructive Apneas (Index)	Mixed Apneas	Total Apneas (Index)	Total Hypopneas (central/ obstructive)	Total Apneas + Hypopneas (Index)	Min Sp O_2	Total time Sp O_2 </=88% (min)
Polysomnogram day of life 5	98 (12.3)	20 (2.5)	3	121 (15.1)	18 (0/18)	139 (17.4)	78%	141 min
Polysomnogram with 0.5 L nasal O_2 day of life 8	22 (2.8)	7 (0.9)	0	29 (3.6)	13 (0/13)	42 (5.3)	81%	10.6 min

A brain and cervical spine MRI showed no cord impingement at the level of the foramen magnum as the CSF space around the cranio-medullary junction was maintained. No foramen magnum narrowing was seen. However, the narrowing of the canal in the cervical and upper thoracic spine caused moderate to severe stenosis, most pronounced at the upper cervical spine levels. The neurosurgery consultant did not recommend surgical intervention. After passing a car seat test, the baby was discharged at 11 days of age on supplemental O_2 with an apnea monitor and plans for outpatient follow-up with otolaryngology and other specialists.

Assessment:

Achondroplasia, the most common type of skeletal dysplasia, is associated with significant health concerns that begin in infancy and extend throughout life. The most serious early problems include cervical cord impingement from a narrow foramen magnum, spinal stenosis, and central and obstructive sleep apnea (1). Untreated, these problems can be lethal, causing a significantly increased risk of sudden infant death (SIDS) in achondroplasia.

"Unexpected infant death occurs in up to 7.5% of infants with achondroplasia (2). Legare et al. (3) reported that acute life-threatening events (ALTEs) occurred in the first year of life in 18 of 477 individuals (3.8%)."

Unexpected infant death occurs in up to 7.5% of infants with achondroplasia (2). Legare *et al*. (3) reported that acute life-threatening events (ALTEs) occurred in the first year of life in 18 of 477 individuals (3.8%). Most ALTEs (14/18, 78%) occurred in the first six months of life and presented as episodes of apnea or seizures, often while infants were in car seats (11/18, 61%).

Although these risks are widely understood, there is no consensus on how to assess the newborn with achondroplasia to minimize these risks. Guidelines from the American Academy of Pediatrics (1) published in 2020 recommend that infants with achondroplasia should have a polysomnogram study in the first month of life or if diagnosed later in infancy, then at the time of diagnosis. An international consortium published in 2022 recommends a sleep study in the first year of life (4). Gooch *et al*. (5)reported their protocol in 2019, which specifies that all newborns with achondroplasia have a polysomnogram prior to discharge, and if abnormal, the infant would have an evaluation by a sleep specialist before discharge. Their medical center in Alabama serves a large area that includes rural communities without local hospitals at some distance from their facility, similar to our region.

For this reason, I followed their lead and completed the sleep study before discharge. Although she had reassuring MRI imaging of her craniocervical junction, need more detailed imaging studies may be needed to demonstrate cord impingement. Kashanian *et al*. (6) describe their protocol for neuroimaging infants with achondroplasia that includes flexion and extension views, which can demonstrate impingement that is not evident in a neutral position.

Although my decision to delay the baby's homecoming by a week to complete her work up, was not a popular one, it was justified in retrospect by the pathology demonstrated in the first polysomnogram and by the improvement in the subsequent polysomnogram with supplemental O_2. There was no outward evidence of central or obstructive apnea while the baby was rooming in with her mother. This argues for performing a polysomnogram in infants with achondroplasia even when apnea is not clinically suspected. Had this baby been discharged without a sleep study, she would have been subject to apnea and its sequelae and to hours of nightly desaturations that could adversely affect her brain development.

"There was no outward evidence of central or obstructive apnea while the baby was rooming in with her mother. This argues for performing a polysomnogram in infants with achondroplasia even when apnea is not clinically suspected."

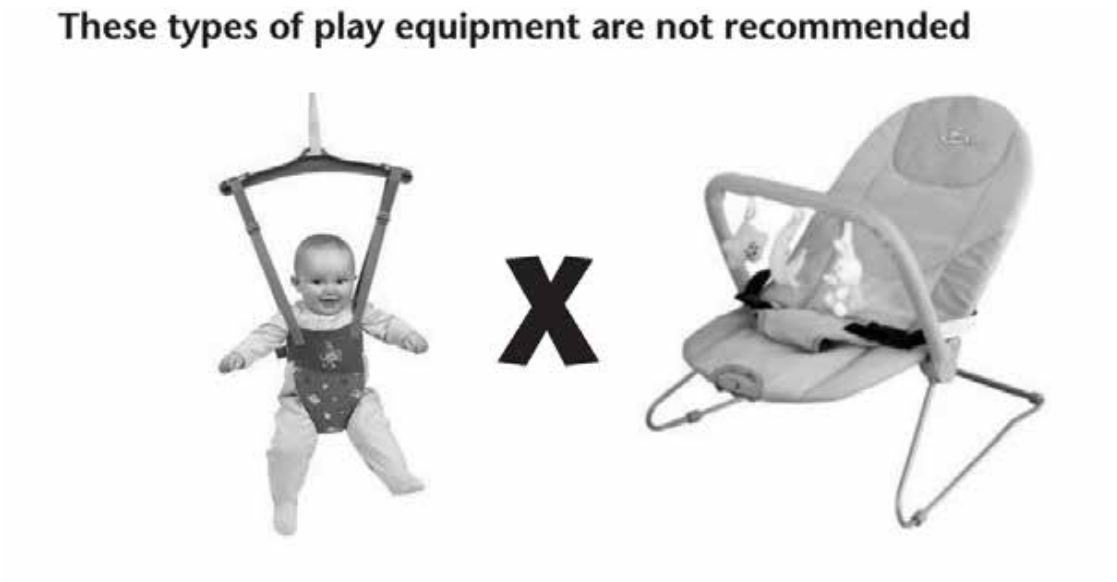
Achondroplasia is the most common type of dwarfism, occurring in 1 in 15-25,000 live births. It is typically caused by one of two recurrent pathogenic gain-of-function variants in *FGFR3*. It is a *de novo* or new mutation in 80% of cases, almost always occurring on the paternally transmitted allele. Twenty percent of the time, the condition is inherited from a similarly affected parent as an autosomal dominant trait. *FGFR3* signaling inhibits chondrocyte proliferation and differentiation. The pathogenic variants respon-

sible for achondroplasia cause a gain-of-function in this pathway that increases signaling and inappropriately suppresses chondrocyte proliferation and differentiation at the growth plate.

New therapeutic agents are designed to block the pathway downstream from this gain-of-function FGFR3 signal and reduce its effectiveness. One drug, Vosoritide (BioMarin), has been FDA-approved in the United States for achondroplasia from age 5 (in Europe, it is approved for use from age 2). It enhances the growth of long bones and increases height. Infants are being treated with Vosoritide on a research basis to determine if this therapy may ameliorate the risk of severe co-morbidities, including craniocervical compression at the foramen magnum and SIDS.

"Meanwhile, efforts should also be focused on reducing the risk of injury to the cervical cord. New parents of infants with achondroplasia need detailed education about how to handle their baby, specifically, the need to support their baby's head, neck, and spine."

Meanwhile, efforts should also be focused on reducing the risk of injury to the cervical cord. New parents of infants with achondroplasia need detailed education about how to handle their baby, specifically, the need to support their baby's head, neck, and spine. A baby with achondroplasia should have head support when in a car seat. Soft infant carriers such as baby slings, front-loading baby carriers, umbrella-type strollers, or soft-backed infant seats that allow the head to flex forward onto the chest should be avoided. The baby should not use a bouncer. Educational materials about caring for infants with achondroplasia designed for new parents are available. (7,8). The illustration below (8) shows examples of seating that should be avoided for infants with achondroplasia.



Parents should be instructed to notify their healthcare provider immediately if there is any change in their baby's baseline status, such as asymmetric use of the extremities or weakness.

The neonatal care team is instrumental in ensuring that babies with achondroplasia receive the best medical care by carefully evaluating them in the immediate newborn period and referring them to appropriate specialty services. Optimally, infants with achondroplasia should be followed closely by a multidisciplinary medical team that specializes in skeletal dysplasias.

"Optimally, infants with achondroplasia should be followed closely by a multidisciplinary medical team that specializes in skeletal dysplasias."

Practical Applications:

1. Appreciate that infants with achondroplasia are at an increased risk for sudden infant death, especially in a car seat. They are at risk for central sleep apnea, craniocervical impingement due to a narrow foramen magnum, and spinal stenosis.
2. Incorporate a polysomnogram into the care plan for newborn infants with achondroplasia. This procedure should be done early in life, and in some healthcare settings, the best time to do this would be before hospital discharge after delivery.
3. Understand that obstructive or central sleep apnea may not be apparent to parents or healthcare providers without a polysomnogram.
4. Counsel parents of infants with achondroplasia to always provide head support, especially in a car seat, and use only seats with a hardback. Educate parents to avoid soft-backed infant seats, slings, strollers, or bouncers that allow neck flexion.
5. Refer infants with achondroplasia to a multidisciplinary medical team that specializes in skeletal dysplasias.

References:

1. Hoover-Fong J, Scott CI, Jones MC; COMMITTEE ON GENETICS. Health Supervision for People with Achondroplasia. Pediatrics. 2020 Jun;145(6):e20201010. doi: 10.1542/peds.2020-1010. PMID: 32457214.

2. Pauli RM. Achondroplasia: a comprehensive clinical review. Orphanet J Rare Dis. 2019 Jan 3;14(1):1. doi: 10.1186/s13023-018-0972-6. PMID: 30606190; PMCID: PMC6318916.

3. Legare JM, Smid CJ, Modaff P, Pauli RM. Achondroplasia is associated with increased occurrence of apparent life-threatening events. Acta Paediatr. 2021 Jun;110(6):1842-1846. doi: 10.1111/apa.15760. Epub 2021 Feb 12. PMID: 33452838.

4. Savarirayan R, Ireland P, Irving M, Thompson D, Alves I, Baratela WAR, Betts J, Bober MB, Boero S, Briddell J, Campbell J, Campeau PM, Carl-Innig P, Cheung MS, Cobourne M, Cormier-Daire V, Deladure-Molla M, Del Pino M, Elphick H, Fano V, Fauroux B, Gibbins J, Groves ML, Hagenäs L, Hannon T, Hoover-Fong J, Kaisermann M, Leiva-Gea A, Llerena J, Mackenzie W, Martin K, Mazzoleni F, McDonnell S, Meazzini MC, Milerad J, Mohnike K, Mortier GR, Offiah A, Ozono K, Phillips JA 3rd, Powell S, Prasad Y, Raggio C, Rosselli P, Rossiter J, Selicorni A, Sessa M, Theroux M, Thomas M, Trespedi L, Tunkel D, Wallis C, Wright M, Yasui N, Fredwall SO. International Consensus Statement on the diagnosis, multidisciplinary management and lifelong care of individuals with achondroplasia. Nat Rev Endocrinol. 2022 Mar;18(3):173-189. doi: 10.1038/s41574-021-00595-x. Epub 2021 Nov 26. PMID: 34837063.

5. Gooch C, Robin NH, Hurst ACE. Editorial: Neonatal management of achondroplasia: one hospital's geosocial approach to improve patient outcomes. Curr Opin Pediatr. 2019 Dec;31(6):691-693. doi: 10.1097/MOP.0000000000000814. PMID: 31693574.

6. Kashanian A, Stadler JA 3rd, Danielpour M. Neurosurgical Evaluation and Management of Children with Achondroplasia. Neurosurg Clin N Am. 2022 Jan;33(1):17-23. doi: 10.1016/j.nec.2021.09.003. Epub 2021 Oct 26. PMID: 34801138.

7. https://www.schn.health.nsw.gov.au/files/factsheets/achondroplasia_-_positioning_and_handling_of_babies_with_achondroplasia-en.pdf

8. https://www.nhsggc.org.uk/media/272500/achondroplasia-information-booklet_sept-22.pdf

Disclosures: *There are no reported disclosures*

NT

Corresponding Author

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