OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Craniofacial/Pediatric

Patterns of Change in the Severity of Airway Obstruction with Robin Sequence in Early Infancy

Belema D. Dede, BFor, MD*
Paul D. Robinson, MBChB, FRACP, PhD*†
Chenda Castro, BSc, MScMed*
Karen A. Waters, MBBS, FRACP, PhD*†

Background: Previous studies suggest that infants with Robin sequence show a pattern of steady improvement in the severity of airway obstruction, and of their treatment requirements, during infancy.
Methods: Three infants with Robin sequence and severe obstructive sleep apnea were managed with nasal continuous positive airways pressure (CPAP). Multiple measures of airway obstruction were made during infancy, including CPAP pressure evaluations and sleep studies (screening and polysomnography studies). Parameters reported include obstructive apnea-hypopnea index, oxygen desaturation parameters, and CPAP pressures required for effective airway management.
Results: CPAP pressure requirements increased in all three infants during their first weeks of life. Apnea indices on polysomnography did not track with the CPAP pressure requirements. Peak pressure requirements were at 5 and 7 weeks for two patients, with subsequent gradual decline and cessation of therapy CPAP at 39 and 74 weeks, respectively. The third patient had a complicated course, jaw distraction at 17 weeks, and biphasic CPAP pressure requirement (first peak at 3 weeks, but maximum pressure at 74 weeks), with cessation of CPAP at 75 weeks.
Conclusions: The observed pattern of early increases in CPAP pressure requirements for infants with Robin sequence adds to the complexities of managing this disorder. Factors that may lead to this pattern of change in airway obstruction are discussed.
(Plast Reconstr Surg Glob Open 2023; 11:e4819; doi: 10.1097/GOX.0000000000004819; Published online 22 February 2023.)

INTRODUCTION

Robin sequence (RS) describes a pattern of malformation with the fundamental abnormality of a small, underdeveloped mandible leading to posterior displacement of the tongue. A posterior cleft palate may also be present. The incidence of RS ranges from one in 8500 to one in 14,000 live births. The sequence is more frequently observed in syndromes, including Stickler syndrome.[1] A major clinical manifestation is upper-airway obstruction in newborns.[2] This combination of the aforementioned features results in a clinical picture of airway obstruction and difficulty feeding in newborns. There is a large spectrum of severity in neonates affected by RS, ranging from mild disease that does not require intervention to very severe clinical features[3] that require surgical management and tube feeding.[4]

The airway obstruction in infants with RS translates to a high incidence of obstructive sleep apnea (OSA).[5] Polysomnography (PSG) is the gold standard for evaluating the severity of OSA, with well-described use in infants with RS,[6] with sleep screening studies providing another source of complementary information. Continuous positive airway pressure (CPAP) is one means of treating OSA with many clinical applications, and is the method most commonly used in our clinical service to manage airway obstruction and sleep disordered breathing in infants with RS.[7,8] Other techniques can be utilized for airway obstruction, including insertion of a nasopharyngeal airway, and surgical mandibular distraction, with these typically reserved for more severe sleep disordered breathing in RS patients in our practice.[9,10]

Patterns of growth during early infancy include rapid changes in the airway and the respiratory system. Whether and how these affect the management of airway obstruction in infants with RS is not well documented. We present data for three infants with RS to illustrate the details of the

*From the *Department of Sleep Medicine, Children's Hospital at Westmead, Sydney, Australia; and †University of Sydney, Sydney, Australia.*

Received for publication April 14, 2022; accepted December 15, 2022.

Presented at the Australian Sleep Association's virtual "Sleep Week," October 2020, Sydney, Australia.

DOI: 10.1097/GOX.0000000000004819

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

longitudinal patterns of airway obstruction and treatment seen in those infants.

METHODS

The data on these infants were obtained by retrospective review of their medical records, including raw data from sleep recordings. Sleep recording included PSG and screening studies, with the methods for these studies detailed below.

The infants described herein were born in Sydney between August 2016 and June 2018 and diagnosed with RS. Two were born in nontertiary hospitals; however, all three infants were transferred to Children's Hospital at Westmead (CHW) for management. At CHW, the diagnosis of RS was confirmed by neonatologists, as well as ear, nose, and throat specialists, and included the following features: micrognathia, glossoptosis, cleft palate, and severe upper-airway obstruction (Fig. 1). OSA is defined by an apnea-hypopnea index (AHI) greater than 10 events per hour.[11] Experienced physicians incorporate factors outside PSG results when determining the presence of sleep disordered breathing in infancy, and the discrepancy between AHI and physician severity classification is greatest for children younger than 6 months where the trajectory of disease differs compared with other age groups.[12] Under the CHW management protocol for RS, all patients had early referral to sleep medicine for assessment and management of their airway obstruction (Fig. 2).

Treatment goals for newborns receiving CPAP are as follows:

- Establish CPAP to manage airway obstruction
- Use CPAP for all sleep periods
- Ensure that the CPAP mask has good fit, minimal leak, and is not causing pressure areas.

Efficacy is evaluated using PSG supplemented by oxycapnography, as described for these cases.

The diagnosis of OSA and monitoring of CPAP treatment pressures was monitored by PSGs and/or oxycapnography, and all were treated with home CPAP. Factors taken into consideration when deciding on management strategies included the infants' tolerance of the therapy, and requirements for adjuvant airway therapy (eg, nasopharyngeal airway). The timing of the PSGs and oxycapnography studies were determined on clinical grounds (Fig. 3).

Patient 1 used a Fisher & Paykal SleepStyle CPAP machine with a Mask Medic size 2 nasal mask and size 2 head gear. Patient 2 used a Fisher & Paykal SleepStyle 200 machine with a Mask Medic size 2 nasal mask and personalized head gear (modified to fit by our hospital sewing room). Patient 3 used a Fisher & Paykal SleepStyle 200 machine with a Mask Medic size 2 nasal mask and smaller (yellow) head gear. All CPAP machines were hired from an external company with assistance by staff of the CHW sleep medicine team. The main company that we use is Sleepap Westmead; families hire CPAP machines for $55AUD per month. The other companies that are occasionally used are CPAP Australia – Parramatta for $60AUD per month, and Sleepeasy (Philips) for $100 per month. Parents have face-to-face education with a member of the sleep medicine team supplemented by the provision of written material describing the therapy and providing trouble-shooting advice, and they are

Takeaways

Question: What changes in severity of airway obstruction and treatment requirements occur for Robin sequence during early infancy?

Findings: Airway pressure support requirements and sleep study data revealed two of three infants' requirements peaked between 5 and 7 weeks and ceased between 39 and 74 weeks. A third infant's course was complicated by the need for jaw surgery. Support peaked at 74 weeks and ceased at 75 weeks.

Meaning: Infants with Robin sequence and severe airway obstruction require increased pressure support in early infancy, gradual reduction, and cessation of support later in infancy.

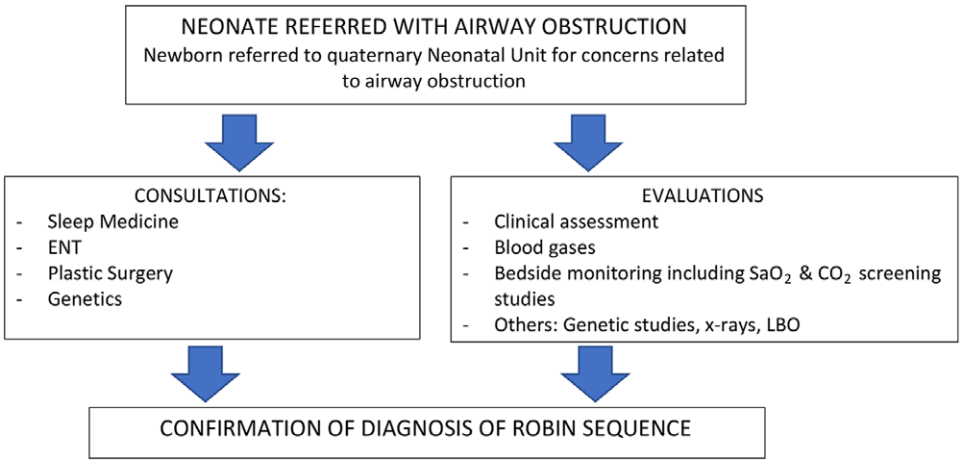

Fig. 1. Diagnostic approach. Approach to diagnosing infants with airway obstruction caused by RS.

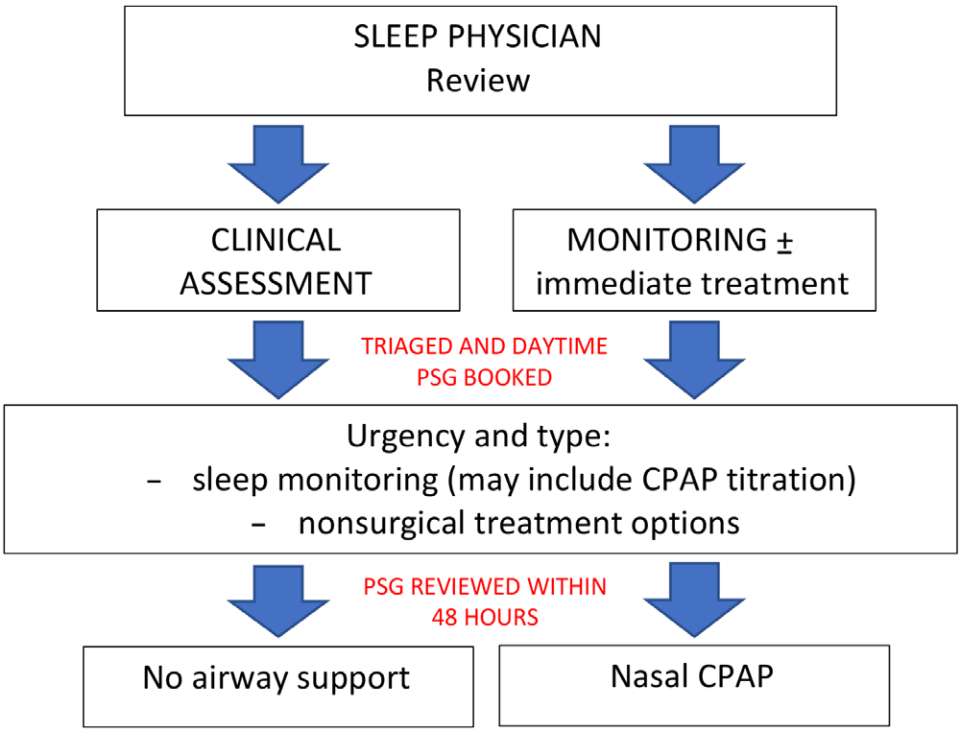

Fig. 2. Sleep physician assessment: assessing whether infants with RS require CPAP therapy to manage their airway obstruction.

given contact information for a member of the treating team should they have any questions or concerns. Initial follow-up is provided by phone, followed by review in the outpatient clinic. The timing of repeated sleep studies or CPAP pressure evaluations are dictated by the treating physician.

PSG recordings included electroencephalography, electrooculography, and submental electromyography to determine sleep state. Respiratory parameters included pulse oximetry, nasal/oral air flow using nasal pressure, chest and abdominal movements with respiratory inductance plethysmography and transcutaneous CO_2 (Radiometer Pacific, Pty, Ltd, Mt Waverly, Victoria, Australia) as well as blood gases. Additional channels included electrocardiography to monitor cardiac rhythm, and position. PSG was analyzed using AASM scoring criteria, with additional input from the Australian Sleep Association.[13] Data were stored in digital format (Grael profusion 4.5Compumedics Ltd, Abbotsford, Victoria, Australia) and where possible, raw data were analyzed. Where raw data were not available, study and clinical reports were accessed from the patient electronic medical record. Data retrieved from PSG studies included the total AHI and obstructive AHI (OAHI), oxygen saturation values (baseline, minimum, desaturation index), and transcutaneous CO_2 values (baseline, maximum, occurrence of episodic CO_2 retention). Obstructive hypoventilation was defined as a partial pressure of CO_2 greater than 50 mm Hg for greater than 25% of sleep time, coupled with snoring, paradoxical thoracoabdominal movement, or flattening of the nasal airway pressure waveform.[14]

Sleep screening studies consisted of overnight screening with continuous recordings of oxygen saturation, heart rate (from the oximetry), and transcutaneous carbon dioxide (Radiometer Pacific, Pty, Ltd, Mt Waverly, Victoria, Australia) with a blood gas taken at the conclusion of the monitoring to confirm CO_2 values. Data retrieved included maximum transcutaneous CO_2, mean CO_2, minimum O_2 saturation, mean O_2 saturation, and frequency of desaturation events. Oxygen desaturation index was assessed as desaturation events per hour greater than 4%. The percentage of time less than 90% O_2 saturation was also recorded. CPAP changes and ages of the patients at which they occurred were also collected. Desaturation score was calculated by adding the oxygen desaturation index and percentage of time less than 90% O_2 saturation (× 2), to highlight more significant obstruction during sleep screening studies.

Ethics approval was obtained from the Sydney Children's Hospitals Network Human Research Ethics Committee (HREC; project number CCR2019/32).

RESULTS

Patient 1

Patient 1 was born at 36 weeks (at a nontertiary hospital) and diagnosed with RS antenatally. The pregnancy was complicated by premature rupture of membranes at 35 weeks gestation. Initial examination of the infant confirmed the presence of a cleft palate. Following establishment of oral

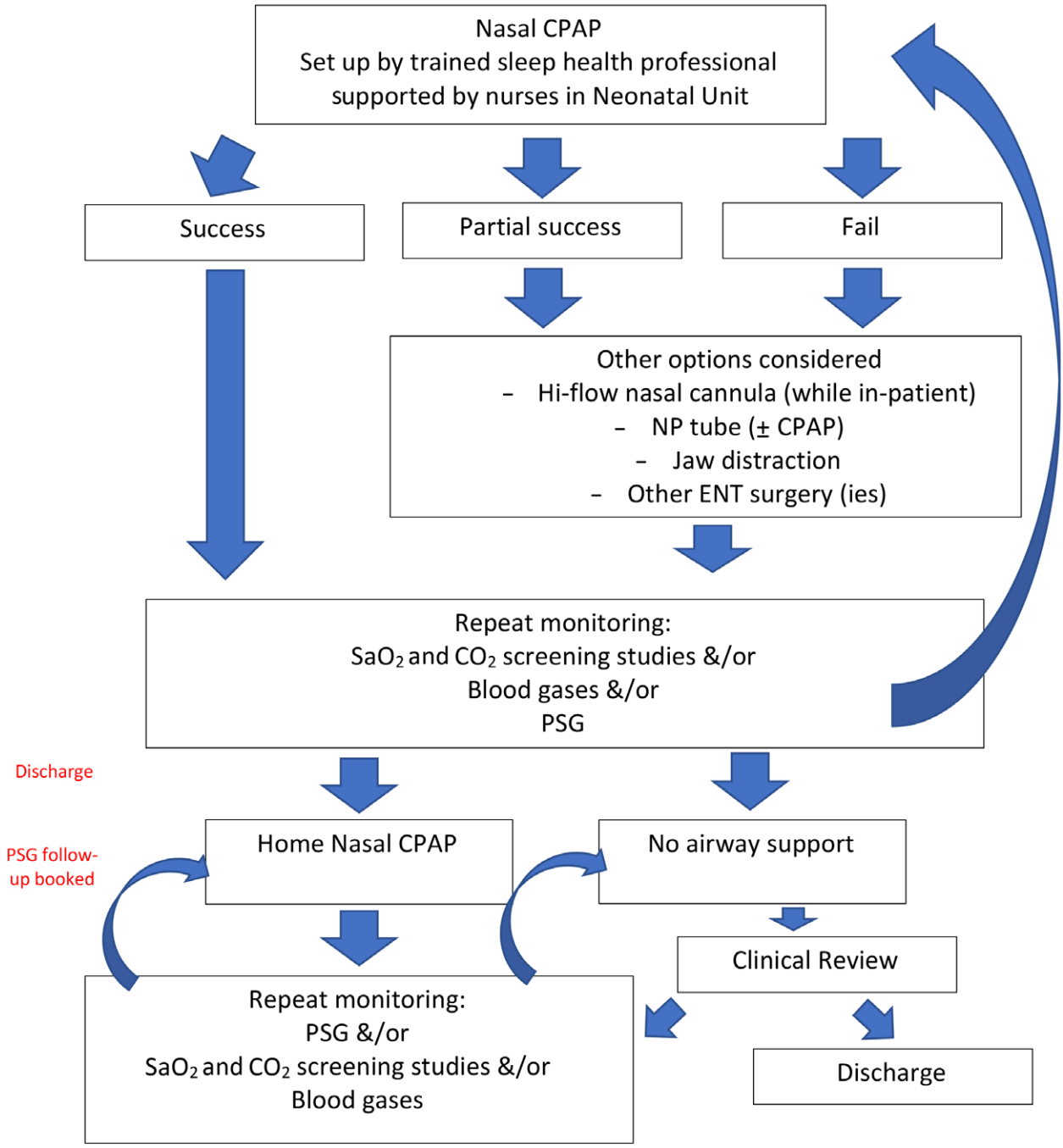

Fig. 3. CPAP initiation, evaluation, and monitoring. Approach to establishing and monitoring CPAP therapy in infants with RS and severe airway obstruction.

feeding in the special care nursery at a regional hospital, the infant was discharged home feeding with a squeeze bottle.

The infant re-presented in the second week of life with large vomits, respiratory distress, and oxygen desaturation. Micrognathia was noted, severe upper-airway obstruction was diagnosed, and the infant was transferred to CHW. At CHW, the infant was commenced on nasal CPAP at a pressure of 5 cm H_2O, and pressures were incrementally increased to a peak value of 8 cm H_2O at 5 weeks of age. A brief trial of a nasopharyngeal airway (NPA) at 10 weeks of age—undertaken due to ongoing sleep disturbance and poor weight gain on CPAP at 8 cm H_2O—was not tolerated. The infant was discharged home on CPAP 6 cm H_2O, and CPAP was ceased at 39 weeks (9 months). Cleft palate repair was undertaken at 67 weeks (15.4 months). The infant has continued to do well without further requirement for respiratory support (Fig. 4).

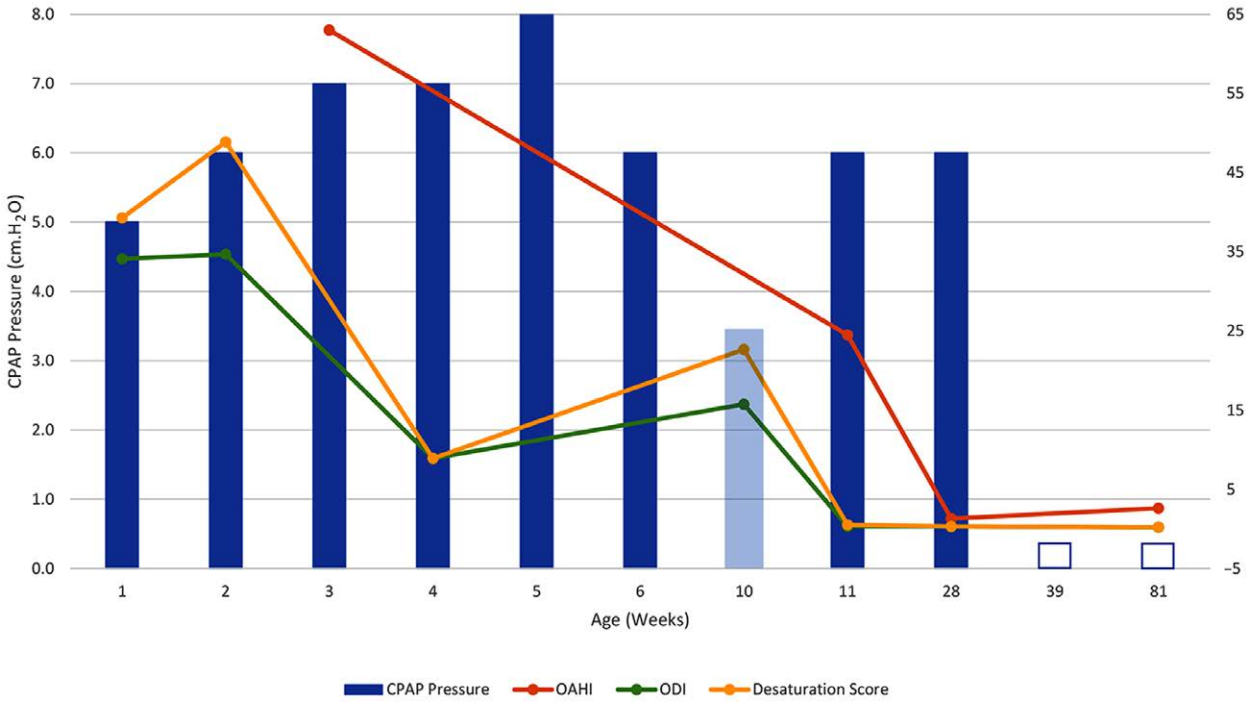

Fig. 4. Patient 1: CPAP titration with age. Nb. At 10 weeks of age, Patient 1 had a failed trial of an NPA in room air before recommencing CPAP, which was finally ceased at 39 weeks.

Patient 2

This infant was born at 39 weeks gestation (in a nontertiary hospital) with a history of suspected RS antenatally, and transferred to CHW on day 2 of life. The diagnostic PSG showed an AHI of 77.2 per hour and nasal CPAP therapy was commenced. CPAP pressure requirement increased during the initial weeks of use before peaking at 10 cm H_2O at 7 weeks, then gradually decreasing and being ceased following cleft palate repair surgery at 74 weeks (Fig. 5).

Patient 3

This infant was born at 38 weeks gestation at another tertiary hospital, and transferred to CHW on day 7 of life, following discharge home and re-presentation with poor feeding and obstructive breathing. The diagnostic PSG on Day 7 showed severe OSA, and the infant was commenced on nasal CPAP therapy. The infant's OAHI peaked at 67.4/hour in week 4 of life.

Management of airway obstruction was difficult and included a trial of NPA in combination with mask CPAP. The infant progressed to mandibular jaw distraction surgery at 17 weeks of age. The jaw was distracted to 17 mm, but infection of a jaw distractor at 20–21 weeks led to its removal. Following jaw distraction, a trial period off CPAP was followed by worsening airway obstruction, a period of treatment with low flow oxygen, and eventual re-initiation of CPAP at 69 weeks, at 6.5 cm H_2O. Peak CPAP pressure requirement was 10 cm H_2O at 73–82 weeks of age. Cleft palate repair was undertaken at 73 weeks of age, and CPAP therapy was discontinued at 82 weeks of age when PSG demonstrated improved AHI (5.5/hour) (Fig. 6).

DISCUSSION

The detailed studies available for these cases showed a trend for increasing CPAP pressure requirements in the first weeks of life with CPAP pressures peaking at 4–7 weeks of life. Cases 1 and 2 demonstrated a pattern we consider representative of uncomplicated cases. Nonetheless, medical management of infants with RS requires recognition of infants' variable tolerance of the strategies for airway management, including NPA and CPAP. Case 3 represents a child whose airway obstruction was severe enough that we went on to recommend jaw distraction, but whose clinical course following that surgery required further intervention with home nasal CPAP therapy.

Our use of nasal CPAP as the therapy of choice for treating airway OSA in infants with RS has led to frequent observation of the pattern documented in these cases, with an early increase in CPAP pressure requirements during the second month of life (in these cases peaking at 4–7 weeks); although it has been previously reported that airway obstruction in RS improves with time.[8,15] As NPAs bypass the upper-airway completely, their reports are limited to providing information about the age at which obstruction resolves/improves. Abel et al reported that gradual improvement in airway obstruction allowed children with RS to wean from airway support after early infancy, without the need for

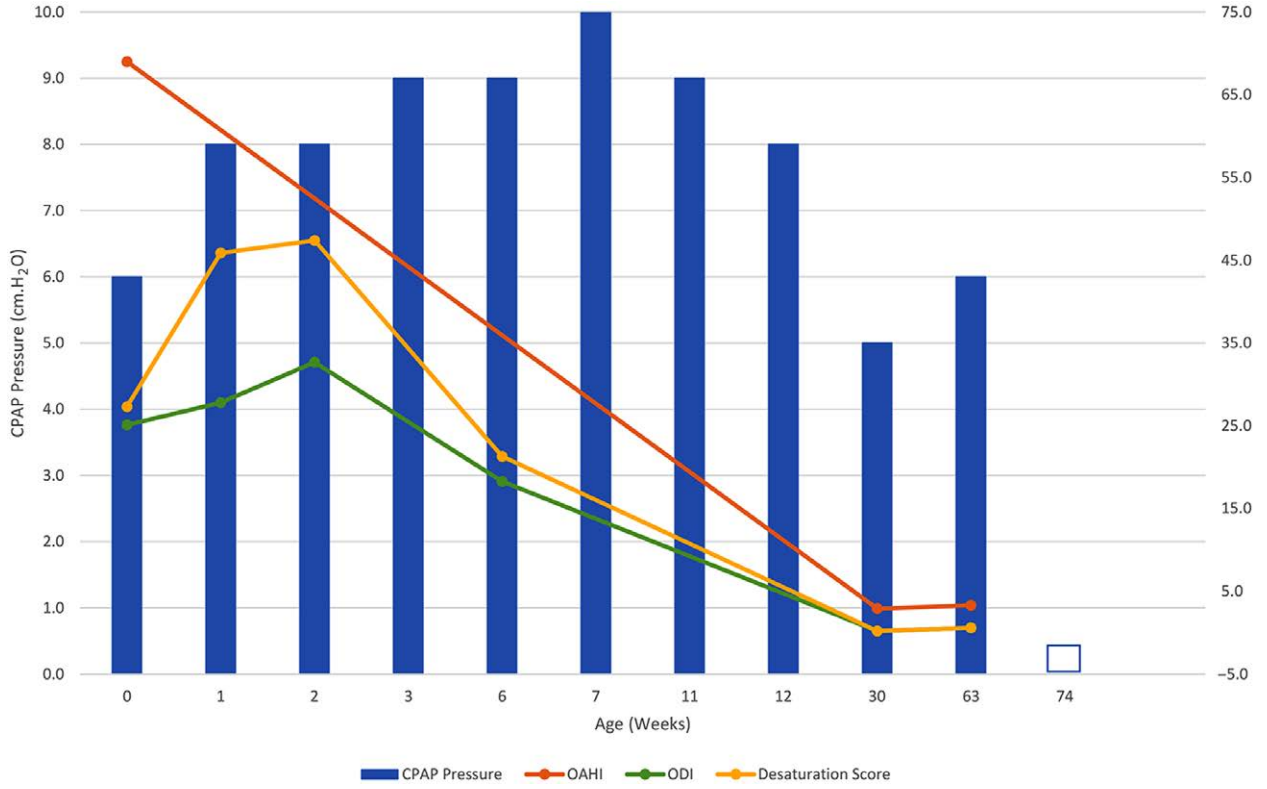

Fig. 5. Patient 2: CPAP titration with age. CPAP was commenced soon after birth and continued until 74 weeks.

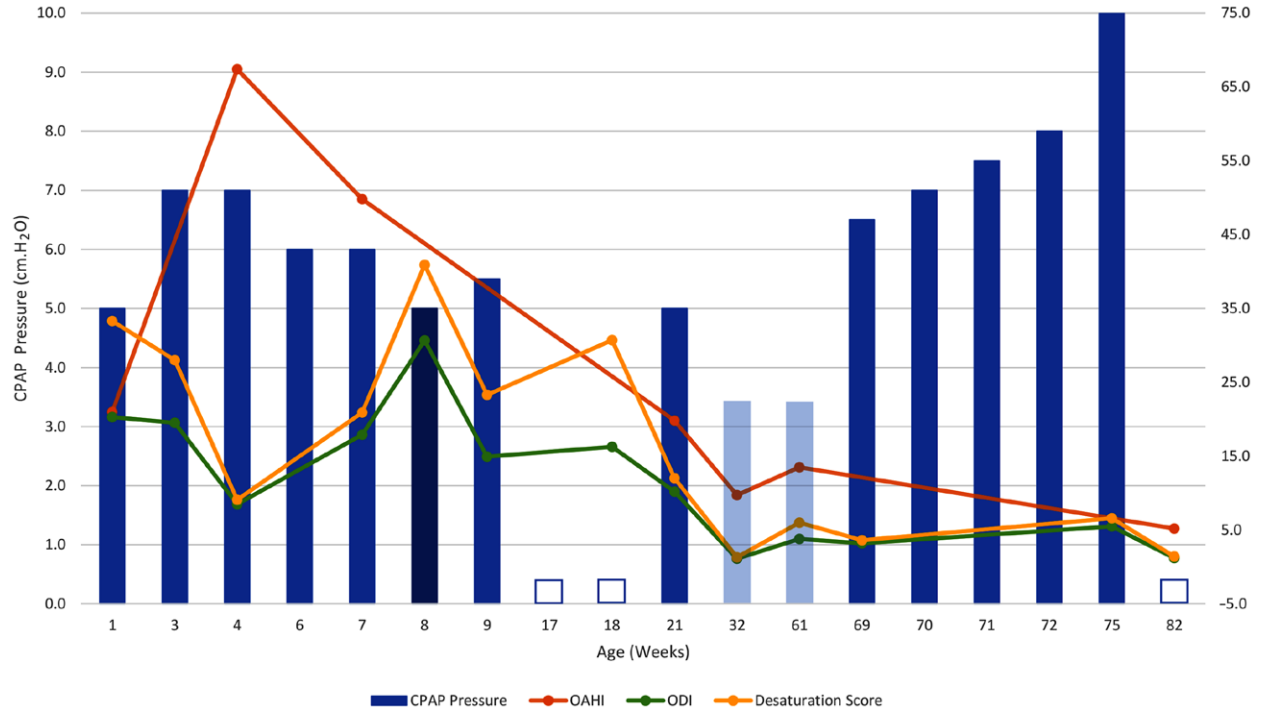

Fig. 6. Patient 3: CPAP titration with age. Patient 2 used an NPA with CPAP briefly at 8 weeks of age. At 17 weeks, they were in room air and at 32 weeks, they went on to home low flow oxygen at 0.5 L/min.

surgical intervention.[16–19] Downey et al also reported that CPAP requirements can improve over time.[20] Together these reports suggest that there would be a gradual reduction in CPAP pressure requirements after initiation of the therapy.

Of interest, the severity of airway obstruction using sleep parameters did not track with the changes in CPAP pressure requirement. Using AHI and OAHI from PSG, or desaturation scores from screening studies, the two infants with relatively uncomplicated clinical courses showed a pattern of progressive improvement in airway obstruction. We postulate that CPAP pressure requirements reflect dynamic changes in the airway tendency to collapse[21] and offer a different evaluation of the severity of airway obstruction to traditional PSG criteria, thereby reflecting changes in other aspects of respiratory development.[12] Several studies suggest that there is concurrent maturation of several systems pertinent to respiratory physiology over the first 6 months.[22–24] Horne described the 2- to 4-month age period as a "developmental window of vulnerability," which coincides with a peak risk of SIDS. In this age group, effects of low blood pressure lead to inadequate flow-metabolism coupling, resulting in reduced cerebral oxygenation.[22] Wong-Riley et al described a similar observation in rats.[23] We believe that changes in pressure requirement are due to underlying maturational changes in respiratory control, neuromuscular development, and/or pulmonary mechanics, but physiological studies would be required to evaluate this further. An additional factor is the way respiratory events are scored on sleep studies, using two-breath duration. As the respiratory system matures and respiratory rates slow, this inevitably leads to a reduced frequency of respiratory events.[12]

Case 3 illustrates the need for access to multiple therapeutic modalities in caring for children with either severe airway obstruction, or who experience complications of surgery. Jaw distraction surgery can be associated with complications, including incomplete alleviation of airway obstruction and infection. In this case, although CPAP therapy was not well tolerated initially, tolerance of CPAP therapy can be influenced by a variety of underlying factors.[25] Cheng et al reported six cases with RS where CPAP treatment failed due to severe airway obstruction, and highlighted the need to evaluate for additional airway problems that require more complex surgery in these cases.[4] In our third case, with maturation and in the presence of documented improvement in the severity of airway obstruction, the infant was able to tolerate a later period of home CPAP therapy.

Limitations of the study include our data quality, given that portions of our data were provided from studies limited to oxygen saturation and transcutaneous CO_2 rather than PSG. Nonetheless, the detailed time course we have illustrated offers new insights into the patterns of airway obstruction in these infants. Such studies provide rapid assessment of the stability of gas exchange when PSG may not be available, especially if changes to CPAP pressure are being made.[26,27] Further studies would also be required to achieve more detailed assessment of the mechanisms underlying the changes in airway obstruction and treatment requirements we have observed.

CONCLUSIONS

This case series of infants with RS illustrates that infants with RS often need an early increase in CPAP pressure. The cases we present showed an early peak in CPAP treatment pressure in the second month of life, before later decreases and potential for cessation of therapy. Changes in CPAP pressure requirements may explain periods of intolerance to the therapy during early infancy.

Belema D. Dede, BFor, MD
Department of Respiratory and Sleep Medicine
Children's Hospital at Westmead
Corner of Hawkesbury Road and Hainsworth Street
Westmead NSW 2145, Sydney
Australia
E-mail: belemadonald.dede@health.nsw.gov.au

REFERENCES

1. Jakobsen LP, Knudsen MA, Lespinasse J, et al. The genetic basis of the Pierre Robin sequence. *Cleft Palate Craniofac J.* 2006;43:155–159.
2. Breugem CC, Evans KN, Poets CF, et al. Best practices for the diagnosis and evaluation of infants with Robin sequence: a clinical consensus report. *JAMA Pediatr.* 2016;170:894–902.
3. Takeshita S, Ueda H, Goto T, et al. Case report of Pierre Robin sequence with severe upper airway obstruction who was rescued by fiberoptic nasotracheal intubation. *BMC Anesthesiol.* 2017;17:43.
4. Cheng ATL, Corke M, Loughran-Fowlds A, et al. Distraction osteogenesis and glossopexy for Robin sequence with airway obstruction. *ANZ J Surg.* 2011;81:320.
5. MacLean JE, Fitzsimons D, Fitzgerald DA, et al. The spectrum of sleep-disordered breathing symptoms and respiratory events in infants with cleft lip and/or palate. *Arch Dis Child.* 2012;97:1058–1063.
6. Khayat A, Bin-Hassan S, Al-Saleh S. Polysomnographic findings in infants with Pierre Robin sequence. *Ann Thorac Med.* 2017;12:25–29.
7. Waters KA, Suresh S, Nixon GM. Sleep disorders in children. *Med J Aust.* 2013;199:S31–S35.
8. Daniel M, Bailey S, Walker K, et al. Airway, feeding and growth in infants with Robin sequence and sleep apnoea. *Int J Pediatr Otorhinolaryngol.* 2013;77:499–503.
9. Sculerati N, Gottlieb MD, Zimbler MS, et al. Airway management in children with major craniofacial anomalies. *Laryngoscope.* 1998;108:1806–1812.
10. Gangopadhyay N, Mendonca DA, Woo AS. Pierre Robin sequence. *Semin Plast Surg.* 2012;26:76–82.
11. Bhushan B, Maddalozzo J, Sheldon SH, et al. Metabolic alterations in children with obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol.* 2014;78:854–859.
12. DeHaan KL, Seton C, Fitzgerald DA, et al. Polysomnography for the diagnosis of sleep disordered breathing in children under 2 years of age. *Pediatr Pulmonol.* 2015;50:1346–1353.
13. Pamula Y, Campbell A, Coussens S, et al. ASTA/ASA addendum to the AASM guidelines for the recording and scoring of paediatric sleep. *J Sleep Res.* 2011;20(Supp. 1):4.
14. Dehlink E, Tan H-L. Update on paediatric obstructive sleep apnoea. *J Thorac Dis.* 2016;8:224–235.

15. Abel F, Bajaj Y, Wyatt M, et al. The successful use of the nasopharyngeal airway in Pierre Robin sequence: an 11-year experience. *Arch Dis Child*. 2012;97:331–334.
16. Monasterio OF, Drucker OM, Molina OF, et al. Distraction osteogenesis in Pierre Robin sequence and related respiratory problems in children. *J Craniofacial Surg*. 2002;13:79–83.
17. Matsas R, Thomson A, Goodacre T. Management of infants with Pierre Robin sequence. *Cleft Palate-Craniofacial Assoc*. 2004;41:219.
18. Bacher M, Sautermeister J, Urschitz MS, et al. An oral appliance with velar extension for treatment of obstructive sleep apnea in infants with Pierre Robin Sequence. *Cleft Palate Craniofac J*. 2011;48:331–336.
19. Amaddeo A, Abadie V, Soupre V, et al. Management of upper airway obstruction by non-invasive CPAP in neonates with Pierre Robin sequence. *Eur Respir J*. 2015;46(Supp 59):PA1567.
20. Downey IR, Perkin RM, MacQuarrie J. Nasal continuous positive airway pressure use in children with obstructive sleep apnea younger than 2 years of age. *Chest*. 2000;117:1608–1612.
21. Bamagoos AA, Eckert DJ, Sutherland K, et al. Dose-dependent effects of mandibular advancement on optimal positive airway pressure requirements in obstructive sleep apnoea. *Sleep Breath*. 2020;24:961–969.
22. Horne RSC. Cardiovascular autonomic dysfunction in sudden infant death syndrome. *Clin Auton Res*. 2018;28:535–543.
23. Wong-Riley MTT, Liu Q, Gao X. Mechanisms underlying a critical period of respiratory development in the rat. *Respir Physiol Neurobiol*. 2019;264:40–50.
24. Horne RSC. Cardio-respiratory control during sleep in infancy. *Paediatr Respir Rev*. 2014;15:163–169.
25. Weiss MR, Allen ML, Landeo-Gutierrez JS, et al. Defining the patterns of PAP adherence in pediatric obstructive sleep apnea: a clustering analysis using real-world data. *J Clin Sleep Med*. 2021;17:1005–1013.
26. D'Souza B, Norman M, Sullivan CE, et al. $TcCO_2$ changes correlate with partial obstruction in children suspected of sleep disordered breathing. *Pediatr Pulmonol*. 2020;55:2773–2781.
27. Khirani S, Amaddeo A, Griffon L, et al. Follow-up and monitoring of children needing long term home ventilation. *Front Pediatr*. 2020;8:330.