Central apnea and periodic breathing in children with underlying conditions

Sergio Ghirardo1,2 | Alessandro Amaddeo1,3 | Lucie Griffon1,3 | Sonia Khirani1,3,4 | Brigitte Fauroux1,3

1 Assistance Publique-Hôpitaux de Paris (AP-HP), Pediatric Noninvasive Ventilation and Sleep Unit, Hôpital Necker-Enfants Malades, Paris, France
2 University of Trieste Department of Medicine, Surgery and Health Sciences, Trieste, Italy
3 Equipe d’Accueil EA VIFASOM, Université de Paris, Paris, France
4 ASV Santé, Gennevilliers, France

Correspondence
Sergio Ghirardo, University of Trieste, Department of Medicine, Surgery and Health Sciences Piazzale Europa 1, Trieste, Italy.
Email: ghirardo.sergio@gmail.com

Summary
Central sleep apneas and periodic breathing are poorly described in childhood. The aim of the study was to describe the prevalence and characteristics of central sleep apnea and periodic breathing in children with associated medical conditions, and the therapeutic management. We retrospectively reviewed all poly(somno)graphies with a central apnea index ≥ 5 events per hr in children aged > 1 month performed in a pediatric sleep laboratory over a 6-year period. Clinical data and follow-up poly(somno) graphies were gathered. Ninety-five out of 2,981 patients (3%) presented central sleep apnea: 40% were < 1 year, 41% aged 1–6 years, and 19% aged ≥ 6 years. Chiari malformation was the most common diagnosis (13%). Mean central apnea index was 20 ± 30 events per hr (range 5–177). Fifty-eight (61%) children had an exclusive central pattern with < 5 obstructive events per hr. Periodic breathing was present in 79 (83%) patients, with a mean percentage of time with periodic breathing of 9 ± 16%. Among periodic breathing episodes, 40% appeared after a sigh, 8% after an obstructive event, 6% after breathing instability and 2% after bradypnea. The highest clinical apnea index and percentage of time with periodic breathing were observed in children with encephalopathy and/or epilepsy (68 ± 63 events per hr and 30 ± 34%). Clinical apnea index did not differ according to age, while periodic breathing duration was longer in children > 1 year old. Watchful waiting was performed in 22 (23%) patients with spontaneous improvement in 20. Other treatments (upper airway or neurosurgery, nocturnal oxygen therapy, continuous positive airway pressure, non-invasive ventilation) were effective in selected patients. Central sleep apnea is rare in children and comprises heterogeneous conditions. Sleep studies are essential for the diagnosis, characterization and management of central sleep apnea.

KEYWORDS
apnea pattern, central sleep apnea, child, infant, periodic breathing
1 | INTRODUCTION

Central sleep apnea (CSA) is an uncommon finding in children outside the neonatal period and is poorly described in childhood (McLaren, 2019), and in particular in relation to specific medical conditions (Ferri, 1997; McLaren, 2019). In children, a CSA is defined as a reduction in airflow of at least 90% without respiratory efforts, lasting at least 20 s, or more than two baseline respiratory cycles associated with an at least 3% reduction in oxygen saturation (SpO₂) and/or an arousal and/or an episode of bradycardia in infants (Berry, 2012). A central apnea index (CAI) ≤ 1 event per hr is widely considered as normal, whereas CAI ≥ 5 events per hr is currently proposed as a pathological threshold (Harman et al., 2020; McLaren, 2019; Scholle, 2011). CSA affects less than 5% of healthy children (Felix, 2016; McLaren, 2019). CSA occurs mainly in children with underlying medical conditions, such as Chiari malformation, with only a few studies reporting CSA in children outside this context (Felix et al., 2016; McLaren et al., 2019). Also, the clinical consequences of CSA as well as therapeutic options have been poorly analysed (Eckert, 2007; Felix, 2016; Harman, 2019; McLaren, 2019; Urquhart, 2013). Therapeutic options comprise weight management, oxygen supplementation or non-invasive ventilation (NIV) without a clear indication about the preferred treatment for specific conditions (McLaren, 2019; Urquhart, 2013).

Periodic breathing (PB) is a particular breathing pattern that is defined by the presence of at least three episodes of central pauses lasting for at least 3 s interspersed by less than 20 s of normal breathing (Berry, 2012). PB may be physiological in preterm infants, due to the immaturity of the breathing centres, but it may also be a pathological finding (Ferri, 1997; Mohr, 2015). Cheyne–Stokes breathing (CSB), which is characterized by a prolonged crescendo-decrescendo pattern of respiration, followed by a central event, either apnea or hypopnea, may overlap with PB, but should be considered a different condition (Berry, 2012; Tinoco, 2017). CSB occurs mainly in adult patients with congestive heart failure, and is much less frequent among children, even in children with congestive heart failure (Peer, 2010). Although the American Academy of Sleep Medicine (AASM) does not define CSB in children, it can be exceptionally observed in children with associated diseases and heart defects (Hoch, 2001). Paediatric literature on PB is mainly focused on the neonatal period or follow-up of preterm subjects (Mohr, 2015), with little data in older children (Driessen, 2012; Kelly, 1985). Sleep bradypnea may also be observed in children, but its description and pathophysiological significance is limited by the lack of well-defined normal values of respiratory rate of children during sleep (Marks, 1993; Scholle, 2011).

Central sleep apneas, PB and bradypnea all seem to reflect an impairment of the central ventilatory centres, either due to brain-stem immaturity or injury, or within the context of a specific disease (Stevens, 2018; Urquhart, 2016). A better description and definition of these entities (CSA, PB and bradypnea) may possibly improve our understanding of these abnormal breathing patterns and, consequently, the management of these children. However, only CSA present a partially defined pathological threshold, whereas the interpretation of PB and bradypnea seems to vary widely between centres outside neonatal age.

The aim of our study was to describe the prevalence and characteristics of CSA and PB in children with underlying conditions, followed at a tertiary university hospital, and the consequent therapeutic management.

2 | METHODS

2.1 | Patients

We retrospectively considered all consecutive patients, aged between 1 month and 18 years, who underwent a respiratory polygraphy (PG) or polysomnography (PSG) at the paediatric sleep unit in Necker Hospital, between October 2013 and October 2019. For all patients, the first PSG with a CAI ≥ 5 events per hr (baseline PSG) was considered for the descriptive analysis. Preterm infants aged less than 6 months of chronological age at PSG were excluded due to the high prevalence of persistent apnea in these infants (Eichenwald, 2016; Zhao, 2011). PSG performed during NIV, continuous positive airway pressure (CPAP) or oxygen therapy were also excluded. Clinical data and consequent therapeutic management were gathered. Successive PSG following treatment were analysed, when available. The study was conducted in agreement with the French regulations, and received appropriate legal and ethical approval from the ethical committee CPP Ile de France II, protocol 2013-A00374-41. All the parents and all the children aged > 6 years old gave their informed consent.

2.2 | PSG recordings

Polysomnography was performed using Alice 6 LDxS™ (Philips Respironics, Carquefou, France), while PG studies were performed using CID102™ (Cidelec, St Gemmes sur Loire, France), Alice 6 LDxS™ or SOMNO HD™ (SOMNOmedics GmbH, Randersacker, Germany). Cardiorespiratory data included airflow (nasal pressure transducer and oronasal thermistor if available), body position, body movements, thoracic and abdominal movements assessed by respiratory inducance belts, respiratory sounds by a microphone, SpO₂, and video recording. For PSG, electroencephalographic recordings were based on the international 10–20 system with the placement of electrodes in positions F1-A2, F2-A1, C3-A2, C4-A1, O1-A2, O2-A1, recording of eye movements, electromyography (EMG) of the chin, electrocardiogram, and left and right tibialis EMG. Respiratory events and sleep stages were scored manually by experienced readers, according to the standard criteria of the AASM (Berry, 2012). We scored as central apneas all the events satisfying AASM criteria regardless of concurrent PB scoring. Transcutaneous carbon dioxide pressure (PtCO₂) recordings were performed simultaneously (SenTec Digital Monitor, SenTec, Therwil, Switzerland).
2.3 Data analysis

The following sleep parameters were analysed.

- Total sleep time (TST): for PSG, TST was considered as the time from sleep onset to the end of the final sleep epoch excluding wakefulness; for PG, TST was the total recording time excluding periods of artefacts and gross body movements.
- Apnea–hypopnea index (AHI), defined as the number of apneas and hypopneas per hour of TST.
- CAI, obstructive apnea index (OAI), mixed apnea index (MAI), hypopnea index (HI), obstructive apnea–hypopnea index (OAHII), defined as the sum of OAI and HI.
- Mean, minimal SpO₂ and the percentage of TST spent with a SpO₂ < 90%; nocturnal hypoxaemia was defined as ≥ 2% of TST with a SpO₂ < 90%.
- Mean, maximal PtcCO₂, and the percentage of TST spent with a PtcCO₂ > 50 mmHg; nocturnal hypoventilation was defined as a PtcCO₂ > 50 mmHg for > 2% of TST (Amaddeo, 2016).
- Oxygen desaturation index (ODI), defined as the number of ≥ 3% SpO₂ desaturations per hour of TST.
- PB was defined as ≥ 3 episodes of central respiratory pauses lasting > 3 s separated by no more than 20 s of normal breathing.
- Total PB duration, percentage of TST spent with PB (PB%), number of PB episodes per hour of TST, and number of patients with Prolonged PB defined as patients spending ≥15% of TST in PB (Finer, 1992).

Specific patterns of PB onset were identified as follows.

1. *Post-sigh/post-overshoot PB*: PB starts within 10 s after a sigh or a respiratory overshoot (Figure 1a; Harman et al., 2020).
2. *Post-obstructive PB*: PB starts within 10 s after an OA or hypopnea (Figure 1b).
3. *Post-bradypnea PB*: PB starts within 10 s after a bradypnea (Figure 1c).
4. *Post-instability PB*: PB starts within 10 s after a crescendo–decrescendo breath or other forms of breath instability (Figure 1d).
5. *Post-awakening PB*, scored only for PSG: PB already present at the moment of falling asleep.
6. *Other PB onsets*.

Patients were then classified into three groups according to the pattern of central apneas.

- Exclusively CSA, defined as an OAHII < 5 events per hr.
- Predominantly CSA, defined as patients with an OAHII ≥ 5 events per hr and a CAI ≥ OAHII.
- Predominantly obstructive sleep apnea, defined as patients with an OAHII > CAI.
TABLE 1 Pathologies and associated pathologies of the population (n = 95)

| Diseases (95 patients) | Age (years) (mean ± SD) | Associated diseases |
|------------------------|-------------------------|---------------------|
| Chiari I malformation (n = 12) | 5.5 ± 5.1 | 1 Syringomyelia 1 Macrocrania 1 Polymalformative syndrome 1 Achondroplasia 1 Obstructive sleep apnea 1 Plagiocephaly 1 Faciocraniosynostosis |
| Upper airway malformation/dysfunction (n = 9) | 0.8 ± 1.3 | 3 Laryngomalacia/vocal cord paralysis 1 Intrauterine growth retardation 1 Macroglossia 1 Beckwith Wiedemann syndrome 1 Treacher Collins syndrome |
| Pierre Robin Sequence (n = 9) | 0.7 ± 1.5 | 1 Cornelia de Lange syndrome 1 Orofacial-digital syndrome |
| Down syndrome (n = 8) | 5.3 ± 5.0 | 1 Achondroplasia |
| Neuromuscular diseases (n = 7) | 3.8 ± 5.9 | 1 Potocki-Lupski 1 TECPR2 mutation 1 Brief resolved unexplained event |
| Cerebral tumour (n = 7) | 5.5 ± 3.1 | None |
| Achondroplasia (n = 6) | 1.9 ± 1.7 | 1 Chiari malformation 1 Occipital stenosis 1 Prematurity |
| Prader Willi syndrome (n = 6) | 4.3 ± 3.3 | None |
| Encephalopathy and/or epilepsy (n = 6) | 7.0 ± 5.5 | 2 Rett syndrome 1 Polymalformative syndrome 1 Cerebral creatine deficiency 1 NBO mutation 1 Anoxic encephalopathy |
| Other (n = 25) | 3.5 ± 4.3 | 5 Developmental delay 4 Brief resolved unexplained event 4 Brainstem dysfunction 2 Cardiopathy 2 Prematurity 2 Storage disease 1 Craniosynostosis 1 Spondyloepiphysyeal dysplasia 1 Hypothyroidism 1 Sensenbrenner syndrome 1 Pulmonary hypertension 1 Idiopathic CSA |

CSA, central sleep apnea.

2.4 Statistical analysis

Discrete variables were reported as numbers and percentages, whereas continuous variables were presented as mean and standard deviation (SD). Comparisons between discrete data were performed using the chi-square test. Comparisons between quantitative data were performed using the one-way analysis of variance or Kruskal–Wallis one-way analysis of variance on ranks. Comparisons of repeated measurements were performed using the paired t-test or the Wilcoxon signed rank test. A p-value <.05 was considered for significance.

3 RESULTS

3.1 Description of central breathing patterns

A total of 4,054 PSG were performed during the study period, comprising 3,888 within the considered age range on a total of 2,981 patients. Of them, 102 patients had a baseline PSG with a CAI ≥ 5 events per hr. Four preterm infants <6 months of age were excluded, two other patients because the PSG was performed during oxygen therapy or NIV, and one PG was not available for retrospective analysis due to a technical issue, which left 95 patients (3%) with a CAI ≥ 5 events per hr. Eighty-eight patients had a PG and seven a PSG, 46 of the patients were boys and 49 girls. Mean age was 3.7 ± 4.5 years; 38 (40%) patients were younger than 1 year old, 39 (41%) aged 1–6 years, and 18 (19%) were ≥ 6 years old. Chiari type I malformation was the most frequent diagnosis, followed by upper airway malformation/dysfunction, Pierre Robin Sequence and Down syndrome (Table 1). Only one patient had no associated disorder.

Mean CAI was 20 ± 30 events per hr (range 5–176.5 events per hr; Table 2). Fifty-eight (61%) had Exclusively CSA, 12 (17%) Predominantly CSA, and 25 (26%) Predominantly obstructive sleep apnea (Table 3). A total of 1,366 PB episodes was identified, with at least one episode of PB in 79 (83%) patients. The mean PB duration was 39 ± 69 min of the total time of analysis, and the mean number of PB episodes per hr was 2 ± 3 (Table 2). The mean PB% was 9 ± 16%, with 19 patients presenting Prolonged PB. Among the 1,366 PB episodes, 552 (40%) were Post sigh PB events, 110 (8%) Post obstructive PB events, 79 (6%) Post instability PB events, 23 (2%) Post bradypnea PB events, and 568 events (42%) presented other onset patterns. Moreover, 34 events (2%) were classified as Post awakening PB events. Only one patient presented all the types of PB onset, three patients presented five types, eight patients four types, 18 patients three types, 28 patients two types and 21 patients only one type. PB% was significantly lower in children <1 year old as compared with children aged 1–6 years (4 ± 9% versus 14 ± 21%) and ≥ 6 years (9 ± 16, p < .001), as was mean PB duration (p < .001) and the number of PB episodes per hr of TST (p < .001). Prolonged PB was less common in infants (5%) than in children aged 1–6 years (28%) or ≥ 6 years (33%) (p = .012; Table 2). Post sigh PB was more frequent in older children as compared with children <1 year old (p < .001), and Post obstructive PB was more frequent in children ≥ 6 years old as compared with children <1 year old (p < .001). Bradypnea was observed in seven patients with Post bradypnea PB events just before the PB onset or interspersed between PB episodes.
TABLE 2 Results of the 95 baseline P(S)G according to the patient’s age

| Age of the patients (years) | < 1 (n = 38) | 1-6 (n = 39) | ≥ 6 (n = 18) | Total (n = 95) |
|----------------------------|-------------|-------------|-------------|--------------|
| TST (min)                  | 255 ± 147*  | 429 ± 93    | 445 ± 106   | 362 ± 145    |
| AHI (events per hr)        | 28 ± 30     | 36 ± 47     | 42 ± 37     | 34 ± 39      |
| OAHl (events per hr)       | 12 ± 16     | 13 ± 34     | 12 ± 15     | 12 ± 24      |
| CAI (events per hr)        | 15 ± 22     | 22 ± 35     | 24 ± 30     | 20 ± 30      |
| PB%                        | 4 ± 9*      | 14 ± 21     | 12 ± 16     | 9 ± 16       |
| PB episodes (number per hr)| 1 ± 2*      | 3 ± 3       | 2 ± 2       | 2 ± 3        |
| Mean SpO₂ (%)              | 95 ± 2      | 94 ± 5      | 94 ± 4      | 95 ± 4       |
| Minimal SpO₂ (%)           | 81 ± 7      | 82 ± 8      | 82 ± 10     | 82 ± 8       |
| Percentage of sleep time with SpO₂ < 90 (%) | 4 ± 9 | 8 ± 22 | 4 ± 8 | 5 ± 15 |
| Number of patients with > 2% of sleep time with SpO₂ < 90% | 10 (26%) | 8 (21%) | 4 (22%) | 22 (23%) |
| ODI (number per hr)        | 39 ± 32     | 37 ± 39     | 50 ± 43     | 40 ± 37      |
| Number of patients with ODI ≥ 10 per hr | 35 (92%) | 33 (85%) | 16 (89%) | 84 (88%) |
| Mean PtcCO₂ (mmHg)*        | 41 ± 5      | 40 ± 4      | 43 ± 4      | 41 ± 4       |
| Maximal PtcCO₂ (mmHg)†     | 45 ± 6      | 45 ± 5      | 48 ± 5      | 45 ± 5       |
| Percentage of sleep time with PtcCO₂ > 50 mmHg (%)‡   | 3 ± 15 | 2 ± 7 | 2 ± 5 | 2 ± 10 |
| Number of patients with > 2% of sleep time with PtcCO₂ > 50 mmHg | 1 (3%) | 2 (6%) | 1 (7%) | 4 (5%)  

Data are presented as mean ± standard deviation, or numbers and percentages.

AHl, apnea–hypopnea index; CAI, central apnea index; ECP, exclusively central pattern; OAHl, obstructive apnea–hypopnea index; ODI, oxygen desaturation index; PB, periodic breathing; PB%, percentage of time with PB; PCP, predominantly central pattern; POP, predominantly obstructive pattern; PtcCO₂, transcutaneous carbon dioxide pressure; SpO₂, peripheral oxygen saturation; TST, total sleep time.

*Significantly different as compared with the two other groups due to nap studies (p < .001).
†PtcCO₂ available for 82 patients.
‡PtcCO₂ available for 82 patients.

The highest mean CAI was observed in patients with encephalopathy and/or epilepsy (68 ± 63 events per hr), followed by patients with cerebral tumour (35 ± 44 events per hr; Table 4). Similar results were observed for the mean PB% (30 ± 34% in patients with encephalopathy and/or epilepsy, and 21 ± 30% in patients with cerebral tumour). The Exclusively CSA group comprised patients with heterogeneous diseases, while the Predominantly CSA group comprised mainly patients with disorders of the central nervous system, and the Predominantly obstructive sleep apnea group, patients with “obstructive” conditions. Of note, the three patterns could be observed in the same disease. Interestingly, mean CAI was higher in the Predominantly CSA group than in the Exclusively CSA or the Predominantly obstructive sleep apnea group (p = .001; Table 4). Maximal PtcCO₂ was lower in the Exclusively CSA group than in the Predominantly CSA group (p = .015), with only four patients, all in the Predominantly obstructive sleep apnea group, presenting nocturnal hypventilation (p = .005).

The mean duration of PB episodes was significantly lower in the Predominantly obstructive sleep apnea group (20 ± 33 min) than in the Predominantly CSA group (58 ± 65 min, p = .031), but not than in the Exclusively CSA group (43 ± 80 min), as well as the PB% (p = .049). Among the 19 patients with Prolonged PB, 14 had Exclusively CSA, four Predominantly CSA, and one Predominantly obstructive sleep apnea (p = .051). The Exclusively CSA group presented a lower number of Post obstructive PB than the Predominantly CSA group (p = .004).

3.2 Consequent therapeutic management

Fifty-five (58%) patients had a follow-up P(S)G (three PSG and 52 RP), with 39 patients having a follow-up CAI < 5 events per hr and 16 a CAI ≥ 5 events per hr. Twenty-six of these patients had a cerebral imaging before baseline P(S)G and, in 27 other patients, the P(S)G results led to a brain magnetic resonance imaging (MRI) within the following 6 months. Following the baseline P(S)G results, 17 patients had a neurosurgical evaluation, 12 an otolaryngological (ENT) evaluation, and one patient a cardiac evaluation. Consequently, 13 patients had a neurosurgical intervention, and eight ENT surgery (Tables 5 and S1). Four patients were treated with nocturnal oxygen therapy, two patients with CPAP, and one with NIV. Two patients were treated with acetazolamide and one with caffeine. Watchful waiting was performed in 22 (40%) patients.

The follow-up P(S)G was performed after a mean of 312 ± 367 days, all P(S)Gs were performed with the ongoing treatment; when a treatment was discontinued before the follow-up P(S)G the patient was classified within the watchful waiting group. Mean CAI decreased from 21 ± 27 events per hr at baseline to 10 ± 21
TABLE 3  Central apnea and PB according to the underlying disorder

|                  | Down syndrome (n = 8) | Upper airway anomaly (n = 9) | Pierre Robin Sequence (n = 9) | Achondroplasia (n = 6) | Prader Willi syndrome (n = 6) | Idiopathic CSA and brief resolved unexplained event (n = 5) | Neuromuscular disease (n = 7) | Cerebral tumour (n = 7) | Encephalopathy and/or epilepsy (n = 6) |
|------------------|-----------------------|-----------------------------|-------------------------------|-----------------------|-----------------------------|---------------------------------------------------|---------------------------|-------------------|---------------------------------|
| CAI              | 7 ± 2                 | 8 ± 6                        | 8 ± 5                         | 10 ± 6                | 12 ± 10                     | 21 ± 16                                           | 26 ± 24                   | 26 ± 37           | 35 ± 44                         | 68 ± 63 |
| OAHI < 5 events per hr | 1 (12%)           | 5 (56%)                       | 5 (56%)                       | 4 (67%)               | 11 (92%)                    | 6 (100%)                                          | 2 (40%)                   | 4 (57%)           | 4 (57%)                         | 2 (33%) |
| CAI < OAHI       | 7 (88%)               | 4 (44%)                       | 4 (44%)                       | 1 (17%)               | 0 (0%)                      | 0 (0%)                                            | 1/5 (20%)                 | 2 (29%)           | 2 (29%)                         | 1 (15%) |
| Percentage of sleep time with PB (%) | 3 ± 3               | 2 ± 3                        | 1 ± 2                        | 4 ± 4                 | 9 ± 9                       | 13 ± 6                                            | 5 ± 4                     | 13 ± 15             | 21 ± 30                         | 30 ± 34 |
| Patients presenting PB | 7 (88%)               | 4 (44%)                       | 5 (56%)                       | 4 (67%)               | 11 (92%)                    | 6 (100%)                                          | 5 (100%)                  | 7 (100%)          | 7 (100%)                        | 6 (100%) |
| Prolonged PB    | 0                     | 0                             | 0                             | 0                     | 3 (25%)                     | 3 (50%)                                           | 0                         | 2 (29%)           | 3 (43%)                         | 3 (50%) |
| Number of types of PB onset | 2 ± 1               | 1 ± 1                        | 1 ± 1                        | 1 ± 1                | 2 ± 1                       | 2 ± 1                                             | 1 ± 1                     | 3 ± 1             | 3 ± 1                           | 4 ± 1 |
| Most prevalent PB onset type | Other n = 4           | Other n = 3                   | Other n = 3                   | Other n = 5           | Other n = 5                 | Other n = 5                                       | Other n = 5               | Other n = 5       | Other n = 5                      | Other n = 4 |
|                  | Post sigh PB n = 1    | Post sigh PB n = 1            | Post sigh PB n = 2            | Post sigh PB n = 4    | Post sigh PB n = 1          | Post sigh PB n = 1                                | Post sigh PB n = 1        | Post sigh PB     | Post sigh PB                      | Post sigh PB |
|                  | None n = 5            | None n = 4                    | None n = 2                    | None n = 2            | Equal n = 1                 | Equal n = 1                                       | Equal n = 1               | Post obstructive PB | Post obstructive PB              | Post obstructive PB |
|                  |                       |                              |                              |                      |                            | Equal* n = 1                                      | Equal* n = 1              | Post instability PB | Post instability PB              | Post instability PB |
|                  |                       |                              |                              |                      |                            | Equal** n = 1                                     | Equal** n = 1              | Post b radypnea PB | Post b radypnea PB               | Post b radypnea PB |
|                  |                       |                              |                              |                      |                            | Post awakening PB                                | Post awakening PB         | Post awakening PB | Post awakening PB               | Post awakening PB |

Data are presented as mean ± standard deviation, or numbers and percentages.
CSA, central sleep apnea; CAI, central apnea index; Equal**, equal number of Post bradypnea PB and other; Equal*, equal number of Post sigh PB and Post instability PB; Equal, equal number of Post sigh PB episodes and other PB; OAHI, obstructive apnea–hypopnea index; PB, periodic breathing.
events per hr at follow-up ($p < .001$), with a mean reduction of 11 ± 30 events per hr. The highest CAI reduction was observed in patients with encephalopathy and/or epilepsy (39 ± 69 events per hr), followed by idiopathic CSA, and brief resolved unexplained events (23 ± 23 events per hr) and neuromuscular diseases (17 ± 60 events per hr). The lowest reduction was observed in achondroplasia (1 ± 6 events per hr) and Down syndrome (4 ± 4 events per hr). Mean PB% was 10 ± 13% at baseline and 7 ± 14% at follow-up, with a mean reduction of PB% of 3 ± 16% ($p = .011$). The highest reduction of PB% was observed in patients with neuromuscular diseases (12 ± 19%), followed by Chiari malformation (10 ± 16%), and encephalopathy and/or epilepsy (8 ± 36%). On the contrary, OAHI, OAI, MAI and HI did not change on follow-up. According to the different management, the mean CAI decreased significantly at follow-up only in the watchful waiting group ($p = .004$; Table S2), with all but two patients having a reduction in the CAI (Table 5).

4 | DISCUSSION

This study is the first to provide a detailed description of CSA and related breathing anomalies such as PB in a large cohort of children with underlying disorders explored at a tertiary paediatric sleep laboratory over a 6-year period. Our results confirm the low prevalence of CSA and the frequent association with PB. Exclusively CSA and Post sigh PB were the most common patterns, with the highest CAI and PB% being observed in children with encephalopathy and/or epilepsy. A spontaneous improvement was observed in ~25% of the patients, with other specific approaches being efficacious in selected patients.

Even if there is a consensus on the definition of CSA in children (Berry, 2012), the CAI threshold that is considered as abnormal remains a matter of debate. Indeed, the threshold to define CSA is set at ≥ 5 events per hr in adults (Berry, 2012; McLaren, 2019), and this threshold is factually adopted in children (Felix, 2016; McLaren, 2019). Using this threshold, the prevalence of CSA is < 5% in children in most of the previously published studies (McLaren, 2019), as well as in the present study. However, when looking at the overnight breathing pattern of these children, one observes that the anomalies of the breathing patterns are far more complex than simple successive central apneas. We thus took the option to perform an exhaustive descriptive analysis of the breathing pattern of children diagnosed with a CSA ≥ 5 events per hr, including the analysis of PB and bradypnea.

Our study confirmed that CSA is variably associated with obstructive events, as observed in previous studies (Orr, 2017). Interestingly, when stratifying the patients according to the respective proportion of central and obstructive events, we observed that patients with Predominantly CSA had the highest CAI (mean 44 ± 40 events per hr), the highest PB% (mean 16 ± 18%), and comprised mainly patients with disorders of the central nervous system. Patients with Exclusively CSA were the largest group (61%), they had a variable CAI, a PB% of about 10%, and better nocturnal gas exchange than the other two CSA groups. Interestingly, the mean age did not differ between the three CSA groups.

Even if there is a definition of PB in children (Berry, 2012), its presence is not always reported, which is quite surprising as PB was observed in 83% of the patients of the present study. PB was more common in children with Exclusively CSA or Predominantly CSA who spent between 10% and 16% of sleep time with PB, as compared with children with Predominantly obstructive sleep apnea, underlining the association between these two entities. PB occurred after various “events”, mainly after a sigh (40%), but also an obstructive event, a bradypnea, a breathing instability, or an awakening. Sighs may physiologically induce PB at 1 month old, but this should decrease at a later age (Khan, 2005), although the total duration of PB did not change between the age of 6 weeks and 2 years using a slightly different PB definition (Poets, 1991). PB may also occur at sleep onset in healthy children or after an arousal but in our population, who presented severe underlying conditions, the prevalence of PB was higher with most PB not occurring at sleep onset (Beck, 2009). A quite surprising finding was that PB episodes could start before an awakening and last until the next sleep onset, and even start during short nocturnal awakenings (supplementary material: PSG findings).

In contrary to CSA, PB was less common in infants < 1 year old as compared with older children. This observation differs from the literature, which suggests a tendency of resolution of PB and Prolonged PB within the first year of life in healthy children (Flores-Guevara et al., 1985; Glotzbach, 1989; Kelly, 1985). These discrepancies may be explained by the specific recruitment of our centre, with nearly all children having underlying medical conditions, mostly rare and severe (Bin-Hasan, 2017; Driessen, 2012; Ferri, 1997). The commonly high gain–low gain model applied to explain PB in adults with heart failure may thus be insufficient to fully understand and explain PB in children with underlying disorders as in the present study. Children with isolated idiopathic CSA present a lower mean daytime PaCO$_2$ due to an increased responsiveness of central respiratory centres to arterial carbon dioxide pressure (PaCO$_2$; Dempsey, 2004, 2010). In these patients, central events reflect the excessive central response (or “respiratory overshoot”) induced by a minimal rise in PaCO$_2$ perceived by the central centres as hypercapnia before the physiological threshold of a 3–6 mmHg increase in PaCO$_2$ (Dempsey, 2004, 2010). The reduced span between euvolemic levels of CO$_2$ and CO$_2$ perceived as an apneic threshold plays a crucial role in respiratory instability (Dempsey, 2004), together with the reduced span between hypoxic and hypercapnic stimulus. This explains why the patients of the Exclusively CSA had higher SpO$_2$ and lower PtCO$_2$ values than the Predominantly CSA and the Predominantly obstructive sleep apnea groups (Table 4).

On the other hand, patients with hypercapnic central apnea present a lower sensitivity to CO$_2$ stimulus, as observed in children with congenital central hypoventilation syndrome (Bradley, 1986). Normally, brief and repeated hypoxic stimuli lead to a fast increase in the sensitivity to hypoxic stimulus as observed in animal models (Neubauer, 2001), and in studies performed on human newborns (Reynolds, 1977), children (Harman et al., 2020) and adults...
TABLE 4 Results of the 95 baseline P(S)G according to the predominant apnea pattern

|                               | Exclusively CSA (n = 58) | Predominantly CSA (n = 12) | Predominantly obstructive sleep apnea (n = 25) |
|--------------------------------|--------------------------|----------------------------|-----------------------------------------------|
| Age (years old)                | 3.9 ± 4.6                | 2.4 ± 3.1                  | 3.7 ± 5.0                                     |
| TST (min)                      | 383 ± 126                | 372 ± 131                  | 303 ± 173                                     |
| AHI (events per hr)            | 23 ± 32*                 | 61 ± 44                    | 45 ± 40                                       |
| OAHI (events per hr)           | 2 ± 1*                   | 16 ± 9                     | 35 ± 38                                       |
| CAI (events per hr)            | 20 ± 31                  | 44 ± 40*                   | 9 ± 7                                         |
| Percentage of sleep time with PB (%) | 10 ± 19                  | 16 ± 18                    | 4 ± 5*                                        |
| PB episodes (number per hr)    | 2 ± 3                    | 4 ± 3                      | 2 ± 2                                         |
| Mean SpO2 (%)                  | 95 ± 3**                 | 93 ± 4                     | 93 ± 5                                        |
| Minimal SpO2 (%)               | 84 ± 7*                  | 78 ± 8                     | 78 ± 9                                        |
| Percentage of sleep time with SpO2 < 90 (%) | 1 ± 3*                   | 7 ± 13                     | 15 ± 26                                       |
| Number of patients with > 2% of sleep time with SpO2 < 90% | 4 (7%)*                  | 5 (42%)                    | 13 (52%)                                      |
| ODI (number per hr)            | 30 ± 30*                 | 64 ± 37                    | 53 ± 42                                       |
| Number of patients with ODI ≥ 10 per hr | 49 (84%)                 | 12 (100%)                  | 23 (92%)                                      |
| Mean PtcCO2 (mmHg)             | 40 ± 3                   | 42 ± 4                     | 43 ± 6                                        |
| Maximal PtcCO2 (mmHg)          | 44 ± 4**                 | 48 ± 5                     | 47 ± 7                                        |
| Percentage of sleep time with PtcCO2 > 50 mmHg (%) | 0                       | 0.2 ± 0.6                  | 7 ± 19                                        |
| Number of patients with > 2% of sleep time with PtcCO2 > 50 mmHg | 0 (0%)                   | 0 (%)                      | 4 (21%)*                                      |

Data are presented as mean ± standard deviation, or numbers and percentages.

AHI, apnea-hypopnea index; CAI, central apnea index; CSA, central sleep apnea; OAHI, obstructive apnea–hypopnea index; ODI, oxygen desaturation index; PB, periodic breathing; PtcCO2, transcutaneous carbon dioxide pressure; SpO2, peripheral oxygen saturation; TST, total sleep time.

*Significantly different as compared with the two other groups.

**Significantly different between Predominantly CSA and Exclusively CSA.

†Significantly different between Predominantly CSA and Predominantly obstructive sleep apnea.

(Safrbaz Mahamed, 2001). This increased sensitivity to hypoxia is carried on through altered genomic expression by glomus cells (Neubauer, 2001). A similar pathogenetic mechanism is speculated for complex sleep apnea syndrome (CompSAS), during which central events appear or worsen after CPAP titration for obstructive sleep apnea syndrome. Such events resolve usually spontaneously within 4–8 weeks. Interestingly, patients who develop CompSAS present a higher loop gain with consequent respiratory drive instability and central apnea (Harman et al., 2020; Sands et al., 2011; Stanchina, 2015; Xie et al., 1995). The higher prevalence of Predominantly CSA in patients having the highest CAI suggests a role of obstructive events-induced hypoxia in causing glomus cells sensitization to hypoxia itself as found for intermittent hypoxia in general (Neubauer, 2001). This may lead to central apnea during periods free from obstructive events. Moreover, it may be possible that fatigue and underbreathing secondary to airway obstruction may play a role. On the other hand, patients with Predominantly obstructive sleep apnea tend to have lower CAI due to the shorter periods free from obstructive events and presented also shorter PB episodes. Of note, also obstructive respiratory events may be caused by brainstem injury or Chiari malformation due to the injury of the cranial nerves (mainly IX and X cranial nerves) causing pharyngeal collapse (Amin, 2015; Dauvilliers, 2007). On average, patients with Predominantly obstructive sleep apnea presented a lower reduction of CAI and PB% at follow-up, as compared with the two other groups, although this difference is not statistically significant. Interestingly, in our population the prevalence of Chiari type 1 malformation was much lower in patients without a CAI > 5 episodes per hr (6.3%). The highest reduction in CAI and PB was observed in patients with Post instability PB (mean CAI reduction 90 ± 23), whereas no significant change was observed in the other PB patterns. This finding is in agreement with the possible previously mentioned immaturity of the respiratory centres.

The therapeutic management depends on the underlying disease, the clinical symptoms and tolerance of CSA, and the P(S)G results with the CAI and the importance of nocturnal gas exchange anomalies. The therapeutic decision may be quite easy in the case of a child with CSA and Chiari malformation with the correction of CSA and PB after cervico-occipital decompression (Tables 5 and S1; McLaren, 2019; Tenconi, 2017). Nocturnal oxygen therapy has shown to reduce CSA in adults and in infants with Prader Willi syndrome (Franklin, 1997; Urquhart, 2013). This treatment was also effective in four children with cerebral tumour, encephalopathy or idiopathic CSA in the present study (Table 5). ENT surgery was able to improve CAI in patients with Predominantly obstructive sleep apnea, except in two patients with neuromuscular disease (Table 5). A watchful waiting was proposed in 22
| Disease type                        | Diseases                        | Intervention                  | CAI at baseline (events per hr) | CAI at follow-up (events per hr) | PB% at baseline (%) | PB% at follow-up (%) | Days between baseline and follow-up P(S)G |
|-------------------------------------|---------------------------------|-------------------------------|--------------------------------|---------------------------------|---------------------|----------------------|------------------------------------------|
| Cerebral                            | Chiari \(n = 9\)                | Neurosurgery \(n = 6\)          | 21 ± 30                         | 1 ± 1                           | 15 ± 18             | 1 ± 1                | 193 ± 160                                |
|                                     | None \(n = 3\)                  |                               | 12 ± 7                          | 1 ± 1                           | 2 ± 1               | 2 ± 1                | 394 ± 230                                |
|                                     | Prader Willi \(n = 6\)          | None \(n = 4\)                 | 10 ± 5                          | 2 ± 1                           | 10 ± 6              | 10 ± 15              | 223 ± 26                                 |
|                                     |                                | Acetazolamide \(n = 2\)        | 43                              | 4                               | 19                  | 3                    | 134                                      |
|                                     |                                | 42                              | 21                              | 20                              | 18                  |                      | 231                                      |
| Tumour \(n = 5\)                   | None \(n = 2\)                  |                               | 30                              | 24                              | 21                  | 38                   | 208                                      |
|                                     |                                | 11                              | 4                               | 4                               | 2                   |                      | 263                                      |
|                                     | Nocturnal oxygen therapy \(n = 1\) |                               | 14                              | 6                               | 2                   | 1                    | 61                                       |
|                                     | Neurosurgery \(n = 2\)          | 6                              | 1                               | 1                               | 1                   | 0                    | 121                                      |
| Encephalopathy and/or epilepsy      | Nocturnal oxygen therapy \(n = 1\) |                               | 132                             | 1                               | 55                  | 0                    | 35                                       |
| \((n = 3)\)                         | None \(n = 1\)                  | 53                             | 88                              | 21                              | 54                  |                      | 643                                      |
|                                     | ENT surgery \(n = 1\)           | 21                             | 0                               | 6                               | 7                   |                      | 133                                      |
| Idiopathic CSA and brief resolved   | Caffeine \(n = 1\)              | 33                             | 5                               | 3                               | 1                   | 8                    |                                          |
| unexplained event \(n = 5\)        | Nocturnal oxygen therapy \(n = 2\) |                               | 7                               | 3                               | 1                   | 1                    | 41                                       |
|                                     | None \(n = 2\)                  | 69                             | 2                               | 11                              | 0                   |                      | 20                                       |
| Atlanto-occipital anomalies \(n = 2\) | Neurosurgery \(n = 2\)          | 52                             | 57                              | 42                              | 47                  |                      | 63                                       |
| Developmental delay \(n = 1\)      | None \(n = 1\)                  | 35                             | 81                              | 13                              | 49                  |                      | 207                                      |
| Obstructive                         | Pierre Robin Sequence \(n = 4\) | CPAP \(n = 1\)                | 5                               | 1                               | 0                   | 0                    | 7                                        |
|                                     | Positional therapy \(n = 1\)    | 6                               | 1                               | 1                               | 0                   |                      | 13                                       |
|                                     | None \(n = 2\)                  | 22                             | 7                               | 1                               | 3                   |                      | 233                                      |
|                                     |                                | 8                               | 1                               | 2                               | 0                   |                      | 49                                       |
| Upper airway anomaly \(n = 5\)     | None \(n = 1\)                  | 35                             | 67                              | 20                              | 50                  |                      | 607                                      |
|                                     | Neurosurgery \(n = 1\)          | 6                               | 0                               | 2                               | 0                   |                      | 365                                      |
|                                     | ENT surgery \(n = 2\)           | 7                               | 1                               | 8                               | 1                   |                      | 866                                      |
|                                     | NIV \(n = 1\)                   | 5                               | 1                               | 1                               | 0                   |                      | 230                                      |

(Continues)
| Disease type        | Diseases                  | Intervention      | CAI at baseline (events per hr) | CAI at follow-up (events per hr) | PB% at baseline (%) | PB% at follow-up (%) | Days between baseline and follow-up P(S)G |
|---------------------|---------------------------|-------------------|---------------------------------|---------------------------------|---------------------|----------------------|------------------------------------------|
| Other               | Down syndrome (n = 5)     | CPAP (n = 1)      | 5                               | 8                               | 1                   | 11                   | 1,498                                    |
|                     |                           | ENT surgery (n = 1)| 6                               | 0                               | 7                   | 1                    | 196                                      |
|                     |                           | Cardiac surgery (n = 1) | 5                               | 0                               | 0                   | 0                    | 9                                        |
|                     |                           | None (n = 2)       | 7                               | 3                               | 1                   | 0                    | 294                                      |
|                     | Achondroplasia (n = 5)    | None (n = 2)       | 12                              | 7                               | 4                   | 2                    | 57                                       |
|                     |                           | ENT surgery (n = 2) | 6                               | 2                               | 0                   | 0                    | 210                                      |
|                     |                           | Cardiac surgery (n = 1) | 5                               | 1                               | 0                   | 0                    | 238                                      |
|                     |                           | None (n = 2)       | 6                               | 4                               | 0                   | 0                    | 412                                      |
|                     | Neuromuscular disease (n = 4) | ENT surgery (n = 2) | 23                              | 33                              | 10                  | 17                   | 244                                      |
|                     |                           | Neurosurgery (n = 1) | 20                              | 30                              | 9                   | 9                    | 568                                      |
|                     |                           | None (n = 2)       | 13                              | 60                              | 2                   | 3                    | 1,727                                    |
|                     | Mucopolysaccharidosis (n = 1) | Neurosurgery (n = 1) | 115                             | 1                               | 46                  | 1                    | 380                                      |
|                     |                           |                   | 12                              | 2                               | 4                   | 0                    | 177                                      |

Data are presented as mean ± standard deviation, or numbers.

CAI, central apnea index; CPAP, continuous positive airway pressure; CSA, central sleep apnea; ENT, ear nose and throat; NIV, non-invasive ventilation; NMD, neuromuscular disease; PB%, percentage of periodic breathing; P(S)G, poly(somno)graphy.
(23%) of the patients, with a spontaneous improvement over time in 20 patients. The treatment was individualized on a clinical basis. A watchful waiting (Tables 5 and S1) was chosen for patients whose disorder might improve with growth (i.e. Prader Willi syndrome; Cohen, 2014), or for patients with a likely growth-related improvement due to anatomical changes (i.e. Chiari type 1 malformation [Strahle, 2011], Down syndrome [Ferri, 1997], achondroplasia or Pierre Robin sequence).

Only two patients of the watchful waiting group increased their CAI; one was a patient with Rett syndrome who discontinued NIV before the follow-up P(S)IG, and the other had a complex malformative syndrome. Of the 55 patients with a follow-up P(S)IG, 20 were < 1 year old, and all presented a reduction of CAI, with a normalization of CAI (<5 events per hr) in 16 of them.

Our study presents some limitations. This is a single-centre retrospective study performed in a tertiary university hospital with the majority of patients presenting rare and complex underlying disorders, which may overestimate the prevalence of CSA. Most studies were PG and not PSG, which may underestimate central events and the time awake, and consequently the CAI and PB due to the absence of arousal scoring. The scoring of bradypnea was limited by the fact that most patients had moderate bradypnea without desaturations or arousals. Lastly, we selected exclusively patients with a CA syndrome; therefore, a possible generalization about PB in patients without CSA should be done judiciously.

In conclusion, CSA is a rare finding in children with underlying disorders and commonly associated with PB. A better description of the clinical and PSG phenotypes of these children, with a thorough analysis of central events, PB and bradypnea should help improving our understanding of the breathing abnormalities of these children, as well as their medical management.

AUTHOR CONTRIBUTIONS
Sergio Ghirardo collected data, performed and wrote the first draft of the manuscript. Alessandro Amaddeo and Lucie Griffon supervised the data collection and revised the first draft. Sonia Khirani performed data analysis and revised the manuscript. Brigitte Faurox designed the study and revised the final version of the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID
Sergio Ghirardo https://orcid.org/0000-0002-6329-4208
Sonia Khirani https://orcid.org/0000-0003-4163-5021

REFERENCES
Amaddeo, A., & Faurox, B. (2016). Oxygen and carbon dioxide monitoring during sleep. Paediatric Respiratory Reviews, 20, 42-44. https://doi.org/10.1016/j.prrv.2015.11.009
Amin, R., Sayal, P., Sayal, A., Massicote, C., Pham, R., Al-Saleh, S., Drake, J., & Naran, I. (2015). The association between sleep-disordered breathing and magnetic resonance imaging findings in a pediatric cohort with Chiari 1 malformation. Canadian Respiratory Journal, 22(1), 31-36. https://doi.org/10.1155/2015/831569
Beck, S. E., & Marcus, C. L. (2009). Pediatric Polysomnography. Sleep Medicine Clinics, 4(3), 393-406. https://doi.org/10.1016/j.jsmc.2009.04.007
Berry, R. B., Budhiraja, R., Gottlieb, D. J. et al (2012). Rules for scoring respiratory events in sleep: Update of the 2007 AASM manual for the scoring of sleep and associated events, American Academy of Sleep Medicine 8(5), 597–619.
Bin-Hasan, S., Khayat, A., Humpf, T., Reyes, J. T., & Al-Saleh, S. (2017). Resolution of periodic breathing in a child with idiopathic pulmonary arterial hypertension. Case Reports in Pediatrics, 2017, 1–5. https://doi.org/10.1155/2017/3280572
Bradley, T. D., McNicholas, W. T., Rutherford, R., Popkin, J., Zamel, N., & Phillipson, E. A. (1986). Clinical and physiologic heterogeneity of the central sleep apnea syndrome. American Review of Respiratory Disease, 134(2), 217–221. https://doi.org/10.1164/arrd.1986.134.2.217
Cohen, M., Hamilton, J., & Narang, I. Clinically important age-related differences in sleep related disordered breathing in infants and children with Prader-Willi syndrome. PLoS One, 9(6), e101012. https://doi.org/10.1371/journal.pone.0101012. eCollection 2014
Dauvilliers, Y., Stal, V., Abri, B. et al (2007). Chiari malformation and sleep related breathing disorders. Journal of Neurology, Neurosurgery & Psychiatry, 78(12), 1344-1348. https://doi.org/10.1136/jnnp.2006.108779
Dempsey, J. A., Smith, C. A., Przybylowski, T. et al (2004). The ventilatory responsiveness to CO 2 below eupnoea as a determinant of ventilatory stability in sleep Sleep effects on ventilatory control stability. Journal of Physiology, 560, 1-11. https://doi.org/10.1113/jphysiol.2004.072371
Dempsey, J. A., Veasey, S. C., Morgan, B. J., & O’Donnell, C. P. (2010). Pathophysiology of sleep apnea. Physiological Reviews, 90(1), 47–112. https://doi.org/10.1152/physrev.00043.2008
Driessen, C., Mathijssen, I. M. J., De Groot, M. R., & Joosten, K. F. M. (2012). Does central sleep apnea occur in children with syndromic craniosynostosis? Respiratory Physiology & Neurobiology, 181(3), 321–325. https://doi.org/10.1016/j.resp.2012.03.017
Eckert, D. J., Jordan, A. S., Merchia, P., & Malhotra, A. (2007). Central sleep apnea: Pathophysiology and treatment. Chest, 131(2), 595–607. https://doi.org/10.1378/chest.06.2287
Eichenwald, E. C. (2016). Apnea of prematurity. Pediatrics, 137, 1. https://doi.org/10.1542/peds.2015-3757
Felix, O., Amaddeo, A., Olmo Arroyo, J. et al (2016). Central sleep apnea in children: Experience at a single center. Sleep Medicine, 25, 24–28. https://doi.org/10.1016/j.sleep.2016.07.016
Ferri, R., Curzi-Dascalova, L., Del Gracco, S., Elia, M., Musumeci, S. A., & Stefanini, M. C. (1997). Respiratory patterns during sleep in Down’s syndrome: Importance of central apnoeas. Journal of Sleep Research, 6(2), 134–141. https://doi.org/10.1046/j.1365-2869.1997.00030.x
Finer, N. N., Barrington, K. J., & Hayes, B. (1992). Prolonged periodic breathing: Significance in sleep studies. Pediatrics, 89(3 SUPPL.), 450–453.
Flores-Guevara, R., Sternberg, B., Peirano, P., Guidasci, S., Durupt, N., & Monod, N. (1985). Respiratory pauses and periodic breathing assessed by cardio- pneumography in normal infants and in SIDS siblings. Neuropediatrics, 17(2), 59–62. https://doi.org/10.1055/s-2008-1052501
Franklin, K. A., Eriksson, P., Sahlin, C., & Lundgren, R. (1997). Reversal of central sleep apnea with oxygen. Chest, 111(1), 163–169. https://doi.org/10.1378/chest.111.1.163
Glotzbach, S. F., Baldwin, R. B., Lederer, N. E., Tansey, P. A., & Ariagno, R. L. (1989). Periodic breathing in preterm infants: Incidence and characteristics. Pediatrics, 84(5), 785–792.
Harman, K., Weichard, A. J., Davey, M. J., Horne, R. S. C., Nixon, G. M., & Edwards, B. A. (2020). Assessing ventilatory control stability
in children with and without an elevated central apnoea index. *Respirology*, 25(2), 214–220. https://doi.org/10.1111/resp.13606. Epub 2019 May 30

Hoch, B., & Barth, H. (2001). Cheyne-stokes respiration as an additional risk factor for pulmonary hypertension in a boy with trisomy 21 and atrioventricular septal defect. *Pediatric Pulmonology*, 31(3), 261–264. https://doi.org/10.1002/ppul.1037

Kelly, D. H., Stellwagen, L. M., Kaitz, E., & Shannon, D. C. (1985). Apnea and periodic breathing in normal full-term infants during the first twelve months. *Pediatric Pulmonology*, 1(4), 215–219. https://doi.org/10.1002/ppul.1950010409

Khan, A., Qurashi, M., Kwiatkowski, K., Cates, D., & Rigatto, H. (2005). Measurement of the CO2 apneic threshold in newborn infants: Possible relevance for periodic breathing and apnea. *Journal of Applied Physiology*, 98(4), 1171–1176. https://doi.org/10.1152/japplphysiol.00574.2003

Mahamed, S., & Duffin, J. (2001). Repeated hypoxic exposures change respiratory chemoreflex control in humans. *The Journal of Physiology*, 534(2), 595–603. https://doi.org/10.1111/j.1469-7793.2001.00595.x

Marks, M. K., South, M., & Carlin, J. B. (1993). Reference ranges for respiratory rate measured by thermistry (12–84 months). *Archives of Disease in Childhood*, 69(5), 569–572. https://doi.org/10.1136/adc.69.5.569

Mclaren, A. T., Bin-hasan, S., & Narang, I. (2019). Diagnosis, management and pathophysiology of central sleep apnea in children. *Paediatric Respiratory Reviews*, 30, 49–57. https://doi.org/10.1016/j.prrv.2018.07.005

Mahr, M. A., Fairchild, K. D., Patel, M., Sinkin, R. A., Clark, M. T., Moorman, J. R., Lake, D. E., Kattwinkel, J., & Delos, J. B. (2015). Quantification of periodic breathing in premature infants. *Physiological Measurement*, 36(7), 1415–1427. https://doi.org/10.1088/0967-3334/36/7/1415

Neubauer, J. A. (2001). Physiological and Genomic Consequences of Intermittent Hypoxia Invited Review: Physiological and pathophysiological responses to intermittent hypoxia. *Journal of Applied Physiology*, 840–847, 90, 1593-1599.

Orr, J. E., Malhotra, A., & Sands, S. A. (2017). Pathogenesis of central and complex sleep apnoea. *Respirology*, 22(1), 43–52. https://doi.org/10.1111/resp.12927

Peer, A., Lorber, A., Suraiya, S., Malhotra, A., & Pillar, G. (2010). The occurrence of Cheyne-Stokes respiration in congestive heart failure: The effect of age. *Frontiers in Psychiatry*, 1, 1–6. https://doi.org/10.3389/fpsyt.2010.00133

Poets, C. F., Stebbens, V. A., Alexander, J. R., & Southall, D. P. (1991). Breathing patterns and heart rates at ages 6 weeks and 2 years. *Archives of Pediatrics & Adolescent Medicine*, 145(12), 1393–1396. https://doi.org/10.1001/archped.1991.02160120061020

Reynolds, E. O. R. (1977). Hypoxia in the newborn infant. *Journal of Clinical Pathology*, S3–11. 134–141. https://doi.org/10.1136/jcp.s3-11.134

Sands, S. A., Edwards, B. A., Kee, K., Turton, A., Skuzu, E. M., Roebuck, T., O’Driscoll, D. M., Hamilton, G. S., Naughton, M. T., & Berger, P. J. (2011). Loop gain as a means to predict a positive airway pressure suppression of Cheyne-Stokes respiration in patients with heart failure. *American Journal of Respiratory and Critical Care Medicine*, 184(9), 1067–1075. https://doi.org/10.1164/rccm.201103-0577OC

Scholle, S., Wiater, A., & Scholle, H. C. (2011). Normative values of polysomnographic parameters in childhood and adolescence: Cardiorespiratory parameters. *Sleep Medicine*, 12(10), 988–996. https://doi.org/10.1016/j.sleep.2011.05.006

Stanchina, M., Robinson, K., Corrao, W., Donat, W., Sands, S., & Malhotra, A. (2015). Clinical use of loop gain measures to determine continuous positive airway pressure efficacy in patients with complex sleep apnea: A pilot study. *Annals of the American Thoracic Society*, 12(9), 1351–1357. https://doi.org/10.1513/AnnalsATS.201410–469BC

Stevens, D., Martins, R. T., Mukherjee, S., & Vakulin, A. (2018). Post-stroke sleep-disordered breathing—pathophysiology and therapy options. *Frontiers in Surgery*, 5. https://doi.org/10.3339/fsurg.2018.00009

Strahle, J., Muraszko, M., Kapurch, J., Bapuraj, J. R., Garton, H. J. L., & Maher, C. O. (2011). Natural history of Chiari malformation Type I following decision for conservative treatment. *Journal of Neurosurgery: Pediatrics*, 8(2), 214–221. https://doi.org/10.3171/2011.5.PEDS1122

Tenconi, R., Khirani, S., Amaddeo, A., Michot, C., Bajuat, G., Coulouigner, V., De Sanctis, L., James, S., Zerah, M., Cormier-Daire, V., & Faurox, B. (2017). Sleep-disordered breathing and its management in children with achondroplasia. *American Journal of Medical Genetics Part A*, 173(4), 868–878. https://doi.org/10.1002/ajmg.a.38130

Tinoco, A., Drew, B. J., Hu, X., Mortara, D., Cooper, B. A., & Pelter, M. M. (2017). ECG-derived Cheyne-Stokes respiration and periodic breathing in healthy and hospitalized populations. *Annals of Noninvasive Electrocardiology*, 22(6), e12462. https://doi.org/10.1111/anec.12462

Urquhart, D. S., Gulliver, T., Williams, G., Harris, M. A., Nyunt, O., & Suresh, S. (2013). Central sleep-disordered breathing and the effects of oxygen therapy in infants with Prader-Willi syndrome. *Archives of Disease in Childhood*, 98(8), 592–595. https://doi.org/10.1136/archdischild-2012-303441

Urquhart, D. S., & Tan, H. L. (2016). Sleep disordered breathing at the extremes of age: Infancy. *Breathe*, 12(1), e1-e11. https://doi.org/10.1183/20734735.001016

Xie, A., Rutherford, R., Rankin, F., Wong, B., & Bradley, T. D. (1995). Hypocapnia and increased ventilatory responsiveness in patients with idiopathic central sleep apnea. *American Journal of Respiratory and Critical Care Medicine*, 152(6), 1950–1955. https://doi.org/10.1164/ajrccm.152.6.8520761

Zhao, J., Gonzalez, F., & Mu, D. (2011). Apnea of prematurity: From cause to treatment. *European Journal of Pediatrics*, 170(9), 1097-1105. https://doi.org/10.1007/s00431-011-1409-6

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.