REVIEW ARTICLE

Investigation and management of childhood sleep apnoea

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Abstract
Sleep-disordered breathing includes disorders of breathing that affect airway patency, e.g. obstructive sleep apnoea syndrome, and also conditions that affect respiratory drive (central sleep disorders) or cause hypoventilation, either as a direct central effect or due to peripheral muscle weakness.
Obstructive sleep apnoea syndrome (OSAS) is an increasingly-recognised clinical entity affecting up to 5.7% of children, which, if left untreated, is associated with adverse effects on growth and development including deleterious cognitive and behavioural outcomes. Evidence exists also that untreated OSAS impacts on cardiovascular risk. Close attention should be paid to assessment and investigation of this relatively common condition, instigating early and appropriate treatment to children with OSAS. First-line treatment in younger children is adenotonsillectomy, although other treatment options available include continuous positive airways pressure (CPAP), anti-inflammatory therapies (nasal corticosteroids and anti-leukotrienes), airway adjuncts and orthodontic appliances.
Central sleep-disordered breathing may be related to immaturity of respiratory control and can be associated with prematurity as well as disorders such as Prader-Willi syndrome. In some cases, central apnoeas occur as part of a central hypoventilation disorder, which may be inherited, e.g. Congenital Central hypoventilation Syndrome, or acquired, e.g. Arnold-Chiari malformation, brain tumour, or spinal injury. The treatments of central breathing problems depend upon the underlying aetiology.Hippokratia 2013; 17 (3): 196-202

Keywords: Sleep-disordered breathing, obstructive sleep apnoea syndrome, OSAS, cognition, polysomnography, adenotonsillectomy, continuous positive airways pressure, CPAP

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Introduction

Sleep-disordered breathing in children incorporates disorders of breathing that relate to airway patency (obstructive sleep apnoea syndrome) and also conditions which affect respiratory drive (central sleep disorders) or cause hypoventilation, either as a direct central effect or secondary to peripheral muscle weakness. This review aims to describe the aetiology, presentation and sequelae of OSAS, as well as reviewing the diagnostic tests available. Central apnoeas and central sleep-disordered breathing will be briefly reviewed.

Definition of respiratory events during sleep in children

Events during sleep are scored using the American Academy of Sleep Medicine (AASM) manual for the scoring of sleep and associated events[1].

An obstructive event is one where respiratory effort continues in spite of reduction or cessation of airflow. An obstructive apnoea in children is scored if the event is associated with an absence (or >90% reduction) of airflow that lasts for 2 or more missed breaths and is associated with maintained (or increased) inspiratory effort[1,2]. An obstructive hypopnoea is described as having a >30% reduction in airflow signal and also lasts for 2 or more missed breaths with preservation of respiratory effort[1,2]. An obstructive hypopnoea needs to be associated with a physiological consequence, namely an arousal, an awakening or a ≥3% fall in oxygen saturations (SpO_2) in order to be scored[1,2]. An example of a sleep study demonstrating obstructive events is given in Figure 1.

A central event is associated with an absence or reduction in both effort and airflow.

A central apnoea is an event associated with absent inspiratory effort and an absence (or >90% reduction) of airflow lasting for > 20 seconds duration, or lasting for ≥2 missed breaths and associated with a physiological consequence (arousal, awakening, a ≥3% fall in SpO_2 or, in infants, bradycardia)[1,2]. A central hypopnoea is scored when a 30% reduction in airflow associated with concurrently reduced inspiratory effort lasting ≥2 missed breaths occurs in association with a physiological consequence[1,2]. An example of a sleep study demonstrating central events is shown in Figure 2.

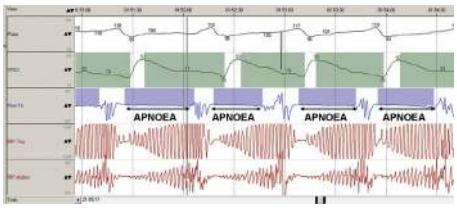

Figure 1: Obstructive events during sleep measured using limited-channel polysomnography (Source: Sleep Laboratory, Royal Hospital for Sick Children, Edinburgh).
SpO_2: Arterial oxygen saturations measured by pulse oximetry, Flow Th: Airflow measured by thermistor, RIP Thorax: Thoracic respiratory effort measured by inductance plethysmography, RIP Abdomen: Abdominal respiratory effort measured by inductance plethysmography.

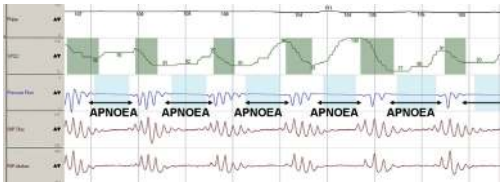

Figure 2: Central events during sleep measured using limited-channel polysomnography (Source: Sleep Laboratory, Royal Hospital for Sick Children, Edinburgh).
SpO_2 : Arterial oxygen saturations measured by pulse oximetry, Flow Th: Airflow measured by thermistor, RIP Thorax: Thoracic respiratory effort measured by inductance plethysmography, RIP Abdomen: Abdominal respiratory effort measured by inductance plethysmography.

Obstructive sleep apnoea syndrome

Obstructive sleep apnoea syndrome (OSAS) is a phenomenon of repeated, episodic reduction or cessation of airflow (hypopnoea/apnoea) as a result of upper airways obstruction. Respiratory effort is preserved or increased at times of apnoea, as the subject attempts to overcome obstruction. OSAS may occur as a result of enlarged tonsils and adenoids[3],be related to airway(s) anatomy for example in those with Pierre-Robin sequence[4], airway(s) tone as in children with muscular weakness[5], or exogenous tissue around the airways in those with obesity[6].

OSAS in children is a common condition affecting up to 5.7% of children[3], and one which carries significant morbidity with deleterious effects on cognition and development[7-12], growth[3], and possibly later cardiovascular risk[13,14].

Presentation of OSAS

Although it is estimated that up to 1 in 7 children snore[15], the numbers with OSAS are estimated at up to 5.7%.[3] The role of history taking as a means of predicting those with OSAS is limited at discriminating those with OSAS from those with primary snoring[16], with recent work on the Paediatric Sleep Questionnaire concluding that the questionnaire can predict sleep study results 'to an extent that is useful for research, but not reliable enough for most individual patients'[17].

Even with those caveats, history-taking is the cornerstone of diagnosis as in any medical condition. Questions on sleep pattern at night are important, including enquiring about snoring, work of breathing (restlessness, sweatiness, and faltering growth), and mouth breathing (whether child sleeps with mouth open, and whether thirsty in the mornings) and the presence of apnoea. The question of whether a child stops breathing is a poor discriminator of apnoea, and is better phrased by asking whether a child sounds 'strangled' during sleep, or whether a period is noted where the child's breathing goes quiet that is then overcome by a gasp. Those with OSAS are more likely than primary snorers to have been witnessed to have an apnoea ($p=0.01$), to have been noticed to be struggling to breathe ($p<0.01$), to have been shaken by parents in order to restart breathing ($p=0.01$) or to have daytime mouth breathing ($p<0.05$)[16].

Questions on daytime functioning are also important, in particular whether any concentration or behaviour problems have been noted. Somnolence is less important in childhood OSAS, in contrast with adults who fall asleep during the day.

Examination findings are directed at examining the tonsils and grading their size (0-4) in accordance with the standardised tonsillar hypertrophy grading scale proposed by Brodsky[18], as well as assessing the nose for mucosal inflammation, turbinate size, septal position, presence of polyps and nasal airflow. The nose may be directly auscultated with the stethoscope or a disposable mirror used to see whether it mists up in association with nasal exhalation[19]. Adenoid size may be assessed directly by either nasoendoscopy or by transoral mirror examination[20]. Mid-face hypoplasia or the "adenoidal facies" may be apparent in chronic OSAS. *Pectus excavatum* secondary to chronic sternal recession is rarely seen nowadays.

Another important aspect of examination is to assess for co-morbidities (obesity, Down syndrome, cleft palate, neuromuscular disease, etc.) and to formally plot growth. Growth is important to measure as OSAS may be a cause of faltering growth[3], whilst obesity is a clear precipitant for OSAS[6].

Investigation of OSAS in children

A variety of modalities exist that may help to make the diagnosis of OSAS. These are briefly discussed.

Polysomnography

The internationally-recognised gold-standard investigation is an attended, night-time, in-laboratory polysomnography (PSG)[3]. PSG utilises electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG) channels to distinguish sleep from wake, and to facilitate sleep staging. In addition, arterial oxygen saturations measured by pulse oximetry (SpO_2) and heart rate are measured, along with airflow (via nasal cannulae or thermistor) which allows detection of apnoea and/or hypopnoea, and respiratory effort which is quantified by inductance plethysmography measured via thoracic and abdominal bands. Thus, obstructive apnoea (effort maintained/increased) can be distinguished from central apnoea (cessation of both effort and airflow)[1]. End-tidal ($etCO_2$) or transcutaneous ($tcCO_2$) measures of carbon dioxide are also made to assess for hypoventilation[1].

The undertaking of PSG requires resources in terms

of time and also personnel to supervise the study. Attempts have been made to do snap-shot PSG studies during daytime sleeps, or so-called 'nap studies'. Whilst these have an excellent positive predictive value (100%) in diagnosing OSAS, their negative predictive value is poor – 20%[21]. OSAS is likely to be worse during rapid-eye movement (REM) sleep, as airway tone falls in REM making obstruction manifest. REM sleep occurs later in the night – i.e. OSAS worsens as the night goes on, and may be missed in a short daytime nap.

The measurement of respiratory events (apnoeas and hypopnoeas) allows one to quantify severity of OSAS in children. The combined number of apnoeas and hypopnoeas per hour is known as the Apnoea/Hypopnoea Index (AHI). An AHI>1 is considered abnormal[22], with normative data demonstrating that AHI values > 1/hour are abnormal[23,24] and many recent studies have considered OSAS to be present when AHI is >1 event per hour[10, 25].

Currently there are no universally accepted guidelines as to when children's OSA is sufficiently severe as to warrant treatment. An AHI >1 is regarded as abnormal with treatment recommended for any child with an AHI >5[26]. Severe childhood OSAS is defined as having an AHI >10 events per hour[27]. How to proceed is less clear in children with AHIs between 1 and 5[26]. Table 1 illustrates the correlation of AHI and OSAS severity.

Table 1: Relationship between apnoea/hypopnoea index (AHI) and severity of obstructive sleep apnoea syndrome (OSAS).

AHI (Events/hour)	OSAS Severity
AHI <1	Normal
AHI ≥1 and ≤5	Mild OSAS
AHI >5 and ≤10	Moderate OSAS
AHI >10	Severe OSAS

AHI: Apnoea/Hypopnoea Index, OSAS: Obstructive Sleep Apnoea Syndrome.

Limited channel polysomnography

Many centres (our own included) undertake cardiorespiratory sleep studies with video camera, effort bands, airflow measures, heart rate and SpO_2 +/- $tcCO_2$ monitoring. This allows confident detection of apnoea, delineation between central and obstructive events, and quantification of the degree of ensuing hypoxia. An AHI can be generated from such studies, enabling one to embark on an appropriate treatment course.

It has been demonstrated that technically-adequate data can be achieved using such limited channel recordings[28]. Sleep stage and the amount of sleep fragmentation can only be speculated upon however, unless a full PSG is performed. Cardiorespiratory studies may be undertaken at home[28] or in hospital.

Oximetry as a single-channel recording

As alluded to above, OSAS is worst during REM sleep, as airway tone is reduced in REM which promotes obstruction. Therefore, there may be periods of sleep where airflow and gas exchange are relatively stable, along with periods (REM) where obstruction is at its' worst. The SpO_2 trace from the overnight hypnogram of the study shown below (Figure 3) illustrates how an oximetry may appear in a child with OSA.

Oximetry relies on changes in SpO_2 as surrogate measures for obstructive events and no direct measure of effort or airflow is made.

The utility of oximetry alone in the detection of OSA has been demonstrated to have limitations. Brouillette and colleagues showed that whilst oximetry is highly specific (98%), it has a sensitivity of only 43%[29]. The positive predictive value of an abnormal oximetry for diagnosing OSA was 97%, suggesting 3% cases where oximetry is abnormal are due to central apnoea. The negative predictive value (value of a negative oximetry in excluding OSA) was only 47%[29], roughly the equivalent of tossing a coin.

Later work from Kirk and colleagues[30] also compared overnight oximetry with PSG and showed sensitivity to be 67% and sensitivity 60% in the detection of moderate OSAS (AHI >5), and they too concluded that oximetry alone is inadequate for the diagnosis of OSAS. This is partly because children may have significant OSAS with arousal and sleep fragmentation but little desaturation, and also because movement artefact can give rise to apparent desaturations when none are occurring[3].

Clinical implications of OSAS

The sequelae of each obstructive event are such that a consequence of the event, namely a desaturation, an arousal or an awakening may occur. Repeated arousals and awakenings are associated with sleep fragmentation which it is thought may be a mechanism by which OSA is associated with delayed growth and development[26].

It is during REM sleep that memory consolidation is postulated to occur[31], such that the sleep fragmentation may affect cognition; whilst Growth Hormone is produced in slow wave sleep[32] and its' secretion may be interrupted by fragmented sleep. The increase in work of breathing to overcome obstruction and its' consequent calorie demand are a further mechanism by which OSA impacts growth.

It has been shown across a number of studies that childhood OSA is associated with a negative effect on cognition and behaviour,[7-9,33,34] and that relief of obstruction is accompanied by improvements in learning.[7,33] Several studies highlight the deleterious relationship of OSA and cognitive performance,[8,9,33] with IQ suggested to be up to 10 points lower than the healthy population even in those with mild OSA.[9] Furthermore, increased rates of inattention and hyperactivity[33] and difficulties with peer interaction and emotional lability[34] are also reported in children with OSA.

Known risk factors for cardiovascular disease in adulthood include hypertension and inflammation. The effects of desaturations and arousals are known to stimulate the sympathetic nervous system with an adrenaline surge and a transient rise in blood pressure. This is a frequent and oft-repeated insult in those with OSA and over time acts as a promoter of systemic hypertension, such that OSA has become an increasingly-recognised cause of adult hypertension[35]. Furthermore, OSA is pro-inflammatory with elevations in C reactive protein (CRP) reported in both adults[36] and children[37], with

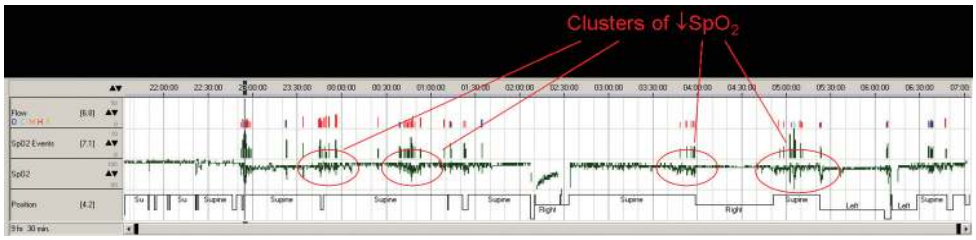

Figure 3: Overnight oximetry findings in a child with OSAS (Source: Sleep Laboratory, Royal Hospital for Sick Children, Edinburgh). SpO_2 : Arterial oxygen saturations measured by pulse oximetry.

OSA, whilst an animal model of intermittent hypoxia and hypercapnia (mimicking OSA) resulted in increased levels of interleukin-6 (IL-6), a precursor of CRP production[38]. Levels of CRP are reported to fall with successful treatment of OSAS[36,39]. CRP is used by the American Heart Association to stratify risk for ischaemic heart disease[40], and has also been shown to correlate with measures of radial artery stiffness and carotid artery intimal thickness in children[41]. In addition, endothelial dysfunction has been demonstrated to be present in a childhood OSAS population[14,42] Thus, it seems plausible that childhood OSAS is a risk factor for later cardiovascular risk. In extreme cases of OSAS, right heart strain and development of *cor pulmonale* have been known to occur[43].

Therefore, there is evidence from animal and human studies that support a deleterious effect of untreated OSAS on a number of key areas including cognition and behaviour, pulmonary hypertension and the potential for later public health consequences of increased cardiovascular risk.

Treatment of childhood OSAS

The mainstay of treatment of OSA is surgical (adenotonsillectomy), although respiratory support with CPAP, medical treatments and the use of airway adjuncts will also be briefly discussed.

Adenotonsillectomy

Adenotonsillectomy (AT) is the recommended first line treatment for childhood OSA.[3] Studies have shown significant improvement in obstruction on follow-up sleep studies[7,44], as well as improvements in quality of life[44], behaviour[44], and school performance[7] following surgical intervention. Following AT, improvement in OSAS is reported to occur in 75-100% children[15], though a multicentre review of 578 children who underwent AT for OSAS reported that although undoubted improvement was noted (AHI falling from 18/hour pre-surgery to 4/hour after AT), complete resolution of OSA (<1 event per hour) was achieved in only 27%[25]. Obese children have been reported as having less satisfactory results following AT[45], with body mass index (BMI) reported as an independent demographic factor that influences AHI post-AT[25]. Other groups with lower success rates following AT include children with Down Syndrome[6,46].

The benefit of AT on ameliorating obstruction is clear with consequential benefits on growth, behaviour and school performance[7,33]. For a some children however, obstruction may persist or recur and careful counselling of parents or carers is required pre-operatively as in some patients other means to alleviate airway obstruction may need to be considered. Such treatments include continuous positive airways pressure (CPAP) therapy, anti-inflammatory therapies, as well as airway adjuncts such as nasopharyngeal airways or orthodontic appliances.

Continuous positive airways pressure (CPAP)

The rationale for CPAP is that one applies a continuous positive airways pressure (CPAP) via a face-mask or nasal mask during sleep[47], pushing upper airway tissues apart to splint the airway open, allowing relief of obstruction, whilst maintaining normal gas exchange and preserving sleep quality. CPAP is instituted in hospital with a team of nurses, play therapists, medical staff and of course parents involved; and sleep studies are undertaken to titrate CPAP pressures to the patients' needs.

CPAP has been used with success in those with obesity and OSAS. Although some children will have obesity hypoventilation and require bi-level support, for those with OSAS and obesity the evidence suggests benefit for CPAP therapy[3]. A study of 29 children that were treated with either CPAP or bi-level support in whom almost 2/3 were obese reported a fall in mean AHI from 27/hour to 3/hour with respiratory support[48]. Children with Down Syndrome who did not improve with adenotonsillectomy, whilst representing a challenging group, are a group who are likely to benefit CPAP[49,50].

Anti-inflammatory treatments

There is some published work on the role of anti-inflammatory agents in the modification of mild OSA, namely topical nasal steroids[51] and also the anti-leukotriene inhibitor, Montelukast[27,52]. Both types of treatment are thought to work by reducing the size of lymphoid tissue, especially adenoids. Small studies report modest benefits in sleep disturbance over the short-term with each of these treatments.

Airway adjuncts

Obstruction frequently occurs in babies with Pierre-Robin sequence due to a small chin (micrognathia) as well as a posteriorly-placed tongue. A nasopharyngeal airway (NPA) fashioned from an endotracheal tube (ETT) is often used to bypass upper airways obstruction in this patient group[53], with the tip of the ETT lying above the laryngeal apparatus. The use of NPAs in older children is limited, but in some children with severe hypotonia and airway obstruction during sleep, such airway adjuncts can be very effective.

Orthodontic appliances, such as mandibular advancement splints, have also been advocated in some centres as

a means of countering the effects of skeletal dysmorphology on airway anatomy.[54]

Other surgical options

There is some evidence supporting rapid maxillary advancement surgery on having benefit on both signs and symptoms of OSAS and also AHI[55-57] in childhood populations. Tracheostomy, whilst effective, is considered a last resort because of its associated significant morbidity.

Central apnoea in children

Central apnoeas represent absences of airflow that are accompanied by an absence of respiratory effort. Infrequent central apnoeas are found in normal children[23,24,58-60], in particular following a sigh[58]. There are some cases where the number of central apnoeas and/or the gravity of associated desaturations are felt to be pathological. Such patterns may be related to immaturity of respiratory control and are associated with prematurity[61] as well as certain medical conditions, such as Prader-Willi syndrome[62]. Finally, some children will have central apnoeas as part of a central hypoventilation disorder, causes for which may be inherited (Congenital Central hypoventilation Syndrome)[63] or acquired (for example as a consequence of an Arnold-Chiari malformation[64,65], brain tumour[66], or spinal injury[67]).

Investigation of central apnoeas in children

In cases of central apnoea, polsomnography with capnometry is recommended[68]. Measures of flow, effort and SpO_2 allow the number and the effect of central apnoeas to be quantified. In addition, simultaneous monitoring of CO_2 (via transcutaneous or end-tidal methods) allows for assessment of hypoventilation in those with central sleep-disordered breathing.

Treatment of central apnoeas in children

A variety of treatments including pharmacological therapies (methylxanthines, acetazolamide), oxygen and ventilator support may be used in the treatment of childhood central apnoea. Each of these, is briefly discussed.

Methylxanthines

Methylxanthines (Caffeine and Theophyllines) have been used mainly for treatment of central apnoeas in premature infants. A recent meta-analysis spanning 5 trials and a total of 192 babies reported a reduction in apnoeas as well as a reduced need for ventilation in the first week of life[69]. The use of these agents has been extrapolated to older children with central apnoeas, though little evidence other than a small number of reported cases[70] exists to support this strategy.

Acetazolamide

There is some evidence for the use of Acetazolamide as a treatment for central apnoea[71,72]. Acetazolamide is a carbonic anhydrase inhibitor which blocks reabsorption of bicarbonate in the proximal tubule. It causes a metabolic acidosis, and it is this change in pH which stimulates ventilation. Thus it is reported that the hypercapnic ventilatory response to CO_2 is left-shifted i.e. ventilation is stimulated at a lower CO_2 level[73].

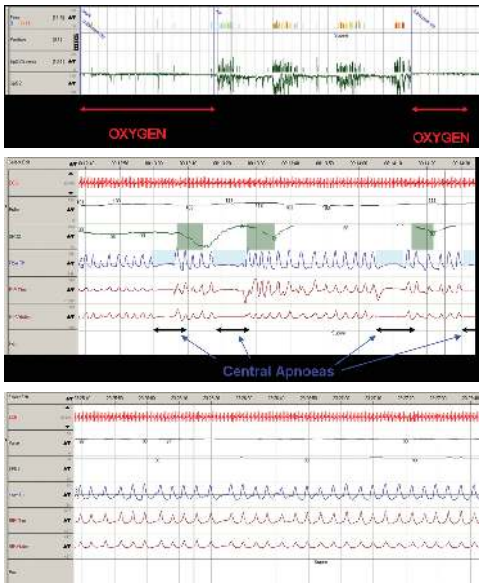

Figure 4: a) Response of repeated central apnoeas to oxygen treatment, b) In air, c) In oxygen at 0.25 L/minute (Source: Sleep Laboratory, Royal Hospital for Sick Children, Edinburgh).
ECG: Electrocardiogram, SpO_2: Arterial oxygen saturations measured by pulse oximetry, Flow Th: Airflow measured by thermistor, RIP Thorax: Thoracic respiratory effort measured by inductance plethysmography, RIP Abdomen: Abdominal respiratory effort measured by inductance plethysmography.

Oxygen

It is known that periodic breathing can be induced under hypoxic conditions in babies[61] and also in adults[74], whilst oxygen therapy in babies has been shown to lead to abolition of periodic breathing[75] and abolition of periodic breathing[76]. A reduction in central apnoeas following oxygen treatment is also reported in infants with Prader-Willi syndrome[62]. Figure 4 (a,b,c) shows a split night sleep study of a child with idiopathic central sleep-disordered breathing in whom a good response to oxygen treatment was observed.

Ventilation

In some cases of central sleep-disordered breathing, apnoea is accompanied by hypoventilation. Such cases require the institution of bi-level ventilatory support with a back-up rate in order to restore normal gas exchange during sleep. As discussed above, causes may be congenital or acquired. Figure 5 (a,b) illustrates a sleep study undertaken on a boy who had undergone cranial irradiation following resection of a posterior fossa tumour. Gas exchange was normalised following the institution of non-invasive bi-level ventilation.

Conclusion

The short-term effects of undetected sleep-disordered breathing in children include detrimental effects on school performance, behaviour, and cognition. Effects in later life affecting cardiovascular risk are also suggested. The stakes are high, as it is the future health and behaviour of our children that we are dealing with. Successful treatments are

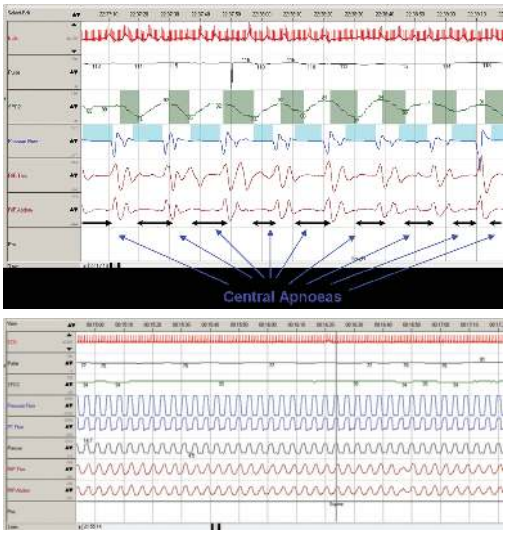

Figure 5: Illustration of central hypoventilation in association with an intracerebral tumour a) Prior to commencing ventilatory support, b) On ventilation (Source: Sleep Laboratory, Royal Hospital for Sick Children, Edinburgh).
ECG: Electrocardiogram, SpO_2: Arterial oxygen saturations measured by pulse oximetry, Flow Th: Airflow measured by thermistor, RIP Thorax: Thoracic respiratory effort measured by inductance plethysmography, RIP Abdomen: Abdominal respiratory effort measured by inductance plethysmography.

readily available. Being mindful of sleep apnoea, taking an appropriate history, and undertaking to investigate and treat appropriately, will all serve to minimise the disease burden of this important group of conditions.

Conflict of interest

There are no conflicts of interest to declare.

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