APNEA IN PRETERM NEONATES: A REVIEW

Estefania Rodriguez, MD¹, Rita P. Verma, M.D., F.A.A.P.²

¹Resident Physician, Department of Pediatrics, Nassau University Medical Center, 2201 Hempstead turnpike, East Meadow, NY 11554

²Rita P. Verma, M.D., F.A.A.P., Attending Neonatologist, Professor of Clinical Pediatrics, Nassau University Medical Center, 2201 Hempstead turnpike, East Meadow, NY 11554

Conflicts of Interest: Nil
Corresponding author: Rita P. Verma

Abstract:
Apnea of prematurity (AOP) is one of the commonest clinical conditions encountered in preterm infants. With decreasing limit of neonatal viability the subject has become of increasing importance to neonatologists. AOP is a developmental maladaptation to extra uterine life secondary to immature neurological control of breathing. It occurs in 100% cases of extremely low gestational age neonates and in over 50% of all preterm infants. AOP may be associated with adverse outcomes, such as, neurodevelopmental deficits, bronchopulmonary dysplasia and retinopathy of prematurity, although its independent contribution to these morbidities is not fully defined due to the confounding effects of concurrent neonatal pathologies. In this review we have presented the current information on the various aspects of AOP, including its definition, classification, etiopathogenesis, clinical-pathophysiological characteristics, management, discharge criteria and potential relationship with post discharge adverse events.

INTRODUCTION

Apnea of prematurity (AOP), reflecting a deficiency in adaptation to extra uterine life consequent to immature control of breathing, is encountered in premature infants admitted to neonatal intensive care units (NICUs) around the world. It is present in approximately 50% of all preterm neonates and in almost 100% of infants who are born at <28 weeks of gestational age (GA) or with a birth weight that does not surpass 1000 grams.¹² The incidence of AOP has an inverse relationship with maturation and at 34 weeks of GA approximately 20% of infants may present with the symptoms ³(Figure 1). A genetic predisposition to AOP has been described by Bloch-Salisbury et al who determined the heritability to be 87% among same-gender twins.⁴

AOP may be directly or indirectly associated with significant long term adverse outcomes. As the survival of more prematurely born infants has increased over the past few decades, the understanding and management of the condition has become of vital importance to neonatologists.⁵⁻⁶ The associated hypoxia and consequent exposure to intermittent supplemental oxygen have been implicated in adverse neurological sequelae and other long-term complications, such as retinopathy of prematurity and bronchopulmonary dysplasia.⁷ However, as the morbidity is inherently directly related to prematurity, it is difficult to establish its primary contribution to such outcomes. Infants who are born at <28 weeks of gestation or suffer from BPD exhibit delayed resolution of AOP and both of these clinical conditions are known to have independent associations with poor neurodevelopment. According to the functional maturation data of preterm infants AOP may resolve only after 44 weeks postmenstrual age (PMA) ²,⁸ and longer duration of apnea in days,
as well as resolution of episodes at more than 36 weeks of PMA are reported to be associated with worse neurodevelopmental outcomes.9-11

DEFINITION AND CLASSIFICATION

Apnea of prematurity refers to apnea that occurs in preterm infants and which usually resolves by 37 weeks of postmenstrual age, whereas, apnea of infancy refers to pathologic apnea that begins in newborns of more than 37 weeks of gestational age. Over the years several variations in the definitions have been forwarded, while a single definition has not been established. The most widely used definition is a pause in breathing for 20 seconds or longer; or a shorter pause which is associated with bradycardia, oxygen desaturation, cyanosis, pallor, abnormal movements and change in muscle tone in infants < 37 weeks of gestation. A drop in heart rate below 100 beats per minute while awake and arterial oxygen saturation (SaO2) < 85% are adjudged as bradycardia and oxygen desaturation and are significant components of AOP in preterm infants.11

Based on the origin of apnea as a neurological deficiency in central nervous or of peripheral neuromuscular control, AOP has been classified as central or obstructive. Central apnea refers to cessation in breathing with no airflow and no chest movements that will indicate respiratory efforts, whereas, obstructive apnea presents with no airflow but irregular, ineffective chest movements suggesting obstruction to air movement. This might happen due to the floppiness and hypotonia of hypo pharyngeal muscles, which prolapse into the airway lumen with negative pressure generated during inspiration, or secondary to an over flexed or extended neck positioning. The third category and the most common one is mixed, which involves a combination of both central and obstructive apneas. These are events in which obstructed airflow results in a central apneic pause, or a central apneic pause results in airflow obstruction (Figure 2). These classifications have implications in management decisions. Mixed apnea may be present in about 50% of all cases of AOP, whereas, about 40% are central apneas, and the rest 10% obstructive in nature. These three categories are inherently interrelated, and documentation of reduced electromyographic activity in the diaphragm during spontaneous obstructed inspiratory efforts suggest that decreased respiratory center output to the respiratory muscles is the common pathway in both central and mixed apneic episodes.12

EPIDEMIOLOGY AND RELATION TO SUDDEN UNEXPECTED INFANT DEATH

AOP is present in almost 100% of infants born before 28 weeks of gestational age and its incidence decreases with increasing gestational age. Henderson-Smart et al reported an incidence of 85% in premature infants born at 30 weeks, with subsequent decrease to 20% in those born at 34 weeks.13 Virtually all premature infants have a risk for apnea and require close cardiorespiratory monitoring. This study further revealed that 92% of infants presented with resolution of AOP by 37 weeks of postmenstrual age, while 98% of infants underwent resolution by 40 weeks of postmenstrual age.13 Home monitoring evaluation studies have determined that significant apnea bradycardia or desaturations may occur post discharge, decreasing significantly only after 43 weeks of post menstrual age.14 Even though prematurely born infants are reported to have a higher risk for sudden unexpected infant death (SUID) no causal association has been established between the two entities.3 Epidemiologically and clinically AOP is resolved in almost all cases by 43 weeks of PMA, which is earlier than the established age for SUID of 53 weeks in term and 47 weeks in extremely low gestational age infants of 24-28 weeks.13,14 Home monitoring does not prevent SUID and is not recommended for its prevention, although it may be used in selected cases at the discretion of the caretaking physician.14

PATHOPHYSIOLOGY

AOP consists of an unstable breathing pattern that reflects immaturity of the respiratory system and resultant maladaptation to extra uterine life. Several factors play roles in the development of AOP, including central nervous system (CNS) respiratory control, positional and anatomical proclivity to airway obstruction, and difficulty in coordinating sucking and swallowing with respiration (table 1).
Respiratory control

The brain in preterm infants is poorly myelinated and has fewer, immature neuronal connections as well as chemoreceptors. These lead to either limited or exaggerated responses to airway stimulation, along with hypoxemia and hypercapnia.

Increased function of peripheral chemoreceptors: Peripheral chemoreceptors, located in the carotid bodies in the bifurcation of the carotid arteries in thorax, play the most important part in regulating breathing in response to hypoxia. They act as the sensors for changes in blood levels of pH, pCO₂ and pO₂. Under conditions of decreased blood pO₂ or pH, and increased pCO₂ levels, the chemoreceptors are activated and centrally stimulate respiration via 9th and 10th cranial nerves. Activity of these chemoreceptors is increased in neonates compared to adults, reportedly because neonates have decreased levels of O₂ in blood.

Peripheral chemoreceptors have a very high firing threshold; however, their response becomes rampant once a certain level of pO₂ is reached. Changes in arterial pO₂ have zero to little response until its level drops below 100 mmHg. At this point the firing rate increases exponentially and small changes in oxygenation might result in big changes in ventilation. Small increases in oxygen may also trigger apneic episodes in the neonate once the threshold is met. Preterm neonates display a biphasic response to hypoxia with an initial hyperventilation followed by hypoventilation and apnea. This biphasic response can persist up to 38 weeks of post menstrual age and is alleged to play role in apneas which continue beyond 37 weeks.

Decreased function of central chemoreceptors: Central chemoreceptors, located in the medulla, are responsible for the hypercapnic ventilatory response. These respond to the levels of CO₂ in blood by increasing minute ventilation and are the main promoters of regular respiratory pattern. Having decreased function of these chemoreceptors, premature infants require higher levels of CO₂ in order to trigger a ventilatory response, which in turn is also influenced by levels of O₂ in blood. As opposed to adults in who CO₂ response increases in the presence of hypoxemia, the positive ventilatory response to high blood CO₂ level becomes blunted and attenuated under conditions of low pO₂ in premature infants. This leads to apnea and worsening hypoxemia and hypercapnia. Furthermore, chest wall activity increases linearly during efforts to initiate breathing while the response of upper airway muscles to hypercapnia may be weak, absent or delayed. This results in upper airway instability and obstructed inspiration after a period of central apnea as is commonly seen in mixed apneic episodes.

Hyper activated laryngeal chemoreceptors: Laryngeal chemoreceptors are located in the laryngeal mucosa and their main function is to protect the airway from aspiration. They are stimulated by mechanical or chemical triggers via superior laryngeal nerve afferents and lead to inhibition of breathing, resulting in periods of apnea with bradycardia and hypotension. Preterm neonates have exaggerated inhibitory responses and poor coordination of upper airway muscles, both of which promote apnea. This reflex is of particular importance as it is thought to be the cause for apneic episodes triggered by feeding or presence of regurgitated food material in oropharynx. However, it is demonstrated that apnea may precede rather than follow gastroesophageal reflux. Despite numerous studies, the association of gastroesophageal reflux disease (GERD) with AOP has not been established and anti-reflux medications have no role in its treatment or prevention. Hypoxia and apnea are shown to be accompanied by a reduction in lower esophageal sphincter pressure, which may predispose to gastroesophageal reflux. Sensory input from these upper airway receptors travels to the CNS by means of cranial nerves V, VI, IX, X, XI, and XII. They may strongly affect respiratory rate and rhythm, heart rate, and vascular resistance. With maturation, apneic episodes secondary to laryngeal chemoreceptor activation are decreased.

Decreased apnea threshold: The major drive for ventilation comes from CO₂ concentration of blood which acts on central brainstem receptors and to some extent peripheral chemoreceptors located in the carotid and aortic bodies.
pCO2 apneic threshold, defined as the minimal level of CO2 required to maintain respiration, is lower in preterm neonates compared to adults and the difference between pCO2 levels for eupnea and apnea is very narrow. This translates into vulnerability to and higher risk for breathing instability and apneic episodes. Recent publications have suggested that the closer the eupneic pCO2 is to the threshold pCO2, the more prone the patient is to instability of breathing. Khan et al showed that the average CO2 apneic threshold in preterm infants is only 1.5 mm Hg lower than the actual or baseline pCO2, whereas in adults it is 5 mm Hg lower. Moreover, the ventilatory response to CO2 is found to be lower in age and weight matched preterm infants with AOP than in controls. As pointed out earlier, the blunted CO2 response is exaggerated by hypoxia in preterm infants and providing slightly higher concentration of inspired O2 improves the slope of CO2 and minute ventilation relationship. In addition, in preterm infants while protective respiratory reflexes are depressed, Hering-Breuer reflex activity is increased which inhibits inspiration by sending signals via vagus nerve to the inspiratory area in the medulla and apneustic center of the pons.

Role of Neurotransmitters: Preterm neonates display increased sensitivity to inhibitory neurotransmitters, such as gamma-aminobutyric acid (GABA), adenosine, serotonin, and prostaglandins. GABAergic neurons are activated in response to hypercapnia as demonstrated in animal models and this in combination with a heightened sensitivity to GABA may be partly responsible for depressed respiratory response to hypercapnia in premature states. Adenosine formed as a consequence of metabolic and neural activity in the brain during hypoxia, interacts with GABA in the regulation of breathing. Adenosine receptors are expressed in GABA-containing neurons and the binding of adenosine to its receptor may release GABA and thus inhibit respiration leading to apnea. Methylxanthines block adenosine and by virtue of this property, are used as the mainstay of pharmacological therapy of AOP.

Increased Sleep state

Newborn infants spend 80% of their time sleeping compared to 30% in adults, and a much higher percentage of their sleep time in spent in REM state. AOP occurs most frequently during active or REM sleep and is relatively infrequent during non REM quiet sleep unlike periodic breathing. REM sleep is associated with changes in respiration pattern. It increases the incidence of periodic breathing and apnea and decreases the ventilatory response to CO2. It also enhances the hypoxia induced late decrease in ventilation. It increases the rate of sighs and promotes chest distortion leading to muscle fatigue and increased oxygen consumption. Furthermore, it inhibits pulmonary reflexes and decreases upper airway tone and post inspiratory diaphragmatic activity leading to partial lung collapse during expiration. Chest distortion, which may ultimately lead to apnea, is thought to be caused by the spinal moto neural inhibition of muscle groups responsible for maintaining chest wall stability during active sleep, such as intercostal muscles and diaphragm. With a very compliant rib cage, paradoxical chest movement becomes common for these reasons in premature babies and predisposes them further to apnea by decreasing functional residual capacity (FRC) and thereby, limiting oxygenation.

Positional and anatomical proclivity to obstruction

Upper airway patency is essential for maintaining respiratory steadiness and preterm neonates present several anatomic characteristics that interfere with this. They have a highly compliant chest wall, less rigid airways, highly collapsible pharynx and poor control of neck flexion. These lead to inadequate lung volumes during expiration, and when combined with positional changes and lack of coordination of respiratory and pharyngeal musculature, result in an increased risk for obstructive apnea. Infants with mixed and obstructive apnea have decreased activation of their genioglossus muscle in response to occlusion which may reflect their inability to recruit dilating muscles of the upper airway during spontaneous airway obstruction.

DIAGNOSIS

Electrocardiographic signaling, impedance probes and infrared light absorption monitors are used to
detect heart rate, respiratory rate and saturation of O2 in blood, respectively. These are conventionally used in NICUs, and in combination with nursing reports, aid in the diagnosis of AOP. However, the impedance monitors may not always be able to pick up obstructive apneas, as they function by detecting chest movement which may be intact in these cases. Apnea in such conditions is detected by the presence of bradycardia and hypoxemia as recorded on specific monitors. AOP is a diagnosis of exclusion and other neonatal pathological conditions must be ruled out in order to establish prematurity per se as the cause. The clinical conditions that may present with secondary apnea are as follows: sepsis and meningitis, hypoglycemia, electrolytes anomalies, pulmonary diseases, cardiac disorders and arrhythmias, seizure, hyper or hypothermia, pathological ductus arteriosus, necrotizing enterocolitis (NEC), intraventricular-periventricular hemorrhage (IVH), pain, clavicular or other fractures, air leak syndromes, anatomical anomalies of upper airway, vocal cord paralysis, tracheo-bronchomalacia, over or under hydration, hypothermia, anomalies in ambient temperature, anemia, congestive heart failure, acid base disorders, maternal-fetal sedation, maternal drugs like MgSO4, birth asphyxia etc. Recently high blood level of unconjugated hyperbilirubinemia has been implicated in apnea of prematurity.  

TREATMENT
Understanding the etiologic basis of AOP is key to prevent, manage, and treat. If there is a definable clinical condition triggering apnea it should be treated first. In conditions where no such events are identified the diagnosis of AOP is made. Prevention is the first step and optimization of the baby’s environment by way of regulating ambient and body temperature is necessary. Preterm infants are poikilothermic needing external heating and any aberration of their environmental temperature might lead to apneic events and a need for supplemental oxygen. Positioning and airway patency are other crucial factors that should be paid attention to.

Preventive Measures

Ambient and body temperature: Neonates should be placed in neutral thermal environments with body temperature within a range of 97.7°F–98.2°F or 36.5°C–36.8°C. Temperature fluctuations and extremes might precipitate apneic events and should be avoided. A mild increase in body temperature in infants enhances the instability of breathing pattern. Apnea is found to be less common at an incubator temperature of 30.4°C than at 32.5°C. Both under and overheating can precipitate apnea. A specific environmental temperature that will reduce the incidence or severity of AOP is not known.

Body position: Adequate positioning of the neonate helps stabilize the chest wall and minimize airway obstruction. Prone position has been recommended in several studies, with tilting of the head end approximately to 30 degrees. Avoiding extreme bending or stretching of the neck prevent airway obstruction and should be sought.

Airway Patency and avoiding hypoxemia: Apart from body positioning, airway patency may be compromised by the presence of secretions. Gentle suctioning if necessary, cleaning secretions surrounding nose and oral cavity, and using oxygen delivery equipment of adequate size for the neonate are important. Based on the available information maintaining SaO2 between 90 and 95 percent in preterm infants, who receive supplemental oxygen and are continuously monitored by pulse oximetry, is considered as optimum.

Specific measures
Although there are no guidelines or clear consensus on how to treat, treatment options, like preventive measures, are targeted towards the classification and etiopathogenic conditions that lead to or facilitate AOP. Apnea secondary to conditions associated with prematurity may need to be treated if they persist even after elimination of the precipitating cause. Pharmacological intervention and O2 and positive airway pressure supplementation, either singly or in combination are the commonly practiced modalities of management.

Pharmacological Intervention:
Methylxanthines, specifically caffeine citrate and theophylline are the pharmacologic agents
universally used in the treatment of AOP. These drugs block adenosine receptors, an action that stimulates respiratory drive and results in excitation of respiratory neural output, leading to increased minute ventilation, as well as improved CO2 sensitivity, diaphragmatic contractility and lung compliance. 34 Caffeine citrate is preferred over theophylline due to its longer half-life (100 vs. 30 hours), 16 and better therapeutic index, as a result of which, fewer daily doses are required and blood level monitoring is not warranted. Aminophylline is administered orally or intravenously in a loading dose followed by maintenance doses every 8 to 12 hours. Its therapeutic range is between 7 mcg/mL to 12 mcg/mL and levels need to be followed in order to assure effectiveness and avoid toxicity. Caffeine citrate, administered orally or intravenously via a loading dose followed by maintenance doses every 24 hours has a broader therapeutic range at 5 mg/L to 25 mg/L. The Caffeine for Apnea of Prematurity Trial, the largest randomized controlled trial on the subject studied the effects of caffeine citrate during the first 10 days of life in premature infants weighing between 500-1250 grams at birth, compared to placebo, and demonstrated that neonates treated with caffeine citrate have lower duration of mechanical ventilation, decreased incidence of bronchopulmonary dysplasia and increased survival with better neurological outcomes at 18 months of life. 34,35 Treatment with caffeine is recommended for all infants born at or before 28 weeks of gestational age. 16 Beyond 28 weeks use of caffeine may be discretionary for neonatologists. Some recommend treating infants with caffeine between 28 to 32 weeks of GA as a preventive measure, considering the incidence of AOP to be significant at this level of immaturity, while others may want to wait for symptoms to appear. At higher than 32 weeks of gestational age, most neonatologists agree on treating the neonates on an “as needed basis”. Adverse effects of methylxanthines are generally related to increased basal metabolism, and manifest as tachycardia, arrhythmias, emesis, increased oxygen consumption, jitteriness, and rarely, seizures. 16 Discontinuation of caffeine is usually attempted at 33 to 34 weeks of postmenstrual age and after apnea episodes have been absent for 5-7 days. Patients should be observed for at least 5-7 days after cessation of therapy.

**Oxygen and Positive Pressure Support:** Provision of oxygen with or without positive airway pressure is the next level of intervention in cases of AOP. Oxygen can be delivered alone via nasal cannula or in combination with continuous positive airway pressure (CPAP), synchronized nasal intermittent positive pressure ventilation (NIPPV), high flow nasal cannula, and mechanical ventilation. 2 These interventions, in conjunction with methylxanthines have proven to be effective in the management of most of the cases of AOP. CPAP is the most widely used initial technique. Provided at the pressures of 4-6 mmHg, it maintains the airway patency, improves and prevents atelectasis, establishes and enhances functional residual capacity and reduces the work of breathing, all of which lead to increased oxygenation and ventilation. It works best in obstructive and mixed apneas and can have positive effect on central apnea secondary to augmented oxygenation and ventilation. The use of NIPPV and high flow nasal cannulas are effective alternatives to CPAP. It is demonstrated that Variable-flow nasal continuous positive airway pressure may be more effective in treating AOP than a conventional ventilator using NIPPV mode. 36 Mechanical ventilation should be considered as last resort after failure of other treatment options and be used for the least possible period with minimal ventilation parameters in order to prevent lung injury.

**Other Treatment options**

Other options in the management of AOP are treatment of gastroesophageal reflux disease (GERD), mechanosensory stimulation, blood transfusion and doxapram, a respiratory stimulant drug. These measures however are not well studied and have not clearly demonstrated evidence based efficacy or utility in the treatment of AOP.

**Sensory stimulations:** Mechanosensory stimulation via acoustic mattresses is an unproven intervention that was proposed to reduce the incidence of apneic episodes and desaturations. Tactile and olfactory stimulation have been used in the treatment or prevention of AOP. Tactile
stimulation may decrease occurrence of apnea by 35% via induction of nonspecific excitatory neuronal activities in the brainstem center that stimulate respiration. A systematic review failed to show kinesthetic stimulation to be effective at preventing the apnic episodes and therefore, this intervention is not recommended. Vanillin, a stimulus known to affect the olfactory nerve, may be of benefit in cases refractory to caffeine and doxapram but needs additional information to gain acceptance.

**CO₂ inhalation:** Increasing pCO₂ by 1 to 2 mmHg above the apnea threshold might reduce or abolish apnea. A randomized controlled trial revealed that inhalation of a 0.08% CO₂ in premature infants may be as effective as theophylline in decreasing apnea without any adverse effects on cerebral blood flow velocity. Its long term adverse effects are undetermined and currently the measure is not followed by neonatologists.

**Red blood cell transfusion:** Transfusing RBCs in neonates as a part of treatment of AOP is a topic of ongoing controversy. Although increasing oxygen carrying capacity and consequent tissue oxygenation sounds logical in the prevention of apneic events, studies have shown the effects to be transient and with no long-term benefits. A retrospective study in extremely low birth weight infants noted that while red blood cell transfusion was not associated with reduction in apnea frequency, it increased the risks of bronchopulmonary dysplasia and necrotizing enterocolitis.

**Doxapram:** Doxapram is a chemoreceptor stimulant. It, independent of blood oxygen levels, directly stimulates the peripheral carotid chemoreceptors, possibly by inhibiting the potassium channels of type I cells within the carotid body. This results in release of catecholamines, reversal of respiratory depression and increase in respiratory drive. The effects are short lived and the drug is given as continuous intravenous infusion. It has significant side effects and only limited studies have been conducted to evaluate its efficacy and safety. Dani et al. investigated the effects of doxapram on cerebral hemodynamics in premature infants using cerebral Doppler ultrasonography and near-infrared spectroscopy and found that the drug increases cerebral oxygen consumption and decreases oxygen delivery to brain tissues.

The short term side effects of doxapram are irritability, hypertension tachycardia, tremor, gastric retention and vomiting, while its long term side effects are undetermined. Due to its side effects Doxapram is not recommended for AOP at this time.

**CRITERIA FOR DISCHARGE IN RECOVERING INFANTS**

Discharging neonates from NICU might bring some uncertainties as medical professionals attempt to transition the infant to an environment where 24 hours continuous cardiorespiratory monitoring is not available. The decision making process is judicious and may be challenging due to a lack of guidelines and complete information on the subject. The general consensus is to start the process at PMA of 33-34 weeks and after discontinuation of caffeine following 5-7 apnea free days. Lorch et al suggested that there is very low risk for subsequent occurrence of apneic episodes after a 5-7 day event free period and reported resolution of AOP in 94-96% of such cases. This success rate was, however, lower in VLBWI and it was proposed that for infants born at >30 weeks of gestation a 95% success rate threshold should be a minimum of 3 apnea free days, whereas, for infants born at 27-28 weeks and at < 26 weeks the duration should be 9 and 13 days respectively. The National Institute of Child Health and Human Development [NICHD] states “The observational period needed after therapy for apnea of prematurity is unknown, and an appropriate duration of surveillance off therapy is needed to reasonably prevent acute life-threatening events”. In general, a PMA of > 34 weeks with body weight > 1800 g and 5-7 apnea free days post cessation of methylxanthine therapy, in addition to regular weight gain in acceptable range on full nipple feeding, maintenance of body temperature on normal ambient temperature and absence of any other limiting clinical condition are criteria followed by most neonatologists to make a decision for a safe discharge.
Figure 1: Incidence of AOP according to gestational age

Figure 2: Classification of apnea based on recordings of pulse oximetry, respiratory efforts and nasal air flow

Table 1: Factors contributing to AOP

| Increased function of peripheral chemoreceptors |
| Decreased function of central chemoreceptors |
| Lower CO2 apneic threshold |
| Hyperactivation of laryngeal chemoreceptors |
| Sleep state |
| Proclivity to obstruction |

Figure 3: Pathogenesis of AOP: Roles of Central and peripheral chemoreceptors
OUTCOME AND PROGNOSIS

AOP resolves in almost all cases by 43 postmenstrual age even in the most premature infants. Even though it has been associated with complications, it is difficult to separate its adverse neurodevelopmental outcome from those of prematurity and related morbidities. It does not have causal relationship with SUID although ELGAN infants displayed a higher incidence of SUID than term neonates. It had been demonstrated that infants with clinically significant AOP do not perform as well as prematurely born infants without recurrent apneas on neurodevelopmental follow-up testing. Untreated recurrent severe apneas may result in IVH, prolonged mechanical ventilation and adverse neurodevelopmental outcomes. Recent studies have shown an association between apnea and intermittent hypoxia with retinopathy of prematurity, bronchopulmonary dysplasia and neurologic disabilities. Chronic episodes of intermittent hypoxia due to apneas and periodic breathing may induce the expression of inflammatory mediators in the central nervous system and this effect may produce increased respiratory instability, alter growth and cardiovascular regulation and increase the risks of retinopathy of prematurity and neurologic disability.

FUTURE DIRECTION

Despite ample information on AOP significant knowledge gaps exist, esp in regards to its implications in neurological and other significant adverse outcomes. The future research needs on the subject were identified by the Apnea of Prematurity group, which concluded that a large prospective study is needed to distinguish the role of apnea from the many confounding conditions and other predictors of neurodevelopmental outcome, including gestational age, neuroanatomic abnormalities, exposure to mechanical ventilation, sepsis, postnatal steroid treatment, and occurrence of bronchopulmonary dysplasia. It should be a randomized, primary or co-primary hypotheses driven study, well powered to assess long term follow up and done with rigorous control of potentially confounding variables.

SUMMARY

Apnea of prematurity, one of the most important clinical problems in NICU, that improves with advancing gestational age, represents a physiologic maturational deficiency of the neurological control of breathing during adaptation to extra uterine life. The magnitude and implications of the problem were best summarized by the National Institutes of Child Health and Human Development (NICHD) group who conducted a workshop on AOP and published the proceedings. They conceded that there is no consensus on definition, diagnosis, or treatment of AOP and the real-time events associated with apnea are not well documented by the current technology. Moreover, the confounding conditions that influence the occurrence of AOP are poorly recognized and not well integrated into care. While the relationship between gastro esophageal reflux and AOP requires additional investigation, other confounders associated with brain injury in preterm infants as causes of abnormal child development are difficult to separate from those of AOP. They commented that an improved characterization of the effects of apnea of prematurity on neurodevelopment during infancy and childhood is needed. AOP is a diagnosis of exclusion and a developmental process involving prematurely delivered and otherwise healthy neonates, which may require specific therapy during its course in postnatal adaptation period and which eventually resolves, however, with a caveat of unrealized potential association with adverse neonatal outcomes.

REFERENCES


7. Alvaro RE. Control of Breathing and Apnea of Prematurity. NeoReviews 2018;19;e224 DOI: 10.1542/neo.19-4-e224


24. Simakajornboon N, Beckerman RC, Mack C, et al. Effect of supplemental oxygen on sleep architecture and cardiorespiratory events in


Sudden Unexpected Infant Deaths in the United States. Pediatr 2017; Volume 140, number 1:e20163334


