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Sleep Development and Apnea in Newborns

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1. Introduction

One of the major problems in neonatal care, is the presence of sleep apnea in premature infants. This is due, that respiratory disturbances placed at high-risk and in immediate danger to newborn infants because alteration in adaptation to extra-uterine environment. Apnea during sleep can be the principal symptom of maturational dysfunction of the control of the central nervous system (CNS) on the infant respiratory patterns, or can be present secondarily to other brain or non-brain pathologies. Frequency of apnea is inversely related to gestational age at birth. In this chapter, we revisited the process of sleep development from fetal to neonatal age focused in the presentation of respiratory alterations, such as the apnea. Afterward, we reviewed the clinical features of apnea for its clinical diagnosis and therapeutics.

2. Development of sleep

Different neuronal networks underlying brain function maturing during fetal life beginning as early as 10 weeks of gestational age (GA). For example, the human fetus displays spontaneous movements that can be visualized by means of ultrasonography (USG), which can document eye-opening and –closure, and rhythmic body movements. On the other hand, fetal heart rate can be electronically recorded by means of serial electrodes placed in the abdominal skin of the mother, fetal heart rate variations reveals the fetal well-being. Both tests, allow estimation of fetal state transitions underlying fetal behavior including the sleep. Recently, Magnetoencephalographic (MEG) recordings of the fetal and neonatal cortical magnetic activity constituted as a promising technique in the study of sleep physiology. At earlier stage of development, no clear sleep state can be well defined. The sleep stages appears clearly at the end of fetal period near at the time of birth.[1] One study carried out in our laboratory suggested a high correlation of fetal sleep with those sleep measurements developed after birth in neonates.[2]

After birth serial recording of several physiologic functions during sleep or polysomnography (PSG) can be obtained by continuous monitoring of electroencephalographic (EEG) signal; eye movements (EOG); electromyographic (EMG) signal of axial and limb muscles; electrocardiographic (EKG) recording; different measurements of respiratory function, such as those obtained by a nasal thermistor, chest and abdominal movements; blood

concentrations of oxygen and carbon dioxide sensors are placed in neonates in order to study the organization of the functional state.[3]

Preterm infants born at 24 weeks of gestational age (GA) show predominant cyclic rudimentary sleep functional state called Transitional or Indeterminate sleep (IS). Scarce burst of electro-cortical activity over a flat background in EEG are presents which is called Discontinuous activity or *Tracé Discontinu*.[4] When time intervals are measured between successive epochs of PSG signal, EEG activity shows variable Discontinuous activity depending on GA with larger flat EEG periods at earlier GA. By 34 weeks of conceptional age (CA = GA + post-natal legal age in weeks. Is the better parameter to measure and correct maturational effects of preterm birth and early post-natal life on the EEG and PSG recordings when are compared with those of newborns born at-term and with some weeks of post-natal age) a Rapid eye movements (REM) sleep-like state emerges, and is called Active sleep (AS). Around 37 weeks of CA Quiet sleep (QS) differentiates and appear as alternating intervals of variable span according to CA changes of different EEG frequency and amplitude patterns called *Tracé Alternat*, while in AS periods appears with continuous EEG activity or *Tracé Continu*. Cycle times vary between sleep periods, but usually range between 40 and 60 min. Behavioral estimations of IS approximate amounts 95% of sleep in the 30 weeks of CA studies, decreasing progressively and disappearing by near-term ages.[5]

There is a relative continuity of sleep state from intrauterine through neonatal age, from last weeks of pregnancy to 44 weeks of CA. Such physiologic continuity may reflect the need for sleep state homeostasis of both the fetus and newborn during the transition from intrauterine to extra-uterine environments,[2] requiring approximately one postnatal month of brain development before infant sleep patterns emerge. These physiologic interrelationships defining neonatal state, persist to 4–6 weeks of postnatal life after which infant sleep patterns subsequently emerge to eventually resemble those of adult sleep rhythms by between the first and second years of life. Similar temporal relationships are expressed by preterm neonates in an extra-uterine environment. However, a review of medical literature regarding fetal wakefulness suggests no convincing evidence that the fetus is awake as often as the preterm neonate. A state of cortical arousal similar to IS inhibits the awake state in the fetus as a defense response of brain plasticity.[6]

3. Development of sleep respiratory patterns

The recognition of sleep states in newborns and infants was initially based on differences in respiratory rate. The breathing rhythm was more irregular during AS and IS and more regular during QS segments. Related changes in these respiratory patterns first were noted when sleep state differentiation was recognized.[7] There are a number of features of respiratory patterns that will be briefly summarized, including central respiratory pauses, breathing regularity versus irregularity, breathing frequency, and the percentage of paradoxical breathing as it refers to out-of-phase thoracic and abdominal breathing movements. Central respiratory pauses are of short duration and are normally seen in the newborn and can be documented also during the waking state following body movements. However, they primarily occur during sleep.[8] The apnea index, defined by the percentage of non-breathing time,[9] is significantly higher during AS than QS. It remains high until 38 weeks of CA and decreases significantly both during AS and QS by term age. Preterm infants corrected to term age as well as gestational-age infants who are small for their age also have a greater number of respiratory pauses than is appropriate for gestational-age infants of the same CA.

After 35 weeks of CA, respiratory frequency is higher during AS and QS. During both components of the sleep cycle, respiratory frequency increases with increasing gestational age to term and continues to increase during the first two months of life. Thereafter, at older ages, the respiratory rate progressively decreases. Phase shifting or paradoxical breathing between thoracic and abdominal breathing movements is commonly seen during the first several months of life and is closely related to inter-costal muscle inhibition, particularly during active sleep, in part reflecting high chest wall compliance. By the at-term age of pregnancy, the time spent with 180º out-of-phase shift between thoracic and abdominal breathing movements remains unchanged but is significantly greater during AS than QS.[10]

4. Definition and different types of apnea

Apnea in newborns is defined as absence of breathing for 20 sec or longer, or at a shorter time if bradycardia of <100 beats/min, cyanosis, hypoxia, and/or hypotension is present.[11] Apnea is classified as central, obstructive, and mixed. Central apnea is present when epochs of absence of nasal air flow and thoracic breathing are identified, obstructive apnea is recognized when respiratory thoracic movements are present but nasal air flow is inadequate, and mixed type is present when events begin or end with central or obstructive apnea and change to the other type of apnea.[12] PSG is the most adequate electrophysiologic test to identify apnea in preterm and at-term newborns, and must be performed in all infants with risk factors.

5. Risk factors for different types apnea

We carried-out a study at a tertiary-level medical center for care of high-risk newborns at Neonatal Intensive Care Unit in Mexico City. Newborns were selected if they presented any risk factor for apnea during neonatal period (such as preterm birth, low Apgar score, sepsis, and others) when infants were stable and not mechanically ventilated. The sample was divided in infants that presented and those that did not presented apnea events on PSG studies. Newborns were studied by a neurologic examination, transfontanelar ultrasonography, and laboratory tests. Two hundred twenty three patients were studied (Table 1). One hundred twenty nine were females (57.84%). One hundred thirty one patients were born weighting <1,500 g (58.74%). Apgar score at 1 min was ≤3 in 53 patients, other clinical data were obtained from hospital records.

We detected apnea events in 55 patients (24.66%). Comparison of clinic characteristics between infants with and without apnea is shown in Table 2, significant differences were found with regard to age, weight, and cephalic perimeter at birth, with lower values in the group of infants with apnea as expected by previous literature. No statistical differences in main risk factors such as: sepsis, intraventricular hemorrhage, hyperbilirubinemia, hypoxic-ischemic encephalopathy, meningitis and TORCH in infants with and without apnea were seen. Although each patient can have more than one type of apnea, forty patients showed central apnea events (72.72%), six manifested obstructive events (10.90%), and nineteen demonstrated mixed events (34.54%). Some infants presented only one type of apnea: central (n = 31), obstructive (n = 5) and mixed (n = 10). Comparison of characteristics among these groups showed significant differences in weight at birth, cephalic perimeter, and one-min Apgar score with lower values in infants with central and obstructive apnea than infants with mixed apnea (Table 3). Significant differences in weight at birth between central and mixed groups with regard to infants with obstructive events; and in cephalic perimeter

among group of mixed apnea to the other two groups; and in Apgar score at one min in groups of obstructive and mixed apnea to group of infants with central events were observed. Frequency of three main risk factors identified in patients with only one type of apnea showed significant differences when compared with infants without apnea in birthweight <1,500 g in the group of infants with central apnea; and in hyperbilirubinemia and gastroesophagic reflux in infants with obstructive apnea; and in hyperbilirubinemia and sepsis in infants with mixed events of apnea (Table 4). The main pharmacologic agents used for apnea treatment were theophylline (*n* = 21, 38.18%) and aminophylline (*n* = 14, 25.45%), nonetheless twenty patients (36.36%) were without treatment at time of study because they were not identified as having apnea events previously.[13]

Risk Factor	*n*	Percentage
Low birth weight (≤ 1,500 g)	131	58.74
Sepsis	120	53.81
Mechanical ventilation	118	52.91
Low Apgar score at minute (≤ 3)	53	23.76
Intracranial hemorrhage	41	18.38
Neonatal seizures	32	14.34
Hypoxic-ischemic encephalopathy	25	11.21
Hydrocephalus	19	8.52
Meningitis	16	7.17
Hyperbilirubinemia (blood exchange)	11	4.93
Cerebral malformation	7	3.13
TORCH	3	1.34
Head trauma	3	1.34

n = number of patients. Each subject can have more than one risk factor

Table 1. Neonatal risk factors in the sample (n = 223 patients)

Variable	Apnea	*x*	*sd*	*p*
Age at birth (weeks)	present	32.82	2.03	0.01
	absent	33.83	3.55	
Weight (g)	present	1405.09	468.44	<0.001
	absent	1738.36	842.88	
CP (cm)	present	28.18	2.58	0.04
	absent	29.16	3.58	
Apgar score 1 m	present	5.56	2.40	n.s.
	absent	6.20	2.36	
Apgar score 5 m	present	8.25	1.17	n.s.
	absent	8.17	1.26	

x = mean. sd = standard deviation. p = probability. n.s. = no significant. CP = Cephalic perimeter

Table 2. Comparison of characteristics of infants with (n = 55) and without apnea (n = 168)

Feature	Type of apnea	x	sd	p
Age at birth (weeks)	Obstructive	32.68	2.23	n.s.
	Mixed	33.76	2.36	
	Central	32.58	2.12	
Weight at birth (g)	Obstructive	1245.09	355.94	0.03
	Mixed	1635.50	421.67	
	Central	1427.41	519.76	
CP (cm)	Obstructive	28.00	2.73	0.04
	Mixed	29.52	2.52	
	Central	28.20	2.70	
Apgar score 1 m	Obstructive	7.2	2.38	0.02
	Mixed	8.00	0.66	
	Central	5.64	2.49	
Apgar score 5 m	Obstructive	8.41	1.34	n.s.
	Mixed	9.00	0	
	Central	7.96	1.35	

x = mean. sd = standard deviation. p = probability. n.s. = no significant. CP = Cephalic perimeter

Table 3. Comparison of characteristic of infants with different type of apnea

Central	n/%	Obstructive	n/%	Mixed	n/%
Preterm birth	30/96.77*	Preterm birth	5/100	Preterm birth	9/90
Sepsis	16/51.61	HB	5/100*	HB	8/80*
HB	13/41.93	GR	3/60*	Sepsis	5/50*
Anemia	12/38.70	HNa	2/40	HM	3/30
HM	11/35.48	IH	2/40		
HNa	9/29.0	BD	2/40		
GR	9/29.03				
BD	8/25.8				
PFC	8/25.8				
FGR	8/25.8				

HB = Hyperbilirubinemia. HM = Hyaline membrane. GR = Gastroesophagic reflux.
HNa = Hyponatremia. IH = Intraventricular hemorrhage. BD = Bronchopulmonar dysplasia.
PFC = Persistent Fetal Circulation FGR = Fetal growth retard. * ($p < 0.001$)

Table 4. Main risk factors found in infants with different type of apnea

6. Pathophysiology

Several mechanisms have been proposed to explain apnea pathophysiology, such as: immaturity of respiratory control center at brainstem, CO_2 lower ventilation response at REM sleep, lower number of synapsis and myelination at respiratory control center.[10,14]

7. Diagnosis and treatment

The diagnosis is clinical, and is established in basis of a high degree of suspicion of apnea in premature high-risk infants. However, some immature at-term infants may also present

apnea. Breathing observation and respiratory pauses identification are the cornerstone signs for the diagnosis. However, infants with obstructive and mixed apnea may present some difficulties for the diagnosis. The PSG is the gold standard study for apnea diagnosis of any type because can identify objectively and measure central obstructive and mixed respiratory pauses than can be forgetting by visual observation. Thus, every infants with risk factors or suspicion for apnea must be send to PSG study. Clinical examination must underline in cardio-respiratory and neurological tests. Laboratory studies may include as follows: blood test and culture; lumbar puncture; glycemia and calcium measurements; oxygen and carbon dioxide levels determination; chest, abdominal and gastro-esophagic serial X-ray; echocardiogram; ultrasonography of the brain, and continuous O_2 determination.[15]

For treatment there are several useful interventions: pharmacological and no-pharmacological. We will comment one by one as follows. Methylxanthines increase chemoreceptor sensitivity as well as respiratory drive and can also improve diaphragmatic function. Of the substances available, caffeine has a wider therapeutic range and fewer side effects than theophylline. There were concerns, however, that caffeine, being an adenosine antagonist, could reduce tolerance to hypoxia and might thus be harmful to infants with recurrent hypoxia.[16]

Aminophylline will be given at loading dose of 6-8 mg/Kg and a maintenance dose of 1-3 mg/Kg/dose three times daily to produce a desired plasmatic concentration of 5-12 μg/ml. Theophylline will be given at a loading dose of 7.5 mg/Kg and a maintenance dose of 3 mg/Kg three times daily to produce plasmatic concentrations of 13-20 μg/ml. Caffeine could be administered at a loading dose of 25 mg/Kg caffeine citrate and at a maintenance dose of 6 mg/Kg to produce plasmatic concentrations of 13-20 μg/ml.[17]

Six trials reported on the effect of methylxanthine in the treatment of apnea (three trials of theophylline and three trials of caffeine). Five trials that enrolled a total of 192 preterm infants with apnea evaluated short term outcomes; in these studies, methylxanthine therapy led to a reduction in apnea and use of mechanical ventilation in the first two to seven days. The *post-hoc* analysis of the large Central Apnea of Premature Trial comparing caffeine to control in a subgroup of infants being treated for apnea reported significantly reduced rates of Persistence of Ductus Arterial ligation. Moreover, postmenstrual age at last oxygen treatment, last endotracheal tube use, last positive pressure ventilation; and reduced chronic lung disease at 36 weeks were significantly associated. Methylxanthine was effective in reducing the number of apnea attacks and the use of mechanical ventilation in the two to seven days after starting treatment. Caffeine is also associated with better longer term outcomes.[18]

Other substance used to treat apnea is Doxapram. Doxapram stimulates peripheral chemoreceptors at low, and the central at high doses. It shows a clear dose–response curve, with a 50% reduction in apnea rate occurring in 47, 65, 82 and 89% of infants at a dose of 0.5, 1.5, 2.0 and 2.5 mg/kg/h respectively. Most studies used a continuous intravenous infusion, although some suggest that the i.v. solution may also be given orally at twice the dose with good effect (enteral absorption is approximately 50%). Short-term side effects become quite common at doses above 1.5 mg/kg/h and include irritability, myoclonus, elevated blood pressure and gastric alterations.[19]

In the other hand, Continuous-positive airway pressure (C-PAP) has been shown to reduce extubation failure in preterm infants, despite the fact that most systems currently available

do not reduce work of breathing. C-PAP can be applied via a nasopharyngeal tube or (bi-) nasal prongs. Reintubation rates are 40% lower with the latter device, number needed to treat, which is why this should be the preferred mode when applying C-PAP. An extension to this is Nasal-Intermittent positive pressure ventilation (N-IPPV), which has a high effectiveness over C-PAP in preventing extubation failure. Typically, an inspiratory pressure of 15–20 cm H_2O, applied at a rate of 10–20/min., is combined with a C-PAP level of 5–6 cm H_2O.[20]

Other interventions has been studied such as prone head-elevated positioning, keeping environmental temperature at the lower end of the thermoneutral range, oscillating waterbed and tactile and olfactory stimulation, oxygen administration, increase inspiratory CO_2 concentration, red blood cell transfusions, and branched-chain amino acid supplementation.[16] However, these techniques are under study and deserve more investigation before be accepted.

8. References

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