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Visual evoked potentials are similar in polysomnographically defined quiet and active sleep in healthy newborns

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ABSTRACT

Morphology and late components of evoked potentials change depending on wake-sleep stages in adults. Visual Evoked potentials (VEPs) have been frequently studied in newborns to identify abnormal development of visual pathways; however, large variability has been reported and there is uncertainty as to the effect of sleep stages on VEPs in neonates.

Objective: To describe the characteristics of VEPs in one month old, healthy full-term newborns during active sleep (AS) and quiet sleep (QS), defined by simultaneous polysomnography (PSG).

Methods: VEPs were obtained by monocular LEDs stimulation of each eye during AS and QS, in 20 healthy full-term newborns (gestational age 37–40 weeks) with normal birth weights and normal prenatal Doppler ultrasound indices. Latencies and amplitudes of N2, P2 and N3 components in AS and QS were compared, and their association with absolute power of EEG frequency bands, assessed.

Results: There were no significant differences in VEP morphology, latencies and amplitudes between sleep states. Typical wave forms were obtained in all newborns in AS; however, no VEPs could be identified clearly in 3 newborns in QS; QS VEPs were less reliable than in AS: more averaging was required; correlation was significantly lower between the VEP averages; and a larger number of babies needed more than two averages to obtain replicable responses needed for clinical purposes.

Conclusions: These results indicate that changes in amplitude and latency of some VEP components observed in NREM and REM sleep in adults are not yet present in one month old newborns probably due to immaturity of cortical and sleep mechanisms. VEPs are more reliable during AS than QS in newborns. Systematic VEP recording during AS, and polysomnographic control to identify this stage, are highly recommended as methods that can increase there liability of neonatal VEPs.

1. Introduction

There is a bidirectional interaction between behavioral states and sensory processing (Vellutti, 1997). Sensory perception during sleep is not abolished but it is considerably attenuated. It is well known in the human adult that the sensory threshold is increased during sleep as compared to wakefulness (Bonnet et al., 1978) and that the brain response to auditory, visual and somatosensory stimuli -as assessed by evoked and event related potentials- is modified depending on the level of arousal and sleep stages (Campbell et al., 1992; Näätänen and Michie, 1979). While early components like those of Brainstem Auditory Evoked Potentials remain unaffected by the sleep stage in both adults and newborns (Husain, 2011), mid-latency and late components associated with complex processing –likely of cortical origin– do vary in relation to sleep stages in the adult (Kakigi et al., 2003; Coenen, 1995; Campbell et al., 1992). Even if Visual Evoked Potentials (VEP) during sleep in the human adult have not as often been recorded as auditory potentials, it has been found that some of its components are enhanced during sleep while others are reduced or even disappear (Okusa and Kakigi, 2002).

Whereas sleep is not yet fully developed in newborns, and even though its characteristics are different from those of the adult, as early

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as the first month of life, three sleep states, recorded behaviorally and through polysomnography (PSG), can be clearly distinguished: Quiet Sleep (QS), Active Sleep (AS) and Wakefulness (Grigg-Damberger, 2016; Mizrahi et al., 2011; Prechtl, 1974; Anders et al., 1971). QS displays high-voltage slow activity alternating with flat periods or *tracé alternant* with no rapid eye movements, behavioral quiescence, closed eyes and regularity of breathing. AS reveals EEG low-voltage irregular activity, with rapid eye movements, irregular breathing and frequent facial movements. QS and AS states are precursors of non REM sleep (NREM) and rapid eye movement (REM) sleep respectively. Wakefulness is characterized by strong diffuse motor activity, open eyes and irregular breathing and a fourth behavioral state, indeterminate state, gradually disappears with age. Hence, the presence of different electrical activity during QS and AS in the newborn suggests a different brain response to visual stimulation during QS and AS; however, even though VEPs have often been studied in newborns to assess neurodevelopment and identify abnormal development of the visual pathways (Cruz et al., 2015; McGlone et al., 2013; Kato and Watanabe, 2006), not all studies in newborns have taken into account the behavioral state of infants when recording VEPs, thus the effect of sleep states on neonatal VEPs remains unclear.

Some studies in newborns have carried out VEPs recording only during wakefulness (Roy et al., 2004; Kraemer et al., 1999), some others differentiated between wakefulness and sleep and found significant differences in amplitude and latencies between the two states but did not analyze AS and QS separately (Cruz et al., 2015; Benavente et al., 2005; Tsuneishi et al., 1995). Those studies separating VEPs in QS and AS, based only on behavioral observation found no differences between the two states (Shepherd et al., 2000; Mercuri et al., 1995). Only a few studies have distinguished QS and AS using polysomnography for sleep state identification, but either the number of same age newborns was very small ($n < 7$) or diverse age ranging between preterm and few months were included in the sample without age discrimination (Shepherd et al., 2000; Mercuri et al., 1995; Apkarian et al., 1991; Hrbek et al., 1973). As a result of these outcomes, the controversial results reported in VEPs characteristics is hardly surprising thus the uncertainty regarding the effect of sleep states on VEPs in newborns persists.

Another source of variability is the type of stimulus used to elicit the VEPs. Some studies employed flashes of white light (Benavente et al., 2005; Kraemer et al., 1999; Apkarian et al., 1991; Hrbek et al., 1973), less consistent than light emitting diodes (LEDs) (Kato and Watanabe, 2006; Taylor et al., 1987). Mercuri et al. (1995) employed LEDs, but their distinction between AS and QS was based only on behavioral criteria in a very small sample of six newborns.

The early detection of abnormal development of the central nervous system of at-risk newborns is crucial for successful early intervention (Harmony et al., 2016; Spittle et al., 2015).VEPs have often been used because they are objective, sensitive to structural and functional brain damage, and do not require patient cooperation (Huang et al., 2016; McGlone et al., 2013). In newborns, a normal visual evoked response indicates adequate neural maturation of the cerebral cortex, according to the newborn's age (Cruz et al., 2015; Kato and Watanabe, 2006). Therefore, besides the significance of analyzing the effect of sleep upon brain response to visual stimulation, it is important to obtain better, more reliable, characterizations of VEPs in normal, full-term newborns in AS and QS.

In this study we analyzed, as a first approach, amplitude and latency of monocular left and right VEPs recording using LEDs goggles in AS and QS sleep states unambiguously defined by simultaneous polysomnography in 20 full-term babies during the first month of life.

Table 1
Neonatal and anthropometrical data of the group.

	Mean	Standard Deviation	Range
Gestational age at birth (weeks)	39.02	1.03	37 - 40
Postnatal age(days)	24.5	10.7	8 - 47
Birth weight(g)	3117	378	2530 - 4065
5-minutes Apgar	9	0	

2. Method

2.1. Participants

Twenty healthy full-term newborns between 37 and 40 weeks of gestational age at birth (12 girls, 8 boys; 55% spontaneous vertex delivery) participated in this study. All were born at the Children's and Women´s Specialty Hospital of Querétaro, Mexico, between December 2012 and November 2015. They were referred as normal control babies after neurological normal examination. They were deemed eligible applying the following inclusion criteria: 1) singleton newborns with gestational age at birth of 37–40 weeks defined by a first trimester prenatal Doppler ultrasound study; 2) normal birth weight (between the 10th and 90th percentile according to local standards); 3) normal prenatal Doppler ultrasound pulsatility index in the umbilical artery, middle cerebral artery and uterine arteries; and 4) absence of neonatal morbidity. Special care was taken to include only babies of similar postnatal age within narrow limits (Table 1).

The exclusion criteria applied were: congenital malformations, chromosomal abnormalities, and prenatal infections such as cytomegalovirus. The experimental protocol was approved by the Hospital's Ethics Committee and follows the principles of the World Medical Association's Helsinki Declaration. Written consent for participation was obtained from all parents involved.

2.2. Recording procedures

The VEP studies were carried on by appointment. All babies were asymptomatic at the time of the VEPs studies. In all 20 newborns, VEPs and spontaneous sleep polysomnography were recorded simultaneously. Polysomnographic studies lasted 60–90 min to allow VEP recording during AS and QS. Only VEPs that were recorded during polysomnographically clearly identified AS and QS were stored for off line analysis. VEPs recording was suspended if the newborn cried, or if transition to another state occurred.

With the baby resting in a hospital crib, after gently cleaning the babies' skin, gold cup electrodes were placed for simultaneous sleep and VEP recordings at F3, F4, C3, C4, T3, T4, O1 and O2 referred to linked mastoids for sleep recording, and at Cz and Oz for VEP bipolar recording of the 10–20 International System. The ground electrode was placed on the right mastoid. Electrode impedances were below 5 kOhm.

2.3. Sleep recording and analysis

For sleep, additionally ocular movements (EOG), and sub-mental electromyography (EMG) were recorded, in accordance with the published standards for newborns (Grigg-Damberger, 2016). EOG were recorded in two channels from two electrodes, one placed 1 cm above the external canthus of the left eye, the other 1 cm below the external canthus of the right eye, also referred to linked mastoids. Filters were set between 1–30 Hz for sleep EEG and EOG, and between 10–100 Hz for EMG. Polygraphic signals were digitized at a sampling rate of 256 Hz and stored in a Medicid 3E EEG system (Neuronic Mexicana S.A., Mexico City).

Behavioral states were classified as QS, AS, wakefulness, and indeterminate sleep (Grigg-Damberger, 2016) by an experienced