Sleep cycle studies in babies of undernourished mothers

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SUMMARY Polygraphic sleep cycle studies—comprising simultaneous recording of electroencephalogram (EEG), electrocardiogram (ECG), electro-oculogram (EOG), phasic body activity, and respiration—were performed on 19 term newborn babies born to severely undernourished mothers, and results compared with 19 healthy newborn babies. The sleep cycle in babies of undernourished mothers showed disorganisation during active rapid eye movement (REM) sleep and quiet nonrapid eye movement (NREM) sleep. The sleep disorganisation was more pronounced during quiet NREM sleep when frequent phasic activity and ocular movements were registered, thereby leading to a significant increase in the content of intermediate sleep. Furthermore, the duration of total sleep cycle and its components, active REM and quiet NREM sleep, were significantly shortened.

Early nutritional deprivation in animals leads to a decrease in the number and size of brain cells, deficient dendritic arborisation, and to alterations in the reticular formation. Furthermore, the content of neurohumoral agents—namely, 5-hydroxytryptamine, acetylcholine, and gamma-amino-butyric acid (GABA)—is also greatly altered.¹⁻⁵ However, the nutritional demands of the fetus during the early stages of gestation are so small that maternal undernutrition has no limiting effect on the growth and maturation of the central nervous system.⁶ The early maturing reflexes and neuromotor features are therefore less likely to be affected. As the neuromotor behaviour and reflex pattern in the newly born are mainly subcortical in origin, the conventional neuromotor evaluation may not show changes in the various regions of the neocortex.

Some investigators have shown that bioelectric brain activity, sleep cycle, and various other electroencephalographic patterns make their appearance and mature at a constant rate in accordance with conceptional age, and are unaffected by low birthweight.⁷⁻¹⁰ Polygraphic study is therefore a sensitive index for evaluating deficits in maturity and

organisation during intrauterine growth. In the present study polygraphic recordings were used to evaluate the pattern of sleep cycle in babies suffering from severe intrauterine nutritional deprivation.

Material and methods

Subjects. A sample was taken of 19 newborn babies of severely undernourished mothers, who had haemoglobin levels <8 g/dl and serum albumin levels <25 g/l (mean $\pm$ SE; 5.5 ± 0.19 g/dl and 17.2 ± 0.96 g/l respectively), and weights $<$ the 25th centile of that expected for height (40.8 ± 0.89 kg). An equal number of healthy newborn babies were chosen as controls from mothers who had had regular antenatal care, and haemoglobin >11 g/dl (12.6 ± 0.29) and albumin >35 g/l (36.1 ± 0.77). These mothers had weights above 50.0 kg (54.9 ± 1.35) and heights above 150.0 cm (155.1 ± 0.97). The mothers in both groups had uncomplicated antenatal and obstetrical history, and knew the exact dates of their last menstrual periods.

Only term newborn babies with gestations of 280 ± 2 days were studied. These babies did not suffer from any birth injury or anoxia and had remained in hospital for a normal period of time.

Methods. The following parameters were recorded simultaneously. These comprised the polygraphic

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studies. (1) electroencephalogram (EEG), 8 channels; (2) electrocardiogram (ECG); (3) electro-oculogram (EOG); (4) respiratory patterns; (5) phasic body activity, using observation code.

Bipolar EEG recordings were made in a 16-channel polygraph machine (Kaizer), using Ag-AgCl polarised disc electrodes. Paper speed was 15 mm/second, time constant was 0.1 second, and high frequency cut filter was used. Electrode resistance was kept <10 k ohms.

ECG was recorded using lead I. EOG was recorded using 2 electrodes and by visual observations. Respiration was observed continuously during the recording and 3 types of patterns were found—namely, regular, irregular, and periodic/apnoeic.

A continuous record of body movements was made with precise discrimination using the following observation code: *Grade I*, slight movement/movement of one component of an extremity. *Grade II*, moderate grade of movements, head rotation not crossing midline. *Grade III*, gross, high amplitude movements, rolling over, cry. Each recording lasted between 2½ and 3 hours.

Sleep cycle

Active REM sleep. If 4 of the following criteria were present the baby was said to be having active REM sleep: (1) low voltage-high frequency EEG, (2) frequent phasic activity, (3) irregular respiration, (4) irregular heart rate, (5) presence of rapid eye movements.

Quiet NREM sleep. If 4 of the following criteria were present the baby was said to be having quiet NREM sleep: (1) high voltage, low frequency EEG, or 'trace-alternant EEG', (2) absence of phasic body activity, (3) regular respiration, (4) regular heart rate, (5) absence of ocular movements.

Sleep which could not be designated to either state was categorised as 'intermediate'.

Blood samples were collected from the mothers before delivery to estimate haemoglobin, total proteins, and albumin.¹¹ Wet placental weight was recorded, after trimming the membranes to the margin and cutting the cord at insertion.

Results

Babies born to undernourished mothers had severe

Fig. 1 Undernourished group of newborn babies, showing shortened and disorganised sleep cycle with frequent ocular movements and phasic activity. Heart rate is irregular. Vertical lines across phasic activity denote 'startles'.

Fig. 2 Control group of newborn babies showing organisation of parameters.

intrauterine growth retardation, the mean weight with standard error being 2007.97 ± 9.09 g compared with 3178.47 ± 78.18 g in the control group. The placental weight was reduced in proportion to the baby's weight, demonstrating a direct correlation, the value of 'r' being $+0.45$ and $+0.47$ for the undernourished and control groups respectively. These correlation coefficients were significant ($P < 0.05$; Table 1).

The graphic presentation of the sleep cycle showed that the organisation of the various parameters (EEG, respiration, heart rate, body activity, and ocular movements) during sleep was poor in most of the babies born to undernourished mothers (Fig. 1), while babies in the control group showed a

fairly good degree of organisation for these parameters (Fig. 2). The disorganisation in the former group occurred mainly during quiet NREM sleep when frequent body movements were registered, the heart rate was often irregular, and there were many ocular movements. This disorganisation led to a significantly increased amount of intermediate sleep compared with the controls ($P < 0.01$; Table 2).

Normal newborn babies showed reduction of heart rate during quiet NREM sleep by 7.9 ± 1.09 beats/minute compared with active REM sleep, but this reduction was less evident in the undernourished group (4.85 ± 0.93 , $P < 0.05$). Ocular movements and their variations during active REM and quiet NREM sleep were found to be similar in both groups (Table 3).

The mean durations of the total cycle, quiet sleep,

Table 1 Placental weight, protein content, and mean birthweight in control and undernourished groups (mean $\pm$ SE)

	Control group (n = 19)	Undernourished babies (n = 19)
Placental weight (g)	449.2 ± 13.03	$285.4 \pm 12.91^{***}$
Placental protein content (mg/g wet tissue)	63.74 ± 0.54	$57.0 \pm 1.12^{***}$
Birthweight (g)	3178.47 ± 78.18	$2007.97 \pm 9.09^{***}$

*** $P < 0.001$.

Table 2 Percentage distribution of active, quiet, and intermediate sleep in babies born to control and undernourished mothers (mean $\pm$ SE)

Sleep state	Control group (n = 19)	Undernourished babies (n = 19)
Active	44.1 ± 2.21	39.7 ± 2.38
Quiet	38.3 ± 1.70	34.5 ± 2.61
Intermediate	17.6 ± 1.67	$25.8 \pm 1.74^{**}$

** $P < 0.01$.

Table 3 Heart rate, ocular movements, and percentage differences in the two sleep states (mean $\pm$ SE)

Group	Active sleep	Quiet sleep	Difference
Heart rate/min			
Control	121.5 $\pm$ 3.23	113.6 $\pm$ 3.61	7.9 $\pm$ 1.09
Undernourished	126.0 $\pm$ 2.85	121.2 $\pm$ 4.23	4.8 $\pm$ 0.93*
Ocular movements/min			
Control	6.8 $\pm$ 2.80	0.97 $\pm$ 0.57	5.9 $\pm$ 0.49
Undernourished	6.5 $\pm$ 4.21	0.83 $\pm$ 0.22	5.7 $\pm$ 0.92

*P<0.05.

Table 4 Duration of total sleep cycle, active, and quiet sleep in babies born to control and undernourished mothers (mean $\pm$ SE)

Sleep cycle/min	Control group (n = 19)	Undernourished babies (n = 19)
Total cycle	51.6 $\pm$ 1.36	41.6 $\pm$ 1.81***
Active sleep	26.9 $\pm$ 1.29	20.4 $\pm$ 1.28***
Quiet sleep	24.7 $\pm$ 0.75	21.3 $\pm$ 0.84**

P<0.01, *P<0.001.

Table 5 Distribution of sleep cycle/min according to birthweight (mean $\pm$ SE)

Birthweight (g)	Total cycle (min)	Active sleep (min)	Quiet sleep (min)
>2500 (mean, 3178.5) (n=19)	51.6 $\pm$ 1.36	26.9 $\pm$ 1.29	24.7 $\pm$ 0.75
2500-2000 (mean, 2146) (n=9)	44.3 $\pm$ 1.85 <i>t</i> = 3.15**	22.3 $\pm$ 1.89 <i>t</i> = 2.0*	21.0 $\pm$ 1.07 <i>t</i> = 2.7**
<2000 (mean, 1870) (n=10)	40.2 $\pm$ 2.64 <i>t</i> = 3.85***	18.3 $\pm$ 1.60 <i>t</i> = 3.99***	21.5 $\pm$ 1.32 <i>t</i> = 2.14*

*P<0.5, **P<0.01, ***P<0.001.

and active sleep are shown in Table 4. The duration of the total sleep cycle was significantly shorter in babies born to undernourished mothers (41.6 $\pm$ 1.81 min) compared with the control group (51.6 $\pm$ 1.36 min). The values for active REM and quiet NREM sleep of the control group were 26.9 $\pm$ 1.29 and 24.7 $\pm$ 0.75 min respectively. The corresponding values for the undernourished group were 20.4 $\pm$ 1.28 and 21.3 $\pm$ 0.84 min respectively. Both differences were highly significant.

The sleep cycle in the babies of birthweights between 2000 and 2500 g (mean 2146) resembled that of babies weighing under 2000 g (mean 1870). In the latter group, duration of active sleep was further reduced while quiet sleep remained unaltered. The difference was however, not significant (P<0.1; Table 5).

In several EEG recordings of the babies in the undernourished group there was pronounced inter- and intrahemispheric asymmetry and abnormal paroxysmal discharges were recorded. It was still possible to identify the sleep cycle in such records.

Discussion

The values of duration of the total sleep cycle, active sleep, and quiet sleep of the control group in the present study were similar to those of Roffwarg *et al.*⁹ and Stern *et al.*¹² who reported the duration of the total sleep cycle as 43.4-61.2, and 47.0 minutes respectively. Similarly the content of active REM sleep has been reported to vary from 40%¹³ to 50%.^{9,14-15} Parmelee *et al.*¹⁰ reported the mean percentage of active sleep to be about 49% and quiet sleep about 34%; the rest they designated as transitional sleep.

The babies of undernourished mothers in the present study demonstrated (1) shortening of sleep cycle; (2) reduced duration of both active REM and quiet NREM sleep, and a still greater reduction in duration of active REM sleep for babies weighing < 2000 g; (3) generalised disorganisation of sleep, leading to significantly increased content of intermediate sleep, and (4) in some, inter- and intra-hemispheric asymmetry and abnormal paroxysmal discharges.

In term babies of mothers addicted to heroin and in infants at risk for CNS impairment, Schulman¹⁶ showed that there was excessive activity during active REM sleep and he failed to exhibit any well organised quiet NREM sleep. Immature sleep patterns have been reported in small-for-date babies of toxæmic mothers by Schulte *et al.*¹⁷ Such changes suggest generalised dysmaturation of the developing brain; they may even indicate brain damage due to varied intrauterine insults.

The evident physiological changes in the sleep polygrams indicate pathological deviations and maturational lags in development due to intrauterine insult. Although no comparable study so far has been reported in babies born to undernourished mothers, it seems likely that intrauterine nutritional deprivation is responsible for these changes. Recent studies show that REM and NREM sleep are controlled by anatomically distinct monoaminergic systems. 5-Hydroxytryptamine (5-HT) containing neurones in the midline pontomedullary raphe nuclei initiate quiet NREM sleep, whereas nor-adrenaline-containing neurones in the locus ceruleus modulate active REM sleep.¹⁸ Shoemaker and Wurtman³ and Im *et al.*⁴ found reduced synthesis of noradrenaline and 5-HT, and raised cholinesterase activity in whole brain of rats subjected to early undernutrition. Studies have shown that reduction of both 5-HT and acetylcholine reduces the duration and induction of total and paradoxical sleep.¹⁸⁻²⁰ It is difficult to assess whether the reduction of these neurohumoral agents in the total brain is reflected in sleep regulating centre(s).

Disorganisation of the sleep cycle and the reduction in REM sleep content may be important in the development of intellectual and neurointegrative functions of the infant. REM sleep is considered to be ontogenetically primitive, and constitutes the major proportion of sleep in preterm and term infants.^{9 12 21} It offers intense stimulation to the CNS, considered to be essential to the developing brain *in utero*, and later in early extrauterine life when external stimuli are limited.⁹ The percentage of REM sleep may decrease owing to environmental deprivation²² or it may increase after a period of intense learning.²³ REM sleep deprivation may lead to poor acquisition or retention of several kinds of learning.¹² These studies are particularly relevant since severe intellectual and neuromotor deficits have been noticed in babies of low birthweights.²⁴

References

- Platt B S, Heard C R C, Stewart R J C. Experimental protein calorie deficiency. In: Munro H N, Allison J B, eds. *Mammalian protein metabolism*, vol. 2. New York: Academic Press, 1964; 446–521.
- Fish I, Winick M. Effect of malnutrition on regional growth of developing rat brain. *Exp Neurol* 1969; **25**: 534–40.
- Shoemaker S W J, Wurtman R J. Perinatal under-nutrition: accumulation of catecholamines in rat brains. *Science* 1971; **171**: 1017–19.
- Im H S, Barnes R H, Levitsky D, Krook L, Pond W G. Postnatal malnutrition and regional cholinesterase activity in brain of pigs (abstract). *Fed Proc* 1972; **31**: 697.
- Katiyar G P, Agarwal K N, Shanker R, Nagchaudhuri J. Effect of protein energy deprivation on the brain enzymes of glutamic acid in preweanling rats. *Nutr Metab* 1976; **20**: 396–403.
- Dobbing J, Smart J L. Vulnerability of developing brain and behaviour. *Br Med Bull* 1974; **30**: 164–8.
- Ellingson R J, Lindsley D B. Brain waves and cortical development in newborn and young infants. *Am Psychol* 1964; **4**: 248–9.
- Dreyfus-Brisac C. The electroencephalogram of premature infant and full term infant: normal and abnormal development of waking and sleeping patterns. In: Kellaway P C, Peterson K G I, eds. *Neurological and electroencephalographic studies in infancy*. New York: Grune & Stratton, 1964: 186–207.
- Roffwarg H P, Muzio J N, Dement W C. Ontogenetic development of the human sleep-dream cycle. *Science*, 1966; **152**: 604–19.
- Parmelee A H, Jr, Schulte F J, Akiyama Y, Wenner W H, Shultz M A, Stern E. Maturation on EEG activity during sleep in premature infants. *Electroencephalogr Clin Neurophysiol* 1968; **24**: 319–29.
- Lowry O H, Rosenbrough N J, Farr A L, Randall R J. Protein measurement with the folin phenol reagent. *J Biol Chem* 1951; **193**: 265–75.
- Stern E, Parmelee A H, Jr, Akiyama Y, Schultz M A, Wenner W H. Sleep cycle characteristics in infants. *Pediatrics* 1969; **43**: 65–70.
- Petre-Quadens O. On the different phases of the sleep of the newborn with special reference to the activated phase or phase d. *J Neurol Sci* 1966; **3**: 151–61.
- Dreyfus-Brisac C, Monod N. Sleep of premature and full terms. Polygraphic study. *Proc R Soc Med* 1965; **58**: 6–7.
- Monod N, Pajot N. Le sommeil du nouveau-né et du prématuré. I. Analyse des études polygraphiques (mouvements oculaires, respiration, et EEG) chez le nouveau-né à terme. *Biol Neonate* 1965; **8**: 281–307.
- Schulman C. Alterations of sleep cycle in heroin-addicted and 'suspected' newborns. *Neuropediatrics* 1969; **1**: 89–93.
- Schulte F J, Hinze G, Schrempf G. Maternal toxemia, fetal malnutrition, and bioelectric brain activity of the newborn. *Neuropediatrics* 1971; **2**: 439–60.
- Jouvet M. Some monoaminergic mechanisms controlling sleep and waking. In: Karczmar A G, Eccles J C, eds. *Proceedings of a Symposium on the brain and human behavior*, Logola University, Chicago, 1969. Berlin: Springer, 1972: 131–61.
- George R, Heslett W L, Jenden D J. A cholinergic mechanism in the brain stem reticular formation: induction of paradoxical sleep. *Neuropharmacology* 1964; **3**: 451–2.
- Baxter B L. Induction of both emotional behaviour and a novel form of REM—sleep by chemical stimulation applied to cat mesencephalon. *Exp Neurol* 1969; **23**: 220–9.
- Parmelee A H, Jr, Wenner W H, Akiyama Y, Flescher J. Electroencephalographic and brain maturation. In: Minkowski A, ed. *Regional development of the brain in early life*. Oxford: Blackwell, 1967: 459–76.
- McGuity D J. Effect of prolonged isolation and subsequent enrichment on sleep pattern in kittens (abstract). *Electroencephalogr Clin Neurophysiol* 1969; **26**: 335.
- Lucero M A. Lengthening of REM sleep duration consecutive to learning in the rat. *Brain Res* 1970; **20**: 319–22.
- Fitzhardinge P M, Steven A M. The small for dates infants. Neurological and intellectual sequelae. *Pediatrics* 1972; **50**: 50–7.

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