Sleep–wake cycle disturbances in protein–energy malnutrition: effect of nutritional rehabilitation

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تأثير التأهيل التغذوي على اضطرابات دورة النوم واليقظة لدى الرُّضَّع المصابين بسوء التغذية بالبروتين والطاقة

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الخلاصة: تم في هذه الدراسة توزيع استبيان موحَّد حول النوم، وإجراء الاختبار المتعدِّد المعايير polysomnograph لتقييم أنماط النوم لدى 26 من الرضَّع الذين يعانون من سوء التغذية بالبروتين والطاقة. وتم تكرار ذلك بعد حوالي شهرين من تنفيذ برنامج للتأهيل التغذوي وفقاً للدلائل الإرشادية لمنظمة الصحة العالمية. وتمت مقارنة مجموعات الدراسة مع 10 من الرضَّع الأصحاء. كما أُجريت القياسات البشرية مع قياس مستويات سيروتونين المصل. ولوحظ بعد التأهيل التغذوي انخفاض يُعتدُّ به إحصائياً في النسبة المئوية للنوم في مرحلة الحركة غير السريعة للعين، وفي مدة الحركة السريعة الثانية للعين، وفي عدد مرات نوم الكمون والنوم في مرحلة الحركة السريعة للعين. ولوحظ أيضاً ارتفاع يعتدُّ به إحصائياً في النوم في مرحلة الحركة السريعة للعين، وفي مستويات سيروتونين المصل. ويبدو من الدراسة أن سوء التغذية بالبروتين والطاقة يؤثِّر على دورة النوم واليقظة. وقد يكون اضطراب مستويات سيروتونين المصل من بين العوامل المسؤولة عن ذلك.

ABSTRACT A standard sleep questionnaire was given to the parents of 26 infants with protein–energy malnutrition who underwent polysomnographic evaluation. These investigations were repeated approximately 2 months after enrolment in a nutritional rehabilitation programme based on World Health Organization guidelines. Anthropometric values and serum serotonin levels were also measured. After nutritional rehabilitation there was a significantly higher percentage of non-rapid eye movement (REM) sleep; 2nd REM time, and latency times for sleep and REM sleep increased. Percentages of REM sleep and serum serotonin levels decreased significantly. Protein–energy malnutrition seems to affect the sleep–wake cycle; disturbed serotonin levels may be among the factors responsible.

Troubles du cycle veille-sommeil dans la malnutrition protéinocalorique : l'effet de la récupération nutritionnelle

RÉSUMÉ Un questionnaire normalisé sur les habitudes de sommeil de leur enfant a été administré aux parents de 26 nourrissons souffrant de malnutrition protéinocalorique, lesquels ont subi un examen polysomnographique. Ces évaluations ont été répétées 2 mois environ après inclusion des nourrissons dans un programme de récupération nutritionnelle conforme aux directives de l'Organisation mondiale de la Santé. Les paramètres anthropométriques et la sérotoninémie ont également été mesurés. À l'issue de la récupération nutritionnelle, on a pu constater une augmentation significative du pourcentage du sommeil NREM (pour *non-rapid eye movement* – sans mouvements oculaires rapides), ou sommeil lent, ainsi qu'un allongement de la durée de la deuxième phase de sommeil REM (*rapid eye movement* – à mouvements oculaires rapides), ou sommeil paradoxal, de la latence d'endormissement et de la latence du sommeil paradoxal. Il a en outre été noté une diminution significative du pourcentage du sommeil REM et de la sérotoninémie. La malnutrition protéinocalorique semble retentir sur le cycle veille-sommeil; il est probable que l'instabilité de la sérotoninémie figure parmi les facteurs responsables.

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Introduction

Nutritional deficiencies are a major health problem in tropical and subtropical regions of the world [*1*]. Malnutrition is still a problem especially in developing countries, where the total number of underweight and stunted children has not changed dramatically since 1980 [*2*]. In Egypt, the incidence of protein–energy malnutrition (PEM) was found to be 16.5% [*3*].

Reduction in the supply of energy and several essential nutrients during the early stages of life has profound effects on the nervous system structural and functional development. Malnutrition impairs brain development, decreasing the number of cell replication cycles, reducing total brain DNA and restricting dendritic arborization, thus reducing the connection between neurons [*4*]. Cintra and colleagues [*5*] stated that prenatal and chronic malnutrition produces important alterations in the homeostatic and circadian process of sleep, thus altering the sleep–wake cycle.

Several neuropeptides affect the sleep–wake cycle [*6*] and a role for gamma-aminobutyric acid (GABA) transmission has been hypothesized [*7*]. Lechin et al. investigated the changes of circulating neurotransmitters (noradrenaline, adrenaline, dopamine, platelet serotonin, plasma serotonin and tryptophan) during the sleep–wake cycle to correlate the profile of circulating neurotransmitters with the well-known central neurocircuitry functioning during the sleep–wake cycle [*8*]. Among many factors associated with PEM, increased levels of the neurotransmitter serotonin were reported to be the cause of sleep disturbances in malnourished rats [*9*].

Since PEM is still a problem in many countries, its effects on children's development and cognition is a concern of many investigators. As far as we know, sleep disturbances in PEM patients have rarely been studied before as most of the data on malnutrition from sleep laboratories is from animal models [*5,9,10,11*] or anorectic adults [*12,13*]. This study was therefore designed to detect disturbances in the sleep–wake cycle of Egyptian infants with PEM, comparing oedematous and non-oedematous cases before and after a nutritional rehabilitation programme, and to correlate the detected abnormalities to the level of the neurotransmitter serotonin.

Methods

Patients

The present study was conducted on 26 infants diagnosed with PEM according to the Wellcome classification [*14*]. They were recruited from the nutritional unit of the Children's Hospital and assessed at the Institute of Psychiatry, Ain Shams University. The patients were further divided into 2 groups according to the 2 clinically distinct disorders of PEM, oedematous and non-oedematous, Heird's preferred terms for kwashiorkor and marasmus respectively [*3*].

Group 1 was 12 infants with the non-oedematous form of PEM (8 males and 4 females), with a mean age of 8.5 months [standard deviation (SD) 3.8 months]. Group 2 comprised 14 infants (8 males and 6 females) with the oedematous form of PEM, with a mean age of 13.7 (SD 7.5) months. Patients of both groups were compared with group 3, 10 clinically healthy age- and sex-matched controls (5 males and 5 females), with a mean age of 12.6 (SD 6.8) months. The controls were recruited from among those presenting for dietetic advice, vaccination or circumcision (in males) at the outpatient clinic in the Children's Hospital.

All the recruited patients and controls were from underprivileged families (having low socioeconomic standard according to Park and Park [*15*]) and had been breastfed for at least 6 months and afterwards weaned while receiving artificial milk products. None of the infants was on any medication or vitamin supplementation at the time of enrolment in the study.

Investigations

An informed written consent was signed by the parents or the legal guardians after obtaining the approval of the ethical committee at the Children's Hospital, Ain Shams University. Each studied infant was then enrolled in the 3-phase study: pre-interventional assessment (phase 1); a nutritional rehabilitation intervention programme according to World Health Organization (WHO) guidelines [*16*] (phase 2); and a post-interventional assessment 2 months (SD 2 weeks) after enrolment (phase 3).

The WHO nutritional rehabilitation programme starts feeding with a diet which is low in protein, fat and sodium and high in carbohydrates (calorie intake 80–100 kcal/kg/day) as almost all severely malnourished infants have infections, impaired liver and intestinal functions and problems related to electrolyte imbalance. At the rehabilitation stage as the infant's appetite returns, the calorie intake is increased to 150–200 kcal/kg/day with an increase in amounts and decrease in frequency. A high protein diet is given and vitamins and minerals (potassium, magnesium and zinc) are continued in increased amounts. Iron is given during this stage to treat the anaemia present. The infant remains in the hospital during the early phase of rehabilitation (at least 3 weeks after admission), and is then followed up in the nutritional rehabilitation outpatient clinic.

Assessment in phases 1 and 2 included detailed dietetic history and clinical examination, with special emphasis on the anthropometric measurements and signs of malnutrition as well as the laboratory workup and recording the sleep data.

Laboratory workup

For the laboratory workup, samples of blood were collected from all subjects and processed as clotted venous blood and EDTA anticoagulated blood. Serum samples were used for the determination of liver and kidney functions (Synchron CX-5 Delta, Beckman Inst. Inc., Scientific Instruments Division, Fullerton, USA). Serum level of serotonin was estimated as well in all studied cases by enzyme-linked immunosorbent assay (ELISA) according to Chauveau et al. [*17*]. The EDTA blood was used for complete blood count (Coulter T660, Miami, USA).

Assessment of sleep

Assessment of sleep was done through a standard sleep questionnaire in simple Arabic language that was answered by the parents [*18*] in addition to polysomnographic evaluation of the study infants and controls who were left to sleep spontaneously without any intervention. The apparatus used was the Neurofax EEG-2110 digital electroencephalograph (Nihon Koden Corporation, Tokyo, Japan), with 3 dedicated respiratory inputs at the headbox and 4 available DC channels. The EEG 2110 can record a variety of biopotential activities necessary for the sleep laboratory. Polysmith TM software provided the immediate staging, scoring and reporting of the polysomnographic recordings.

Hypnographic sleep EEG provided the following variables: sleep continuity (including sleep latency and efficiency and

number of arousals) as well as sleep architecture, including percentage of rapid eye movement (REM) sleep, non-REM (NREM) sleep and slow wave sleep (SWS), as well as REM, NREM and SWS latency periods. The analysis of sleep architecture did not include a differential percentage of each sleep stage (I, II, III, IV), but rather NREM or SWS was considered as a whole.

Statistical analysis

Statistical analysis of the results was done using *SPSS*, version 10 and *Statsoft,* version 5. Non-parametric data were detected by the Shapiro–Wilk test. Student *t*- and paired *t*- tests were used for parametric quantitative data and Mann–Whitney U and Wilcoxon matched pairs tests for non-parametric quantitative data in addition to the correlation studies. The numerical data were represented in mean and standard deviation (SD) and median (interquartile range). The differences were considered significant at $P < 0.05$.

Results

Anthropometric data

The present study revealed significantly lower anthropometric measurements—weight, length and mid arm circumference—in PEM patients compared with those of the controls at the pre-assessment phase (Table 1). These measurements showed significant improvements after nutritional rehabilitation in both oedematous and non-oedematous patients, although the values did not reach control values (Table 2). The same findings were observed regarding haemoglobin and serum albumin levels (Tables 1 and 2). As regards liver and kidney functions, their values were within the normal range for age and sex according to Nicholson and Pesce [*19*] from the start of the study.

Serum serotonin levels were significantly higher in both studied PEM subgroups compared with those of the controls (Table 1) and these decreased significantly after nutritional rehabilitation (Table 2).

The study also revealed significantly lower skull circumference (% of median for age) and serum albumin with significantly higher serum serotonin in the oedematous compared with the non-oedematous patients (Table 1).

Sleep data

Analysis of the sleep questionnaire findings revealed that caregivers reported sleep complaints in 76.9% of cases, mostly disturbed sleep rhythm, in both subgroups of PEM infants.

As regards the sleep data before nutritional rehabilitation, there was no significant difference between both PEM groups before nutritional rehabilitation (Table 3). Comparing both groups of PEM infants with the control infants showed a significantly lower percentage of NREM sleep, REM latency time and 2nd REM time. In addition, the number of minutes of sleep latency was lower in both PEM groups compared with the controls but this result was significant only in non-oedematous patients. On the other hand, the percentage of REM sleep was higher in both PEM groups compared to the controls but this result was significant only in oedematous patients (Table 3). In addition, initial SWS latency time and the percentage of SWS were not significantly different in both subgroups compared with the controls.

Table 4 shows the sleep parameters measured after nutritional rehabilitation. Sleep latency increased in both groups and this was significant in non-oedematous infants. The percentage of NREM sleep and the amount of 2nd REM sleep time increased in both groups, with a statistically significant

Table 1 **Anthropometric measurements and laboratory parameters of infants with non-oedematous and oedematous protein–energy malnutrition before nutritional rehabilitation compared to the controls**

Variable	Mean (SD) [Median (interquartile range)]			Statistics		
	Non-oedematous Group 1 (n = 12)	Oedematous Group 2 (n = 14)	Control Group 3 (n = 10)	Group 1 vs 3 t/Z values	Group 2 vs 3 t/Z values	Group 1 vs 2 t/Z values
Weight (% of median for age)	61.2 (12.5) [58.5 (14.7)]	62.9 (8.9) [66.0 (16.0)]	93.6 (6.7) [94.9 (6.5)]	–3.82[a] (P < 0.001)	–4.10[a] (P < 0.001)	–0.82[a] (P > 0.05)
Length/height (% of median for age)	88.1 (3.7) [88.7 (5.2)]	84.9 (8.8) [87.3 (4.3)]	97.1 (1.1) [97.6 (1.6)]	–3.96[a] (P < 0.001)	–4.10[a] (P < 0.001)	–0.62[a] (P > 0.05)
Skull circumference (% of median for age)	92.3 (1.5) [92.8 (2.5)]	90.6 (4.6) [90.4 (5.0)]	95.6 (1.5) [95.8 (2.0)]	–3.96[a] (P < 0.05)[a]	–4.10[a] (P < 0.05)	–2.16[a] (P < 0.05)
Mid arm circumference (cm)	8.5 (1.0) [8.5 (1.0)]	9.0 (1.6) [9.0 (3.5)]	13.1 (0.8) [13.0 (1.2)]	–3.96[a] (P < 0.001)	–4.10[a] (P < 0.001)	0.93[a] (P > 0.05)
Serum albumin (g/dL)	3.2 (0.5) [3.1 (0.7)]	2.2 (0.2) [2.2 (0.2)]	4.2 (0.5) [4.3 (0.6)]	–3.51[a] (P < 0.001)	–4.12[a] (P < 0.001)	–4.35[a] (P < 0.001)
Haemoglobin (g/dL)	8.9 (1.0) [8.9 (9.0)]	9.7 (1.8) [9.0 (9.7)]	12.1 (1.6) [12.3 (1.5)]	–5.27 (P < 0.001)	–3.23 (P < 0.01)	–1.11 (P > 0.05)
Serum serotonin (ng/mL)	434.7 (270.3) [251.5 (360.4)]	646.5 (238.1) [745.2 (374.8)]	190.5 (34.2) [175.4 (48.2)]	–3.10[a] (P < 0.01)	–4.10[a] (P < 0.001)	–2.57[a] (P < 0.05)

[a]*Non-parametric data were tested by Shapiro–Wilk test. The test of significance was Mann–Whitney test.*
SD = standard deviation.

Table 2 **Comparison between anthropometric measurements and laboratory parameters of infants with non-oedematous and oedematous protein–energy malnutrition before and after nutritional rehabilitation**

Variable	Non-oedematous (n = 10) Mean (SD) [Median (interquartile range)]			Oedematous (n = 10) Mean ± SD [Median (interquartile range)]		
	Before	After	Statistics t/Z values	Before	After	Statistics t/Z values
Weight (% of median for age)	61.2 (12.5) [58.5 (14.7)]	71.2 (9.9) [68.5 (11.1)]	3.18[a] (P < 0.01)	62.9 (8.9) [66.0 (16.0)]	74.1 (10.3) [72.7 (21.1)]	–3.47[a] (P < 0.001)
Length/height (% of median for age)	88.1 (3.7) [88.7 (5.2)]	88.8 (5.3) [87.9 (8.9)]	–0.54 (P > 0.05)	84.9 (8.8) [87.3 (4.3)]	89.0 (6.8) [89.8 (13.2)]	2.41[a] (P < 0.05)
Skull circumference (% of median for age)	92.3 (1.5) [92.8 (2.5)]	93.8 (2.5) [94.0 (1.9)]	2.02[a] (P < 0.05)	90.6 (4.6) [90.4 (5.0)]	93.0 (2.8) [93.8 (4.0)]	–7.15 (P < 0.001)
Mid arm circumference (cm)	8.5 (1.0) [8.5 (1.0)]	9.8 (0.9) [9.8 (1.5)]	–16.58 (P < 0.001)	9.0 (1.6) [9.0 (3.5)]	9.9 (1.8) [9.7 (3.5)]	–8.33 (P < 0.001)
Serum albumin (g/dL)	3.2 (0.5) [3.1 (0.7)]	3.95 (0.3) [3.9 (0.4)]	7.35 (P < 0.001)	2.2 (0.2) [2.2 (0.2)]	3.6 (0.1) [3.5 (0.2)]	25.24 (P < 0.001)
Haemoglobin (g/dL)	8.9 (1.0) [8.9 (9.0)]	9.96 (0.8) [9.5 (9.5)]	–7.98 (P < 0.001)	9.7 (1.8) [9.0 (9.7)]	10.5 (1.2) [10.3 (11.1)]	–4.31 (P < 0.01)
Serum serotonin (ng/mL)	434.7 (270.3) [251.5 (360.4)]	152.1 (63.9) [127.9 (80.9)]	–3.06[a] (P < 0.01)	646.5 (238.1) [745.2 (374.8)]	220.9 (34.2) [238.0 (114.1)]	–3.30[a] (P < 0.01)

[a] *Non-parametric data were tested by Shapiro–Wilk test. The test of significance was Wilcoxon matched pairs test.*
SD = standard deviation.

Table 3 **Sleep data of infants with non-oedematous and oedematous protein–energy malnutrition before nutritional rehabilitation compared with the controls**

Variable	Mean (SD) [Median (interquartile range)]			Statistics		
	Non-oedematous Group 1 (*n* = 15)	Oedematous Group 2 (*n* = 15)	Control Group 3 (*n* = 10)	Group 1 vs 3 *Z* value	Group 2 vs 3 *Z* value	Group 1 vs 2 *Z* value
Sleep latency (min)	2.8 (1.1) [3.1 (1.9)]	4.1 (2.1) [3.2 (3.2)]	5.5 (2.2) [5.1 (3.7)]	–3.03 (*P* < 0.01)	–1.35 (*P* > 0.05)	–1.44 (*P* > 0.05)
Sleep efficiency (%)	95.2 (2.1) [95.3 (4.1)]	93.6 (1.9) [93.2 (2.7)]	94.4 (1.5) [94.4 (2.2)]	–0.86 (*P* > 0.05)	–1.35 (P > 0.05)	–1.65 (*P* > 0.05)
NREM sleep (%)	44.5 (12.0) [44.0 (19.1)]	49.6 (10.3) [50.0 (20.8)]	60.6 (8.9) [63.5 (7.9)]	–2.77 (*P* < 0.01)	–2.58 (*P* < 0.01)	–1.23 (*P* > 0.05)
SWS (%)	20.0 (11.6) [19.4 (14.5)]	18.6 (4.8) [18.5 (2.3)]	13.7 (8.8) [19.0 (14.0)]	–0.92 (*P* > 0.05)	–0.23 (*P* > 0.05)	–0.62 (*P* > 0.05)
REM sleep (%)	41.2 (6.1) [39.0 (11.9)]	43.8 (6.2) [43.0 (12.0)]	36.6 (3.7) [36.5 (7.0)]	–1.85 (*P* > 0.05)	–2.63 (*P* < 0.01)	–1.44 (*P* > 0.05)
SWS latency (min)	17.0 (12.7) [23.5 (26.0)]	19.6 (13.4) [27.0 (31.0)]	13.2 (11.8) [19.0 (20.0)]	–1.12 (*P* > 0.05)	–1.46 (*P* > 0.05)	–1.13 (*P* > 0.05)
REM sleep latency (min)	6.5 (8.3) [2.0 (17.0)]	13.0 (10.1) [13.0 (21.0)]	27.3 (14.3) [31.5 (23.0)]	–2.84 (*P* < 0.01)	–2.34 (*P* < 0.05)	–1.23 (*P* > 0.05)
2nd REM sleep (min)	56.2 (7.3) [56.0 (14.0)]	61.6 (8.4) [59.0 (17.0)]	70.3 (4.4) [70.5 (6.0)]	–3.63 (*P* < 0.001)	–2.52 (*P* < 0.05)	–1.85 (*P* > 0.05)
Arousal index	0.9 (0.35) [0.9 (0.3)]	1.2 (0.5) [1.2 (0.6)]	0.9 (0.5) [1.0 (0.8)]	–0.66 (*P* > 0.05)	–0.88 (*P* > 0.05)	–1.44 (*P* > 0.05)

All data are non-parametric data detected by Shapiro–Wilk test. The test of significance was Mann–Whitney test.
SD = standard deviation; REM = rapid eye movement; NREM = non-rapid eye movement; SWS = slow wave sleep.

Table 4 **Comparison between sleep data of infants with non-oedematous and oedematous protein–energy malnutrition before and after nutritional rehabilitation**

Variable	Non-oedematous (*n* = 10) Mean (SD) [Median (interquartile range)]			Oedematous (*n* = 10) Mean (SD) [Median (interquartile range)]		
	Before	After	Statistics *t*/*Z* values	Before	After	Statistics *t*/*Z* values
Sleep latency (min)	2.8 (1.1) [3.1 (1.9)]	3.9 (0.6) [3.9 (0.5)]	2.02[a] (*P* < 0.05)	4.1 ± 2.1 [3.2 (3.2)]	4.2 ± 3.0 [2.8 (5.9)]	–0.19 (*P* > 0.05)
Sleep efficiency (%)	95.2 (2.1) [95.3 (4.1)]	94.0 (1.1) [94.2 (2.0)]	0.86[a] (*P* > 0.05)	93.6 ± 1.9 [93.2 (2.7)]	94.6 ± 1.8 [94.6 (3.5)]	1.34[a] (*P* > 0.05)
NREM sleep (%)	44.5 (12.0) [44.0 (19.1)]	50.1 (7.5) [52.1 (4.1)]	0.87[a] (*P* > 0.05)	49.6 ± 10.3 [50.0 (20.8)]	58.7 ± 5.9 [60.8 (8.1)]	–5.80 (*P* < 0.001)
SWS (%)	20.0 (11.6) [19.4 (14.5)]	13.1 (8.9) [12.7 (12.4)]	2.46 (*P* < 0.05)	18.6 ± 4.8 [18.5 (2.3)]	13.3 ± 7.5 [19.3 (14.0)]	0.27[a] (*P* > 0.05)
REM sleep (%)	41.2 (6.1) [39.0 (11.9)]	43.0 (3.8) [41.8 (8.4)]	0.87[a] (*P* > 0.05)	43.8 ± 6.2 [43.0 (12.0)]	39.1 ± 3.2 [39.2 (5.2)]	–2.73 (*P* < 0.05)
SWS latency (min)	17.0 (12.7) [23.5 (26.0)]	16.8 (9.8) [18.0 (11.0)]	0.32[a] (*P* > 0.05)	19.6 ± 13.4 [27.0 (31.0)]	17.1 ± 11.8 [23.0 (27.0)]	2.85[a] (*P* < 0.01)
REM sleep latency (min)	6.5 (8.3) [2.0 (17.0)]	6.1 (7.3) [2.8 (14.0)]	0.41[a] (*P* > 0.05)	13.0 ± 10.1 [13.0 (21.0)]	16.1 ± 13.6 [21.0 (20.5)]	0.87[a] (*P* > 0.05)
2nd REM sleep (min)	56.2 (7.3) [56.0 (14.0)]	61.5 (4.8) [61.5 (5.0)]	–0.29[a] (*P* > 0.05)	61.6 ± 8.4 [59.0 (17.0)]	59.7 ± 5.9 [69.0 (10.0)]	3.47[a] (*P* < 0.001)
Arousal index	0.9 (0.4) [0.9 (0.3)]	1.1 (1.0) [0.9 (0.7)]	0.32[a] (*P* > 0.05)	1.2 ± 0.5 [1.2 (0.6)]	0.8 ± 0.7 [0.7 (1.2)]	1.34[a] (*P* > 0.05)

[a]*Non-parametric data were tested by Shapiro–Wilk test. The test of significance was Wilcoxon matched pairs test.*
SD = standard deviation REM = rapid eye movement; NREM = non-rapid eye movement; SWS= slow wave sleep.

difference in the oedematous group only. The percentage of REM sleep decreased significantly in the oedematous group while the non-oedematous one showed a non-significant increase. Moreover, SWS latency time decreased in both subgroups and this was significant only in oedematous patients. As regards percentage of SWS, it decreased significantly in the non-oedematous group, while the oedematous one showed a non-significant increase. However, in spite of the changes occurring after nutritional rehabilitation, most of the sleep EEG parameters of both groups of PEM infants did not reach the control values.

Figure 1 shows the polysomnography of a PEM patient, showing no clear stage differentiation of NREM sleep, while Figure 2 shows the polysomnography of the same patient after nutritional management with greater differentiation of sleep stages.

Anthropometric and sleep data correlations

As regards the correlation studies, the present study revealed significant positive correlation between the rate of change of REM sleep in non-oedematous PEM infants and both of weight and serum albumin (r =

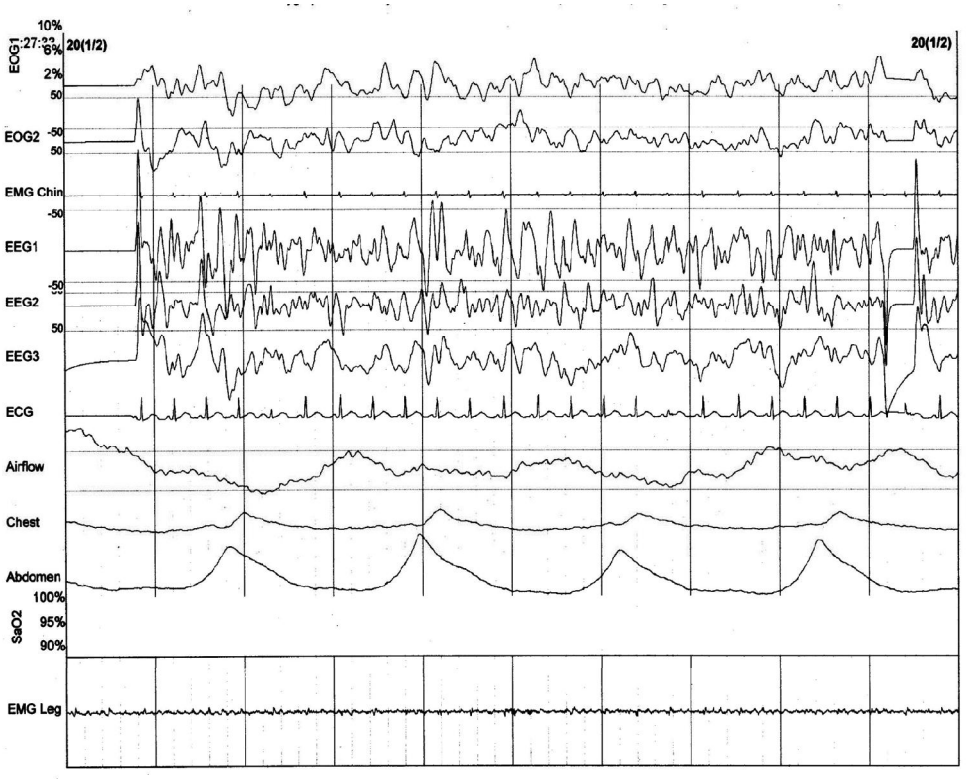

Figure 1 **Polysomnography of protein–energy malnutrition infant showing non-rapid eye movement sleep with no clear stage differentiation before nutrition rehabilitation**

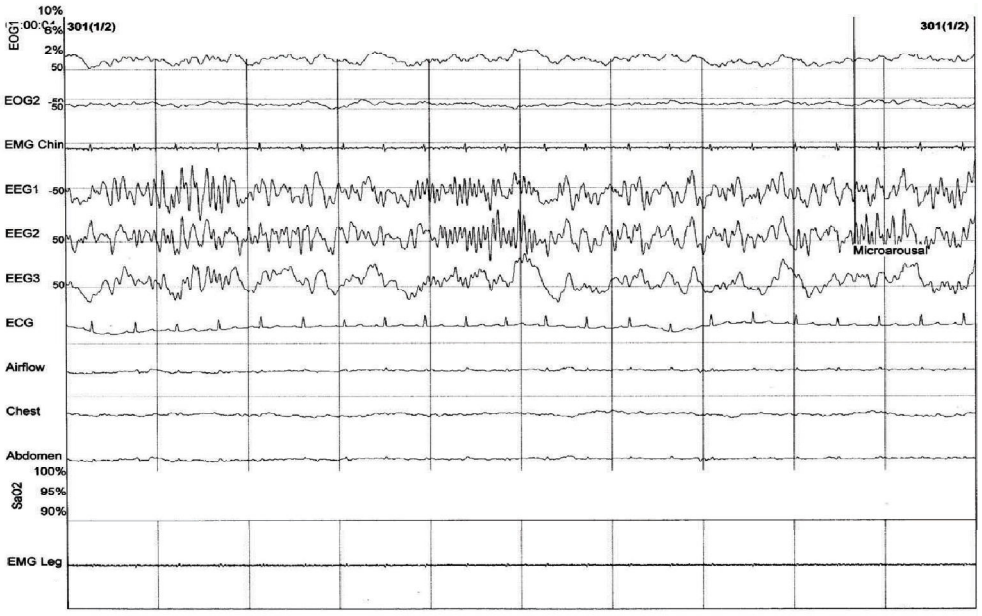

Figure 2 **Polysomnography of a protein–energy malnutrition infant showing greater differentiation of sleep staging after nutritional rehabilitation**

0.88 and 0.80 respectively and $P < 0.05$ for both). In addition the rate of change of REM sleep showed a negative correlation to serum albumin level in oedematous PEM patients but this was not statistically significant ($r = –0.45$). There was also a significant negative correlation between the rate of change of SWS and weight in non-oedematous PEM patients ($r = – 0.72$ and $P < 0.05$).

Discussion

The sleep data of the PEM infants in our study showed that the sleep latency was significantly lower in the non-oedematous malnourished group before nutritional rehabilitation compared with the controls. However, in the oedematous malnourished group sleep latency was lower than in the controls, but not significantly so. After nutritional rehabilitation the sleep latency increased in both subgroups of PEM infants, both non-oedematous and oedematous. This indicates that after nutritional rehabilitation, patients of both PEM types needed more time to fall asleep than in the acute phase of PEM illness which denotes an improvement in their condition, i.e. they are less sleepy or lethargic.

The percentage of NREM sleep was significantly lower in both non-oedematous and oedematous malnourished cases before nutritional rehabilitation compared with the controls. After nutritional rehabilitation, NREM sleep improved in the non-oedematous malnourished group, but was

still significantly lower than the control values. Moreover, the oedematous malnourished group showed improvement after nutritional rehabilitation but the percentage of NREM sleep was still lower than the control values, although not significantly. The failure of complete recovery may be attributed to the short period of nutritional rehabilitation and the immature brain development at this age.

Before nutritional rehabilitation the percentage of SWS was higher in the non-oedematous subgroup of PEM compared to the control values but this was not of statistical significance. This, in addition to the significantly higher serotonin levels detected in the PEM patients, agrees with Datta et al. [*9*]. Their animal study found that the mean percentage of SWS in malnourished rats (73.30%) was significantly higher than in well-nourished ones (61.23%) and they attributed this to increased brain serotonin levels. The same results were stated by Mokler et al. [*20*] who found that malnutrition in rats leads to increased serotonin production in the brain which leads to an increase in the percentage of SWS.

After nutritional rehabilitation, the percentage of SWS in the non-oedematous subgroup of PEM decreased and nearly reached the control levels. This is further supported by the significant negative correlation between the rate of change of SWS and weight in the non-oedematous PEM infants. Similarly Cintra et al. demonstrated that malnourished rats showed a significant reduction in SWS in the nutritional recovery period pre- and postnatally [*5*].

Before nutritional rehabilitation the percentage of REM sleep in the non-oedematous malnourished infants was higher than in the controls, but with no statistical significance. However, in the oedematous malnourished group the percentage of REM sleep was significantly higher than the controls. This may be attributed to immature brain development. After nutritional rehabilitation the percentage of REM sleep in the non-oedematous malnourished group increased but not significantly. This was further demonstrated by the significant positive correlation between the rate of change of REM sleep and that of weight and albumin in the non-oedematous group of PEM patients. On the other hand, the percentage of REM sleep decreased significantly in the oedematous malnourished subgroup, which is the normal expected pattern. This finding is further supported by the negative correlation between the rate of change of REM and that of albumin levels in these patients.

Our results of percentage REM sleep in non-oedematous patients are not consistent with Siegal who suggested that food consumption could produce an increase in REM sleep [*21*]. More recently, Cintra et al. found that there was increase in REM sleep during nutritional rehabilitation in rats with PEM [*5*].

The normalization of REM sleep to near control levels in both subgroups is important, as Shaffery et al. proposed that the primary purpose of the REM phase is to act as an inducer of CNS development in the fetus as well as the neonate [*22*] and we suggest that it might still be of the same importance during infancy.

We hypothesize that the increase in REM sleep in non-oedematous PEM might be related to a transient relative increase in REM following a period of decrease (the so called "REM rebound"), which is supposed to be followed by the stabilization period.

It is worth mentioning here is that in spite of the changes occurring after nutritional rehabilitation, most of the sleep EEG parameters of both groups of PEM infants did not reach the control values. This could be explained by the work of Robinson

et al., who detected electrophysiological abnormalities, persisting despite somatic rehabilitation, of 10 severely malnourished children, and added that this must be associated with the chronic rather than the acute aspects of malnutrition, and can be used to detect any deviation of brain function from normality [*23*].

In conclusion, the ability to maintain normal progression in sleep–wake maturation is an important index of brain development and may serve to assess how environmental factors, including essential nutrient supply, affect central nervous system development. The present study showed that PEM can have an effect on the sleep–wake cycle, which improves after adequate nutritional rehabilitation. The disturbed serotonin levels in PEM could be one of the factors responsible for such changes and this needs further study, together with assessment of the role of other neurotransmitters involved in the central nervous system functional development in PEM.

The changes that we have demonstrated in the sleep pattern in PEM infants should be considered seriously, as they could be detrimental to the development of social, behaviour and cognitive functions. We thus recommend proper and early nutritional rehabilitation for PEM infants not only to improve the physical growth parameters but also to improve their sleep pattern. Follow-up of these patients for longer periods is also recommended to ensure that the residual sleep changes are reversible and that there are no permanent changes. Further studies on PEM patients are advised on a larger scale to support the current results and to measure the specific dietetic elements which could be the causal factors for the sleep disturbances.

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