PHYSIOLOGICAL AND CLINICAL DATA ON RELATIONS OF MAGNESIUM AND SLEEP

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Literature review

It is surprising that in spite of frequent occurrence of sleep disorders in magnesium deficiency and in the spasmophilic syndromes, only a small number of publications in this field appeared. We can mention the papers of *Durlach* (5,8), *Poenaru* et al. (19,20), *Popoviciu* (26), and *Popoviciu* et al (22, 23, 24, 25, 30, 31). Some of these papers (22, 23, 24, 25) were devoted to sleep disorders in spasmophilic patients with hypocalcemia (sometimes associated with hypomagnesemia). But in the last years, together with the precise identification of the neurogenic spasmophilic syndromes (NSS) generated by the magnesium deficits (5, 8, 19, 20, 25, 30, 31), we performed some systematic polysomnographic researches in sleep disorders associated with magnesium deficiency.

It is known that in our clinical practice we sometimes meet certain cases in which the establishment of the diagnosis needs complex paraclinical and laboratory examinations. It often happens so in cases of spasmophilia. On one hand it is due to the multiple factors in its pathogenesis, and on the other hand to the

great variety of symptoms that might be caused by it, imitating those of other affections (neurosis, migraine, epilepsy etc). The coexistence of spasmophilia with one of these affections exerts a mutual influence and exacerbation, which makes the problem more difficult. The diagnosis of spasmophilia is important because of the very good response of this affection to adequate treatment, and this justifies the great number of new investigations in this field.

First some problems of physiopathology of central nervous system (CNS) disorders in magnesium defficiency (5,8) must be summarized. A reduction of the cAMP/cGMP ratio in all the regions, especially in the thalamus-hypothalamus, midbrain and in cortex (33) was found in the CNS of adult rats deficient in Mg.The changes in neuromediators and neuromodulators in the CNS during magnesium deficiency can be summed up basically as an increased turnover of biogenic amines (serotonin, acetylcholine and catecholamines), associated with a reduction in the turnover of GABA and taurine (5, 8, 6, 9, 13, 21, 33). These complex modifications conduct to the increasing of cGMP and the reducing of cAMP. The neuromuscular hyperexcitability in magnesium deficiency seems to be based on a tendency towards reduction of the ratio of the two principal cycle nucleotide second messengers, cAMP/cGMP (8). During magnesium deficiency, the aminergic neuromediators exhibit increased turnover (8, 9, 21). Conversely, turnover of GABA and taurine is most often reduced. These changes tend to increase cGMP and decrease cAMP, with the exception of certain cAMP-dependent catecholamine receptors (8). The level of Mg in the CNS during magnesium deficiency can play a direct role in reducing activity of adenylate cyclase or stimulating the activity of guanylate cyclase (8). But these modifications necessarily involve calcium overloading and disturbances of its distribution in the cells, in conjunction with the modifications in the levels and in the distribution both of calmodulin (17) and of its cercebral antagonist calcineurin (16) and of taurine (6, 7, 8, 13, 33).

We may suppose the implication of magnesium in the regulation of sleep and wakefulness by the biochemical functions of magnesium, especially by the participation of this element in the synthesis and activity of a very great number of the enzymes with important role in the carbohydrate metabolism, in the nucleic acid and protein metabolism, in the lipid metabolism, in the activity of other enzymes:phosphatases, cholinesterase, ATP-ase a.s.o. In this respect we send the reader to the synthetic papers of *Aikawa* (1), *Durlach* (8), *Jouvet* (14), *Hartmann* (15), *Wollemann* (38) and *Popoviciu* and *Arseni* (29). It is important to point out the relations established between neuroses and secondary magnesium deficits, both of these creating reciprocal vicious circles in determining sleep disorders. Neuroses constitute major "conditioning factors" for stress (8, 9, 23, 24, 26). Neurotics are "specifically" exposed to the loss of magnesium during the physical and psychical stress (8, 23, 26). Neuroses thus very frequently produce secondary magnesium deficits (10,11). At the same time, magnesium deficit produces neurotic disorders, both generating sleep disorders. When signs of magnesium deficit are associated with symptoms of neuroses, it is very difficult to appreciate the primordial role of the magnesium deficit or of the neurosis(5, 6, 8, 30).

We studied clinically 1320 EMG and EEG well verified neurogenic spasmophilic syndromes (NSS) cases, of which we retained 397 patients with clinical and biochemical well-substantiated NSS presenting hypomagnesemia. Out of the 397 patients, only three groups were selected for this study : I) 240 subjects suffering from nocturnal insomnia, counterbalanced by diurnal sleepiness. II) 15 patients suffering from hypersomnia. III) 27 patients suffering from nonepileptic nocturnal episodic manifestations (NEM).

I) *Insomnia in patients with magnesium deficiency:* 240 subjects. Some of our results have been recently published (31).

The dosing of the seric and erythrocytic Mg was performed by means of a colourimetric method with xylidyl blue (Mann and Yoe method) (31), while the readings were carried out on a PYE UNICAM spectrophotometer. The EEG and EMG changes were studied by means of an original method of simultaneous recording of the EEG and EMG (24, 25, 26, 34), before, during and after hyperpnoea. In 35 selected cases we carried out 8 hours of continuous night polysomnographical recordings by means of polygraphic devices provided with either 8 or 16 channels, which investigated the eye movements (EM), the menton electromyogram (MEMG) and the electrocardiogram (ECG), as well as the EEG (several channels), the respiration and the actogram (ACTO). The estimation of the stages of slow wave sleep (SWS) and of REM sleep was according to the criteria of *Rechtschaffen* and *Kales* (34) and of *Popoviciu* et al. (26). In establishing the normal percentages of the REM periods, we guided by the normal values ranging from 18 to 25 percent of the total sleep (26). There were computed: a) The total sleep time (TST); b) The sleep latency (SL); c) The REM latency (RL); d) The total wake time (TWT); e) The sleep stages organization (duration and percentages).

Table 1 shows that in the studied patients we found decreases of the seric and erythrocytic Mg.

Table 1.

Mean values ($\bar{x} \pm SD$) of the serum and erythrocyte Mg. in controls and in NSS with insomnia in mmol/l

	Controls (N=50)	Patients with NSS with insomnia (N=35)	T (P<0.01)
Serum Mg	0.941 ± 0.170	0.824 ± 0.087	4.151/S
Erythrocyte Mg	2.359 ± 0.282	1.643 ± 0.390	9.293/S

The *Chwostek* and *Trousseau* signs were positive in all the cases, marking the neuromuscular hyperexcitability. In all the cases, the EEG anomalies were noted during hyperpnoea, under the form of sinusoidal slow waves and slow polyspikes-and-waves on all the derivations, pointing out the presence of the spasmophilic syndromes.

Table 2 illustrates the mean values of total sleep time (TST), of the total wake time (TWT) during 8 hours of polysomnographic recordings, of the sleep latency (SL) and of the REM latency (RL). It can be observed that the patients slept only for 213.32 min. per night and that they spent 266.28 min. in several split periods of wakefulness. The mean values of SL were of 48.20 min., while the RL was of 131.18 min. (i.e. much longer than in normal subjects).

Table 2.

Mean values of TST, TWT, SL and RL

	Total sleep time		Total wake time		Sleep latence		REM latency	
	Controls (N=15)	NSS (N=35)	Controls (N=15)	NSS (N=35)	Controls (N=15)	NSS (N=35)	Controls (N=15)	NSS (N=35)
Mean values ($\bar{X}$) min	424.40	213.32	55.60	266.28	29.40	48.20	86.50	131.18
Standard deviation (SD) min	90.40	76.52	40.22	76.56	16.25	82.41	22.40	32.25
T (P<0.01)	13.951/S		12.697/S		1.292/NS		5.621/S	

Table 3 and Figures 1, 2, 3 and 4 display the sleep organization. One can see important sleep anomalies both in the course of sleep cycles (involving various and repeated stage changes) and in the composition of these cycles. In all the cases, as shown in the table 3 and in the figures 1-4 there was a clear-cut prevalence of the light slow wave sleep (LSWS) and an important diminution of the deep slow wave sleep (DSWS - stages III and IV), or even the total absence of this DSWS in 12 cases.

Table 3.

Sleep organization

	Stages I A		Stages I B		Stages II		Stages III - IV		REM	
	Controls (N=15)	NSS (N=35)	Controls (N=15)	NSS (N=35)	Controls (N=15)	NSS (N=35)	Controls (N=15)	NSS (N=35)	Controls (N=15)	NSS (N=35)
Mean values ($\bar{X}$) min	16.40	43.99	40.40	88.46	144.50	40.48	108.10	10.26	95.00	30.53
Standard dev (SD) min	17.40	33.15	19.50	22.36	45.31	58.19	31.40	21.52	26.35	49.55
%Total sleep time	8.58	20.43	9.52	41.47	34.05	18.98	25.47	4.81	22.38	14.31

Regarding the wakefulness states, the histograms of the recordings (Fig. 1-4) showed that wakefulness states were present not as long- lasting states at the beginning and at the end of the night, but as more or less long periods of awakening states, dividing the various stages of sleep into fragments. In 33 of the cases , a significant decrease of number, duration and percentages of the REM sleep was found (from only 16. min. to 40 min. during the entire night). The mean percentage value of REM sleep for all the patients was of 14.41 percent (in 6 patients not more than 3.00 percent and in 2 patients of 0 percent).

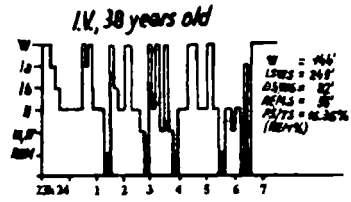

Fig. 1: Polysomnographic diagram of the patient I.V., 38 years old. Diagnosis: Hypomagnesian spasmophylic syndrome with insomnia. One can see the nocturnal sleep disorganization with many periods of wakefulness, with predominance of the LSWS and with a slight reduction of the REM sleep (16.36%).

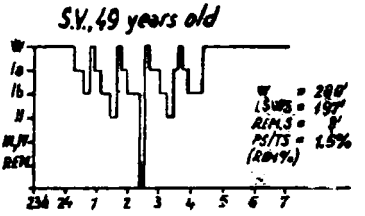

Fig. 2: Polysomnographic diagram of a female, 49 years old. Diagnosis: Hypomagnesian spasmophilic syndrome with neurotic picture and insomnia. Important sleep disorganization, with many periods of wakefulness with LSWS, absence of DSWS and with only a short stage of REM sleep (3 min. i.e. 1.5%).

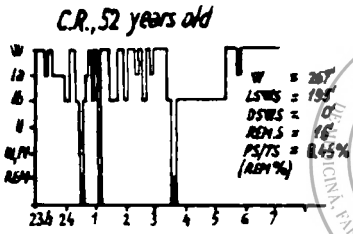

Fig. 3: Polysomnographic diagram of the patient C.R., 52 years old. Diagnosis: Hypomagnesian spasmophilic syndrome with neurotic picture and insomnia. One can see important fluctuations of the LSWS with many periods of wakefulness. Absence of the DSWS and only three very short stages of REM sleep (only 8.45% of REM sleep)

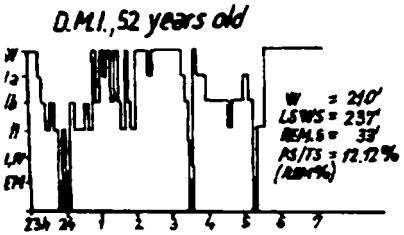

Fig. 4: Polysomnographic diagram of the patient D.M.I., 52 years old Diagnosis: Hypomagnesian spasmophilic syndrome. One can see predominance of the LSWS and of the wakefulness, the absence of the DSWS and an important reduction of the numbers and of the percentages of the REM sleep (12.12%).

In 25 cases we observed frequent occurrence of bursts of ample sharp slow waves, slow sinusoidal waves, polyspikes-and-waves and of degraded spikes-and-waves (usually being generalized ones), during stages Ib and II and very seldom during the REM phases (Figs. 5a and b). None of these cases ever presented epileptic seizures.

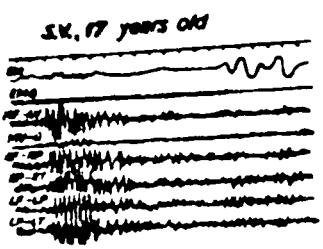

Fig. 5a: Polygraphic recording in patient S.V., 17 years old, female. Diagnosis: Hypomagnesian spasmophilic syndrome with neurotic picture, insomnia and sometimes with short and simple loss of consciouness. Stage Ib (before a transition to REM sleep). One can see a discharge of hypervolted 3c/sec degraded spines and waves, bilateral, synchronous and symmetrical.

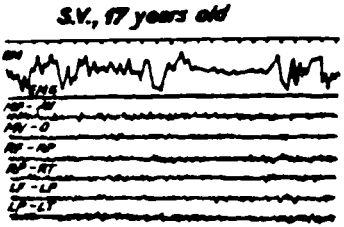

Fig. 5b: A REM sleep polygraphical recording of the same patient S.V., 17 years old, from Fig. 5a. One can see the dissapearance of the epileptic-like discharges.

As we mentioned above, it is known, according to Durlach (8), Poenaru et al. (19,20) and Popoviciu et al. (22, 23, 24, 25, 26, 30) that sleeplessness is a very frequent symptom in spasmophilia, being even able to suggest the spasmophilic disease itself. The nocturnal insomnia in NNS with magnesium deficiency is very similar to the one described by us in some previous papers (22, 26) in NSS with calcium deficiency. In the majority of cases there is not a real total insomnia, but a very poor sleep, with important sleep disorganization, with appearance of LSWS soon after the beginning of the recordings, with many periods of wakefulness, with the predominance of LSWS, with absence of DSWS and with only short stages of REM sleep.

According to our present and previous data, many patients are asleep for a rather long period of time, but their sleep is predominantly a LSWS, with various phase alternations broken up by numerous awakenings of various durations. These frequent awakenings make the patients feel that they have not slept at all, or that they have slept for a very short time. The lack or insufficiency of the DSWS produces their sensation of morning tiredness and the lack of the resting-character of their sleep as well. The low percentage of REM phases corresponds to the subjective statements of the patients who think that they did not dream. Poenaru et al. (19, 20) using a special electropolygraphic method of sleep study (sleep in the afternoon), described some pictures of the insomnia due to the primary magnesium deficiency. These authors related the shortness of the sleep cycles, the increase of the percentages of stages IA and IB, the decrease of percentages of the stages II and especially the significant amputation or even dissapearance of the stages III and IV. The paradoxical sleep was absent and the patients presented many awakenings, creating a feature with battlements of the sleep histogram. The falling asleep latency was very short, but the sleep remained superficial and broken up by frequent awakenings. This dyssomnia was responsible for the matinal astenia. Poenaru et al. demonstrated that some hypomagnesian patients are not real insomniac, very often

they being "hypoagnostic" in the sense that they think that did not sleep. The bursts of EEG discharges of the epileptic-like character which occurred during the recordings of sleep in about all the patients studied by us had a bilateral-synchronous-symmetrical appearance. They occurred during the different stages of SWS and only seldom during the REM phases. These findings suggest (22, 23, 24, 25, 26, 27, 28, 30, 31) that they are of subcortical origin, being produced at the level of the oral portion of the reticulate formation. In fact, as we had demonstrated in previous papers, (Popoviciu et al. 1970, 1971, 1976, 1984, 1985, 1987) the so called "spasmophilic" syndromes constitute a meso-diencephalic reticulate neuronal hypersynchrony, manifested, on one hand by the occurrence of the EEG phenomena (sharp slow waves and/or high voltage sinusoidal waves of 3-6 Hz, bilateral, synchronuos and symmetrical - sometimes asymmetrical - during the day, induced by hyperpnoea test, and during sleep) and, on the other hand, by the peripheral muscular and EMG changes.

II) *Hypersomnia in patients with magnesium deficiency:* 15 patients.

We had the possibility to observe 15 patients (9 females and 6 males) aged from 24 to 42 years, who presented complaints of periodic or more or less continuous hypersomnia. All the clinical, EEG and laboratory examinations were negative, excepting an evident magnesium deficiency. The mean value of Mg in the 15 patients from this group were 0.811 ± 0.068 Mmol/l serum Mg and 1.603 ± 0.190 Mmol/l erythrocyte Mg. We performed for all these cases the "Maintenance of Wakefulness" tests of *Browman* et al. (3), modified by us (32), and we found an important hypersomnia in SWS (Table 4). This "Maintenance of Wakefulness" test (MWT) was used by us in the following manner (32): The subjects were placed in a sleeping room (insonorized and perfectly obscure) and they were maintained in bed for five sessions of 20 min. each, (at 10.00; 12.00; 14.00; 16.00; 18.00 hrs). Each session was exactly concluded after 20 min., irrespective of the patient's stage (of wakefulness or sleep). In order to evaluate the slow wave sleep (SWS) and REM sleep stages, well-known standard criteria have been used (26, 34). The wakefulness-sleep polygraphical recordings have been carefully read and exactly interpreted and computed in minutes: wakefulness (W) time, SWS and REM sleep time, the sleep latency and the REM latency. In Table 4 one may see that the patients with symptomatic hypersomnias with magnesium deficiency have slept a little more than those with narcolepsy, but with important amounts of SWS (mean value 12.33 min.) as compared to the reduced durations of the REM sleep (1.57 min).They could maintain the wakefulness state for a mean period of only 6.10 min.

Table 4.

Mean values for all 5 sessions of MWT

	W (min)	SWS (min)	REM sleep (min)	Sleep Latency (min)	REM Latency (min)
Controls (N=75)	19.40	0.20	0.00	19.40	20.00
Narcoleptics (N=20)	4.07	11.55	4.38	4.09	8.14
Symptomatic hypersomnia in patients with magnesium deficiency (N=15)	6.10	12.33	1.57	6.20	16.40

during the 20 min. of the all 5 MWT sessions. However, the sleep latency was of 6.20 min. and the REM sleep latency scored a mean of 16.40 min. for all the five sessions.

It is interesting that some of these patients presented in the clinical picture periodic hypersomniac attacks of narcoleptic aspects, with short duration (but without other narcoleptic symptoms), mimicking a narcoleptic-like hypersomnia. The hypersomnia of these patients was characterized by recurrent diurnal falling asleep, but habitually without abrupt "sleep attacks", because the falling-asleep was not so irresistible as in narcolepsy. The sleep in some cases was both fast and long, but not so resting and preceded by long periods of somnolence. Subsequently an appropriate treatment with magnesium products brought about the disappearance of this hypersomnia and the recovering of these patients. In this situation we can call the attention to the hypersomniac form of the magnesium deficiency. This new nosological entity, not yet described in the literature, raises some problems. It is known that hypersomnia is symptomatic and functional.The symptomatic (or secondary) hypersomnia appears in some organic diseases of the CNS (tumoral, encephalitic, postencephalitic, vascular, toxic, metabolic a.s.o.) and in some hepatic, renal, hormonal affections (27). We think that till now, some of these rare hypersomnias, because of the non-understanding of the real physiopathological basis by the omission of the analysis of the magnesium metabolism, were integrated in the group of idiopathic functional hypersomnias. These idiopathic functional hypersomnias represent a group of functional hypersomnias with falling asleep in SWS (NREM), which are caused neither by a known organic cerebral disease, nor by other metabolic or toxic factors and which do not have a psychogenic origin (2, 18, 27, 35, 36, 37).

III) *Non-epileptic nocturnal episodic manifestations (NEM) or parasomnias :* 27 patients.

In our sleep disorders laboratories we systematically analysed in the last 20 years more than 1700 non-epileptic nocturnal episodic manifestations (NEM), some of our material being published in a previous book (28). But only in the last three years we were able to observe that in the etiopathogeny of some NEM the magnesium deficiency may play a definite role. In this way, we selected 27 patients (between 5 and 29 years old) with pavor nocturnus (PN), associated with nocturnal motor automatisms (NMA) and with nocturnal verbal automatisms (NVA). Five cases presented sometimes bruxisms (B).

The clinical and paraclinical observations eliminated other factors which can generate such NEM. On the contrary Table 5 shows that in these 27 patients studied by us we found significant decrease of the seric and erythrocytic Mg.

Table 5.

Mean values ($\bar{x} \pm SD$) of the serum and erythrocyte Mg in controls and in patients with NEM

	Controls (N=50)	Patients with NEM (N=27)	T (P<0.01)
Serum Mg	0.941 ± 0.170	0.689 ± 0.065	9.298/S
Erythrocyte Mg	2.359 ± 0.282	1.583 ± 0.160	19.4/S

In all the cases with NEM during diurnal standard EEG investigations we found no important EEG anomalies, besides the neuronal hypersynchrony (slow sinusoidal waves and sharp slow waves) generated by the hyperpnoea, which drew the attention upon the spasmophilic feature of these EEG anomalies.

In all the cases, 8 hours polysomnographical recordings showed important disorders in sleep organization. We found in about all the cases an agitated sleep, with the increase of stages of LSWS, with frequent periods of awakening, with rapid changes affecting the various stages of sleep and with the decrease of the DSWS and especially of the REM sleep (Table 6).

Table 6.

Sleep organization (8 hrs continuous polysomnegraphical recording) in 27 patients with nocturnal episodic manifestations (NEM)

Periods of awakenings (min)(%)	Stages I A (min)(%)	Stages I B (min)(%)	Stages II (min)(%)	StagesIII-IV (min)(%)	REM sleep (min) (%) (reported to total sleep)
99.8	75.3	116.2	92.4	54.1	42.2
(28.79)	(15.69)	(24.21)	(19.25)	(11.27)	(11.10)

In all these cases we found EEG anomalies, manifested by long discharges of slow waves, of sinusoidal slow waves and of sharp slow waves, appearing in the SWS (especially in the Ib, II and III stages), with disappearance in the REM sleep (Figs. 6, 7, 8 and 9).

Fig. 6: Polysomnographic recording (stage III) of the child N.L., 11 years old. Diagnosis: Non-epileptic nocturnal episodic manifestations (pavor nocturnus, bruxism and motor automatisms). One can see: irregular respiration, a long, continuous and ample tonic muscular activity (on the menton EMG), which corresponds to the beginning of the clinical seizure (monitorized in infra-red video-TV). During all the seizure (lasting 30 sec.), on the EEG tracings one can observe a slow activity (2-3c/sec.).

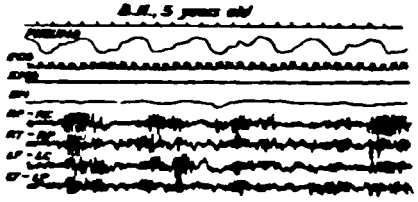

Fig. 7: Polysomnographic recording (stage Ib) of the child B.H., 5 years old. Diagnosis: Non-epileptic NEM (pavor nocturnus, sleep talking and motor automatisms). On the EEG tracings one can see several periodic generalized bursts of hypervolted sharp slow waves and sinusoidal slow waves.

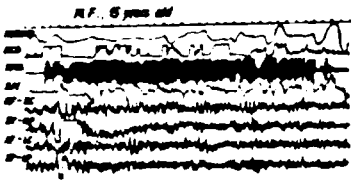

Fig. 8: Polysomnographic recording (stage III) during a seizure with pavor nocturnus, sleep talking and bruxism of the child M.F., 15 years old. One can see: a) Very irregular respiration; b) Many artifacts on the EEG; c) EMG: an important muscular tonic activity lasting 30 sec.; d) Frequent and irregular eye movements; e) EEG: ample slow waves at 2-3 c/sec. on all the derivations during all the time of seizure (monitorized in infra-red video-TV).

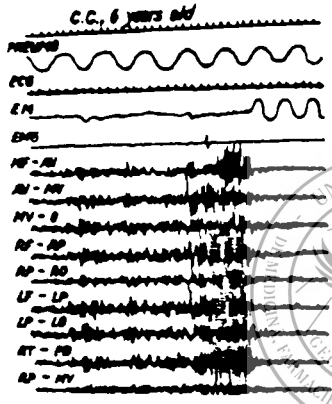

Fig. 9: A sequence of a polysomnographical recording of the child C.C., 6 years old, during a NEM (sleep talking and laughing attack, monitorized in infra-red video-TV), appeared in a transitional stage from stage II to REM sleep. One can see a burst of 3c/sec. bilateral and quasi-symmetrical sharp waves (a little ampler on the left temporal region).

We think, that perhaps these anomalies represent the expression of the brain damage caused by magnesium deficiency, or they represent the electrographic manifestations of the reticulate neuronal hypersynchrony exacerbated by the sleep.

Conclusions

1) It is suprising that in spite of the frequent occurrence of sleep disorders in magnesium deficiency and in the spasmophylic syndromes, there is only a small number of publications in this field.

2) It seems that the understanding of the new physiopathological disorders of the central nervous system in magnesium deficiency, regarding the changes in neuromediators, in neuromodulators and especially in the turnover of biogenic amines may conduct to a lot of sleep disorders, not so well identified and comprehended till now.

3) In neuropsychiatric practice especially three groups of sleep disorders can be met: insomnias, hypersomnias and nocturnal episodic manifestations (parasomnias). We think that they must be accurately and multidisciplinarily studied (polysomnographically inclusively) for a better physiopathological understanding and for an adequate treatment.

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kw: neurology; magnesium; sleep;

Summary

PHYSIOLOGICAL AND CLINICAL DATA ON RELATIONS OF MAGNESIUM AND SLEEP

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The aim of this study was to expose the physiological and clinical data existing in the literature about the relations of magnesium and sleep. After the introduction and the exposure of the actual knowledge in this new field, there are presented some personal clinical EEG, EMG and polysomnographical contributions to the investigations on insomnia in patients with magnesium defiency (240 subjects), on hypersomnia generated by magnesium defiency (15 patients) and non-epileptic nocturnal episodic manifestations in 27 spasmophilic patients with hypomagnesaemia.

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