Blood — CSF barrier of magnesium in CNS infection and acute lymphatic leukaemia*)

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Zusammenfassung

Die Tatsache, daß Mg-Mangel und Überschuß die Funktionen des ZNS negativ beeinflussen, ist bekannt. Gilt auch das Umgekehrte? Die Frage wurde durch Mg-Bestimmungen mittels AAS im Liquor (L) und Serum (S) bei drei Gruppen von Kindern untersucht. Gruppe I (n = 14): Kontrollen; Gruppe II (N = 40): Tuberkulose des ZNS; Gruppe III (n = 11): Akute lymphatische Leukämie (ALL). Gruppe III wurde untersucht a) vor Behandlung, b) nach Beendigung des 1. Abschnittes der systematischen Therapie; c) nach intrathekaler Chemotherapie plus Schädelbestrahlung mit 2400 rad.

Die Mittelwerte und Standardabweichungen für Liquor bzw. Serum betragen (mg %):

Gruppe I		: 2,63 ± 0,35 und 2,48 ± 0,70
Gruppe II		: 2,39 ± 0,36 und 1,79 ± 0,46
Gruppe III	a)	: 2,48 ± 0,19 und 1,78 ± 0,81
	b)	: 2,53 ± 0,25 und 1,63 ± 0,56
	c)	: 2,78 ± 0,23 und 1,49 ± 0,67

Bei keinem Patienten wurden ausgeprägte Hyper- oder Hypomagnesämien beobachtet. Bei Tuberkulose des ZNS und ALL waren jedoch L-Mg und S-Mg signifikant erniedrigt. Systematische Behandlung (IIIb) beeinflußte das L-Mg günstig, das sich weiter unter IIIc erholte. S-Mg blieb während der Beobachtungszeit erniedrigt. Somit bestehen Beziehungen zwischen 2 Erkrankungen, die neurologische Ausfälle verursachen, und den Mg-Gehalten in zwei wichtigen Flüssigkeitskompartimenten des Körpers.

Summary

The fact that magnesium excess or deficiency affects the nervous system adversely, has been well demonstrated. Does the reverse occur? This question was examined by atomic absorption spectrometric estimation of magnesium levels of the cerebro-spinal fluid (CSF) and serum in three groups of children. Group I (n = 14) controls, Group II (n = 40) tubercular infection of the Central Nervous System; Group III (n = 11) acute lymphatic leukaemia (ALL); a) pre-treatment b) on cessation of first stage of systemic therapy, c) after intrathecal chemo-therapy combined with 2400 rads external cranial irradiation.

Mean ± S. D. values for CSF and serum were respectively (mg %):

Group I		: 2,63 ± 0,35 and 2,48 ± 0,70;
Group II		: 2,39 ± 0,36 and 1,79 ± 0,46;
Group III	a)	: 2,48 ± 0,19 and 1,78 ± 0,81;
	b)	: 2,53 ± 0,25 and 1,63 ± 0,56;
	c)	: 2,78 ± 0,23 and 1,49 ± 0,67.

Neither hyper — nor hypo-magnesaemia was noted in any patient. However, levels of magnesium in both CSF and serum were significantly lower in neuro-tuberculosis and ALL. Stage one treatment had a beneficial influence on CSF magnesium levels which were further elevated after intrathecal chemo-therapy combined with irradiation of the brain, choroid plexuses and the ventricular CSF pool. Serum magnesium remained significantly depressed throughout the period of observation.

The study demonstrates a cor-relation between two diseases known to cause neurological lesions and the levels of magnesium ion in the two major pertinent fluid compartments of the body.

Résumé

Le fait qu'un excès ou un déficit en Mg affecte le système nerveux de façon défavorable a été bien démontré. L'inverse se produit-il? Cette question a été examinée par l'estimation par spectrométrie d'absorption atomique des taux du Mg du liquide céphalo-rachidien (LCR) et du sérum chez 3 groupes de patients. Groupe I: contrôle (n = 14); groupe II: (n = 40) infection tuberculeuse du SNC; groupe III: (n = 11) leucémie lymphoïde aiguë (LLA); a) avant le traitement, b) à la cessation du premier stade du traitement général, c) après une chimiothérapie intrathécale associée à une irradiation crânienne externe de 2400 rads.

Les valeurs moyennes ± ES pour le LCR et le sérum ont été respectivement (mg %):

groupe I		: 2,63 ± 0,35 et 2,48 ± 0,70
groupe II		: 2,39 ± 0,36 et 1,79 ± 0,46
groupe III	a)	: 2,48 ± 0,19 et 1,78 ± 0,81
	b)	: 2,53 ± 0,25 et 1,63 ± 0,56
	c)	: 2,78 ± 0,23 et 1,49 ± 0,67

Il n'a été noté ni une hpyer-, ni une hypomagnésémie chez aucun des patients. Cependant, les taux du Mg, à la fois dans le LCR et le sérum ont été significativement plus faibles dans la neuro-tuberculose et la LLA. Le premier stade de traitement a présenté une influence bénéfique sur les taux de Mg du LCR qui se sont encore élevés après la chimiothérapie intrathécale associée à l'irradiation du cerveau, des plexus choroïdes et du pool ventriculaire du LCR. Le Mg sérique est resté significativement déprimé tout au long de la période d'observation.

L'étude démontre une corrélation entre deux affections connues pour provoquer des lésions neurologiques et les taux de l'ion Mg dans 2 compartiments liquides de l'organisme en rapport avec ces affections.

Introduction

The interest initially aroused in the correlation between blood magnesium levels and neurological pathologies in experimental animals, is now

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gathering momentum with the investigation of homo sapiens [1—12]. Not only have histological abnormalities been observed in the brain (as also in the liver and myocardium), but definite symptomatology has been consistently encountered. Thus hyper — excitability, twitchings, tremors, convulsions are associated with hypo — magnesaemia, while lethargy, paresis, respiratory depression, cardiac conduction defects and coma are associated with hyper — magnesaemia. Technical facilitation by atomic absorption spectrometry has combined with the physiological stability of the magnesium pool (less than 15 % variation), to render feasible and reliable a study of this trace element.

The present series analyses the cerebrospinal fluid (CSF) and blood (serum) compartments of three groups of children. Due to the medical ethics involved in performing a lumbar puncture, the control group could not be composed of absolutely healthy patients: subjects being investigated for febrile convulsions, therefore formed the base — line of this study.

Targets of interest were two groups of subjects known to have histological devastation of the central nervous system (CNS): neuro — tuberculosis with a clinical spectrum ranging from uncontrolled convulsions to coma; and acute lymphatic leukaemia with paucity of clinical neurological manifestations despite cellular infiltrates and a massive therapeutic assault of 2400 rads Xrays to the brain, combined with intrathecal methotrexate (table 1).

Material and method

1. Patients

Table 1 details the groups studied. Their socio-economic strata was comparable and the nutritional status differed only slightly.

All patients of Groups I and II had abnormal neurological complaints, whereas only one child in group III had experienced a convulsive episode, while another had symptoms of a generalised increase in his intracranial tension; 27 patients of Group II and only two from Group III exhibited meningism.

Routine hematology, urine, faeces, serum chemistry and CSF examinations were done in all members, but cultures, cell surface antigen determination, EEG and scintigraphy were carried out in pertinent subjects only.

2. Magnesium estimations

Magnesium levels of CSF and serum were measured by atomic absorption spectrometry in all patients initially, and twice subsequently in leukaemic children (table 2).

Results

Classical hyper — and hypo — magnesaemic values were not encountered, but both compartments were significantly effected in Groups II and III. The blood pool was more contracted than the CSF pool and it continued to diminish during anti — leukaemic treatment, though the CSF pool improved (table 2).

Comparison of published normal values with those of Group I patients suggests that the results of Groups II and III might have reflected a more significant deviation than has been expressed in table 2.

Discussion

Magnesium ions activate enzymes engaged in the transfer and hydrolyses of phosphate groups such as hexokinase, alkaline phosphatase, and

Tab. 1: Patient data.

Group	Patients N	Age years	Diagnosis	CSF		
				Cells per cmm	Proteins mg %	Sugar mg %
I	14	0,5—4	Febrile Convulsions	0—5	10—15	58—75
II	40	0,5—14	Neuro-Tuberculosis	15—1280	10—600	0—45
III	11	3—12	Ac. Lymphatic Leukaemia	0—5	10—25	40—90
a)	Pre-treatment					
b)	At remission following oral prednisolone 40 mg/m² with i. v. vincristine 1,4 mg/m²					
c)	Immediately on completion of intra-thecal methotrexate 10 mg/m² × 5 doses with 2400 rads cranial radiotherapy.					

Tab. 2: Magnesium levels of cerebrospinal fluid (CSF) and serum: mg/100 ml.

Group	CSF			Serum		
Published data: Normal values	2,8—3,3			2—3		
I	2,63 ± 0,35			2,48 ± 0,7		
II	2,39 ± 0,36	I:II	t = 2,12	1,79 ± 0,46	I:II	t = 2,73
III						
a)	2,48 ± 0,19	I:III a	t = 1,23	1,78 ± 0,81	I:III a	t = 2,07
b)	2,53 ± 0,25	I:III b	t = 0,5	1,63 ± 0,56	I:III b	t = 2,06
c)	2,78 ± 0,23	I:III c	t = 0,84	1,49 ± 0,67	I:III c	t = 2,2

creatine kinase. Also, $Mg^{+2} - ATP^{-4}$ complex formation is an essential step in all enzyme reactions involving ATP. It is therefore not surprising that both hypo — as well as hyper — magnesaemia adversely effect the nervous system which preferentially utilizes glucose for its energy requirements.

But the reverse need not hold true. Neuropathologies may not upset the magnesium homeostasis. It was, therefore, necessary to ascertain the correlation between clinical symptoms, signs and the magnesium levels in such diseases.

The present series revealed that comatosed children did not have classical hyper — magnesaemic values; nor did those with continuous generalised convulsions or decerebrate rigidity yield low levels commensurate with the classification of hypo — magnesaemia. However, it was evident that diffuse CNS pathology did upset magnesium homeostasis as judged from the compartments sampled (table 2).

The finding of low CSF values in the pre — treatment phase of acute lymphatic leukaemia suggests that infiltrates may be present at the time of the initial diagnosis and do not occur only after systemic eradication of the disease. It may, therefore, be judicious to administer cranial therapy earlier.

The results imply the existence of a blood — CSF barrier for magnesium, because the serum levels are more profoundly effected than the CSF levels initially, and in ALL, they continue to decline after cranial irradiation combined with intrathecal methotrexate, when the CSF values improve. Irradiation produces hyperaemia with augmented capillary permeability. So it is pertinent to recall that 64—70 % serum magnesium is in an unbound form, free to enter the CSF; furthermore, the CSF concentration of this element is somewhat higher than the serum level, even in normal subjects. It is therefore possible that the barrier operates in favour of the more important compartment, attempting to maintain a satisfactory level of a critical ion where it is most needed.

We conclude that the postulates arising from these observations need to be confirmed by turn — over studies using radiomagnesium in patients suffering from acute lymphatic leukaemia and tubercular infection of the brain and the meninges. It is possible that such an academic pursuit might eventually aid a more comprehensive and correct therapeutic approach. Furthermore, magnesium may act as a marker for assessing the activity of these disease processes.

However, it is essential to emphasize that the changes in Mg^{++} levels are not specific for any particular etiology, occurring in infections as well as in proliferative pathologies effecting the central nervous system.

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