Magnesium in Cerebro-Spinal-Fluid (CSF) of Preterm Infants with Seizures

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Zusammenfassung

Im Tierversuch können cerebrale Krampfanfälle durch Magnesiummangel provoziert und nach Magnesiumsubstitution unterbrochen werden. Magnesium, ein Antagonist von N-methyl-D-aspartat (NMDA) Rezeptoren des Gehirns, wirkt als endogenes Antikonvulsivum. Erhöhte Liquor-Magnesiumwerte konnten kürzlich bei epileptischen Kindern mit günstiger Prognose nachgewiesen werden, wohingegen bei therapieresistenten Anfällen die Magnesiumspiegel im Normbereich blieben. Bis heute ist über Liquor-Magnesiumkonzentrationen bei Frühgeborenen mit Krämpfen nichts bekannt. Wir untersuchten deswegen 59 zu früh geborene Kinder. 19 von ihnen hatten Krämpfe, 21 Apnoen, 19 altersentsprechende Kinder konnten als Kontrollgruppe untersucht werden. Die Liquorwerte des Magnesiums lagen höher als die des Serums, eine intakte Magnesiumpumpe ist demnach bereits bei einem Gestationsalter von 27 Wochen anzunehmen. Liquor-Magnesiumkonzentrationen stiegen an bei Kindern mit Krämpfen und Apnoen, beides Zeichen für Hyperexzitabilität des unreifen Gehirns. Mit zunehmendem Gestationsalter kam es zum Abfall sowohl der Serum- als auch der Liquor-Magnesiumspiegel.

Summary

In experimental animals seizures can be provoked by magnesium deficiency and stopped by substitution of this cation. Magnesium, an antagonist of the N-methyl-D-aspartate (NMDA) receptor of the brain, acts as an endogenous anticonvulsant. Increased magnesium levels in CSF have been documented recently in epileptic children with a good prognosis of the seizures, whereas normal values are present in untractable epilepsy. Until today nothing is known about CSF magnesium values in preterm infants with seizures. We therefore studied 59 preterms. 19 had seizures, 21 apnoeas and 19 were age matched normal infants. CSF magnesium levels were higher than serum concentrations indicating an intact mechanism of the magnesium pump in the blood brain barrier already at the age of 27 weeks of gestation. CSF magnesium increased in patients with seizures and apnoeas, both signs of hyperexzitability of the immature brain. There was a decrease of serum and CSF magnesium with increasing gestational age.

Résumé

Des expériences sur l'animal montraient que des convulsions cérébrales peuvent être provoquées par une carence en magnésium et qu'elles peuvent être interrompues par une substitution de magnésium. Le magnésium, un antagoniste des récepteurs de N-méthyle-D-aspartate (NMDA) du cerveau, exerce la fonction d'un anticonvulsivant endogène. Récemment, on pouvait détecter un taux de magnésium augmenté dans le CSF chez des enfants épileptiques avec prévision favorable, tandis que le taux de magnésium restait normal dans les attaques résistantes au traitement. Jusqu'à aujourd'hui rien n'est connu sur les concentrations de magnésium dans le CSF chez les enfants prématurés qui souffrent de convulsions. C'est pourquoi nous avons fait une étude sur 59 enfants nés avant terme – 19 d'eux souffrant de convulsions, 21 d'apnée et 19 enfants normals, selon la phase de gestation, qui faisaient fonction de groupe de contrôle. Le taux de magnésium du CSF était plus élevé que le taux sérique; par conséquent on peut présumer une pompe intacte de magnésium déjá pendant une phase de gestation de 27 semaines. Les concentrations du magnésium du CSF augmentaient chez les enfants souffrant de convulsions et d'apnée, ce qui est un symptôme d'une hyperexcibilité du cerveau immature. Avec une période de gestation plus avancée, le taux sérique de magnésium ainsi que le taux du CSF diminuait.

Introduction

The variability of CSF-magnesium in children with seizures is well known. The concentration of magnesium varies with the type of the seizures, it depends on the duration and on the prognosis of the illness as well as on structural abnormalities of the brain (*Breyer, U.; Kanig, K.* (1970); *Dralle, D.* et al. (1994); *Tanuma, S.* et al. (1982)). In cases with normal blood-brain-barrier there is an increase of CSF-magnesium in the beginning of the disease. The values become normal after successfull anticonvusant therapy (*Debus* 1990).

In neonates, magnesium deficiency seizures can be observed. By systemic substitution of magnesium the seizures can be interrupted (*Holtmeier, H.J.* (1988); *Nagy, E.* et al. (1993); *Schmalheiser, N.R.; Swanson, D.R.* (1994); Peltner, H.U.; Dralle, D. (1977)). In these patients the blood-brain-barrier is less stable than in older children and magnesium is able to pass rapidly through this barrier (*Bachtler, K.* et al. (1993); *Chan, A.W.K.* et al. (1992); *Joo, F.* (1987); *Lefauconnier,*

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J. M. (1990)). Differences of magnesium concentrations in the blood in this age immediately result in similar differences in the CSF. Therefore the beginning and the end of magnesium deficiency seizures are nearly synchronous to the blood values of the cation.

In experimental animals it could be demonstrated that magnesium is an antagonist to the N-methyl-D-aspartate (NMDA) receptor in the brain. The NMDA-receptor is important in generating excitatory postsynaptic potentials (EPSP). Magnesium is able to block this receptor voltage dependently. On the other hand, magnesium deficiency results in depolarisation of the receptor cell and in seizures (*Gean, P. W.* et al. (1988); *Heinemann, U.* et al. (1989); *Johnson, J. W.; Ascher, P.* (1991); *McDonald, J. W.* et al. (1990); *Taylor, L. A.* et al. (1995); *Zhang, C. L.* et al. (1995)).

Patients and Method

Until to day nothing is known about CSF magnesium values in preterm infants with seizures. We therefore studied 59 preterms of 27–37 weeks of gestation. 19 infants suffered from seizures. In 21 preterm infants apnoeas were observed without any cardiorespiratory distress and apnoeas were suspected to be an equivalent to seizures even in case of normal EEG recording. In 19 infants meningitis was excluded by lumbar punction, they were regarded as a control group. All preterm infants were under intensive care, all received several drugs, most of them had parenteral nutrition. Under these conditions it is to be suspected, that magnesium values are influenced by many different factors.

Serum and CSF samples were taken within 24 hours after a seizure. Magnesium was analyzed by atomic absorption spectrophotometry (AAS).

In all infants EEG recordings and ultrasound of the brain were performed.

Results

Serum magnesium levels vary between 0.55 and 1.03 mmol/l in normals. Hypomagnesiemia (magnesium levels below 0.7 mmol/l) was not always correlated with seizures or apnoeas. Some preterm infants with seizures or apnoeas had additional therapy with magnesium either oral or parenteral some minutes after the seizure was observed. As a result in these infants serum magnesium is higher than in the control group.

As in older children and newborns, in all preterm infants serum magnesium levels are in a lower range than CSF values. This means an active transport of magnesium through the blood-brain-barrier even in immature infants.

The levels of CSF magnesium in normal preterm infants are between 0.98 and 1.27 mmol/l. In those with seizures, and in those with apnoeas CSF magnesium is increased compared with the normal control group.

With increasing age there is a decrease of both serum and CSF magnesium concentration. To demonstrate these results more strikingly, we show the decrease from 27 to 42 weeks of gestation, using additionly the results of a previous study of neonates (38–42 weeks) (*Bachtler, K.* et al. 1993). (Fig. 1 and 2).

There is no correlation between CSF magnesium on the one hand and the prognosis of seizures and development of the infants during the first 3 month of life on the other. No correlations are seen between CSF magnesium and structural abnormalities of the brain, as well as between CSF magnesium and EEG findings.

Discussion

The values of serum and CSF magnesium of the investigated preterm

Tab. 1: Serum magnesium in preterms with seizures and apnoeas compared with normal preterms. * $p < 0.01$.

	serum magnesium (mmol/l) median (range)
control group (n = 10)	0.81 (0.55–1.03)
preterms with seizures (n = 16)	0.94 (0.68–1.31)*
preterms with apnoeas (n = 19)	0.91 (0.70–1.08)

Tab. 2: Cerebrospinal fluid (CSF) magnesium in preterms with seizures and apnoeas compared with normal preterms. * $p < 0.01$

	CSF magnesium (mmol/l) median (range)
control group (n = 19)	1.14 (0.98–1.27)
preterms with seizures (n = 19)	1.24 (1.13–1.39)*
preterms with apnoeas (n = 21)	1.20 (0.99–1.52)

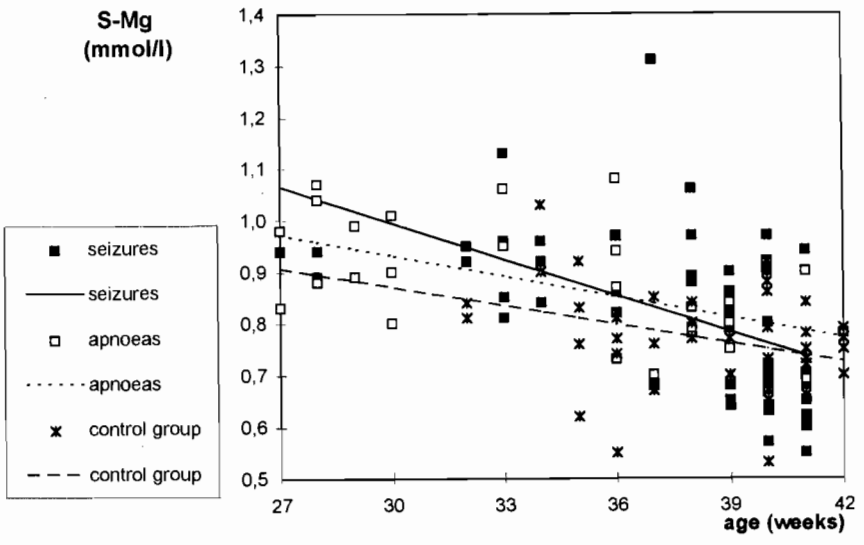

Fig. 1: Serum magnesium (S-Mg) in preterm infants and neonates from 27 to 42 weeks of gestation.

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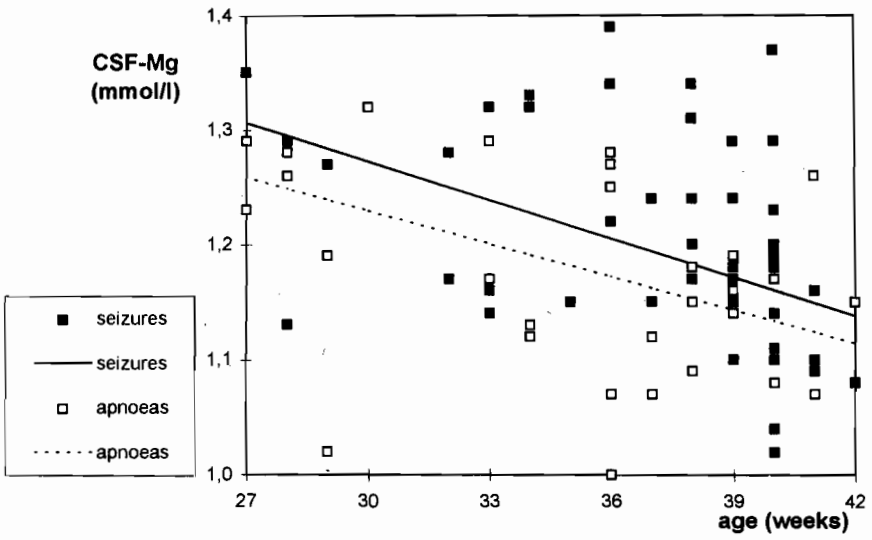

Fig. 2: Cerebrospinal fluid magnesium (CSF-Mg) in preterm infants and neonates from 27 to 42 weeks of gestation.

infants are in a larger range than the values of older children and newborns due to the morbidity of the preterms under intensive care (*Bachtler, K.* et al. (1993); *Dralle, D.* et al. (1991) and (1992)).

However in all immature infants CSF magnesium is higher compared to serum levels. It is not known at which time the active transport mechanism in the blood-brain-barrier is able to increase CSF magnesium against a concentration gradient, but obviously, it must be before the age of 27 weeks of gestation.

As in older children, CSF magnesium is increased in preterm infants with seizures. This reaction of the organism in case of hyperexcitability is already present since the 27th week of gestation. The increased magnesium pump mechanism leads to higher magnesium levels in the CSF, and it can be suspected that this leads to higher magnesium concentrations at the site of the NMDA receptor. This enables the brain to use magnesium as an endogenous anticonvulsive substance.

In preterms with apnoeas there was also an increase of CSF magnesium. This is an additional indication that these apnoeas are seizures. From this we conclude, that apnoeas without cardiorespiratory distress may be equivalent to seizures, despite the absence of abnormalities in the EEG.

From 27 to 42 weeks of gestation there is a decrease in both serum and CSF magnesium. During this time body weight is doubled and magnesium is required for the growth of bones and other organs. So it is necessary to provide a sufficient substitution of magnesium at the end of pregnancy for a normal development of the fetus and to prevent seizures in the neonate.

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