Prognostic Value of Cerebrospinal Fluid (CSF) — Magnesium in Infantile Spasms

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Zusammenfassung

Wir untersuchten 27 Kinder mit BNS (Blitz-Nick-Salam) Krämpfen. Alle hatten klinisch typische Anfallsmuster in Serien und im EEG eine Hypsarrhythmie. Die Diagnostik umfaßte Sonographie, Computer- und/oder Magnetresonanztomographie des Gehirns und Screeninguntersuchungen auf connatale Infektionen sowie Stoffwechselerkrankungen.
Der Liquor wurde durch Lumbalpunktion gewonnen, Magnesium und Calzium wurden mit Hilfe der Atomabsorptionssepektrophotometrie (AAS) bestimmt. Zellzahl und Eiweißgehalt lagen im Normbereich. Während Liquor-Calzium-Konzentrationen normal waren, fanden sich bei 20 Kindern erhöhte Magnesiumwerte.
Patienten mit normalem Liquor Magnesium hatten häufiger schwere Hirnatrophien als solche mit erhöhten Werten.
Kinder mit Normalwerten waren häufiger therapieresistent, ihre psychomotorische Entwicklung war stärker retardiert.
Antikonvulsive und neuroprotektive Eigenschaften des Magnesiums, die aus neurophysiologischen Untersuchungen bekannt sind, werden in diesem Zusammenhang diskutiert.

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Summary

We studed 27 patients with infantile spasms. All had the typical serial seizures and on EEG the pattern of hypsarrhythmia. The diagnostic program included sonography of the brain, cerebral computertomography and/or magnetic resonance tomography, screening for connatal infections and metabolic disorders.
CSF was taken by lumbar punction, magnesium and calcium were determined by atom-absorption-spectrometry (AAS). CSF cell count and protein were within normal ranges. While CSF calcium did not differ from normal values, there was a marked increase of CSF magnesium in 20 patients.
In infants with normal CSF magnesium severe brain atrophy was more frequent than in patients with increased CSF magnesium.
Treatment failed more often in infants with normal values and psychomotor development was more delayed in this group.
Anticonvulsant and brain protective properties of magnesium as could be demonstrated in neurophysiological studies are to be discussed in this respect.

Résumé

Nous avons étudié 27 patients atteints des spasmes infantiles. Ils présentaient des crises de type spasmes infantiles aves à l'EEG une activité hypsarythmique. Dans le but diagnostique nous avons inclu l'échographie, la tomographie computérisée et/ou la résonance magnétique nucléaire cérébrale et les recherches des infections connatale et des désordres métaboliques.
Le liquide cephalo rachidien (LCR) était obtenu par ponction lombaire, le magnésium et le calcium étaient déterminés par l'atomabsorptionspectrométrie (AAS). Le compte des cellules du LCR et la protéinorachie étaient normaux.
Alors que le calcium du LCR n'était pas différent des valeurs normales, il y avait une importante augmentation du magnésium du LCR chez 20 patients.
Chez les enfants avec magnésium du LCR normal une atrophie cérébrale était plus fréquente que chez ceux avec augmentation du magnésium.
Il y avait par ailleurs plus fréquemment un échec thérapeutique chez les enfants avec valeur normale et le developpement psychomoteur était plus retardé dans ce groupe.
Le rôle anticonvulsivant et protecteur cérébral du magnesium comme il pouvait étre démontré dans les études neurophysiologiques, doit être discuter dans cet aspect.

Infantile spasms or West syndrome are nonspecific but age-related epileptic reactions of the immature brain to a variety of lesions during early stages of development.
Etiologically embryofetal, perinatal or postnatal incidences must be considered. Brain malformations, hypoxic encephalopathies, and cerebral infarcts, amino-acidopathies, meningocerebral calcinosis in connatal infections and tuberous sclerosis, cerebrovascular or inflammatory lesions and brain atrophy, Down syndrome and Aicardi syndrome are cerebral disorders which can be associated whith infantile spasms [1, 2, 6]. The incidence of idiopathic forms varies in literature from 0–48 % [10].
Manifestation occurs almost entirely during the first year of life espescially between 6 to 9 months. Some patients suffered from neonatal seizures before.
Clinical signs are characterised by typical serial seizures with flexor spams of the body and extremities as well as myoclonic jerks, tonic or atonic components. An EEG pattern with hypsarrhythmia is almost pathognomonic. In addition psychomotor retardation or mental deterioration and severe neurological sequelae with a multiplicity of handicapping variations are characteristic for the West syndrome [9, 14].
Therapy in epilepsies with infantile spasms is still an unsolved problem. Seizures often do not respond to conventional anticonvulsant drugs. ACTH, steroids, vitamine B and immunoglobulines have been found to

improve seizures in som cases. However, prognosis remains poor for most patients, especially with regard to psychomotor and mental development [2, 4, 5, 12, 13, 15].

We studied 27 patients with infantile spasms reffered to our hospital between 1986 and 1990. Only two of them were older than one year (13 and 15 months). All had the typical serial seizures and showed the features of hypsarrhythmia in their EEGs. The diagnostic program included sonography of the brain, cerebral computerized tomography and/or magnetic resonance tomography, lumbar punction and tests on CSF, screening for connatal infections and metabolic disorders.

Etiologic factors were malformations of the brain, Down-syndrome, hypoxic-encephalopathy, intraventricular hemorrhage, neonatal meningitis and sepsis. In 12 patients with brain atrophy etiology of the atrophy remains unclear.

In 24 patients treatment started within one month after the onset of seizures. Clonazepam and phenobarbitone were given to all patients. In 15 infants ACTH and steroids could be administered with parental informed consent.

Lumbar punction was performed in 11 infants before, and in 16 patients shortly after inition of therapy. CSF cell-count and protein were within normal ranges. CSF calcium and magnesium were determined by atom-absorption-spectrometry (AAS).

While CSF calcium did not differ from our normal values (1.0–1.15 mmol/l) [3], there was a marked increase of CSF magnesium in 20 patients.

In 70 children without any neurological symptoms or risk factors and without an infection of the central nervous system CSF Mg had been found to vary between 0.95 and 1.15 mmol/l [3].

In 15 patients with symptomatic seizures 4 had normal and 11 had increased CSF Mg. This did not differ from relations of CSF Mg in 12 infants with brain atrophy of unknown etiology, where 3 patients had normal and 9 had elevated CSF Mg levels (tab. 1).

Tab. 1: CSF-Mg in infantile spasms with symptomatic and with idiopathic etiology of brain atrophy.

Etiology	CSF-Mg in patients with infantile spasms: CSF-Mg 0,95–1,15 (mmol/l)	CSF-Mg 1,16–1,31 (mmol/l)	total (n)
symptomatic	4	11	15
idiopathic	3	9	12

In all patients computerized tomography of the brain revealed signs of atrophy even before ACTH therapy. Severe atrophy was diagnosed, when more than one third of the brain substance was replaced by CSF. In moderate stages there was a slight enlargement of ventricles as well as of subarachnoid space, whereas mild atrophy showed some isolated enlargement of the ventricles. 5 out of 7 infants with normal CSF Mg showed severe atrophy of the brain, whereas 14 of the 20 patients with elevated CSF MG had mild or moderate atrophy (tab. 2).

Tab. 2: CSF-Mg in infantile spasms with mild to moderate and with severe brain atrophy.

Brain atrophy	CSF-Mg in patients with infantile spasms: CSF-Mg 0,95–1,15 (mmol/l)	CSF-Mg 1,16–1,31 (mmol/l)	total (n)
mild-moderate	2	14	16
severe	5	6	11

The follow up of all patients was evaluated during a period of at least one year.

Treatment failed in 6 of the 7 infants with normal CSF Mg and in 9 patients with increased values. There was an improvement of seizures during therapy in 11 children with elevated CSF Mg but only in one child with a normal Mg level (tab. 3).

Mental development and statomotor functions were delayed in all children.

Tab. 3: CSF-Mg in infantile spasms and response to therapy.

Seizures under Therapy	CSF-Mg in patients with infantile spasms: CSF-Mg 0,95–1,15 (mmol/l)	CSF-Mg 1,16–1,31 (mmol/l)	total (n)
seizures-free	1	6	7
improvement of seizures	0	5	5
seizures resistant to therapy	6	9	15

In severe cases development deteriorated. In moderate retardation there was some developmental progress whereas in mild retardation cerebral dysfunctions were only detected by careful neurological examination.

Severe developmental retardation was seen in 14 patients, 6 of them had normal CSF Mg. However, of the 13 infants with mild to moderate neurological sequelae there was only one child with normal Mg (tab. 4).

Tab. 4: CSF-Mg in infantile spasms and neurodevelopmental progress.

Development	CSF-Mg in patients with infantile spasms: CSF-Mg 0,95–1,15 (mmol/l)	CSF-Mg 1,16–1,31 (mmol/l)	total (n)
normal	0	3	3
moderate retardation	1	9	10
sereve retardation	6	8	14

In conclusion, during early stages of disease prognosis with regard to outcome seems to be better when infantile spasms are associated with increased CSF Mg. Children with normal CSF Mg had a higher risk of brain

atrophy, they were more often resistent to therapy and their psychomotor development was almost always severely retarded.

From neurophysiological experiments we know, that Mg physiologically is antagonistic to NMDA receptors. Most of our findings are in accordance with this mechanism.

NMDA receptors are essential in excitatory neurotransmission. After binding of NMDA agonists on the receptor a channel opens and permeability increases to sodium, potassium and calcium. The activated conductance for these ions depolarizes the membrane. If threshold depolarisation is reached an action potential is initiated. Voltage dependent Mg is able to block this mechanism [7, 19].

Moreover, in Mg depletion seizures are provoced which can be blocked by amino-phosphono-valerate (APV), a NMDA receptor antagonist [8, 16, 18].

NMDA receptors are located in a high amount in the hippocampus, a brain structure, often involved in seizures. As *Wolf* and coworkers (1990) could demonstrate, cytotoxic edema and even cell death occur in hippocampus neurons after the application of a NMDA agonist (quinolinate) in high concentration. Cell damage can be prevented when Mg is applicated synchronously [11]. Our results are consistent with these findings, indicating that anticonvulsant as well as brain protecting properties are to be expected in infantile spasms associated with increased CSF Mg levels.

These findings were part of the forces responsible for encouraging us to initiate a therapeutic experiment. Patients with normal CSF Mg values had lower serum Mg levels being in a range between 0.81 and 0.91 mmol/l, the median was 0.86. In comparision serum Mg was between 0.80 and 1.04 mmol/l with a median of 0.90 in children with increased CSF Mg. Serum and CSF samples were taken at the same day (tab. 5).

In two patients with untreatable seizures and low serum as well as low CSF Mg we substituted a 10 % Mg solution intravenously in a dosage of 1 ml per kg body weight once a day. However, after one week patients did not recover clinically, serum and CSF Mg levels remained unchanged.

Tab. 5: CSF- and serum Mg in infantile spasms.

	CSF-Mg in patients with infantile spasms	
	CSF-Mg 0,95–1,15 (mmol/l)	CSF-Mg 1,16–1,31 (mmol/l)
Serum-Mg (mmol/l)	0,86 (0,81–0,91)	0,90 (0,80–1,04)
total n	7	20

It seems possible that to penetrate the blood-brain-cerebrospinal fluid barriers higher concentrations of Mg would have been necessary. However, being afraid of neuromuscular blockage and cardiac problems we did not applicate Mg in higher doses.

Perhaps in future it will be possible to increase CSF Mg by special drugs acting on the blood-CSF-barrier without severe side effects. Some of the conventional anticonvulsants are able to do so as we could demonstrate previously [3].

Moreover Mg agonistic agents inhibiting NMDA receptors may be effective in epilepsies with low Mg concentration [17].

However, conclusive results in infantile spasms are missing until today. So this problem deserves further study.

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