Aluminium in spinal fluid of uremic patients

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RESUMEN

Concentración de aluminio en el líquido cefalorraquídeo de pacientes urémicos.
Los niveles de aluminio en líquido cefalorraquídeo no se correlacionan con el aluminio sérico, electroencefalograma, velocidad de conducción motora y tiempo en diálisis. Todos los pacientes con trastorno neurológico tenían un aluminio superior a 5 µg/l. en el líquido cefalorraquídeo.

SUMMARY

Aluminium in spinal fluid of uraemic patients.
Aluminium levels in spinal fluid did not correlate either with serum aluminium levels, or electroencephalography, or nerve conduction, or time on dialysis. Nevertheless, patients with neurological derangement presented aluminium spinal fluid concentrations above 5 µg/l.

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Introduction

Dialysis encephalopathy syndrome has been reported for the first time in the mid seventies [1, 2]. At that time we did not know the causative agent of this syndrome, which was characterized clinically by dysphagia, dyspraxia of speech, tremulousness, myoclonus, asterixis, epilepsy and progressive dementia [1].

During the following years a series of clinical reports confirmed the existence of the disease and its epidemic nature, involving individual dialysis units or specific geographic areas [3].

In 1976 aluminium was proposed to be the possible cause of dialysis encephalopathy [4]. The close relationship between aluminium levels in water supply for dialysis fluid and the occurrence of encephalopathy was subsequently confirmed by other reports [5, 6]. Later on, other important source of aluminium was established: aluminium containing phosphate binders. In some patients the intestinal absorption of aluminium from phosphate-binding gels appears to have been the dominant mechanism in the development of an excess body burden of aluminium [7].

In the meantime other clinical entities were related to aluminium intoxication: a vitamin D resistant osteodystrophy, which was first described as "Newcastle Bone disease" [8], ron-unresponsive microcytic anaemia [9] and parathyroid suppression [10] were also observed.

Considering this fairly wide spectrum of clinical consequences to an increased aluminium body burden, it is not understood why a group of patients may develop dialysis encephalopathy while others present osteomalacic osteodystrophy and do not have any sign of aluminium toxicity, assuming that all patients are apparentely comparable in terms of aluminium content in the dialysate, dialysis schedule and oral aluminium intake.

We report here our studies aimed to assess the role of the blood brain barrier in the pathogenesis of dialysis encephalopathy [11-13].

Patients and methods

Eighteen informed patients were included in a neurological protocol, whose objective was to evaluate the existence of alterations in the spinal fluid composition of aluminium intoxicated patients. The majority of the patients was selected as they presented neurological or skeletal signs suspected to be related to aluminium intoxication; additionally, other patients on regular dialytic treatment presented unexpected high levels of plasma aluminium (> 100 µg/l) and, for this only reason, they were included in the protocol.

For all patients dialysis schedule was comparable: they were treated for 4 hours, three times a week, using 1 sqm cuprophane dialyzers. Water was treated by reverse osmosis or deionization in order to obtain levels of Al in the final dialysate below 10 µg/l; all patients were taking moderate amounts of aluminium gels in order to maintain their phosphate plasma levels below 1.7 mmol/l (5 mg/dl).

Our neurological protocol included clinical history, neurological examination, EMG and EEG tracing, and lumbar puncture. Analysis of cerebrospinal fluid (CSF) included the assessment of blood brain barrier (BBB) permeability to Albumin and IgG, and determination of aluminium levels.

Spinal fluid and blood samples were taken using uncontaminated material. A basal measurement was performed on cerebrospinal fluid samples (250 microliters), added in 1:1 ratio to a magnesium nitrate solution directly into the autosampler plastic container; a 2.5 g/l solution in double distilled water of $Mg(NO_3)\cdot 6H_2O$ Suprapur Merck was used. In addition, since it was conceivable that aluminium concentration in CSF could be too low to match the sensitivity of the instrument (Perkin Elmer Model 430 atomic absorption spectrophotometer equipped with a deuterium background corrector), other three aliquots of sample (250 microliters) were diluted in the same way with magnesium nitrate solutions containing 5, 10 and 20 µg/l of aluminium, respectively. All measurements were repeated five times.

BBB permeability to plasma proteins was assessed calculating the selectivity index (ratio spinal fluid/serum IgG to spinal fluid/serum Albumin), where normal values are below 0.6; the Albumin spinal fluid/serum ratio is also considered a reliable indicator of BBB derangement and values (X 1000) > 7.4 are considered highly indicative for an increased permeability to albumin [14].

The clinical and neurological examination was performed by two experts in the field and neurological status was assessed using arbitrary scores.

Results

Table I shows data obtained from the 18 patients included in our study: aluminium concentrations in plasma and spinal fluid, spinal fluid aluminium/serum aluminium ratio, blood brain barrier index and blood brain barrier selectivity to albumin are indicated.

All patients had plasma aluminium levels in a pathological range, while only 13 of them presented spinal fluid levels higher than 5 µg/l (normal values <1 µg/l).

We could not find any statistically valid correlation between dialysis age and spinal fluid aluminium levels, as well as between serum and spinal fluid aluminium levels.

Comparing plasma and spinal fluid aluminium levels, along with the presence of clinical neurological abnormalities and EEG abnormalities, we were able to subdivide our patients into two groups.

The first one includes seven patients without neurological abnormalities, who had low aluminium levels in their spinal fluid, even when high plasma aluminium levels were present. The mean dialytic age of this group was 67.7 months (range 6 - 204): this observation justifies the absence of correlation between dialytic age and spinal fluid aluminium levels.

A second group includes patients presenting clinical and/or EEG evidence of neurological involvement and higher aluminium concentrations in their spinal fluid. Among them we can find patients with serum aluminium levels only slightly elevated (i.e. patient VT, whose serum aluminium concentration was 14 µg/l, and spinal fluid level was 12 µg/l). Patient PG, with a serum aluminium concentration strikingly high (1300 µg/l) also had the highest spinal fluid level (43 µg/l), but this was the only case that could make us postulate a possible correlation between very high serum levels and high spinal fluid levels.

As shown in figure 1, our results suggest that while high plasma aluminium levels may or may not be associated with neurological involvement (left panel), spinal fluid aluminum levels correlate more precisely with neurological symptoms; indeed all patients presenting neurological derangement had spinal fluid

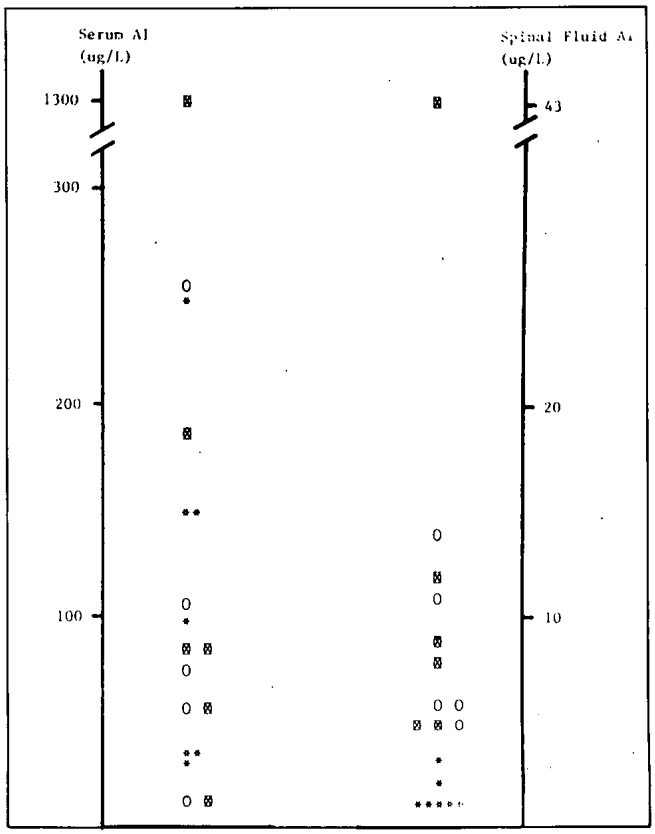

Fig. 1.—Serum aluminium levels do not depict the neurological involvement of patients on regular dialytic treatment, while cerebrospinal fluid aluminium levels (right panel) indicate the population possibly prone to encephalopathy (levels > 5 mcg/l). Reproduced with permission from reference n. 11.

Table I. Spinal fluid and plasma aluminium concentration, BBB index and spinal fluid albumin/plasma albumin × 1000 (see below)

Patient	Spinal fluid aluminium	Serum aluminium	Aluminium SF/S × 1000	BBB index	SF alb/S alb × 1000
BB	< 1	27	30	0.36	5.56
AA	< 1	36	20	0.30	3.71
VT	12	14	850	0.47	9.57
LR	5	85	50	0.66	5.48
AS	< 1	147	6	0.29	2.78
PM	< 1	34	30	0.43	6.83
GT	5	85	60	0.44	6.66
MA	3	98	30	0.27	3.32
ME	1	150	6	0.23	2.26
CC	6	19	330	0.33	3.72
EE	6	67	90	0.41	5.00
ZMG	9	65	110	0.46	3.32
PC	5	188	26	0.47	2.99
ZR	11	260	40	0.54	2.71
RG	8	85	90	0.43	4.98
PG	43	1300	30	—	—
MR	2	259	7	—	—
MA	14	114	120	0.58	9.73

$$\text{BBB Index} = \frac{\text{Spinal fluid IgG}}{\text{Serum IgG}} \Big/ \frac{\text{Spinal fluid albumin}}{\text{Serum albumin}} \quad \text{(normal value} < 0.6\text{)}.$$

Spinal fluid albumin/serum albumin × 1000 = BBB selectivity to albumin (normal value < 7.4).

aluminium concentrations higher than 5 µg/l (right panel).

Discussion

The comparative analysis of our data seems to suggest that aluminium intoxication with neurological derangement is not a time-related pathology. In fact we failed to observe any correlation among EEG, motor and sensory nerve conduction, clinical symptoms and dialytic age. The same parameters also failed to correlate with plasma aluminium levels.

Again, spinal fluid and plasma aluminium levels do not correlate.

From the analysis of our data we postulate that some factors may be responsible for aluminium deposition in the central nervous system: only patients with spinal fluid aluminium levels higher than 5 µg/l seem to be prone to neurological impairment, thus supporting the hypothesis that a blood brain barrier derangement with increased permeability to aluminium might play a role in inducing encephalopathy.

In addition, our data concerning blood brain barrier selectivity to plasma proteins confirm that blood brain barrier permeability to plasma proteins do not necessarily predict permeability to aluminium. In fact only two patients have a blood brain barrier unselectivity to plasma proteins, while all patients with neurological derangement presented spinal fluid aluminium > 5 µg/l.

We therefore presume that spinal fluid aluminium assessment may be of crucial importance in the identification of the population suspected for dialysis encephalopathy. The role of this laboratory determination can be similar to that of desferrioxamine test in giving information about the aluminium skeletal burden [15].

In conclusion we believe that spinal fluid aluminium assessment, in spite of its invasive procedure, should be included in an investigative protocol for uremic patients who present neurological derangement.

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