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SPINAL FLUID ALUMINIUM IN HAEMODIALYSED URAEMIC PATIENTS

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Summary

To elucidate the possible role of the blood brain barrier in inducing encephalopathy, 18 uraemic patients were included in a neurological protocol which included the assessment of aluminium, IgG and albumin in plasma and in spinal fluid. Our data, correlated with EEG and clinical neurological status, support the hypothesis that patients on haemodialysis who present neurological impairment also have a blood brain barrier increased permeability to aluminium.

Spinal fluid aluminium might be a reliable index to identify patients at risk of possible encephalopathy.

Introduction

Patients on regular haemodialysis may have an increased aluminium body burden [1]. This intoxication is not a rare syndrome in Europe [2] and it may induce progressive neurological derangement, dialysis encephalopathy, and also osteomalacic osteodystrophy with spontaneous fractures [3,4].

It is not understood why a group of patients may develop dialysis encephalopathy while others present with osteomalacic osteodystrophy, assuming that both groups are apparently comparable in terms of aluminium content in the dialysate, dialysis schedule and oral aluminium intake.

This study elucidates the possible role of the blood brain barrier derangement as a pathogenetic factor in inducing encephalopathy in uraemic patients on dialysis.

Patients and methods

After informed consent, 18 patients – all treated in Regione Lombardia – were included in the present protocol. Many of them were selected as they presented neurological or skeletal signs suspected to be related to aluminium intoxication;

additionally, other patients on haemodialysis presented unexpectedly high plasma aluminium and, for only this reason, they were included in the study. Table I shows data concerning their diagnosis, age, duration of dialysis and the percentage of their life spent on dialysis.

TABLE I. Patients included in the present study

Patient	Age (years)	Diagnosis	Duration on dialysis (months)	Percentage of life spent on dialysis
BB	55	PK	60	9
AA	60	PK	36	5
VT	44	RPGN	120	22
LR	31	RPGN	60	16
AS	41	CRGN	204	41
PM	52	CRGN	84	13
GT	40	HSP	96	20
MA	62	CRGN	48	6
ME	29	CRGN	6	1
CC	30	REFLUX N	156	43
EE	45	CRGN	36	6
ZMG	47	CRGN	144	25
PC	54	NSC	72	11
ZR	47	CRGN	48	8
RG	50	NSC	180	30
PG	55	CRGN	60	9
MR	45	CRGN	36	6
MA	56	CRGN	84	12

PK=polycystic kidneys; RPGN=rapidly progressive glomerulonephritis; CRGN=chronic glomerulonephritis; HSP=Henoch Schönlein Purpura; REFLUX N=reflux nephropathy; NSC=nephrosclerosis

The dialysis schedules were comparable: they were treated for four hours, three times a week, using $1 m^2$ cuprophan dialysers. In all dialysis units, where the patients were treated, water treatment was reverse osmosis or deionization in order to allow a controlled low level of aluminium in the dialysate, mostly $<10 \mu g/L$; in addition a minimum amount of aluminium containing gels was given to all patients in order to maintain their plasma phosphate $<5 mg/dl$.

The neurological protocol included spinal fluid and plasma aluminium measurement, blood brain barrier permeability to albumin and IgG, EEG, CT brain scan and a clinical neurological examination.

Spinal fluid and blood samples were taken using uncontaminated material and sent to the Laboratorio di Tossicologia dell'Istituto Superiore di Sanità in Rome; aluminium determination was made by an expert technician using a Graphite Furnace Spectrophotometer. Blood brain barrier permeability to

plasma proteins was assessed calculating the index of selectivity (ratio IgG $\frac{L}{S}$/ Alb $\frac{L}{S}$) where normal values are below 0.6; the ratio albumin $\frac{L}{S}$ is also considered a reliable indicator of blood brain barrier derangement and the value (x1000) >7.4 are highly indicative of increased permeability [5].

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

Results

Aluminium concentrations in plasma and spinal fluid and their ratio and the blood brain barrier permeability to plasma proteins of the 18 patients included in the present study are given in Table II. While all plasma values of aluminium

TABLE II. Spinal fluid and plasma aluminium concentration
Blood brain barrier (BBB) index and spinal fluid (SF) alb/plasma alb x 1000 (see below)

Patient	Spinal fluid Al µg/L	Serum Al µg/L	Al SF/S x1000	BBB index	SF alb/S alb x1000
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

$$\text{Blood brain barrier index} = \frac{\text{Spinal fluid IgG}}{\text{Serum IgG}} / \frac{\text{Spinal fluid albumin}}{\text{Serum albumin}} \quad \text{(normal value <0.6)}$$

Spinal fluid albumin/serum albumin x 1000 = blood brain barrier selectivity to albumin (normal value >7.4)

were in a pathological range, 11 of the 18 patients presented high levels in spinal fluid (n.v. <1µg/L). There was no correlation between length of time on dialysis and spinal fluid aluminium. Figure 1 shows a split of the patients into a group

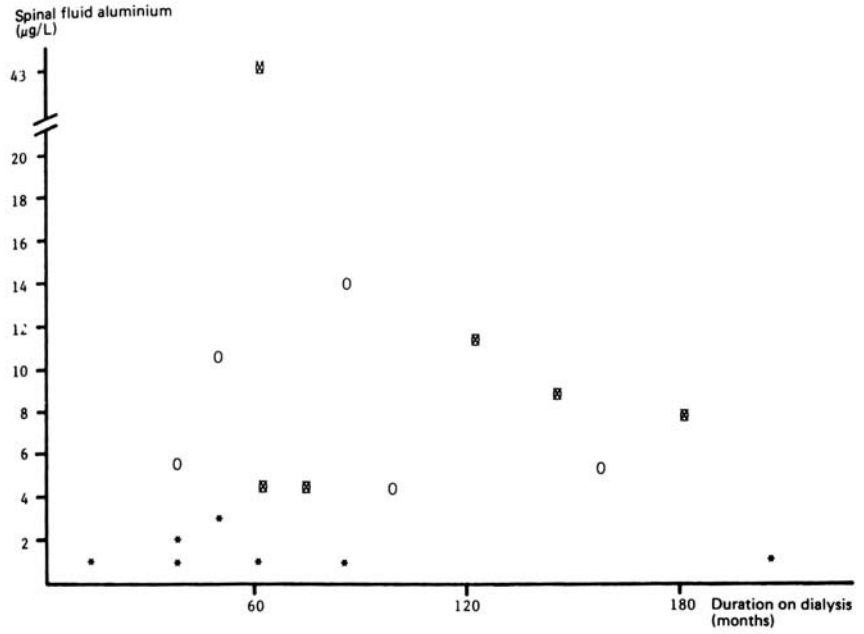

Figure 1. 0=neurological clinical abnormalities; X=EEG abnormalities; *=no abnormalities

who do not have any clinical or EEG abnormalities and who have low aluminium values in their spinal fluid, even after a long time on dialysis, and a second group of 12 patients who have clinical and/or EEG evidence of neurological involvement and higher concentration in spinal fluid. In this second group there is a trend of correlation between aluminium and time spent on dialysis. More specifically, Figure 2 compares the clinical involvement and plasma or spinal fluid aluminium concentration; while aluminium in plasma does not depict the neurological involvement, spinal fluid aluminium correlates more precisely with neurological symptoms as no patient with neurological derangement has a spinal fluid concentration $<5\mu g/L$.

Additionally no correlation was found between CT brain scan and the above mentioned parameters and no correlation was found between blood brain barrier selectivity to plasma protein and neurological impairment.

Discussion

The comparative analysis of the data collected in our patients 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, CT brain scan, motor and sensory nerve conduction, clinical symptoms and time spent on dialysis. In addition we also failed to correlate the plasma values with each of the above mentioned parameters and with the duration of dialysis treatment.

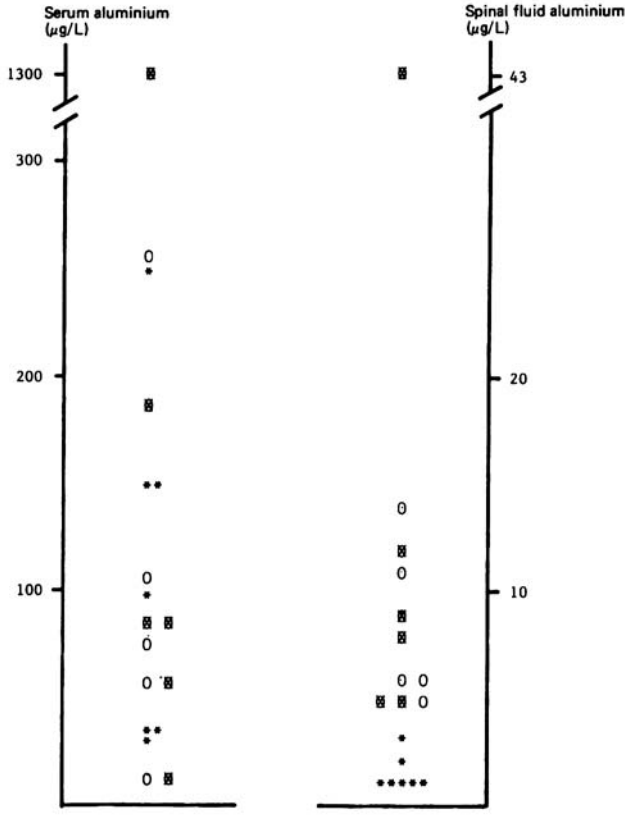

Figure 2. 0=neurological clinical abnormalities; X=EEG abnormalities; *=no abnormalities

It is, however, more than an impression that some factors may be responsible for aluminium deposition in the central nervous system; our results show that only patients with spinal fluid aluminium >5μg/L are prone to neurological derangement, thus supporting the hypothesis that a blood brain barrier derangement with increased permeability to aluminium may 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 present spinal fluid aluminium >5μg/L. We therefore presume that spinal fluid aluminium assessment may be of crucial importance in the identification of the population at risk of neurological danger, similar to the role of the desferrioxamine test in giving information about the aluminium body burden [6]. Spinal fluid aluminium should be included in an investigative protocol for uraemic patients who present neurological derangement.

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