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The Contribution of Aluminium to Alzheimer's disease: A Neuropathological Investigation of Renal Dialysis Cases

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Abstract

Whilst controversial, the role of aluminium in Alzheimer's disease (AD) has not been adequately explained as models of aluminium exposure are not generally available. Renal dialysis (RD) patients are exposed to aluminium through phosphate-binding compounds for controlling hypophosphatemia and because of impaired renal excretion accumulate aluminium in tissues including the brain.These individuals represent a suitable population to study the role of aluminium exposure in inducing AD changes in the brain.We studied the brains of 28 RD individuals, with a history of haemodialysis or peritoneal dialysis, for the presence of AD-type changes and glial pathology, and related these to aluminium exposure and to Apolipoprotein E (*APOE*) genotype. RD patients had increased Aβ deposition compared to controls but this did not relate to brain aluminium. RD cases carrying the *APOE*ε4 allele were more likely to show Aβ deposition, though cases not carrying the *APOE*ε4 allele also showed Aβ deposition. Neurones immunostaining with AT8 against a phosphorylated epitope of Tau were identified in RD brains though neurofibrillary tangles were not observed. A slight increase in the numbers of microglia was also identified in the brains of RD cases compared to controls. Whilst neuropathological changes suggestive of early AD-type pathology associate with RD, they could not be attributed to aluminium exposure but may be related to the presence of the *APOE*ε4 allele acting in conjunction with other RD pathological processes. Aluminium therefore does not appear to be a major risk factor contributing to AD.

Keywords

Renal dialysis, Aluminium, Alzheimer's disease, Astrocytes, Microglia

Abbreviations

AD: Alzheimer's disease

RD: Renal Dialysis

Aβ: Amyloid beta

NFT: Neurofibrillary tangles

Al: Aluminium

APOE: Apolipoprotein E gene

GFAP: Glial Fibrillary Acidic Protein

Introduction

Genetic factors and age appear to play a primary role in the development of Alzheimer's disease (AD) with the Apolipoprotein E gene (*APOE*) being the main risk factor for late onset sporadic AD [1]. That non-genetic risk factors contribute to the progression of AD cannot be discounted, since numerous studies have shown factors such as head trauma [2], non-steroidal anti-inflammatory drug use [3] and gender [4] have an effect on disease outcome and progression.Though controversial, aluminium (Al) has been suggested by some to play a role in the development of AD, with Al being found to be present in Senile Plaques (SP) and Neurofibrillary Tangles (NFT), the major pathological features of AD [5,6]. The incidence of AD is also suggested to correlate with the levels of Al in the drinking water [7-9]. Biochemical evidence suggests that Al is neurotoxic and can act upon several important pathways involved in neuronal functioning [10]. Whilst this provides circumstantial evidence of Al being involved in AD, no directly relevant animal models to address this issue are available. Patients undergoing dialysis for chronic renal failure may provide a model for studying the effects of long term Al exposure on AD biology. Past use of tap water in haemodialysis procedures led to a fatal neurological disorder, dialysis encephalopathy,

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which was attributable to the presence of Al in the dialysate fluid [11]. Renal dialysis (RD) patients are still chronically exposed to high levels of blood Al due to the ingestion of large quantities of aluminium containing phosphate binding compounds used to control hyperphosphataemia, and the inability to excrete Al because of their impaired renal function [12]. Whilst overt dementia is not seen in RD patients, cognitive function is impaired, potentially related to renal function and toxaemia [13,14] and CT scan abnormalities are observed which correlate with the amount of Al ingested during treatment [15]. Neuropathologically, such cases show the presence of Amyloid beta (Aβ) immunoreactive SP in about one third of cases, at an age where such changes are not common [16], and also show alterations in Tau protein processing, the major constituent of NFT, which correlate with brain Al levels [17]. Because of the finding of AD-like changes in the brains of RD patients we have quantitatively assessed these changes, along with glial markers, and related these to the levels of Al found in the brains of these cases.Additionally we have also assessed the effect of Apolipoprotein E (*APOE*) ε4 allele dosage, the major genetic risk factor for sporadic AD, to determine if the presence of this risk factor has an effect on pathology.

Materials and Methods

All studies were approved by the Local Research Ethics Committee. Brains were obtained at post-mortem following informed consent from 28 individuals who had undergone either haemodialysis or continuous ambulatory peritoneal dialysis for chronic renal failure (Table 1). None of the cases had any evidence of dialysis associated encephalopathy/dementia, though one case showed evidence of mild cognitive impairment.Brains from five individuals dying of non-neurological causes and having no history of renal impairment, or of neuropsychiatric disease were used as controls (3 male, 2 female, mean age 63(±8) years). Control cases were not significantly different in age at death from renal dialysis cases (p=0.34, unpaired t-test).Brains were obtained and the tissue processed as described previously [16] (see Supplementary Methods).

Results were analysed using ANOVA and Student t-test where appropriate with $p<0.05$ being regarded as significant. *APOE* genotypes were analysed using Chi-squared test with Yates correction for small sample sizes. The study had at 80% power and alpha of 0.05 the ability to detect an effect size of 1.42.

Results and Discussion

Renal dialysis cases showed increased levels of Aβ deposition compared to the control group, which was significant in the frontal cortex (RD, 0.56% vs control, 0.03%; p=0.033, see Table2). Trends for increased Aβ deposition were apparent in the temporal cortex and hippocampus but these failed to reach significance (Temporal, p=0.12; hippocampus, p=0.16). The deposition of Aβ in RD cases did not appear to correlate with age (r=0.019, p=0.92) or with aluminium concentration (r=0.257, p=0.19), though did show a slight association with *APOE* genotype, *APOE* ε4 positive individuals (n=7) showing higher Aβ levels than *APOE* ε4 negative individuals (n=21) though in no region was this significant. Given the low numbers of control cases used, statistical power to show significant differences may have been a limitation in this study since the study was only powered to detect robust changes (effect size 1.42). Further studies with greater sample sizes for both control and renal dialysis cases will be needed to confirm these changes.

Silver staining (Palmgren) failed to reveal the presence of NFT in control or RD cases.No control case showed any evidence of AT8 immunostaining, whilst 17 of the 29 RD cases showed positivity (~58%, p<0.0001), primarily located in the hippocampus though in some cases also in the cortex.This positivity consisted of scattered immunostained pyramidal neurones in the hippocampal CA1 layer and in the parahippocampal gyrus in 8 of the 17 cases.In the remainder of the cases, multiple immunostained neurones and accompanying neurites in the neuropil, were observed throughout the hippocampal formation, primarily in CA1, CA4, and the parahippocampal gyrus. In all cases AT8 immunostaining was of Braak stage 0-1. AT8 immunostaining did not appear to correlate with age or cortical aluminium levels (data not shown). AT8 immunopositive cases showed a slightly lower mean brain aluminium concentration than AT8 negative cases though this was not significant (AT8 positive, 4.5±3.3 mgAl/g tissue; AT8 negative, 6.7±4.2 mgAl/g tissue; p=0.14). Conversely, *APOE*ε4 positive cases showed a slightly, but not significantly, higher AT8 score than *APOE* ε4 negative cases (ε4 negative, 0.7±0.3; ε4 positive, 2.1±0.8, p=0.13).

There was an increase in the numbers of astrocytes of approximately 20% in frontal and temporal cortex of RD cases compared to controls but this did not reach significance, and in the hippocampus the number of astrocytes was reduced, though again, not significantly so.The numbers of activated astrocytes (increased branching and strong GFAP staining) was increased in the frontal and temporal cortex from RD cases, this increase reaching significance in the temporal cortex (p=0.004, two tailed t-test), though in the hippocampus the number of activated astrocytes remained unchanged. Total microglial numbers were elevated in all areas, though this only reached significance in the temporal cortex (p=0.005, two tailed t-test).Activated microglia were reduced in the

No.	Age	Gender	C.o.D.	*APOE*	Al µg/g ‡
1	59	F	ARF, PE	E2/3	10.2
2	66	M	Spt	E3/3	1.8
3	64	M	MI	E3/4	2.7
4	68	F	Spt	E3/4	5.4
5	59	M	CRF	E3/3	1.4
6	68	F	Spt	E3/4	2.1
7	59	M	SAH	E3/3	8
8	66	M	na	E2/3	5.5
9	56	F	na	E3/3	8.7
10	73	F	na	E3/4	2.3
11	37	F	Spt	E3/4	1.2
12	61	M	MI	E3/3	2.7
13	47	F	CRF	E3/3	13.1
14	37	F	CRF	E3/3	5.6
15	49	F	CRF	E3/3	14.1
16	54	M	MI	E3/4	5.6
17	64	F	na	E2/3	6.3
18	69	M	na	E2/3	7.9
19	55	M	MI	E3/3	3.9
20	67	M	na	E3/3	6
21	38	M	na	E3/3	3.5
22	69	F	na	E3/3	3.7
23	69	F	na	E3/3	3.1
24	51	F	CRF, BPN	E3/4	2.8
25	70	M	MI, CRF	E3/4	6.3
26	64	M	na	E3/3	2
27	64	M	na	E2/3	12.3
28	62	F	LVF, CRF	E3/3	2.6
29	62	F	MC, ARF	nd*	nd*

C.O.D: Cause of Death; ARF: Acute Renal Failure; BPN: Bronchopneumonia; CRF: Chronic Renal Failure; LVF: Left Ventricular Failure; MI: Myocardial Infarction; SAH: Subarachnoid Haemorrhage; Spt: Septicaemia; MC: Metastatic Carcinoma; PE: Pulmonary Embolism; na: Cause of Death Not Available.

‡: Aluminium Levels in Frontal Cortex;µg/G: Dry Weight Determined by Atomic Absorption Spectrophotometry

nd* not determined, no frozen material available

Table 1: Case details, *APOE* genotype and brain Aluminium concentrations in cases of chronic renal dialysis

	Renal dialysis	Control
Aβ (%) - frontal	0.56 ± 1.25 *	0.03 ± 0.075
Aβ (%) - temporal	0.37 ± 1.17	0.02 ± 0.04
Aβ (%) - hippocampus	0.03 ± 0.12	0.00 ± 0.00
AT8 - frontal	0.00 ± 0.00	0.00 ± 0.00
AT8 - temporal	0.00 ± 0.00	0.00 ± 0.00
AT8 - hippocampus	1.07 ± 1.59 **	0.00 ± 0.00
Total astrocytes - frontal	103.8 ± 44.9	82.8 ± 22.8
Total astrocytes - temporal	96.1 ± 37.5	75.5 ± 25.2
Total astrocytes - hippocampus	52.1 ± 26.6	60.1 ± 31.9
Activated astrocytes - frontal	61.2 ± 34.2	47.0 ± 19.4
Activated astrocytes - temporal	61.7 ± 33.1 **	36.9 ± 10.0
Activated astrocytes - hippocampus	25.0 ± 23.0	25.4 ± 35.9
Total microglia - frontal	184.9 ± 62.9 ‡	147.8 ± 33.7
Total microglia - temporal	187.1 ± 56.8 **	106.7 ± 42.1
Total microglia - hippocampus	160.5 ± 62.5	144.1 ± 63.6
Activated microglia - frontal	29.5 ± 35.6	46.5 ± 30.3
Activated microglia - temporal	30.7 ± 31.3	24.7 ± 23.1
Activated microglia - hippocampus	33.5 ± 30.4	56.4 ± 35.3

Total amyloid-β load (Aβ (%)) was determined using imaging morphometry and values expressed as mean grey

matter area covered in percent. All other determinations are specific object counts per mm^2 of grey matter area. *, $p<0.05$; **, $p<0.01$; ‡, $p<0.1>0.05$. Aβ: Amyloid Beta; AT8: Hyperphosphorylated tau antibody.

Table 2: Neuropathological analysis of renal dialysis and control cases for Alzheimer pathology and glial cell density

frontal cortex and hippocampus and elevated in the temporal cortex but nowhere was this significant. No correlations were observed between astrocyte or microglial numbers and age or brain aluminium in any region studied.

Because of the finding that high aluminium in dialysate can lead to the development of dementia and that, in certain species such as the rabbit, administration of aluminium salts can lead to formation of NFT-like structures in neurones, RD cases have been studied in order to elucidate the role of aluminium in Alzheimer's disease. The pathology of dialysis encephalopathy/dementia is relatively non-specific with the presence of spongiform change in the upper cortical layers being the only significant finding [18]. Some authors have suggested that argyrophilic inclusions distinct from NFT are present in cortical neurones [19, 20], and that Aβ and senile plaque deposition may also occur [16,21].

In the present study, we have sought to relate quantitative measures of pathology to aluminium exposure and *APOE* ε4 allele status in a series of RD cases previously shown to have Aβ deposition at an age when this finding is infrequent [16]. In this group of RD cases, overall there was increased deposition of Aβ, though this was not at a density comparable to that found in AD (RD, 0.5%; AD, 4-5%, [22]). This might suggest that RD cases have either increased deposition or reduced clearance of Aβ. The deposition of Aβ was however not related to the burden of Al found in the cortex. There was however a trend towards increased deposition of Aβ in those cases carrying the *APOE* ε4 allele though this relationship was not distinct since study of individual case details demonstrated that a case with the protective ε2/3 genotype [23] shows neocortical SP at a similar age and brain aluminium content to the more predisposed ε3/4 genotype (e.g. case 3, case 8, supplementary Table 1). In these instances and in ε3/3 cases, *APOE* genotype alone may not account for the presence of Aβ, indeed, even cases with an AD predisposing *APOE* genotypes do not always progress to develop AD [24]. It may be that *APOE* ε4 acting as a predisposing risk factor interacts with the general pathological processes associated with RD to produce Aβ deposition as has been suggested for *APOE* and head trauma [2,25]. RD patients suffer from a considerable number of metabolic impairments due to their renal failure and there is clear evidence of cognitive impairment [26] and such changes may predispose to accelerated AD changes.

The presence of AT8 immunopositive neurones, indicating hyperphosphorylated Tau may be related to the previous finding of protease-resistant hyperphosphorylated Tau in the brains of this group of RD patients using a biochemical assessment [17,27]. The finding of elevated Tau in the previous study was found to be correlated with aluminium exposure though in this study we were unable to identify any such link. This may be due to the biochemical rather than immunohistochemical approach used, allowing a differentiation between soluble and insoluble forms of Tau. The presence of AT8 immunostaining was however related to the APOE ε4 allele and may indicate a general AD pathological process to be occurring in the brains of RD cases independently of aluminium.

There does not appear to be any major change in the numbers of astrocytes in the brains of RD patients, though in some regions the microglial response appears elevated. This does not however appear to be associated with any inflammatory changes since HLA-DR expressing microglia appear to be normal or even reduced. One possibility is that the metabolic disturbances because of renal failure which occur prior to and during dialysis [26] affect neuronal or glial integrity which in turn leads to increased microglial numbers. The presence of altered immune function in cases undergoing chronic renal dialysis may however prevent an adequate microglial response from occurring, resulting in increased microglial numbers but a failure to induce HLA-DR expression [28]. Alternatively, the elevation in microglial numbers may relate to the presence of Aβ in some renal dialysis cases, though we were unable to demonstrate any association with Aβ deposition, the *APOE* ε4 allele and microglial numbers.

Supplementary Methods

Histopathology was performed on the formalin fixed right hemisphere. Previous studies have shown the presence of Aβ deposition as fibrillar aggregates in RD patients but have failed to demonstrate NFT using silver staining methods in RD [16]. Blocks were cut from the superior frontal gyrus (frontal cortex) at the anterior limit of the corpus callosum, from the superior temporal gyrus (temporal cortex) at the level of the amygdala, and from the hippocampus at approximately the level of the lateral geniculate nucleus and embedded in paraffin wax. Sections, 10 μm, were stained with anti-Aβ (clone 6F/3D against 11-17 of Aβ, Dako, UK; 1:100 dilution) to demonstrate Aβ, anti-phosphorylated Tau (clone AT8, Innogenetics, Belgium) to demonstrate NFT and Tau accumulation, anti-GFAP (polyclonal anti-bovine GFAP, Dako, UK; 1:4000 dilution) to demonstrate astrocytes, anti-ferritin (polyclonal anti-human liver ferritin, Dako, UK; 1:1000 dilution) to demonstrate all microglia [29], and with anti-HLA-DR/DP/DQ (clone CR3/43, Dako, UK; 1:100 dilution) to demonstrate MHC class II expression on activated microglia. For each antigen, sections were stained in a single run to minimise potential variation in staining. Sections were dewaxed and taken to water, then for AT8, GFAP, ferritin, and HLA-DR, boiled in a microwave for 10 minutes in 0.1M sodium citrate buffer (pH 6.0). Sections were allowed to cool and then endogenous peroxidise activity quenched by incubation of the sections for 20 minutes in methanol containing 3% hydrogen peroxide. For the demonstration of Aβ, sections were incubated in 98% formic acid for 3 minutes, and the sections subsequently washed extensively in running tap water. Non-specific binding was blocked by incubation of the sections in 1% normal horse serum in Phosphate Buffered Saline (PBS), and the sections then incubated with the primary antibodies at room temperature for 1 hour.Sections were given three five-minute washes in PBS and then incubated with biotinylated secondary antibody (Vectastain Elite, Vector Laboratories, UK) for 30 minutes at room temperature then given three five-minute washes in PBS.Sections were incubated with streptavidin-biotin horseradish peroxidise complex (Vectastain Elite, Vector Laboratories, UK) for 30 minutes at room temperature, given three five-minute washes in PBS, and

the antibodies visualised by incubating the sections in 0.25 mg/ml diaminobenzidine tetrahydrochloride in 0.003% hydrogen peroxide in PBS for 10 minutes at room temperature. Sections were then washed extensively in running tap water, given a light haematoxylin counterstain, dehydrated, cleared and mounted.

Aβ load was calculated using imaging densitometry as the percentage grey matter covered by Aβ determined in 3 non-adjacent ribbons of cortex from the pial surface to the white matter, or in three areas of the CA1 pyramidal cell layer of the hippocampus [30]. Because AT8 immunostaining demonstrated neurones, neurites in the neuropil and SP-associated neurites containing NFT/Tau phosphorylated at Ser 202, a semi-quantitative method of assessment was used based on a scale from 0, no staining; 0.5, 1-2 neurones/neurites per cm^2; 1-5, increasing levels of immunostaining up to levels that are seen in AD cases. Cell counts for total and reactive astrocytes/microglia were made using an eyepiece graticule in 3 non-adjacent ribbons of cortex or CA1 region of the hippocampus.

Brain aluminium levels were determined in frontal cortex as described previously [31] and *APOE* genotyping was performed using standard methods [32,33].

Conclusion

In summary, we have determined indices of AD neuropathology in renal dialysis cases and attempted to relate them to aluminium exposure. Whilst RD cases show elevated AD-type pathology compared to a control group, and this may be related to the presence of the *APOE* ε4 allele, no single factor, including aluminium, could account for the elevated AD pathology, although a limitation of the study may be sample size given the multifactorial nature of late onset neurodegenerative disorders. The factors giving rise to AD pathology appear to be complex and several factors may interact to produce the final picture of mildly increased AD pathology.

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Conflict of Interest

The authors declare no perceived conflict of interest

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