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Toxicology

Aluminium in brain tissue in familial Alzheimer's disease

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ABSTRACT

The genetic predispositions which describe a diagnosis of familial Alzheimer's disease can be considered as cornerstones of the amyloid cascade hypothesis. Essentially they place the expression and metabolism of the amyloid precursor protein as the main tenet of disease aetiology. However, we do not know the cause of Alzheimer's disease and environmental factors may yet be shown to contribute towards its onset and progression. One such environmental factor is human exposure to aluminium and aluminium has been shown to be present in brain tissue in sporadic Alzheimer's disease. We have made the first ever measurements of aluminium in brain tissue from 12 donors diagnosed with familial Alzheimer's disease. The concentrations of aluminium were extremely high, for example, there were values in excess of 10 μg/g tissue dry wt. in 5 of the 12 individuals. Overall, the concentrations were higher than all previous measurements of brain aluminium except cases of known aluminium-induced encephalopathy. We have supported our quantitative analyses using a novel method of aluminium-selective fluorescence microscopy to visualise aluminium in all lobes of every brain investigated. The unique quantitative data and the stunning images of aluminium in familial Alzheimer's disease brain tissue raise the spectre of aluminium's role in this devastating disease.

1. Introduction

Genetic mutations associated with both the expression [1] and metabolism [2] of amyloid precursor protein (APP) are, in general, the basis for a diagnosis of familial Alzheimer's disease (fAD). They, along with evidence from Down's syndrome [3], provide strong support for the amyloid cascade hypothesis [4,5] and a central role for the neuropathology and biochemistry of amyloid-beta (Aβ) in Alzheimer's disease [6]. In many ways, familial AD has been used as a blueprint for understanding and treatment of sporadic or late-onset AD.

Aluminium is present in human brain tissue [7] and in a recent study involving 60 human brains the median aluminium content of 712 tissues across all four main lobes was 1.02 μg/g dry wt. with 75% of all values being <2.01 μg/g dry wt. tissue [8]. The association of aluminium and AD has a significant history [9,10] and yet there remains no consensus as to a role for this known neurotoxin in the disease [11]. However, recent reports concerning sporadic AD [12] and environmental [13] and occupational [14] exposure to aluminium have allowed the conclusion to be drawn that, under certain conditions, it is inevitable that aluminium will contribute towards AD [11,15]. The suggestion is made that wherever in the brain the concentration of aluminium is pathologically-concerning (>2.00 μg/g dry wt.) that this aluminium will contribute towards any ongoing AD and will result in the disease being earlier in onset with a more aggressive aetiology [15].

Familial AD is characterised by an earlier age of onset and yet there are no data to describe the aluminium content of brain tissue in this 'signature' form of AD. Herein we have obtained brain tissue from 12 autopsy-confirmed cases of familial AD and we have carried out the first ever measurements of brain aluminium content in familial AD. We have also supported our quantitative measurements with imaging of brain aluminium by aluminium-selective fluorescence microscopy.

2. Materials and methods

There was ethical approval from The MRC London Neurodegenerative Diseases Brain Bank at King's College, London (08/MRE09/38 + 5).

Samples of cortex of approximately 1 g frozen weight from temporal, frontal, parietal and occipital lobes were obtained from 12

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