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Axonal Preservation in Deep Subcortical White Matter Lesions in the Ageing Brain

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Abstract

Cerebral white matters lesions (WML) are seen in 94% of the population aged 64 and over and are associated with cognitive decline and depression. We used immunohistochemistry and stereological methods on post mortem brain samples derived from the Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS) cohort to investigate the axonal density within deep subcortical lesions. There was no significant difference between the lesional and control white matter, therefore, we conclude that there is axonal preservation within these lesions that are characterized by demyelination.

Keywords: Deep subcortical lesions; Axonal density; Ageing.

Introduction

Hyperintense White matter lesions (WML) are often identified by T2-weighted magnetic resonance imaging (MRI) in periventricular or deep, subcortical regions of ageing brains. Deep subcortical lesions (DSCL) are seen in 86% of the population aged 64 and over [1] and are associated with cognitive decline and depression [2].

This laboratory has demonstrated that DSCL are associated with severe myelin loss and high levels of amoeboid, phagocytic microglia [3,4].

The current study used stereological methods to investigate the hypothesis that deep subcortical white matter lesions would be characterized by axonal loss.

Materials and Methods

DSCL and non-lesional white matter were identified by MRI of post mortem brain tissue derived from the MRC-CFAS cohort [3]. Blocks of tissue were sampled from these regions, fragmented, processed and embedded in paraffin wax with random orientation. Sections (5 μm) stained by immunohistochemistry for neuro filament protein, and the number of cut ends of axon within a superimposed frame were counted, according to stereological rules. From these, the length density of axons in DSCL in lesional and non-lesional tissue was calculated.

Results

The length density (L_v) was calculated as 359.7 (SD 41.0) m/mm³ for controls and 353.1 (SD 31.9) m/mm³ for lesions. There was no significant difference between the control and lesional tissue (P=0.528).

Conclusions

The estimated L_v of 360 and 353 m/mm³ for control and lesional tissue compares well with other estimates of axonal density in white matter [5]. Surprisingly, it appears that deep subcortical white matter lesions are characterized by relative axonal preservation. This stands in interesting contrast to our existing demonstration of a loss of myelin [3]. The demonstration of relative (if not complete) axonal preservation in the context of myelin loss clearly has parallels with multiple

sclerosis [6]. In this context it is interesting that microarray studies have demonstrated that both deep subcortical lesions [7] and multiple sclerosis plaques [8] occur against background field changes in the so-called 'normal appearing white matter'. Studies of gene expression in the normal appearing white matter of brains with white matter lesions stress the importance of genes involved in immune response, proteolysis, cell cycle progression and control, as well as ion transport [7].

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