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White Matter Ageing: Etiology and Prognosis

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Abstract

The present study continues our previous efforts to explore the roles played by white matter in initiating diseases. In this study, we explored the ageing of white matter from different points of views including gender, age, histology, genetic and biomarkers involved in its ageing. We also explored the involvement of white matter ageing in some neurodegenerative diseases including Alzheimer Disease. Due to the important roles of white matter in initiating diseases, it is important to take appropriate measures to concentrate on this topic by scientific communities and to probably design some programs to detect cases at an early stage, particularly because the ageing of white matter precedes the clinical onset of diseases. Taken together, white matter ageing is an important topic for future intervention programs.

Keywords

White matter;
Ageing;
Neurodegenerative diseases;
Alzheimer Disease;
Biomarkers

INTRODUCTION

Normally, ageing is not only triggered by genetic directed programs, but also through limited abilities to keep hemostasis of organs [1]. Several theories have been set up to demonstrate mechanisms underlying normal ageing include continuous breakdown of DNA, continuous deterioration of control of protein quality, in addition to decreased capability of regeneration of stem cells [2]. It is thought that decreased volume of white matter (atrophy of white matter) with ageing is due to a continuous lack of small diameter myelinated fibers [3]. The maximal changes in white matter volume were observed in parietal and occipital regions due to age [4]. Other studies showed that males have larger volume of white matter than females [5,6].

Normal brain ageing implies loss of cognitive functions which are accompanied by loss of volume of WM as well as loss of its integrity in the prefrontal cortex [7]. It implies the occurrence of a group of structural and functional changes [2], including small brain volumes [8,9], decreased thickness of cortex [10], and increased ventricular system [11]. There cerebral pathologic changes associated with ageing such as WM lesions, infarction, and cerebral microbleeds [10]. Ageing is also accompanied with changes in functions of brain such as lowered motor abilities [9], and partial loss of sensory function [12]. With ageing, declining levels of neurotransmitters were reported including dopamine [13], acetylcholine [14], serotonin [14], and norepinephrine [15], and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [16]. Rathee et al (2016) [17] studied changes in microstructure of white matter in terms of diffusivity indices and macrostructures of white matter volume in healthy persons in the age range of 20-85 years. Study findings showed that there were differential changes in structure of volume of white matter and diffusion indices based on age and gender.

The components of white matter include myelinated neurons and glial cells are important for brain ageing and influenced differently with age in mammals [18].

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The ideas of having age related changes in volume of white matter and different integrity indices have been reported by Ge et al (2002) [19]. The study of Svennerholm et al (1994) [20] showed that there was a continuous decrease in the concentration of myelin lipid over time. Other studies made an explanation of declining of cognitive process with age based on continuous breaking down of myelin [21-23]. In their study, Hsu et al (2008) [24] did not find uniform effects of age and gender in various areas of white matter coping with normal ageing.

It has been interestingly reported that verbal fluency and semantic memory are not affected by normal ageing, which is plausible due to dependency of these skills on previous experience from long past [2].

Genetic changes accompanying white matter ageing

Sri et al (2013) [25] conducted a study the contribution of genetic factors involved in the ageing of white matter. As evidenced from family studies, it has been suggested to encounter inheritance of white matter integrity measures changes over time. These changes include measures of DTI, fractional anisotropy (FA), and show large impacts of inheritance among adults. Loci on chromosomes 3 and 15 have been linked to genetic variants for WM integrity. However, genetic studies are still in their infancy and much work is required. Some studies investigated the APOE ε4 polymorphism. The APOE ε4 allele was linked with lowered integrity of white matter in the cingulum, corpus callosum and parahippocampal gyrus.

Histological studies

Histological studies showed that there is a decrease in the number of myelinated fibres in addition to alterations of myelin sheath with age [3,26,27]. Several studies have found that cerebrovascular changes are likely to participate to the microstructural changes of white matter with ageing [28,29]. Studies have also indicated that the observed age-related WM decline is not uniform [10].

It was interestingly reported that the process of myelination is affected by ageing so that recent myelinated regions are more likely to be subjectd to atrophic changes compared with that with early myelinated regions [21].

Degeneration of white matter follows certain patterns including an anterior–posterior gradient, or a superior–inferior gradient which implies that degeneration of white matter is a complicated process [30-34].

Biomarkers of ageing

Racine et al (2017) [35] conducted a study to investigate Cerebrospinal fluid (CSF) for biomarkers related to Alzheimer disease pathology including phosphorylated-tau/Aβ42 ratio, axonal degeneration (neurofilament light chain protein, NFL), dendritic degeneration (neurogranin), and inflammation (chitinase-3-like protein 1, YKL-40). The results showed that these biomarkers predict deterioration of white matter health.

CONCLUSIONS

The present study put emphasis on the importance of white matter ageing from various points of view including gender, genetics, histology, and biomarkers. A very important question was asked about any future possibilities to establish early intervention programs to detect early ageing of white matter.

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