

Does Myelin Play the Leading Role in Alzheimer's Disease Pathology?

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Abstract

Although Alzheimer's disease (AD) has been mainly considered as a grey matter disorder, there is emerging evidence that myelin impairment may play an important role in AD pathology. These data come from animal neuropathological studies, but also from human pathological, biochemical and brain MRI studies. Classical neuropathological changes in AD such as the accumulation of aggregated A β 42 and the presence of neurofibrillary tangles are responsible for neuronal loss, but they may also induce death of oligodendrocytes and myelin impairment. Accelerated deposition of A β in brains of AD patients induces damage to oligodendrocytes and results in impaired myelin production. What is more interesting, there is also evidence that myelin pathology may precede A β and tau pathologies in AD. Recent studies suggest that A β and tau proteins may be by-products of myelin repair in AD, instead of being the primary underlying cause of dementia. This seems possible, considering the fact that attempts to control clinical symptoms of AD by removing A β from the human brain have been unsuccessful. In this article, current knowledge on the place of myelin in AD pathology and its interactions with A β and tau pathology is reviewed.

Keywords: Alzheimer's disease; Myelin impairment; Glial derived antigens; Oligodendroglia; Biomarkers

Alzheimer's disease (AD) is known for some well-characterized pathological changes including the extracellular accumulation of amyloid plaques, intra-neuronal presence of neurofibrillary tangles, glial hypertrophy and neuronal death [1-3]. Paradoxically, myelin pathology in human AD has not been widely studied, even though it has been more than a century since Alois Alzheimer described myelin disruption in AD in 1911 [4,5]. It is unclear why the phenomenon of myelin impairment has been forgotten for more than 100 years. Classical neuropathological changes in AD, such as amyloid plaque deposition and the presence of neurofibrillary tangles in the brain, are responsible for neuronal damage and synapse loss, but there is also emerging evidence that oligodendroglial degeneration and myelin impairment are present in the brains of AD patients [6-9].

Data from animal models suggest that focal demyelination is mainly found in the proximity of beta amyloid plaques within the neocortex [10-12]. Schmued et al. have provided evidence for the complete disruption of myelinated fibers passing through A β plaques in the regions adjacent to the plaques in the rat hippocampus [12]. At the same time, myelin impairment may aggravate neuronal dysfunction, as myelin supports axonal survival. Clinically, such impairment translates into deterioration of cognition, as different myelination disorders result in cognitive decline.

At present, the knowledge of the role of myelin in human AD is mostly limited to MRI neuroimaging studies [9,13-15]. The most recent data indicate that beta amyloid deposition in the brain may change the white matter microstructure, as confirmed by brain MRI, and this phenomenon can be found even in early stages of the disease [9]. In addition, there is a strong correlation between a decrease in A β levels in the cerebro-spinal fluid of subjects in the preclinical phase of AD and a decrease in selected MRI myelin measures indicative of myelin damage [9].

As mentioned above, the neurodegenerative process in AD has been classically perceived as being initiated by the accumulation of aggregated A β 42 and the presence of neurofibrillary tangles. This process probably causes neuronal death; however, there is evidence that it may also lead to the damage of myelin and myelin-producing oligodendrocytes [16,17]. Still the exact nature of the interaction between AD pathology and myelin damage remains unclear.

Some studies suggest that myelin damage in AD may even precede A β and tau pathologies [17]. Myelin basic protein (MBP), which is an intracellular protein and a major structural protein component of myelin, has been proven to bind β amyloid and inhibit β amyloid fibril formation in AD, which may have a regulating role in the deposition of A β 42 and the formation of amyloid plaques in the extracellular space of the brains of AD patients [18,19]. MBP is also responsible for β amyloid degradation *in vitro* [18]. MBP levels are significantly decreased in the white matter of AD patients [20], and there is a strong association between decreased MBP levels and the increase in A β 42 in the brain tissue of AD patients [9]. It is therefore possible that the loss of myelin and the decrease in MBP levels result in accelerated deposition of A β and increased deposition of A β plaques in the brains of AD patients. On the other hand, as mentioned above, the deposition of A β in the human brain deteriorates the state of myelin. It has been shown that A β induces death of oligodendrocytes and inhibits myelin formation [21]. Thus, the loss of myelin in AD may be involved in a kind of vicious circle which promotes further neuronal loss and disease progression.

The above data are also in accordance with the results of our previous study in which we observed increased levels of antibodies against different glial derived antigens (anti-MOG, anti-MAG, anti-MBP, anti-PLP) in sera of AD patients in comparison to healthy control subjects [22]. The increased antibody levels against different antibodies of the myelin sheath are probably secondary to myelin damage in AD patients. Of course, it is not quite clear whether the antibodies found in AD reflect a diffuse CNS injury or contribute to this injury. Nevertheless, the process of myelin damage probably leads to the presentation of new antigens to the immune system, and subsequent activation of T

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and B cells. A hypothesis on how the immune system may be involved in the pathogenesis and progression of neurodegenerative disorders was proposed by Monahan in 2008 [23]. Activated B cells or specific autoantibodies may enter the CNS across dysfunctional BBB, produce cytokines which activate microglia and release autoantibodies. This may lead to further inflammation and subsequent cell death [23]. This conception would rather support the hypothesis that myelin damage precedes classical A β and tau pathology in AD. Our results also support the hypothesis that not only neuronal cells but also oligodendroglial cells undergo neurodegeneration in AD, with subsequent presentation of new antigens to the immune system. In the light of data from animal studies on early demyelination of the hippocampal region, our results may, in the future, help determine biomarkers of early memory loss in AD. The hippocampus is among the first structures affected by AD pathology in the human brain.

Data from animal models also provide evidence on the interaction between tau pathology and myelin degradation. Firstly, tau protein hyperphosphorylation may occur during the remyelination process [24]. Recent findings suggest that myelin impairment may even precede neurofibrillary tangles deposition in certain cortical regions in AD. A defect in myelin biosynthesis has been found in AD subjects even in very early, preclinical stages of the disease, such as Braak stage I/II within the temporal cortex. Interestingly, hyperphosphorylated tau protein, which is a hallmark of axonal and neuronal loss, has also been found in other demyelinated disorders.

What is interesting, the spread of AD pathology reflects the myelination pattern in reverse. Later myelinated brain regions, such as the temporal and frontal lobes, develop AD pathology first, whereas early myelinating regions, mainly motor and sensory systems may remain intact in AD until very late stages of the disease [25-27]. Some studies also suggest that AD is a developmental disorder, which cannot occur before myelination has been completed [26,28]. It is worth noting, that unlike the formation of neurons of the CNS, the process of myelination in humans progresses slowly throughout the childhood and young adulthood [29]. In humans, the process of myelination in the corpus callosum is not complete until the second decade of their lives [30] and in frontal lobes may not even be finished by the age of forty [31-33]. More accurate data show that AD is rather a remyelination disorder [32], as a defect in myelin lipid biosynthesis has been found.

Intriguingly, there exists an association between the presence of an ApoE4 allele and the level of myelin damage in AD. ApoE, a confirmed risk factor for the disease, plays an important role in the transportation of endogenously produced brain lipids and recycling of these lipids, which is crucial for myelin production, its maintenance and repair [31,34]. It has been proven that apoE4 allele carriers have lower levels of ApoE molecules in serum and brain tissue than non-carriers [35]. An Apo E4 allele decreases the formation of myelin in the human brain and promotes age-related myelin damage [36].

In conclusion, data from recent studies suggest that A β and tau proteins may potentially be products of myelin repair in AD instead of being the main underlying cause of dementia [9,31]. These data are also supported by the fact that previous attempts to control clinical symptoms of AD by removing A β from the human brain have failed, although different agents turned out to be successful in eliminating A β from the brain tissue.

There also exists evidence for myelin damage in the normal aging brain [9,24,31]. Nevertheless recent data suggest that AD pathology is additionally affected by myelin damage [9]. Also neuroimaging studies

of patients with MCI reveal white matter damage and myelin impairment in these patients, before the fifth decade of their lives [37].

In conclusion, although AD pathology has over the years been typically linked with neuronal degeneration, most recent data show that it is strongly associated with oligodendrocyte and myelin pathology [9,22,31]. Evidence comes from human MRI neuroimaging studies, but the finding is also supported by the presence of increased levels of different autoantibodies against proteins of the myelin sheath in sera of AD patients compared to healthy controls. There is emerging evidence that myelin plays a more important role in AD pathology than previously thought, but further serological, neuroimaging and pathological studies are necessary to explain the exact role of myelin in AD.

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