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Involvement of the Spinal Cord in the Alzheimer's Disease: A Literature Review

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Abstract

Context: Pathologic studies often show an involvement of the spinal cord in the early stages of the Alzheimer's (AD) disease; clinical studies further show a statistically-relevant frequency of gait impairment and an increased risk of falling. Therefore, the spinal cord is possibly involved in the Alzheimer's disease and has a role in the appearance of some symptoms.
Evidence Acquisition: Medline literature search.
Results: Several pathologic studies in animals and humans show abnormalities in the spinal cord and particularly in the anterior horn lesions that are typical of AD. Several clinical studies show frequent and precocious impairment of the gait, which is possibly related to the pathology of the spinal cord.
Conclusions: The AD disease does not only affect the brain, and cognitive symptoms, as well as non-cognitive symptoms are typical of the early stages of the disease.

Keywords: Alzheimer's Disease, Spinal Cord in Alzheimer's Disease, Non-Cognitive Symptoms in Alzheimer's Disease

1. Context

The chief symptoms of the Alzheimer's disease (AD) are cognitive; however in the earlier stages of the disease non-cognitive symptoms can also appear (1). Anatomopathological studies have shown lesions typical of the AD outside the regions of the brain typically involved in AD (2) or even outside the brain (1). The aim of this report was to review the potential involvement of the spinal cord in the AD and its role in the appearance of some symptoms.

2. Evidence Acquisition

The Medline literature was scanned until august 2015 using 'AD disease", "spinal cord and AD", "non-cognitive symptoms in the AD" as keywords. Other studies were identified by reviewing relevant bibliography quoted in original studies. Clinical studies were included if they could meet these threshold criteria: 1) AD diagnosis according to the NINCDS-ADRDA criteria (3); studies including patients with dementias other than AD were only considered when sufficient data on AD were provided; 2) Use of standardized instruments for evaluation.

3. Results

Pathological studies on animals and humans were retrieved. Several studies on transgenic animals showed lesions that are typically associated with AD in the spinal cord. Probst et al. (4) showed high levels of tau isoform both in the brain and in the spinal cord of the transgenic mouse AL217; most tau immunostained neurons were located in the anterior horn. The authors underlie that, unlike the cerebral spheroids, the spinal spheroid show a strong reactivity to several anti-tau antibodies. The axonopathy was abundant in the spinal cord and motor deficit appeared at the age of one to three months. Similar observations were reported by Wirths et al. (5) in the transgenic APP/PS1 mouse with elevated intraneuronal amyloid β42 levels. The authors showed early alterations mostly in the ventral horn and severe axonal pathology mostly along the ventral horn but also in the intermediolateral and dorsal horn. Lazarov et al. (6) showed an impairment of the fast axonal transport responsible of functional motor deficits in the transgenic mouse expressing presenilin 1 variants. In the transgenic Tg2576 mouse, overexpressing a mutant form of the amyloid β precursor protein, motor deficits appeared at the age of 10 months along with a severe reduction in the number of neurons present in the lumbar spinal cord (7). Wirths et al. (8) drew attention to

the inflammatory processes that are present in the mouse APP/PA1K1 both in the brain and in the spinal cord; the authors hypothesized that the early inflammatory reaction contributes to the axonopathy and thus to motor impairment. Severe axonopathy and motor impairment was studied in another model of the transgenic mouse 5XFAD (9). Yuan et al. (10) studied amyloid β deposition in the central part of the dorsal column corresponding to the corticospinal tract pathway and its projection region in the TgCRND8 mouse. The authors hypothesized that neurons in the sensorimotor cortex are the source of the amyloid β deposited in the spinal cord. Tesseur et al. (11) showed axonal degeneration and gliosis in the brain and in the spinal cord of the transgenic mouse expressing human APOE4, often associated with AD.

There are only a few pathologic studies in humans. Ogomori et al. (12) showed amyloid deposits in the spinal cord of 3/9 patients with onset of dementia before the age of 65 years. Saito et al. (13) showed tau-related pathology in 11/11 AD patients, mainly in the anterior horn but also in the intermediate zone and in the posterior horn; seven patients also showed neurofibrillary tangles. These lesions were more abundant at the cervical level and decreased progressively at the thoracic and lumbar level. Small tau reactivity was also noticed in 7/10 neurologically normal subjects although none showed neurofibrillary tangles. Schmidt et al. (14) showed neurofibrillary lesions in 18/19 patients with AD or one of its variants (not specified). The lesions were mostly in the substantia intermedia and to a lesser extend in the lateral, dorsal and ventral horns. In the detailed work of Dugger et al. (15) the Authors examined tau's presence in the spinal cords of 46 AD patients and in 37 control patients. Tau immunoreactivity was noticed in 95.6% of the patients at the cervical level, in 68.9% at the thoracic level, in 65.2% at the lumbar level and in 53.5% at the sacral level. Controls also showed tau immunoreactivity but significantly lower than that of the patients: in 43.2% at the cervical level, in 36.7% at the thoracic level, in 26.7 at the lumbar level and in 12.9% at the sacral level. In two subjects classified at the Braak stage (16) 0 spinal tau was absent whereas it was noticed in 4/10 subjects classified as Braak stage 1. On the basis of these data, the authors hypothesized that the spinal cord's involvement is precocious but does not precede the involvement of the transentorhinal cortex. Spastic paraparesis is often described in the familial AD due to mutations in presenilin 1 or 2. In five patients with familial AD and mutations in presenilin 1, Verkkoniemi et al. (17) described degeneration of the lateral corticospinal tracts at the level of the medulla oblongata and of the spinal cord. Degeneration of the corticospinal tracts was also described by Rudzinski et al. (18) in three members of another family with presenilin 1 mutation.

3.1. Clinical Studies

The acts of standing and walking result from the integration of voluntary and involuntary processes. When triggered emotionally, the regulation of locomotion processes originate in the cerebral cortex or in the limbic-hypothalamic system, whereas the automatic processes are located in the brainstem and in the spinal cord. Two areas involved in the control of locomotion have been identified in the mesopontine tegmentum: the midbrain locomotor region and the muscle tone inhibitory region. Two pathways descending from the midbrain locomotor region in the ventrolateral and in the dorsolateral funiculi activate the locomotor central pattern generator, which is formed by spinal interneuronal circuits. Inhibitory effects on muscle tone arise from pedunculopontine nucleus, which in turn activates the reticular formation, the medullary reticulospinal neurons and the spinal inhibitory neurons (19). From this short description, it is clear that different lesions at different levels may impair the capacity to stand and walk in different ways. Incomplete spinal cord injuries in experimental animals initially impair their gait coordination (20, 21). In humans, several studies show a clear relationship between dementia and falls (2). Verghese et al. (22, 23) described the motoric cognitive syndrome characterized by slow gait and cognitive complaints. The increased risk for falling was ascribed to specific cognitive deficits, including immediate memory (24) or visuospatial ability (25). However, several studies showed that increased risk of falling was not only related to the early stages of AD and to minimal cognitive impairment (MCI) (26-29) but also to the presymptomatic stages of the MCI (30-32). In particular, Buracchio et al. (31) showed a decline in gait speed approximately 12 years before MCI. According to these data, it seems unlikely that cognitive impairment alone may be responsible for an increased risk of falls in the early stages of the disease, as motor impairment is also likely to contribute. Whether motor impairment is due to brain or spinal lesions is a matter that requires further investigations. Theoretically, medullar damage may provoke urinary disturbances. Several studies showed a statistically-relevant correlation between urinary disturbances and dementia (33-37). Nevertheless, these studies had some limitations: neuropsychological assessment is not always precise and the study's sample was mainly limited to patients with severe AD, so it remains difficult to reach any definitive conclusion. However, a specific study on transgenic animals provided an interesting piece of information: in the AppSL/PS1M146L mouse, Biallosterski et al. (38) showed a clear increase in the number of VAChT+ and NOS+ nerve fibers within the

lamina propria, which are sensory fibers contributing to the afferent output of the bladder. Although it remains difficult to draw a conclusion, this work demonstrates that a possible anatomical substrate may be responsible for some urinary disturbances.

4. Conclusions

The AD is usually viewed as a degenerative disease of the brain associated with cognitive disturbances. However, this understanding is rather limited and likely incomplete. The first interesting remark relates to the presence of typical AD lesions not only in the spinal cord but also outside the nervous system (1). A second relevant remark concerns the sequence of the symptoms. According to the national institute of aging and the Alzheimer association's workgroup (39), the average time between the deposition of the β amyloid and the clinical syndrome of the AD dementia is approximately a decade. We still don't have effective therapies: recognizing the disease in its very early stages would greatly improve drug research and the evaluation of their effectiveness. Third, in light of these observations, the diagnostic criteria of AD (3) could be revised by including non-cognitive symptoms such as psychiatric and motor disturbances. A fourth remark relates to the possible misinterpretation of some tests used in transgenic animals. Indeed some behavioral studies on cognitive processes assume normal motility because the cognitive status is deduced from behavioral performances. However, since some animal models show impairment of the motility, the results of these tests should be judged cautiously (36).

However, two possible weakness of this work need to be recognized:

1) This is a narrative and not a systematic review; 2) suggestions for the involvement of the spinal cord in the AD are strong but the available literature is not definitive.

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