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REVIEW ARTICLE

Non-cognitive symptoms and related conditions in the Alzheimer's disease: a literature review

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Abstract The Alzheimer's disease is considered a progressive cognitive disorder; however, several non-cognitive symptoms accompany all stages of the disease, appearing at times before the cognitive symptoms become manifest. This article reviews the literature on non-cognitive symptoms normally related to the Alzheimer's disease, including gait and balance dysfunction, olfactory dysfunction, diabetes, pain, and psychiatric symptoms.

Keywords Alzheimer's disease · Diabetes · Gait dysfunction · Non-cognitive symptoms · Olfactory dysfunction · Pain · Psychiatric symptoms

Summary

The Alzheimer's disease is considered a progressive cognitive disorder; however, several non-cognitive symptoms accompany all stages of the disease, appearing at times before the cognitive symptoms become manifest. This article reviews the literature on non-cognitive symptoms normally related to the Alzheimer's disease, including: gait and balance dysfunction; olfactory dysfunction; diabetes; pain; and psychiatric symptoms.

The clinical diagnosis of the Alzheimer's disease (AD) is based on progressive cognitive dysfunctions, whose typical onset is characterized by a progressive worsening of the memory and impairments of other cognitive domains [1]. However, extra-cerebral pathological lesions show that, besides cognitive impairments, other symptoms become manifest during the course of the illness. As a matter of example, it is interesting to notice the symptoms of Auguste D., the first Alzheimer's patient, who started with delusional jealousy towards her husband [2]. Similar symptoms often become obvious during the later stages of the disease; they may, however, begin manifesting in the early stages of the disease, or even when cognitive symptoms are not severe enough to trigger an AD diagnosis. It has been suggested that lesions characterizing the disease begin in the transentorhinal region and progress caudo-rostrally in a rather predictable manner. It has also long been assumed that cognitive symptoms appear only with severe involvement of the transentorhinal and entorhinal regions, whereas the earliest stages of the disease are characterized by non-cognitive symptoms [3].

The aim of this work is to provide a review of the literature dealing with certain non-cognitive symptoms and other related conditions in the early stages of the disease. Their identification may be helpful in selecting patients at risk of developing cognitive impairment.

Materials and methods

Medline literature from January 1984 throughout June 2012 was scanned using "extracranial beta amyloid", "extracranial tau", "extracranial tangles" and "non-cognitive symptoms" as keywords. When non-cognitive symptoms or related conditions were identified, the search was narrowed down using "gait dysfunction", "olfactory dysfunction", "psychiatric symptoms", "pain", "neurologic signs" and "diabetes" as keywords. Others studies were identified by reviewing relevant bibliography quoted

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in the original papers. Clinical studies were included if they could meet three fundamental criteria: (1) AD diagnosis according to the NINCS-ADRDA criteria [1]; studies including patients suffering from dementias other than the AD were considered when sufficient data on the AD were provided; (2) Minimum sample of twenty subjects; (3) Use of standardized instruments of evaluation.

This selection of papers aims to provide a description of the cerebral and extra-cerebral pathology, as well as non-cognitive symptoms and other conditions related to the AD.

Results

Cerebral and extra-cerebral pathology in the AD

The pathological hallmarks of the AD are neurofibrillary tangles and extracellular senile plaques. In a recent wide series, Braak and Colleagues [4] have not detected any intra-neuronal inclusions of abnormally phosphorylated tau protein only in 10 out of 2,332 brains, all pertaining to subjects below 23 years of age. The beta amyloid plaques occurred in the neocortex only after the taupathy's onset in the brainstem. Some authors have examined the occurrence of typical AD lesions outside the brain [5, 6], mainly finding the amyloid in the anterior horns and in the cervical region of the spinal cord. Among elderly patients, small deposits of beta amyloid are commonly found in a number of organs and are usually regarded as having no clinical importance. Fibrils have been found in almost all organs: liver, parathyroid, lung, spleen, lymphonodes, kidney, adrenal glands, thyroid, pancreas, stomach, bowel, myocardial, striated muscles, testis, ovary, hypophysis, aorta, tonsils, tongue and lenses [7]. Studies on transgenic animals also provided interesting information: the tau protein was found in the spinal cord, mostly concentrated in the anterior horns and in the cervical tract [8]. The intraneuronal accumulation was detected in animals at the same age in the spinal cord, in the hippocampus and in the cortex. In the APPswe/PS1 transgenic mice, Filali and Colleagues [9] demonstrated non-cognitive behaviors that are remindful of AD symptoms: irritability, dysexecutive symptoms, apathy and depressive behavior. Further, transgenic mice's behavior is characterized by a decreased spontaneous motor activity, disinhibition, reduced body weight, increased frequency and duration of feeding bouts, and an enhanced aggressiveness in males [10]. Despite few in numbers, all studies found a wide diffusion of pathological processes outside the brain. These studies further proved the presence of non-cognitive symptoms in animals. Pathological lesions are also present in cognitive-intact subjects, although less frequently than in patients affected by the AD.

Gait and balance dysfunction

Age-associated motor decline is common in old peoples with a strength reduction ranging between 20 and 40 % from the third to the eight decade. Similarly, almost all sensory functions are diminished in old people [11]. Several studies proved a strong correlation between falls and impairments of the cognitive functions: it is also well known that the risk of falls increases in patients with Mini Mental State Examination (MMSE) scores below 24 [12], and this independently from the typology of dementia [13]. The extent to which non-neurological factors affect the falls frequency largely depends on the etiology of the dementia: older age and high Cumulative Illness Ratings are significantly associated with gait disorders among patients possibly affected by AD [13]. Several studies pointed out that increased falling risks are to be associated with subtle cognitive impairments. Gleason and Colleagues [12] found a statistically relevant association between MMSE scores ranging from 22/30 to 29/30 and fall frequency, thus suggesting that scores below 30 should be considered an independent risk factor for subjects with a history of falls. Some authors tried to correlate the falls with specific cognitive deficits, and particularly with immediate memory deficits [14] and visuospatial ability deficits [15]. According to Verghese and Colleagues [16] the pace factor, a measure of the velocity and stride, can be used to predict the decline in executive functions, whereas the rhythm factor, a measure of the stride cadence and timing, can be used to predict the decline of episodic memory; a decline in both factors predicts the risk of developing dementia. Cognitive deficits certainly increase the chances of falls, albeit other factors cannot easily be dismissed. Since locomotion results from the integration of intentional and automatic processes, gait and balance cannot be considered unitary processes. According to Braak and Colleagues [3], the pathological process begins in the transentorhinal region, with the first cognitive impairments appearing once the process affects the limbic region. However, these regions are also involved in the regulation of the automatic basic locomotion. In the Parkinson's disease, the dysfunctions of the pedunculopontine nucleus have been positively related to an increased likelihood of falls. Although the AD also affects this nucleus, Kotagal and Colleagues [17] were unable to demonstrate thalamic cholinergic denervation in the AD using positron emission tomography (PET) imaging. Lesions in the spinal cord may also increase the difficulties in walking because inputs descending from the midbrain locomotor region activate the interneurons of the locomotor central pattern generator located in the laminae VII, VIII and X of the lumbar cord. Unfortunately, existing anatomical studies are not precise enough to identify any potential lesion in these

pathways. Other factors may contribute towards gait dysfunctions: in an animal model of the AD, researchers observed disorders of small and large peripheral nerve fibers similar to those of diabetic models [18]. Peripheral neuropathy was reported in a study examining the upper limbs of a series of AD patients [19]. The National Institute of Neurological Disorders and Stroke and the Alzheimer's disease (NINCS-ADRDA) AD's guidelines [1] state that "gait disturbances at the onset or very early in the course of the disease make the diagnosis of AD uncertain or unlikely"; in light of the above observations, this definition shall be amended [13].

Olfactory dysfunction

Waldton [20] was possibly the first to notice the involvement of the first cranial nerve in the AD. Several clinical works [21] demonstrated the presence of olfactory impairments in the AD. From the olfactory bulb, the information directly reaches some cortical areas—particularly the entorhinal cortex—and from these cortical areas inputs are channeled to the cortical association areas, where they are integrated with visceral and gustatory inputs and also channeled towards the hippocampus and the hypothalamus [22]. The precocity and severity of the hippocampus and entorhinal cortex' pathologies are well known [3]. Two separate reviews [23, 24] have concluded that, despite the negative results of some studies, the literature suggests the presence of an olfactory identification deficit in AD patients. Evaluations simultaneously relying on MRI exams, neuropsychological tests and the Smell Identification Test can effectively predict the conversion from MCI to AD [25]. Because olfaction is a complex function related to the ability to store, recall and report memories, several attempts have been made to separately examine these different functions. In particular, some rather specific pathways were identified using the PET [26]. The right parietal association cortices, right precuneus, right inferior temporal cortex, and right orbitofrontal cortex were implicated in the odor identification, the left sensorimotor cortex in the odor discrimination, and the subcortical structures, including the thalamus and the cerebellum, in the odor threshold detection. Olfactory dysfunctions are not peculiar of the AD since they also occur in other neurodegenerative diseases, such as the Parkinson's disease and the dementia with Lewy's body.

The genesis of olfactory dysfunctions remains largely unknown. An anatomopathological study [27] correlated the difficulty in identifying odors with the presence of neurofibrillary tangles in the entorhinal cortex and in the hippocampus; on the other side, neuritic plaques were found to have a weaker association, while diffuse plaques had no association at all. In another study using PET, [28] the olfactory dysfunction and beta amyloid burden were found to be unrelated. A functional MRI [29] showed that the perceptual impairment of odors quality discrimination in the mild-stage of the AD occurs with a disruption of odors quality coding in the posterior piriform cortex, whereas the flow of the olfactory informations from the periphery to the piriform cortex remains uninterrupted. Wesson and Colleagues [30] detected hyperactive odor-evoked activity in the piriform cortex of animals during the early stages of olfactory impairment; as the disease progressed, the system became increasingly hypoactive. An association between the difficulty in identifying odors and the presence of εapolipoprotein E was referred [31]. In conclusion, the difficulty in identifying odors is common in the early stages of some neurodegenerative diseases, including the AD, the Parkinson's disease and the dementia with Lewy's body. In the AD, this is likely due to the neurofibrillary pathology in the entorhinal cortex and in the hippocampus [27] and is characterized by the incapability to extract specific information from odors during the identifications and discrimination phases [29].

Pain

A reduced prevalence of pain in elderly subjects has been reported. Although the use of analgesics for acute pain does not significantly differ from the average consumption in healthy subjects, the consumption of analgesics for chronic pain is significantly lower among AD patients [32]. Discriminative aspects of the AD pain are usually preserved, whereas non-discriminative aspects are damaged [33]. These non-discriminative aspects are mediated by the medial pain system, which includes the intralaminar nuclei connected with the limbic regions. Hence, the prevailing hypothesis is that AD patients have emotionally reduced responses to pain [34]. However, Cole and Colleagues [35] did not find any reduced pain-related activity in medial pain regions using functional MRI and subsequently concluded that the AD does not diminish emotional aspects. These authors further observed a prolonged activation of a functional circuit among the periaqueductal gray, the hypothalamus and the dorsolateral prefrontal cortex. Such circuit mediates defensive responses to nociceptive inputs. Using empirical data, the authors suggest that increased arousal is to be associated with noxious events rather than with an increased pain process potentially due to a diminished capacity to interpret unpleasant stimuli.

Psychiatric symptoms

Alzheimer himself described feelings of jealousy among the incipient symptoms of his first patient [2]; psychiatric

symptoms are indeed very frequent and are the most important cause of the disease's early institutionalization. The relevant literature is wide and at times discordant; opinions differ because they reflect different methods of evaluation as well as physiological differences among patients. Depression, apathy and anxiety are more common in the MCI and in the early stages of the AD. A 2009 review [36] found that the most common behavioral symptoms in order of frequency are depression, anxiety, irritability, apathy, agitation, euphoria, disinhibition, delusions and hallucinations. In a prospective study [37] during the 4 years of follow-up, apathy and hyperactivity increased, whereas the prevalence of affective and psychotic symptoms remained unchanged. Some authors [38] claimed a different prevalence of psychiatric symptoms in the two types of MCI: depression and apathy are more frequent in the amnestic type, whereas delusions and hallucinations are more common in the non-amnestic type. According to several authors, psychiatric symptoms predict the evolution from MCI to AD; conclusions are, however, far from univocal. Some authors [39] diagnosed depression symptoms long before the first cognitive impairment became manifest; these conclusions are also disputed [40]. Other authors [41] maintained that depression predicts changes in executive control and not in memory. In other studies, [42] apathy was postulated as a predictive element of evolution toward dementia. Yet other researches [43] suggested that all behavioral disorders in the MCI probably result in an increased risk of progression towards AD. A recent pathological study [44] showed no significant differences in the AD pathology or in vascular damage in the cortex of depressed patients compared with non-depressed patients. In a first series of 28 patients, [45] the authors claimed that severe AD is over-represented among elderly patients committing suicide; however, there were no signs of a higher-than-average prevalence of AD pathologies in a second and largest series of 143 subjects [46].

Psychotic symptoms, mainly delusions and hallucinations, are also very frequent, with a median prevalence of about 41 % [47]. These symptoms may become manifest in all stages but are more frequent in the later stages of the disease. Even if some authors [48] did not find any link with the MMSE, a review [47] showed that the prevalence of psychoses ranged from 25.5 % in initially impaired subjects to 49 % in severely impaired subjects.

Lyketsos and Colleagues [49] suggest grouping the psychiatric symptoms in few sub-syndromes. In their series, 40 % of the subjects showed no symptoms; 19 % only one symptom; 28 % predominantly affective symptoms and; 13 % a psychotic syndrome. The presence of neuropsychiatric sub-syndromes was confirmed by Aalten and Colleagues [50], who described four groups in a large series: hyperactivity, psychosis, affective symptoms and apathy. Psychiatric symptoms in the MCI are so common that, in the absence of prominent cognitive symptoms, some authors [51] suggested introducing the concept of "Mild Behavioral Impairment (MBI)"—a late life syndrome with prominent psychiatric and psychiatric-related behavioral symptoms. This syndrome is common to several dementias, although is mainly found in the frontotemporal dementia; in the authors' series, 28 % of the cases evolved towards the AD. Studies on transgenic models also confirmed the precocity of behavioral symptoms: since 3 months of age, transgenic mice present social abnormalities but no cognitive or non-cognitive abnormalities [52].

Several theories have been suggested to explain psychiatric symptoms in AD patients, focusing in particular on depression; none of them has, however, proved free from criticism. An early theory claims that depression might occur as a psychological reaction to awareness of being affected by the AD, but there is no evidence of a correlation between depression and severity of the dementia [53]. The concept of depression-dementia medius has been proposed more recently [54]: in old individuals with subtle cognitive impairment, depression impairs compensatory mechanisms, thus giving rise to pseudo-dementia; when the depression improves, concentration also improves, and dementia returns to the latency. When dementia worsens, compensatory mechanisms are inadequate and dementia becomes manifest. It was observed that some proposed mechanisms for depression are similar to those implicated in the neurodegeneration [55]. According to these authors, neuroinflammation and reduction of neurotrophic factors are common to depression and to AD and may explain the link between these two diseases. Studies with Positron Emission Tomography [PET] found hypometabolism in the anterior cingulated, in the superior frontal cortex and in the superior temporal cortex [56]. This same study found the involvement of different areas in AD patients with depression and with apathy, thus confirming the involvement of several neuronal circuits. The few studies that examined the amyloid and the tau in the cerebrospinal fluid in AD patients with and without depression [57] found no association between the AD pathology and depression.

In conclusion, the link between psychiatric symptoms and the AD is complex and insufficiently researched. Interesting but still to be perfected is the concept of MBI, positing the MCI as a very precocious stage of the AD.

Diabetes

The hypothesis of an association between diabetes and AD was put forward in the 1990s. Such association was

long disputed; nevertheless, a recent meta-analysis [58] concludes that diabetes is a risk factor for MCI, AD, vascular dementia and any other type of dementia. Subjects with diabetes have a relative risk of developing vascular dementia of 2,49; 1,46 for AD and 1,21 for MCI. Subjects with diabetes and ε4 apolipoprotein carry the highest risk of developing AD [59]. Insulin acts directly on cognitive functions: intranasal administration facilitates memory in the AD [60], while it increases short- and long-term object memory, anxiolytic behavior and odor-discrimination in mice [61]. Anatomopathological studies excluded a significant increase of AD-related pathologies in diabetes [62] while other studies demonstrated beta amyloid and tau deposits in the pancreatic beta cells in type 2 diabetes [63]. The mechanism linking hyperglycemia to the development of Alzheimer's type dementia remains unknown; several hypotheses have been put forward so far. Hyperglycemia may have toxic effects on neurons: promotes early onset of AD-associated disorders in transgenic mice by increasing the vascular deposition of advanced glycation products and reactive oxygen species [64]. Vascular inflammation and amyloid angiopathy with unaltered amyloid beta burden are present in animal models of AD [65]; these neuropathological changes were associated with impairment of brain insulin signaling. This observation may explain the apparent discrepancy between cognitive impairments and the lack of a significant increase of the AD-related pathology in diabetes. Insulin resistance—defined as an inadequate tissue response to insulin—is also understood to play a central role. Abnormalities in insulin and insulin-like growth factors signaling were found in the AD, thus suggesting that the AD represents a neuroendocrine disorder called type 3 diabetes [66]. Although this hypothesis has been criticized [67], insulin resistance is commonly believed to be involved in the origin of the cognitive impairment. Many insulin signaling molecules in CA1 pyramidal cells were highly related to the episodic memory [67] and exenatide, an anti-diabetic molecule that stimulates the insulin signaling and improves cognition in the mice [68]. On the whole, these results show complex interactions between insulin, food intake, cognitive and emotional behavior. It is possible that the weight losses often reported in the neurodegenerative diseases are to be referred to central regulation dysfunctions, since food intake in the AD is usually adequate or even increased [69]. The hypothalamus and particularly the nucleus arcuatus are involved in the regulation of the homeostasis; these regions are often involved in neurodegenerative diseases. According to Ewalds and Colleagues [70], metabolic changes could be mediated by the amyloid precursor protein, which alters hormonal and insulin signaling pathways.

Discussion

This review results in two remarks: the first is that AD anatomopathological lesions mainly affect, but are not limited, to the brain. The spinal cord is often affected, while AD-typical lesions have also been described outside the nervous system—their overall role in the origin and development of some symptoms remains, however, unproved. The second remark concerns the sequentiality of the symptoms' appearance. The AD has a very long course: some neuropathological alterations already appear in the juvenile age, while cognitive symptoms may be preceded or accompanied by several non-cognitive symptoms. According to the National Institute on Aging and the Alzheimer Association's workgroups, the AD pathological process and the AD clinical symptoms should be conceptualized as a continuum that may evolve in parallel. For research purposes, three preclinical stages of AD were defined: Stage 1, characterized by asymptomatic cerebral amyloidosis with evidence of beta amyloid accumulation but no evidence of brain alterations suggestive of neurodegeneration; Stage 2, characterized by amyloid positivity + evidence of synaptic dysfunction and/or early neurodegeneration with evidence of amyloid accumulation and presence of one or more markers of neuronal injury; Stage 3, characterized by amyloid positivity + evidence of neurodegeneration + subtle cognitive decline with the appearance of subtle cognitive decline approaching the border zone with the proposed clinical criteria for MCI.

The postulated time window between the deposition of the beta amyloid and the clinical syndrome of the AD dementia is approximately a decade [71]. Non-cognitive symptoms may also appear in stage 3 and contribute to identify subjects at risk. The proposed concept of MBI appears very interesting despite requiring further examination. It is possible that the association between the MCI and some non-cognitive symptoms may help detecting with higher accuracy those subjects who will evolve towards dementia. Hence, treating the AD as a disease simply characterized by cognitive impairments maybe reductive; perhaps the diagnostic criteria need to be revised to include some non-cognitive symptoms among its early-stage manifestations. Today, we still do not have effective therapies; there is no doubt that recognizing the disease in its very early stage would greatly improve drug research and evaluation effectiveness. For a long time, the Parkinson's disease has been judged as a motor disease: only in relatively recent times non-motor symptoms have been recognized as an integral part of the disease. Equally, the AD is today classified as a purely cognitive disease; non-cognitive symptoms need, however, to be taken into consideration. Recovering a metaphor used for

the non-motor symptoms in the Parkinson's disease [72], it is possible that AD's cognitive symptoms only represent the tip of the iceberg.

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