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Review Article

Behavioral Symptoms in Mild Cognitive Impairment and In the Early Stages of the Alzheimer's disease: A Narrative Review

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Abstract: ***Background***: Behavioral disturbances are commonly found in the Mild Cognitive Impairment (MCI) and during the early stages of the Alzheimer's disease. This review examines the typology and frequency of such behavioral symptoms. ***Method***: Medline literature review until January 2019. ***Results*:** Although there is a vast and sometimes contradictory literature, most Authors agree on the following elements: 1) Behavioral symptoms are highly frequent; 2) Depression and anxiety are among its most common symptoms; 3) Symptoms appear in all types of dementia and also in animal models of the Alzheimer's disease. In fact, behavioral symptoms are so common that some Authors propose the concept of Mild Behavioral Impairment (MPI). ***Conclusion*:** Behavioral disturbances often represent the very first or one of the first signs of cognitive impairment among the elderly

Keywords: Alzheimer's Disease; Mild Cognitive Impairment; Behavioral disturbances.

INTRODUCTION

The Alzheimer's disease (AD) is usually considered a progressive cognitive disorder; although non-cognitive symptoms are often evident, they are typically considered as late symptoms.The Mild Cognitive Impairment (MCI) is a small cognitive deficit that often precedes the AD. In MCI some non-cognitive symptoms may also be present; however, they are often disregarded.This review examines the type and frequency of behavioral symptoms in both the MCI and the early stages of the AD to see if they can be an early symptom.

METHOD

The Medline literature was scanned until February 2019 using the following keywords: “model of AD”; ”MCI and behavior” and “Alzheimer and behavior”. When articles indicating behavioral disturbances were found, the search was subsequently narrowed using the following keywords: “MCI and depression”; “Alzheimer and depression”; “APOE and depression”; “Depression and MRI”; “Depression and PET”; “MCI and cerebrospinal fluid”; “MCI and pathology”. Additional studies were identified by reviewing relevant bibliography quoted in the original papers. Clinical studies were included whenever they could meet the following criteria: 1) AD diagnoses according to NINCDS-ADRDA criteria [1]; 2) studies including dementias other than AD, whenever sufficient data on AD were provided; 3) use of standardized instruments of evaluation.

RESULTS

Animal models. Cognitive deficits have been studied at length in animal models of the AD, while behavioral alterations have also been observed. Lalonde and Coll. [2] and Ognibene and Coll. [3] reported mild anxiety in the mice TG2576. In the same model, Pietropaolo and Coll. [4] showed deficits in social interaction and communication. According to these Authors, social deficit precedes other neuropsychiatric and cognitive deficits. Increased anxiety was also described in other animal models: notably, Lee and Coll. [5] in the mice C57BL/6 at age 11-14 months and; Beauquis and Coll. [6] in the transgenic PDAPP-J20 mouse at age 5 months. At this same age Beauquis and Coll.[6] also found alterations in the hippocampus without amyloid plaques. Pentkowiski and Coll.[7] described increased anxiety but no spatial memory deficits in the transgenic rat TgF344-AD. In studying the tgDimer mouse at age 7-12 months, Abdel-Hafiz and Coll.[8] described anxiety and despair-related behaviors coupled with impairments in non-selective attention and in motor learning. Petrasek and Coll. [9]

described increased anxiety and cognitive deficits in the McGill-R-thy1-APP transgenic rat at age 4-7 months.Increased irritability and escape responses in the absence of any other change were also found in the APP/PS1 transgenic mouse [10]. However, in another transgenic mice carrying both preseniline-1 and amyloid precursor protein, there was no indication of a change in anxiety levels [11].

Injecting soluble oligomers of the amyloid-ß peptide in mice's cerebral ventricles has shown an impact not only on their memory and learning, but also on their mood; treatment with fluoxetine prevented both cognitive impairments and depressive behaviour [12]. Also, following the intracerebroventricular administration of amyloid-ß peptide to mice, the neuropeptide prevented depressive behavior and memory deficits [13].

Behavioral symptoms and dementia

Depression is a frequent condition in the elderly population [14,15]. Many Authors examined the hypothesis that depression may precede dementia. Some works are retrospective: Speek and Coll. [16] evaluated previous depressive episodes in AD patients and showed a positive correlation with episodes that occurred at least ten years before the diagnosis of dementia. Buntix and Coll.[17] examined 19.103 subjects without cognitive deficits and found a positive relationship between the old age depression and dementia. Wetherell and Coll. [18] examined the occurrence of psychiatric illnesses, mainly depressive episodes, in 65 twin pairs discordant for AD. They found a significant association only with psychiatric illnesses that had occurred not more than ten years before the onset of dementia. Green and Coll. [19] observed depressive episodes in 14.2% of 277 patients with AD, but only in 7.4% of 154 subjects without cognitive deficits.

There are also many prospective studies on the subject.

Devanand and Coll. [20] found a greater risk of dementia in 478 subjects without cognitive deficits but with old age depression (relative risk 2.94). Bassuk and Coll. [21] also confirmed a positive correlation between depression and dementia. On the other side, Chen and Coll. [22] reached opposite conclusions while examining 954 subjects. Yaffe and Coll. [23] referred worse performance in 211 depressed women and a positive relationship between the severity of the depression and the risk of dementia. These data were confirmed by Kessing and Coll. [24], who suggested that, for every depressive episode in patients suffering from depressive disorder, there was an increased risk of 13% to develop dementia. This same correlation was found in patients with a bipolar disorder, where for every depressive episode there was an increased risk of 6% to develop dementia. On the other side, Dal Forno and Coll. [25] found a relationship between depression and dementia only in male subjects. Wilson and Coll. [26] followed 1,256 subjects without cognitive deficits for 12 years; of the 482 who developed MCI, most were scoring high on distress assessment scales. Palmer and Coll. [27] in 185 subjects and Geerlings and Coll.[28] in 486 subjects indicated a statistically- significant relation between depression and dementia. On the other side, Becker and Coll. [29] have not found such relation while studying 288 subjects over a period of 3 years. Dotson and Coll. [30] confirmed the relationship between depression and dementia in 1,239 subjects. Similarly, according to Sackzynski and Coll. [31], depression increases the risk of dementia of 1.5 times.

Li and Coll. [32], after having followed 3,410 cognitively normal subjects for 7.1 years on average, confirmed the association between depression and dementia. In their series, the hazard ratio for AD was 1.43; for vascular dementia 1.78; for mixed dementia 2.24 and for other dementias 2.52.

According to Lenoir and Coll. [33], depression is linked to vascular dementia and not to the AD.

While following 2,663 subjects, Heser and Coll. [34] found that depression is a prodromal feature of the AD but not of dementia or other etiologies.

Masters and Coll. [35] found a significant early presence of neuropsychiatric symptoms in those cognitively normal patients who were to subsequently develop cognitive decline. On the other side, Gracia-Garcia and Coll. [36] suggested a relationship with dementia only in severe depressions.

Makizaco and Coll. [37] found a correlation between dementia and depression, and Ritche and Coll. [38] confirmed such a positive correlation also for depressions that had occurred as long as ten years before the AD diagnosis.

Riddle and Coll. [39] followed 273 depressed subjects and 164 newly-depressed subjects for five years, concluding that depressed subjects had a greater cognitive decline than non-depressed subjects. Mortamais and Coll. [40] evaluated the risk of dementia and trait anxiety among 5,234 subjects, but the depressive symptoms shape the association between anxiety traits and dementia. Ringman and Coll. [41] examined 251 subjects with familial AD: no differences could be found between carriers and non-carriers in the pre-symptomatic stage, whereas in the symptomatic stage carriers displayed a higher number of behavioural symptoms.

MCI, behavioral symptoms and dementia

Others Authors considered the hypothesis that depression may precede the MCI. According to Modrego and Coll. [42], 85% of 41 patients affected by MCI and depression developed dementia, compared to only 32% of 73 patients affected by MCI but not depression.

In analyzing a series of patients with MCI, Rozzini and Coll. [43] found a higher frequency of dementia among subjects with depression, apathy or anxiety. Teng and Coll. [44] referred development of

dementia in all patients with MCI and psychiatric symptoms, while Solfrizzi and Coll. [45] calculated the risk of developing dementia in subjects with MCI and depression in 29.6/100 persons-years. Also Chan and Coll. [46] in 321 patients, Brodaty and Coll. [47] in 319 patients and Brendel and Coll. [48] in 371 patients confirmed that dementia develops more frequently among patients with MCI and depression. According to Van der Mussele and Coll. [49] agitation predicts dementia in general, whereas depression predicts the AD in particular. In a retrospective study, Defrancesco and Coll. [50] found that depression increases the chances of MCI turning into AD. Several Authors [27,43,44,49] reported that anxiety may also precede the conversion of MCI into dementia. Pietrzac and Coll. [51] refer that worried symptoms are associated with poorer performances and predict significant decline in visual learning and memory in patients without cognitive deficits. Others [52-55] suggested that several behavioral disorders such as anxiety, depression, irritability, aberrant motor behavior and social impairment may precede dementia.

APOE depression and anxiety

The APOE4 is recognized as a risk factor not only for the AD but also for other pathologies, mainly vascular. Some Authors considered the hypothesis that APOE4 facilitates the depression, reaching conflicting results. While Forsell and Coll. [56] did not find any association between APO status and depression in a population of 806 subjects, Lavretsky and Coll. [57] suggested that APOE4 carriers may have more severe depressive symptoms. According to Yen and Coll.[58], the APOE4 allele may be correlated with severe depression in the elderly.

Locke and Coll. [59] found no association between APOE genotype and longitudinal changes in depression. Instead, according to Skoog and Coll. [60] APOE4 predicts future depression. According to Karlsson and Coll. [61] depression within ten years of the onset of dementia is associated with dementia regardless of APOE status, whereas depression more distal to the onset of dementia is a risk factor only in ε4 carriers.

According to Tully and Coll. [62], APOE4 is not associated with major depression. Michels and Coll. [63] found an association between APOE4 and anxiety in 141 patients with MCI. Holmes and Coll [64] confirmed the association between APOE4 on the one side, and depression and anxiety on the other, in a population of 423 subjects. Other Authors evaluated the hypothesis that APOE status may modify the response to antidepressant drugs. Peters and Coll. [65] found no significant interaction between any genetic polymorphism and the response to sertraline. On the other side, Burke and Coll. [66] found a statistically significant relationship between recent depression, lifetime depression, ε4 carrier status and AD development. However, among users of antidepressant drugs, the hazard was no longer statistically significant.

Other Authors evaluated the hypothesis that APOE4 and depression have synergistic effects on dementia. Almost all agree that APOE4 and depression have synergistic effects both in subjects without cognitive deficits [67-75] and in subjects with MCI [72,76]. On the contrary, Luciano and Coll. [77] found no strong evidence supporting a synergistic effect of depression and APOE status in four cognitive domains.

Imaging

Some Authors evaluated the possibility that carriers of the APOE4 or affected by MCI with behavioral disturbances may have peculiar radiologic characteristics. Data interpretation is however difficult, because of the widespread reduction of gray matter volumes in middle-aged subjects (31.5 +/- 12.4 years) suffering from major depression [78].

Using Magnetic Resonance Imaging (MRI), APOE4 carriers both in young age [79] and adulthood [80] showed reduced hippocampal volumes.

However, other Authors disagree [81]. Shaw and Coll. [82] in APOE4 carriers found cortical thickness among normal subjects below 21 years of age. Guercio and Coll. [83] found that lower inferior cortical thickness and anterior cingulate cortical thickness were associated with greater apathy in subjects suffering from MCI. According to Mah and Coll. [84], anxiety predicts higher rates of decrease in entorhinal cortical volume. Pink and Coll. [85] reported that depressive symptoms were associated with lower global thickness, especially in prefrontal and frontal regions. The same Authors [86] found a statistically-significant association between anxiety and reduced insular thickness.

By recurring to the Positron Emission Tomography (PET) with subjects suffering from MCI and geriatric depression, Tateno and Coll. [87] found that the onset of depression among amyloid-positive subjects was significantly higher than in the rest of the sample. According to Brendel and Coll.[88] subjects with MCI and depressive symptoms have elevated amyloidosis in the frontotemporal regions.

According to Moon and Coll. [89], the MCI to dementia conversion rate is significantly different between subjects suffering from depression (40.8%) and subjects without depression (19.7%). Instead, Chung and Coll. [90] found no association with current depressive symptoms and cortical amyloidosis in MCI patients; similar results were found by Holmes and Coll.[64] and by Perin and Coll. [91] among normal subjects.

Krell-Roesch and Coll. [92] found a significant association between amyloid and anxiety, and only a

marginal significant association with depression. According to Hanseeuw and Coll. [93] higher amyloid in the subcortex (striatum, amygdala, thalamus) — but not in the cortex — was associated with greater anxiety. Such anziety was highest in the APOE4 carriers.

Cerebrospinal fluid and pathology

Data interpretation is difficult because modifications of the cerebrospinal fluid were also found among depressed patients. A meta-analysis [94] found a marginally significant reduction of the Aß42 in the cerebrospinal fluid and higher plasma Aß40/ Aß42 ratio as more reliable findings in the late-life depression. In both MCI and AD, Kramberger and Coll. [95] claimed that depressed patients tend to have lower p-tau levels; however, depression scores were not associated with tau or amyloid levels.

Diniz and Coll. [96] found lower levels of brain-derived neurotrophic factor in MCI patients with late-life depression, and no difference in Aß42 or tau concentration.

In a longitudinal study in subjects without cognitive impairment, Babulal and Coll. [97] found that patients with higher values of tau/Aß42 had increased mood disturbances.

Some anatomopathological alterations were also described among depressed patients, in this case also with conflicting results. In a meta-analysis of the neuropathology of the bipolar disorder [98], the most reliable findings are decreased cortical thickness and glial density in the subgenual anterior cingulate cortex and reduced neuronal density in some amygdalar nuclei. Hendricksen and Coll. [99] compared depressed subjects with or without AD, not finding any loss of serotoninergic neurons, or signs of neuritic pathology in the dorsal raphe nuclei. Instead, Rapp and Coll. [100] found significant differences in the rating of neuritic plaques and neurofibrillary tangles in the hippocampus of AD patients, dependently from the fact that they were suffering from major depression or not.
In a longitudinal study with a mean follow-up of 7.8 years, Wilson and Coll. [101,102] found higher levels of depressive symptoms before an MCI diagnosis, but no with the change in symptoms after the diagnosis. Depressive symptoms were also associated to faster cognitive decline rates. At the same time,depressive symptoms were not associated with any of the neuropathology hallmarks of dementia.

CONCLUSION

The literature relating behavioral disturbances to cognitive impairments is large and sometimes contradictory.

This relationship is also complicated by the presence of cognitive impairments — mainly in the executive function and in the working memory — in the depression [103], as well as by the inverse relationship between higher depression levels and lower cognitive functions [104].

However, most Authors agree on a number of elements.
The first element is the high frequency of behavioral disturbances during the early or pre-symptomatic stages of the cognitive impairment. Such disturbances were described in all dementias, often in the AD, but also in the vascular dementia, in the Lewy body and in the frontotemporal dementias. Differences in reported percentages are likely due to differences in sampling and evaluation methodologies.
It is remarkable that early behavioral disturbances were also described in animal models of the AD; these observations suggest that the psychological origin of such disturbances is unlikely. Among humans, it is well-known that significant events are closely related with late-life depression [105]; in all likelihood, these events act as triggers for physiological changes.

Depression is the most frequent symptom at the beginning, although anxiety is also relatively frequent, whereas other disturbances are rare.
Altogether, these symptoms are so common that some Authors introduced the concept of Mild Behavioral Impairment (MBI). In particular, Taragano and Coll. [106] examined 119 subjects suffering from MBI defined as major persistent changes in behavior without cognitive complaints and compared them with 239 patients with MCI; the patients were followed for up five years. 70% of patients with MBI developed dementia mainly frontotemporal compared to 34% of the patients with MCI.

According to Mortby and Coll. [107] using the ISTAART diagnostic criteria [108] the prevalence of MBI is of 48.9% in the MCI, of 43.1% in subjects at risk and of 27.6% in subjects cognitively healthies.
According to Sheick and Coll. [109] the prevalence is of 85.3% in the MCI and of 76% in subjects suffering from subjective decline.

The second element on which most authors agree, is the temporal relationship between behavioral disturbances and cognitive impairments. As the development of the AD is very slow, it is possible that behavioral disturbances precede the cognitive symptoms even by many years. The natural history of other neurodegenerative diseases is less known; however, in these diseases as well, a long pre-symptomatic stage is often acknowledged [110,111].

Several mechanisms have been put forward in order to explain such relationship, which is riddled in complexity, because of the multiple interactions between genetic, metabolic and environmental factors.

According to Mendes-Silva and Coll. [112], the AD and major depression have in common an abnormal expression of seven types of microRNA. These microRNA interact with several genes related

mainly to the maintenance of genomic integrity, to proteostasis control, to the regulation of apoptotic processes and to neurotrophic support. The Authors suggest that reduced neurotrophic support is an early event and that it makes the neurons more vulnerable.

According to a recent meta-analysis [113], genetic polymorphisms of brain-derived neurotrophic factor — interleukin 1-ß and methylenetetrahydrofolate — increase the risk of late-life depression and AD. A special importance was given to the hypothalamic-pituitary- adrenal (HPA) axis, which regulates the response to stress. Briefly, responding to stress, the neurons of the paraventricular nucleus of the hypothalamus synthetize the corticotropin-releasing hormone that subsequently stimulate the synthesis of the adrenocorticotropic hormone, which at its own turn stimulates the secretion of the glucocorticoids from the adrenal cortex. The receptors of the glucocorticoids are expressed in the hyppocampus, in the hypothalamus and in the prefrontal cortex. High levels of glucocorticoids inhibit the turnover of the cells of the hippocampus and are linked to apoptosis. In the AD, some Authors described higher levels of cortisol, particularly in APOE4 carriers and during the major depression hyperactivity of the HPA [114].

Insulin resistance is also common among depressive disorders, and AD and inadequate glucose utilization result in neuronal damage in brain regions as the limbic system affected in both disorders [115].

Unlike other typologies of depression, late-life depression has a chronic course and poor response to therapies [116,117]. The reason of these differences is not clearly established, although depression may be viewed as a heterogeneous syndrome encompassing a variety of symptoms and different responses to drugs.

In this respect, it is noticeable how — by recurring to the functional MRI —, several Authors demonstrated the involvement of different cerebral networks in otherwise seemingly similar forms of depression [118-122].

Although this is not a systematic review, the frequency of behavioral disorders in the MCI and in the early stages of the AD seems indisputable. This means that furter controlled studies on the diagnostic and prognostic value of these disorders and the mechanisms involved are needed.

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