

Neuropsychiatric Symptoms in Alzheimer's Disease Patients: Improving the Diagnosis

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Abstract

Neuropsychiatric symptoms have been strongly related to higher risk of cognitive decline, elevated clinical deterioration, increased morbidity and mortality, heavy caregiver burden, and early institutionalization. Patients suffering from dementia may be unable to describe their symptoms to the clinician, and caregivers frequently assume the responsibility to communicate the patient's behavioral disturbances. However, the caregiver's emotional distress may interfere with interpretation of the patient's behavior, compromising the diagnosis accuracy. Accurate assessment is a crucial strategy to diagnose patient's symptomatology. The aim of this work is to discuss some aspects related to disagreements between the caregiver report and the clinician impression on neuropsychiatric symptoms of patients with Alzheimer's disease.

Keywords: Neuropsychiatric symptoms; Alzheimer's disease; Dementia; Diagnosis; Caregiver report; Clinician impression; Diagnosis accuracy

Introduction

The purposes of this communication are to consider the neuropsychiatric symptoms currently considered in the clinical criteria for diagnosis of patients with Alzheimer's disease (AD), to comment on neurobiological aspects of these symptoms, and to emphasize some approaches to clinical practice concerning psychopathological manifestations.

Currently, cognitive and functional decline, as well as structural or functional neuroimaging, and cerebrospinal fluid biomarkers have been used to investigate and support the diagnosis of AD [1], and as well as to distinguish AD from Lewy bodies dementia [2]. In addition to these procedures, neuropsychiatric symptoms few years ago were included in diagnosis criteria of the disease [3-5].

Given the progress of knowledge on Alzheimer neuropathology, lately some chemical biomarkers, which reflect changes in amyloid-beta peptide and phosphorylated tau protein in the cerebrospinal fluid, were also incorporated in the diagnosis criteria. Recently, molecular neuroimaging, including tracers for amyloid-beta and neurofibrillary tangles in the brain parenchyma, has been reported as new imaging strategies for increasing specificity of clinical approach [6]. However, consistent cognitive deterioration and functional decline, and therefore, the worsening of neuropsychiatric symptoms currently remain as clinical criteria for diagnosis in AD patients, and they have been strongly recommended for the practical routine.

Neuropsychiatric Symptoms and Cognition

The concept that neuropsychiatric symptoms linearly follow cognitive and functional deterioration is debatable.

The worsening of neuropsychiatric symptoms not always follows the classical cognitive and functional deterioration of AD patients. Distinct psychopathological syndromes tend to be more prominent in mild stages of dementia while other could be detected at moderate or severe stages. For instance, depression and anxiety are common phenomena among patients with mild disease, whereas aggression, agitation, and apathy are more frequent in those patients at severe states of the disease [7].

Other studies conversely have shown that this association does not always occur [8-10]. In another previous investigation, the severity of neuropsychiatric symptoms in dementia did not highlight a uniform correlation with cognitive decline since great behavior variability has been observed in demented patients [3]. Furthermore, a recent study enrolling 156 AD patients found a 'non-linear' correspondence between cognitive or functional deterioration and neuropsychiatric worsening [11]. The authors reported, for example, that apathy was strongly detected among patients with mild, moderate, and severe stages of dementia, being the most clinically prominent syndrome, while aberrant vocalization were relevant only in the severe stage. Depression, anxiety, and irritability were very common symptoms among patients from all stages of dementia.

Another relevant point regards to the occurrence of individual neuropsychiatric syndromes related to deterioration of specific cognitive domains. For instance, apathy and depression may be related to decline of executive functions in late life, with prediction of more functional impairment in dementia [12-15]. Even in mild cognitive impairment, apathy could be an additional risk factor to progress to Alzheimer's disease [16-18].

Although in depression and apathy some symptoms may overlap, cognitive inertia emerges in apathy as a dysexecutive framework comprising decline in planning and reasoning, shifting thought and problems solving, thinking and behavior monitoring, as well as deterioration of working memory and verbal fluency, with behavior impoverishment [14]. Moreover, AD patients with apathy present a rapid lack of autonomy in daily living activities [19]. In addition,

depression and apathy reduce cognitive functioning of patients, and require more brain efforts than controls for cognitive process and less functional dependence [20,21].

An interesting point concerns the occurrence of neuropsychiatric symptoms in the prodromal stages of dementia, even in individuals cognitively preserved. Psychopathological occurrences in patients without cognitive or functional decline, as known as mild behavioral impairment, may represent a predictor for early manifestation of dementia [15,22].

If apparent dissociation between psychopathological manifestations and cognitive deterioration in AD actually exists, distinct as well as interactive pathophysiological mechanisms may underlie neuropsychiatric syndromes. This approach remains a challengeable issue [10].

Neurobiological Aspects Related to Neuropsychiatric Symptoms

Apathy and depression are frequent syndromes useful for an appropriate discussion about pathophysiological aspects on behavior disturbances in dementia. Neurobiological correlates could contribute to the highlighting of no so logical distinctions between apathy and depression. Using the PET scan, for example, Holthoff et al. [23] found different metabolism dysfunctions in AD patients with apathy, and with depression. In this study, apathetic patients presented brain hypometabolism in the left orbitofrontal cortex, and those with depression in the left prefrontal regions. In apathetic patients, alterations of the left orbitofrontal cortex were associated with impaired recognition and reduced modulation of responses to significant stimuli based on cognitive, motivational, and emotional processes. On the other hand, in depressive patients, the left prefrontal regions were unable to inhibit negative affective processes [23].

Benoit et al. [24] compared the brain SPECT scans between AD patients with and without apathy. They found that AD patients without apathy presented prominent hypoperfusion in the posterior regions, while the apathetic patients showed hypoperfusion mainly in the anterior regions. They also found that hypoperfusion in the prefrontal and cingulated regions were related to greater cognitive decline in the apathetic patients. For Benoit et al. [24], this occurrence emerged because the cingulate gyrus represents an important structure linking motivational and emotional drivers that seem to be regulated by limbic system and infero-frontal area. These connections intrinsically interact one each other and are crucial for goal-directed behavior that comprises cognitive processes, motivational mechanisms, and emotional reactions. In another investigation using the brain SPECT scans of AD patients with apathy, Benoit et al. [25] reported that left prefrontal hypoperfusion was involved in emotional blunting, as was measured by the Apathy Inventory [26]. Emotional blunting represents one dimension of apathy among others, such as lack of interest and lack of initiative [26,27]. Within this context, Benoit et al. [25] assumed that limbic system and fronto-subcortical circuits mediate cognitive, behavioral and affective components of motivation.

Also employing brain SPECT scans, Kang et al. [28] more recently compared brain perfusion in AD patients with apathy and those with depression. Although these authors associated distinct brain areas with apathy or depression, they did not identify a strong correlation between each condition and a specific area in the brain. However, they

concluded that both syndromes in AD involve distinct functional pathways.

Based on the fractional anisotropy method, derived from diffusion tensor imaging (DTI), Kim et al. [29] analyzed the white matter microstructure integrity of AD patients with apathy. These researchers observed through this neuroimaging approach that AD patients with clinically relevant apathy showed lower fractional anisotropy in the anterior cingulate cortex in comparison to those without apathy, independent of concomitant depressive symptoms. The authors assumed the hypothesis that apathy in AD patients is associated with changes in microstructural white matter, suggesting that disruption of communication pathways between the anterior cingulate cortex and other brain regions could contribute to the severity of this syndrome [29].

Furthermore, using DTI neuroimaging, Cacciari et al. [30] analyzed mean diffusivity in individuals with mild cognitive impairment (MCI), with and without apathy. These researchers observed that individuals with apathy presented increased mean diffusivity in several brain tracts, including the right temporal segment of the uncinate, the inferior longitudinal and middle longitudinal fasciculi, parathalamic white matter, and the posterior cingulate of the right hemisphere. Loss of fractional anisotropy and increased mean diffusivity represent microstructural changes of white matter, including disruption of axonal integrity, diminished axonal myelination, reduced amount of axons, decreased axonal diameter, and altered axonal interspaces in fiber tracts or bundles. In MCI individuals, microstructural disorganization within these connections increases the risk for progression to AD [31,32].

Another common problem on diagnosis of neuropsychiatric symptoms in AD regards the accuracy of psychopathological manifestations, and some points deserve to be commented. Accurate recognition of symptoms is an important tool since these occurrences represent a complex brain and mind disorganization. It should be mentioned that in this situation the relationship between both the brain and mind functioning is not yet sufficiently understood. Functional imaging contributes to better comprehension of some correspondences between specific brain regions and neuropsychiatric syndromes [33,34]. For instance, using resting-state functional magnetic resonance imaging, a study demonstrated that patients with mild to moderate AD, when compared with controls, presented alterations in the intrinsic connectivity of the anterior silence network, which includes the anterior cingulate cortex, the frontal insula, the amygdala, and the striatum [34]. The authors found correlations between hyperactivity syndrome and alterations in the intrinsic connectivity of silence network, even without anatomic atrophy detected in this area. Furthermore, they reported that disorganization of intrinsic connectivity of this network predict behavioral disturbances in AD patients. Studies involving neurobiological correlates of neuropsychiatric syndromes in AD could contribute to clarify cerebral bases of behavioral disturbances and to improve the accuracy of understanding clinical manifestations of the disease.

Neuropsychiatric Symptoms: Misidentification vs Accuracy

Concerning the neuropsychiatric symptoms in AD, an important question is related to the clinical diagnosis. Specifically, it regards to misidentification of symptoms by the caregiver or family member when they report to the clinician the behavioral disturbances from his

patient. Unsurprisingly, the care giver or family member suffers of depression, emotional distress, daily burden, anxiety, sleep disorders, or irritability. These symptoms may interfere with the quality of information that caregiver and family member provide to the clinician about the patient's behavior. Not uncommonly, the informant over estimates or underestimates the frequency and severity of symptoms when he describes the patient's behavioral disturbances to the clinician. In addition, elderly informants could present cognitive impairment. This occurrence may cause biases of interpretations or misidentification of patient's symptoms [35,36]. Taken together, these aspects could affect the ability of informant to accurately describe behavioral disturbances presented by patient.

In this scenario, to diagnose neuropsychiatric symptoms in AD requires for the clinician the ability to identify real symptomatology observed in the patient, as well as the biases of interpretation, or misidentifications, made by the informant. The accuracy of neuropsychiatric symptoms is crucial for the clinician establish the final diagnosis and to propose appropriate treatment.

Using the Neuropsychiatric Inventory-Clinician rating scale [NPI-C; 35], the clinician is able to significantly improve the accuracy of information about the patient's behavioral disturbances. Besides the clinician interviews the caregiver or family member, he examines the patient and directly observes his psychopathological manifestations. Based on informant's report and on patient's examination, the clinician provides his own judgment about the severity of patient's symptoms and appropriately diagnoses the neuropsychiatric syndrome.

Finally, despite the diagnosis of dementia in general targets cognitive and functional decline, acknowledgement of neuropsychiatric syndromes is crucial for comprehensive approach to appropriately assess clinical condition and to supply adequate treatment. Neuropsychiatric syndromes have been related to increased morbidity, accelerated course of disease, more rapid cognitive and functional decline, earlier institutionalization, more frequent psychotropic medications, higher mortality, as well as increased caregiver burden [37-39]. To early recognize and appropriately diagnose neuropsychiatric symptoms may reduce the patient's global clinical worsening, as well as attenuates emotional distress of family member and diminishes daily care giver burden.

Conclusions

Currently, neurobiological correlates of neuropsychiatric symptoms could improve the knowledge of pathophysiological mechanisms underlying behavioral disturbances in AD. For instance, apathy and depression in AD patients seem to be distinct syndromes involving specific brain regions and selected functional pathways.

A crucial point regarding neuropsychiatric symptoms in dementia concerns the reliability of information about the patient's behavior that caregiver provides to the clinician. In this scenario, caregivers frequently suffer emotional distress, depression, anxiety, sleep disorders, and eventually, cognitive decline when his is older, causing important biases which interfere with his interpretation of the patient's behavior.

The accuracy of symptoms basically depends on clinician impression for behavioural disturbances of AD patients, and his impression not uncommonly is in disagreement with caregiver report.

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