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Perspective

Biomarkers of agitation and aggression in Alzheimer's disease: A systematic review

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Abstract

Introduction: Agitation is one of the most challenging neuropsychiatric symptoms to treat in Alzheimer's disease and has significant implications for patient and caregiver. A major source of difficulty in identifying safe and effective treatments for agitation is the lack of validated biomarkers. As such, patients may not be appropriately targeted, and biological response to pharmacotherapy cannot be adequately monitored.

Methods: This systematic review aimed to summarize evidence on the association between biomarkers and agitation/aggression in patients with Alzheimer's disease, utilizing the National Institute on Aging–Alzheimer's Association Research Framework and the Biomarkers, EndpointS, and other Tools Resource of the Food and Drug Association-National Institutes of Health Biomarker Working Group.

Results: This review identified six classes of biomarkers (neuropathological, neurotransmitter, neuroimaging, apolipoprotein E (APOE) genotype, inflammatory, and clusterin) associated with agitation/aggression, which were mostly diagnostic in nature.

Discussion: Future studies should investigate the predictive, prognostic, and monitoring capacity of biomarkers to provide insight into the longitudinal course of agitation/aggression, as well as predict and monitor biological response to a pharmacological intervention.

Keywords: Alzheimer's disease; Agitation; Aggression; Biomarkers; Amyloid; Tau; Neuropathology; Neuroimaging; Neurotransmitters; Blood-based; Genetics

1. Introduction

Agitation is one of the most challenging neuropsychiatric symptoms (NPS) to treat in Alzheimer's disease (AD). It is highly persistent and has an increased likelihood of occurrence in the more advanced stages of the disease with 20%–50% of those with moderate-to-severe AD experiencing agitation [1–3]. Agitation has also been linked to faster progression to severe AD. The Cache County study reported that the presence of agitation/aggression was associated with an increased likelihood of developing severe AD (hazard ratio 2.95) [4]. Though there is no confirmatory evidence for the association between agitation/aggression and the progression of AD, it has been hypothesized that the pathology of brain regions associated with agitation/aggression may also occur in the more aggressive forms of AD. The presence of agitation/aggression has also been associated with decreased quality of life [5] and

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an increased likelihood of death (hazard ratio 1.94) [4]. However, the use of atypical antipsychotics, which are commonly prescribed for the management of agitation/aggression, is associated with modest benefits and has been associated with a 1.5- to 1.7-fold increase in mortality in randomized controlled trials (RCTs) [6]. Though the presence of agitation/aggression has an undeniable negative impact on patients with AD, it also places a burden on caregivers and society.

Based on the US National Caregiver Study, caregivers of AD patients with prominent NPS, such as agitation/aggression, spend on average 3.5 hours more per day providing unpaid care, compared with caregivers of AD patients who do not have prominent NPS. This can also be translated to an annual loss of $10,709 (USD) in earnings, per ambulatory patient with AD [7]. As the presence of agitation/aggression has been positively correlated with rates of institutionalization, pharmacological intervention, and use of medical services, there is also a socioeconomic burden associated with this NPS. In a prospective cohort study in the United Kingdom, Morris et al [8] reported that health and social care costs approximately doubled over a 1-year period in AD patients who had agitation, compared with those who did not. This may be due to an increased rate of institutionalization in AD patients with agitation/aggression, as one study reported that a 1-month delay in institutionalization in patients with moderate-to-severe AD would result in savings of $1863 (USD) per month [9]. Furthermore, 75% of the costs associated with AD occur in the severe stages of AD, a stage in which the presence of agitation/aggression is prevalent [10]. As such, agitation is an important symptom to identify and treat, as this could have a positive impact on the patient's quality of life, in addition to potentially reducing caregiver and socioeconomic burden.

A major barrier hindering the progress in identifying novel drug therapies is the lack of understanding with regards to the neurobiology of agitation. As such, patients may not be appropriately targeted for drug therapy, as we cannot predict treatment response or prognostic outcomes on a biological level. Monitoring treatment response at a mechanistic level also presents a challenge. Therefore, investigating the neurobiology of agitation in AD will not only lead to the identification of novel biomarkers and potential drug targets but may also assist in developing a personalized risk:benefit ratio to optimize drug therapy.

The National Institute on Aging–Alzheimer's Association (NIA-AA) has recognized the importance of enhancing efforts in further elucidating the neurobiology of AD through revising the definition of AD as an "aggregate of pathophysiologic processes and thus is defined *in vivo* by biomarkers and postmortem by pathologic changes, not by clinical symptoms". To further encourage efforts in AD research, the 2018 NIA-AA work group created a "research framework" that focuses on three groups of biomarkers: those of (1) amyloid-β (Aβ) deposition; (2) tau pathology; and (3) neurodegeneration/neuronal injury (ATN) [11]. These groupings, each of which has a neuroimaging and cerebrospinal fluid (CSF) biomarker, were chosen based on the nature of pathophysiological processes that each of the biomarker categories measure. Biomarkers of Aβ deposition ("A+/−") include CSF-$A\beta_{42}$ levels, Aβ42/40 ratio, and Aβ ligand binding on positron emission tomography (PET). An individual who is positive for an Aβ biomarker (A+) confirms whether or not an individual is on the AD pathophysiologic continuum. Biomarkers of tau pathology ("T+/−") include CSF phosphorylated tau (p_{181}-tau) and tau ligand binding on PET. An individual who is A+, and who is positive for a tau biomarker (T+), provides confirmation for his or her AD diagnosis. Biomarkers of neurodegeneration/neuronal injury ("N+/−") include anatomical magnetic resonance imaging (MRI), 18-fludeoxyglucose positron emission tomography (FDG-PET), and CSF total tau (t-tau). However, these markers are not specific for AD and can only be used to stage the severity of AD. Nonvalidated biomarkers, such as brain hypoperfusion, apolipoprotein E (APOE) genotype, and inflammatory cytokines, have not been added to the ATN research framework. However, the NIA-AA encourages investigators to thoroughly study and validate biomarkers that can be added to the ATN framework, or as an additional category within the framework.

Though not specific to AD research, the Food and Drug Association-National Institutes of Health Biomarker Working Group (FDA-NIH BWG) has identified the importance of biomarkers in clinical research and has defined a number of terms relevant to study end points and biomarkers. These terms, also referred to as the Biomarkers, EndpointS, and other Tools resource, highlight the multifaceted implications biomarkers may have in trials studying agitation/aggression in patients with AD [12]. Diagnostic biomarkers can be used to detect or confirm the presence or severity of a symptom or disease. To evaluate the diagnostic potential of a biomarker, the biomarker and clinical outcome must be investigated at one point in time. As such, postmortem studies or antemortem studies with a cross-sectional design would fulfill this criterion. Prognostic biomarkers provide information regarding the increased likelihood of a future clinical event or disease progression. To evaluate the prognostic potential of a biomarker, a biomarker collected at one point in time (baseline) must be compared against a longitudinal clinical outcome. Predictive biomarkers may be used to identify individuals who are more likely to experience a beneficial or harmful effect after drug exposure. The predictive potential of a biomarker can be studied in drug trials, where a biomarker is collected at one-point in time (baseline) and is compared against a longitudinal clinical outcome following drug treatment. Monitoring biomarkers can be used to identify a biological mechanism of a drug or to biologically assess change in a symptom or disease status after drug exposure. As such, monitoring biomarkers would provide evidence of an intervention effect. To evaluate the monitoring potential of a biomarker, both the biomarker and clinical outcome must be evaluated longitudinally. This