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Biomarkers of aggression in dementia

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ABSTRACT

Dementia is a clinical syndrome defined by progressive global impairment of acquired cognitive abilities. It can be caused by a number of underlying conditions. The most common types of dementia are Alzheimer's disease (AD), frontotemporal dementia (FTD), vascular cognitive impairment (VCI) and dementia with Lewy bodies (DLB). Despite the fact that cognitive impairment is central to the dementia, noncognitive symptoms, most commonly described nowadays as neuropsychiatric symptoms (NPS) exist almost always at certain point of the illness. Aggression as one of the NPS represents danger both for patients and caregivers and the rate of aggression correlates with the loss of independence, cognitive decline and poor outcome. Therefore, biomarkers of aggression in dementia patients would be of a great importance. Studies have shown that different genetic factors, including monoamine signaling and processing, can be associated with various NPS including aggression. There have been significant and multiple neurotransmitter changes identified in the brains of patients with dementia and some of these changes have been involved in the etiology of NPS. Aggression specific changes have also been observed in neuropathological studies. The current consensus is that the best approach for development of such biomarkers may be incorporation of genetics (polymorphisms), neurobiology (neurotransmitters and neuropathology) and neuroimaging techniques.

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1. Introduction

Dementia is a clinical syndrome defined by progressive global impairment of acquired cognitive abilities. The main cause of dementia syndrome is neurodegeneration. It is characterized by progressive worsening in various cognitive domains and diminished capacity for independent living. Dementia cannot be seen and objected as a single diagnosis, but rather as a collection of symptoms that result in the inability to perform the basic social and professional commitments. The aging of population in the past decades has increased the number of older people with dementia. Recent reviews of global prevalence have estimated that over 35 million people are affected by dementia worldwide and it is projected to affect over 80 million individuals worldwide by the year of 2040 (Prince et al., 2013; Ferri et al., 2005). Disorders causing dementia are numerous, but the most common diseases linked with dementia are Alzheimer's disease (AD), frontotemporal dementia (FTD), vascular cognitive impairment (VCI) and dementia with Lewy bodies (DLB). It is becoming more apparent that different types of dementias do not inescapably exist in isolation but that combined factors play significant role in their etiology (Keage et al., 2012).

Despite the fact that cognitive impairment is central to the dementia, non-cognitive symptoms exist almost always at certain point of the illness (Steinberg et al., 2008). These non-cognitive symptoms lead to serious negative consequences for both patients, as well as their caregivers. Terminology used to describe non-cognitive symptoms differs but most commonly used term nowadays is neuropsychiatric symptoms (NPS) in dementia (Geda et al., 2013). This term was previously often entitled behavioral and psychological symptoms of dementia (BPSD). NPS in mild cognitive impairment (MCI) presents higher risk for conversion to dementia when compared to MCI patients without NPS. Mild behavioral impairment (MBI) has been introduced as a diagnostic construct with intention to identify patients with an increased risk of developing dementia, but who may or may not have cognitive symptoms. Very recently, research diagnostic criteria for MBI were proposed, suggesting that although MBI and MCI can co-occur,

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; BPSD, behavioral and psychological symptoms of dementia; CDR-SB, Clinical Dementia Rating Sum of Boxes; ChAT, choline acetyltransferase; CMAI, Cohen-Mansfield Agitation Inv; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; GH, growth hormone; GDS, Geriatric Depression Scale; IPA, International Psychogeriatric Association; MAO, monoamine oxidase; MBI, mild behavioral impairment; MCI, mild cognitive impairment; MMSE, mini–mental state examination; MTA, medial temporal lobe atrophy; NAA, N-acetylaspartate; NPI, Neuropsychiatric Inventory; NPS, neuropsychiatric symptoms; NTs, neurofibrillary tangles; PA, posterior atrophy; P-tau, phosphorylated tau; PD, Parkinson's disease; RCT, randomized controlled trial; SERT, serotonin transporter; T-tau, total tau; VCI, vascular cognitive impairment.

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they are different and both represent a higher risk of dementia (Ismail et al., 2016).

A general opinion exists that NPS are not of primary importance, although a growing body of evidence suggests that they are critical not only as factors influencing patients' distress and caregivers burden but also as potential predictors of disease outcome. Additionally, NPS can be valuable in elucidating the pathophysiological mechanisms implicated in the disease and may be useful in establishing the proper diagnosis. Indeed, NPS were shown to be expressed to different degrees throughout the course of AD (Lyketsos et al., 2011). They are not only providing a valuable insight into AD pathology, but specific NPS may also serve as prognostic markers during the early phase of mild cognitive impairment (MCI).

Many authors have tried to group NPS in dementia into certain batches, but the majority of studies are classifying NPS into three main clusters: agitation, psychosis and mood disorders. Agitation includes both emotional distress and behavioral changes, such as aggression, irritability, pacing or restlessness, and is experienced by roughly 20% of patients suffering from dementia in a community setting. Agitation differs from psychosis and depression of AD because it may be viewed as a single symptom or a symptom complex (Jeste et al., 2006). Recently, an Agitation Definition Working Group of the International Psychogeriatric Association (IPA) has developed a consensus definition of agitation in patients with cognitive disorders. According to that consensus agitation was defined as: a) occurring in patients with a cognitive impairment or dementia syndrome b) exhibiting behavior consistent with emotional distress; c) manifesting excessive motor activity, verbal aggression, or physical aggression; and d) evidencing behaviors severe enough to cause excess disability and not solely attributable to another disorder or a suboptimal care condition (Cummings et al., 2015).

Although male patients are more prone to exhibit both aggressive behavior and agitation (Kitamura et al., 2012), a variable association of gender and age to NPS has been observed. When it comes to aggression, it was shown that men tended to display more physical aggression with women being more likely to display verbal aggressiveness (Zuidema et al., 2009). Aggression represents danger both for patients and caregivers and the rate of aggression correlates with loss of independence, cognitive decline and in general with the poor outcome. It has been observed that there is a strong correlation between the intensity of dementia according to both physical agitation and verbal aggression (Bidzan et al., 2012).

The functional neuroanatomy and the neurochemical background of aggression and agitation in dementia are still not fully elucidated. Among the theories suggested is also the hypothesis that similar mechanisms are involved in the pathophysiology of agitation as in movement disorders. Restlessness, which is an integral part of agitation, is hypothesized to be the result of disturbances in the segregated parallel pathways that project through the limbic and sensorimotor portions of the striatum (Lindenmayer, 2000). Regarding neurotransmitter disbalances, a higher sensitivity to norepinephrine has been shown in AD patients with agitation, while significant evidence on GABAergic deficiency also exists in agitated patients with dementia (Herrmann, 1998). Significant reduction in serotonergic (5-HT) receptors has been detected in various brain areas of patients with AD, indicating reduced serotonergic function (Mintzer and Brawman-Mintzer, 1996).

Several studies have implicated potentially important role of dopamine in the clinical course of AD (Kumar and Patel, 2007; Stefani et al., 2015). Additionally, disruption of the fronto-striatal and mesocortical dopamine networks have also been implicated in the development of cognitive disturbances, especially executive dysfunction, in patients with dementia, including the dementia in Parkinson's disease (PD) (Gratwicke et al., 2015). Subsequently, monoamine oxidases (MAO), namely MAO-A and MAO-B, and their inhibitors have also been studied in patients with dementia, albeit with mixed results. Results of a 2003 Cochrane review on the use of selegiline (an irreversible and (relatively) selective MAO-B inhibitor) in AD patients lead to disappointing conclusions (Birks and Flicker, 2003). However, recent studies have provided renewed hope for treatment of AD patients with MAO-B inhibitors, mostly due to the neuroprotective effect of MAO-B inhibitor rasagiline (Bolea et al., 2013).

As agitated/aggressive behaviors often co-occur with other NPS, relationships between agitated behavior and other NPS is important. Agitation in dementia often co-occurs with psychosis and depression. There is evidence that verbal agitation is associated with depression, and it may be also related to delusions (Jeste et al., 2006). It was shown that psychosis and depression are more frequent in aggressive patients and may be a causative factor of agitation/aggression (Deutsch et al., 1991). Agitation and aggression have also been related to executive or higher-order loss of behavioral control (Tsoi et al., 2008).

Improved methods aimed at detecting and measuring the severity of NPS are necessary. Pharmacological management is frequently used in treatment of aggression but its great limitations are effectiveness and association with a significant risk of side effects. Better understanding of the pathophysiological mechanisms sustaining NPS will result in developing more effective treatments (Panza et al., 2015).

Biomarkers are valuable biological traits and they can be used to objectively differentiate between normal and pathological biological processes (Atkinson et al., 2001). They can be measured in various biological samples such as peripheral blood or cerebrospinal fluid (CSF). Biomarkers are of special interest in the field of neurodegenerative diseases, not only as a diagnostic tool, but also as predictors of disease onset or for monitoring of disease progression. Given the fact that patients' and caregivers' quality of life is severely affected by NPS and their management has proved to be demanding, development of putative biomarkers would be of special value.

This article will review the current literature on NPS in dementia with a special focus on aggressive behavior. The specific aim of this review is to provide better understanding of etiological background for NPS in dementia and to discuss potential genetic (polymorphisms) and neurobiological (neurochemical, neuropathological) biomarkers of aggression.

2. Genetic biomarkers

Studies have shown different genetic factors that can be associated with various NPS including aggression, although some findings are contradictory while others are missing independent replication. Most of the research has focused on AD.

As the correlation between aggression and frontal lobe serotonergic dysfunction is well known, there are number of studies which have searched for potential correlation between aggression characteristics such as presence or severity and serotonin signaling molecules. Aggression in AD has been shown to be linked with polymorphism in the tryptophan (TRP) gene. Male AD patients with episodes of aggressive behavior were more often the carriers of the C-containing genotypes of A218C intronic polymorphism of the tryptophan hydroxylase gene (Craig et al., 2004a). Polymorphisms in the gene for serotonin transporter (SERT or 5HTT) are implicated in development of NPS in AD. Namely, there were significant associations between the presence of a 5-HTT variable number of tandem repeats sequence (5-HTTVNTR) allele 10 and NPS or aggressiveness, suggesting that 5-HTTVNTR affects the risk of NPS or aggressiveness in AD (Ueki et al., 2007). In addition, SERT-linked polymorphic region (5-HTTLPR) long allele was significantly associated with irritability while the 5-HTTVNTR 10-repeat allele was significantly associated with psychosis in AD, indicating that 5HTT might have a role in development of NPS or psychosis in AD (Pritchard et al., 2007a). The 5-HTTPR*L allele and *L/*L genotype of SERT promoter region was shown to be significantly related to aggression in AD (Sukonick et al., 2001), and with a combined aggressive/psychotic phenotype (Sweet et al., 2001). Study by Assal et al. (2004) suggested potential role for serotonin transmission defects

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