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Alzheimer's Disease associated with Psychiatric Comorbidities

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia and has become a severe public health issue. It is estimated that globally, 35.6% of people have some form of dementia. This number is expected to double by 2030, and possibly even triple by 2050. The disease is associated with deficits in cognition/memory and a reduced ability in coping with everyday life. Moreover, patients can experience behavioral alterations such as mood swings, depression and hallucinations. Therefore, it is common to find the presence of neuropsychiatric comorbidities such as depression, schizophrenia and bipolar disorder during the course or development of AD. These disorders can become severe enough to interfere with the patients daily functioning, and can worsen the course of the disease. However, little is known about the causal relationship between psychiatric comorbidities and AD, or the reasons for the predisposition of some individuals to such disorders. Therefore, the purpose of this review is to clarify the causal relationship between depression, schizophrenia and bipolar disorder with AD.

Key words: Alzheimer's disease, bipolar disorder, depression, schizophrenia.

INTRODUCTION

Alzheimer's Disease (AD) is recognized as the major cause of dementia in modern society, and may result in significant limitations for sufferers through cognitive impairment. The most evident symptom in early AD is progressive memory loss (Grundman et al. 2013).

Studies seek to elucidate the pathophysiology of AD which is related to cognitive damage. Possible biochemical causes include the accumulation of amyloid beta protein oligomers, which are responsible for synaptic damage and sequent memory deficit in AD (Krstic and Knuesel 2013). Furthermore, hyperphosphorylation of the

Tau protein is another pathophysiological process involved in AD. Hyperphosphorylation induces the formation of intracellular neurofibrillary tangles, leading to neuronal death and the progressive loss of neuronal function (Krstic and Knuesel 2013), (Serrano-Pozo et al. 2011), (Chu 2012), (Nimmrich and Ebert 2009).

Despite their being studies that indicate possible biochemical causes that lead to acute neurodegeneration over time (Shankar and Walsh 2009), the pathophysiology of AD is not still elucidated. However, it is suggested that some etiological aspects may be involved in the development of AD, such as environmental and genetic factors (Schipper 2011).

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Considering the present limitations of our understanding of AD, the same issues could appear in the form of cognitive symptoms, which are related to memory, learning, agnosia and apraxia. Also could appear in the form of non-cognitive symptoms, characterized by behavioral and psychological alterations, such as aggressiveness, irritability, hallucinations and depression, which are known as the Behavioral and Psychological Symptoms of Dementia (BPSD) (Schiffczyk et al. 2013).

Neuropsychiatric symptoms are visible both during the development of, and throughout the course of AD (Lyketsos et al. 2011). While the cognitive symptoms of dementia are neuropsychiatric features present in the vast majority of the population regardless of age, the presence of depression associated with dementia appears primarily in the elderly (Steffens et al. 2009). Thus, it is probable that depression is the most common neuropsychiatric disorder in AD (Contador-Castillo et al. 2009).

For this reason, AD causes a huge economic and social impact, generated by the high costs involved in the health care of patients, such as those involved in the utilization of drug therapy and the provision of full-time caregiver (Schaller et al. 2014). It is worth mentioning that in the United States of America (USA), about \$604 million dollars are invested annually for the assistance of patients with dementia (WHO 2012).

Thus, this disease has become one of the most severe global public health problems, with its current prevalence effecting 35.6% of people worldwide, with this number expected to double by 2030, and possibly even tripling by 2050 (WHO 2012). Moreover, there is an increased risk of the incidence of dementia in later life, which is associated with the prevalence of diseases such as AD, mainly occurring in the seventh or eighth decade of life (Reitz et al. 2011). This demands that better organizational and assistive solutions are required from the health professionals and public health systems that are dealing with these patients,

which would help reduce the burden being placed on the patients' families, as well as decrease the high costs involved in the treatment of this disease (Franz et al. 2010).

The symptoms associated with AD are the major causes that lead to an early patient hospitalization (Sansoni et al. 2013). A study performed with 1014 patients, showed that 90% of the patients studied had BPSD, and 44% also showed depressive symptoms. In addition to this, the group also presented a high prevalence of other symptoms such as illusions, hallucinations and delusions in those patients with high scores in the scales of psychiatric symptoms (Fernandez et al. 2010). Furthermore, depression and apathy appear more frequently during AD, with hallucinations, delusions and aggressiveness also being common (Lyketsos et al. 2011).

Considering the high impact that non-cognitive symptoms have upon both the caregivers and the patient's own health, there are considerable costs involved for the public health system. Therefore, the objective of this review is to describe the findings of previously published scientific literature, illustrating the possible associations between patients with AD, and the presence of psychiatric comorbidities including, bipolar disorders, depression and schizophrenia.

BIPOLAR DISORDER AND ALZHEIMER'S DISEASE

Bipolar disorder (BD) is a psychiatric disorder characterized by episodes of mania or hypomania and depression (Brenner and Shyn 2014). The DSM (Diagnostic and Statistical Manual of Mental Disorders) is a document that reflects the consensus among leading academics, physicians and researchers in the field of mental health and psychiatric diseases (Vahia 2013). The latest version of the document was published by the American Psychiatric Association (APA) in May 2013, this being its fifth edition (DSM-5 or DSM-V). This latest edition of the DSM brings some modifications

to the concepts of bipolar disorder, mainly affecting the inclusion and exclusion criteria.

BD is still classified as bipolar disorder I and II. Bipolar disorder I is characterized by manic episodes (extremely elevated mood), mixed states (dysphoria) and major depression. Bipolar disorder II is characterized by episodes of major depression and at least one hypomanic episode (elevated mood and increased energy). As in DSM-IV, the presence of five of the nine diagnostic symptoms are required with at least one manic episode lasting a week or more (bipolar I) or at least one hypomanic episode lasting four days or more (bipolar II), leading to a total change in the life of the patient (APA 2013).

Before the diagnosis of BD can be confirmed, any medical condition, substance or drug that could induce manic symptoms should be excluded. This is especially significant in geriatric patients, who may have other comorbidities that can cause delirium and/or depression, such as AD. However, more recent studies have demonstrated clinical evidence for a link between AD and BD, beyond them sharing similar symptoms. Many epidemiological studies have linked these two diseases (Kessing and Andersen 2004), (Zilkens et al. 2014), (da Silva et al. 2013) and have shown findings such as neuroimaging alterations (Rej et al. 2014), dysregulation of neural calcium signaling (Berridge 2013) and epigenetic changes (Rao et al. 2012).

Studies undertaken on BD patients have demonstrated that they have a greater risk of getting a dementia diagnosis than in controls matched by the gender and age of the general population. The risk of dementia increases by 6% with every episode of bipolar disorder that leads to the hospitalization of the patient. The authors had to indicate that the study only included patients who had been hospitalized at least once, and that affective episodes were included only if they resulted in hospitalization, since the study was conducted using records from hospital admissions in Denmark (Kessing et al. 1999), (Kessing and Andersen 2004). Therefore, the increased risk of dementia in these patients may

have been underestimated. However, it should be noted that this evidence is dependent on clinical and demographic variables.

Epidemiological studies have also been conducted on other populations. A matched case-control study using Western Australian state-wide hospital records relating to inpatient, outpatient, mental health and emergency admissions which were linked to deaths, demonstrated that in Western Australians aged between 65-84 years, the chances of bipolar disorder patients developing AD was twice as high, while the chances of these patients developing non-specific dementia was six times as high (Zilkens et al. 2014). However, a study by da Silva et al. (2013), which conducted a systematic review on the risk of individuals with affective disorder history developing dementia, demonstrated that the risk of developing dementia was higher when associated with depression than with bipolar disorder, and that depression may be a an important confounding factor, since bipolar patients have alternating depressive episodes.

Bipolar disorder and dementia may share common etiological factors, such as oxidative stress and reduced neurotrophic factors that are both key mediators in the pathophysiology of mood disorders (Bauer et al. 2014) and AD (Heneka et al. 2014), as well as neuroinflammation (Stich et al. 2014), which occurs in both comorbidities, with increases shown in pro-inflammatory interleukin, tumor necrosis factor alpha (TNF- α) and arachidonic acid cascade enzymes in the postmortem brains taken from BD and AD patients (Kim et al. 2011), (Rao et al. 2011).

Another of the etiological factors common to the comorbidities being discussed are the vascular changes that are observed in patients affected by AD (Luchsinger et al. 2008), (Brickman et al. 2012) which are also seen in BD patients (Sodhi et al. 2012). However, there is still some disagreement over the data pertaining to the cerebrovascular changes found between various studies, because of the different age of the patients and the regions where these changes are found (Almeida et al.

2009), (Haller et al. 2011), (Rej et al. 2014). Further research is needed to establish the relationship between bipolar disorder and AD, and to ascertain whether these changes are directly related to the cognitive deficits found in both conditions. However, it is known that even after remission of the depressive state, BD patients demonstrate impaired executive function and attention deficits; similarly, euthymic individuals with bipolar disorder have deficits in declarative semantic memory and executive function (Robinson et al. 2006), these alterations also being observed in patients suffering with AD (Bondi et al. 2008)

Another pathway common to both conditions is the inhibition of Glycogen synthase kinase-3 (GSK3). Lithium is a traditional medicine used for treating BD, and it is known that in BD, one of the main intracellular targets of lithium is the inhibition of GSK-3 β , which regulates the activity of the transcription factors (CREB and β -catenin) responsible for the expression of BDNF and Bcl-2. These control neurogenesis and neuronal survival, as well as having mood stabilization effects. In addition, lithium increases Bcl-2 expression and decreases the levels of cytosolic calcium by inhibiting the release of Ca⁺ from the endoplasmic reticulum (Berridge 2013). The use of lithium has recently been advocated in the treatment of AD, and the action of the drug may be a bridge between AD and BD, by operating via the same mechanisms (Stutzmann et al. 2006), since dysregulation of Ca⁺ signaling occurs in both conditions. It may also simply be acting by decreasing the phosphorylation of the Tau protein, which occurs via the action of GSK-3 β , as already noted (Hernandez et al. 2013).

Studies have reported reductions in the levels of BDNF and synaptic proteins in the brains of both AD and BD patients (Rao et al. 2011), (Kim et al. 2010), and in addition to this, there have been observations of changes in the expression of inflammatory (Kim et al. 2011) and apoptotic genes (Kim et al. 2010) common to BD and AD. In a study by Rao et al. (2012), post-mortem brains from patients suffering with BD and AD showed statistically significant

epigenetic changes in global DNA methylation for both BD and AD, and these epigenetic changes are related to neuroinflammation, synaptic integrity, neuroprotection and arachidonic acid metabolism in the frontal cortex. However, while global histone H3 acetylation was found to have increased in the brains of BD patients. However, it was not found altered in AD patients. It should be noted that the medications taken by the patients may have also interfered with the changes found in the epigenome.

Other studies have analyzed the levels of amyloid metabolites contained in the cerebrospinal fluid (CSF) of BD patients, and discovered that there were lower concentrations of the soluble forms of APP (α and β) in bipolar patients, when compared to healthy controls or AD patients (Piccinni et al. 2012), (Jakobsson et al. 2013) in which the decrease in β A-42 in the CSF is inversely proportional to the number of amyloid plaques. An association between low concentrations of A β and an increase in the severity of bipolar disorder type I was also observed, but no other evidence of neurodegeneration for the Alzheimer type was found in bipolar patients (Jakobsson et al. 2013). This finding is in agreement with a previous study in which no increases in amyloid plaques or neurofibrillary tangles were found in the postmortem brain tissues of psychiatric patients (Damadzic et al. 2002).

Thus, the existence of consistent points and similar findings for both BD and AD are clear. However, although both disorders seem to have similar underlying mechanisms, there is not enough evidence to say that the cognitive impairment found in BD has the same pathophysiology as that found in AD, nor is it possible to assert that BD patients are predisposed to AD. The main findings and conclusions are presented in Table I.

DEPRESSION AND ALZHEIMER'S DISEASE

Depression is a mental disorder characterized by the presence of a number of symptoms including: a depressed mood, a loss of interest in pleasurable

TABLE I
Associations between AD and bipolar disorder, depression and schizophrenia.

Psychiatric Comorbidities associated with AD	Article	Authors	Conclusion
Bipolar disorder	Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder?	Kessing and Andersen (2004)	The risk of dementia seems to increase with the number of episodes in depressive and bipolar affective disorders.
	Plasma beta-amyloid peptides levels: a pilot study in bipolar depressed patients	Piccinni (2012)	Changes in plasma levels of different A β peptides might represent increase of the risk for cognitive decline in bipolar patients, such as AD.
	Epigenetic modifications in frontal cortex from Alzheimer's disease and bipolar disorder patients.	Rao et al. (2012)	Brains from BD and AD patients showed epigenetic changes in global DNA methylation related to neuroinflammation, synaptic integrity, neuroprotection and arachidonic acid metabolism.
Depression	Depression and Risk for Alzheimer Disease: Systematic Review, Meta-analysis, and Metaregression Analysis	Ownby et al. (2006)	There is a high relationship between depressive symptoms and depression as a risk factor for the development of AD.
	Prevalence of depression among older Americans: the Aging, Demographics and Memory Study	Steffens et al. (2009)	Individuals with dementia had among the highest prevalence of current depression.
	Contribution of Depression to Cognitive Impairment and Dementia in Older Adults	Potter and Steffens (2007)	The prevalence of depression is highly in most dementias. In AD may be less intense.
	The risk of developing depression when suffering from neurological diseases	Thielscher et al. (2013)	51.4% of patients developed depression, one year after the diagnosis of the AD.
	Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies	Diniz et al. (2013)	Association between late-life depression with the development of AD.
	Increased Hippocampal Plaques and Tangles in Patients with Alzheimer Disease with a Lifetime History of Major Depression	Rapp et al. (2006)	Was found that of a lifetime history of depression, is associated the presence of a higher number of neuritic plaques and neurofibrillary tangles the hippocampus of the patients with AD.
	Plasma amyloid β , depression, and dementia in community-dwelling elderly	Direk et al. (2013)	The presence of a higher number of neuritic plaques and neurofibrillary may be present in patients with depression without AD. Depression may also be associated with the accumulation of these plaques in elderly individuals
	Serum amyloid beta protein in young and elderly depression: a pilot study.	Kita et al. (2009)	Serum Abeta40/42 ratio was higher in depressive patients.
Schizophrenia	Neuropsychiatric symptoms in MCI subtypes: the importance of executive dysfunction.	Rosenberg et al. (2011)	Impairment in executive functions, were more severe in patients with depression and anxiety. People with features of depressive symptoms also associated with mild cognitive impairment, was found an increased risk for the development of AD.
	Dementia in middle-aged patients with schizophrenia	Nicolas et al. (2014)	Identified 14 schizophrenic patients with dementia among 96 elderly, but only two were diagnosed with likely AD.
	A common brain network links development, aging, and vulnerability to disease	Douaud et al. (2014)	Suggested a common spatial pattern of abnormalities in a brain network in AD and schizophrenia.
Bipolar disorder, depression and Schizophrenia	Dysregulation of neural calcium signaling in Alzheimer disease, bipolar disorder and schizophrenia	Berridge (2013)	Dysregulation of the Ca(2+) signaling pathway is responsible for development of neural diseases such as Alzheimer disease, bipolar disorder and schizophrenia.
	Severe psychiatric disorders in mid-life and risk of dementia in late-life (age 65-84 years): a population based case-control study.	Zilkens et al. (2014)	Severe depression, bipolar disorder, schizophrenia and alcoholic dependency disorder in mid-life are important risk factors for AD in the late-life.
Bipolar disorder and depression	Affective disorders and risk of developing dementia: systematic review	da Silva et al. (2013)	Increased risk for dementia in individuals with depression, and bipolar disorder

activities, changes in appetite and in sleep patterns, and alterations in psychomotor activities such as difficulty in thinking, concentrating or making decisions (APA 2013). This disorder is commonly associated with an increased risk of morbidity and mortality, an increased utilization of health services, and a reduced response to therapeutic regimens. There is also an increased risk of suicide (Paradela et al. 2005), (Rotheneichner et al. 2014).

There is an increased rate of depression within developed countries when compared to countries of low to middle income (Bromet et al. 2011), (Kessler and Bromet 2013), adulthood is still related to the onset of symptoms, and women have twice the risk of developing depression over a lifetime when compared to men of the same age (Bromet et al. 2011), (Kessler and Bromet 2013). In addition, a population-based study has assessed the prevalence of depression in the Brazilian population, finding a greater rate of depressive symptoms in individuals over the age of 60 (da Silva 2013).

Globally, the prevalence of depressive disorders in the elderly population is between 10% and 20%, depending on their cultural situations, indicating that it is the most common psychological disorder in the senescence population (Barua et al. 2011). The features attributed to the onset of a major depressive disorder in later life, are also associated with a higher frequency in the development of cognitive impairment (Potter and Steffens 2007), (Steffens et al. 2009).

Studies indicate that there is a strong relationship between depressive symptoms and depression as a risk factor for the development of AD (Ownby et al. 2006), (Thielscher et al. 2013). Two meta-analysis (Diniz et al. 2013) and (Ownby et al. 2006) and one systematic review (da Silva et al. 2013) found an association between late-life depression and the development of AD.

A neuropathological study was performed which assessed the *post-mortem* brains of 153 participants. It was evident from the findings that depression may be related to neuronal loss in specific brain regions, such as the hippocampus,

which also occurs in AD. However, there was no evident association between the effects of depression and AD in the neurofibrillary tangles or neuritic plaques, which are both characteristic symptoms of AD (Tsopelas et al. 2011). Wilson et al. (2003) also found no correlation between plaques, tangle formation and current depressive symptoms in AD patients.

A separate prospective study, which conducted a neuropathological evaluation of the *post-mortem* brains of patients with a mean age of 81 years, found the presence of a higher number of neuritic plaques and neurofibrillary tangle formations in the hippocampus of patients with AD with a history of depression, as compared with brains of AD patients without depression history (Rapp et al. 2006).

These findings reinforce the hypothesis that neuronal changes are caused by AD. However, these changes may also be present in patients with depression who are not suffering with AD (Direk et al. 2013), whereas the formation of neurofibrillary tangles and neuritic plaques are one of the main processes involved in the pathophysiology of AD (Nimmrich and Ebert 2009), (Serrano-Pozo et al. 2011), (Krstic and Knuesel 2013). Depression may also be associated with the accumulation of these plaques in elderly individuals (Kita et al. 2009).

Other studies have shown a positive relationship between a depressive state at the time of death, and the presence of neuritic plaques in Alzheimer's disease, which is independent of the clinical severity of dementia. A pre-clinical study has shown that beta-amyloid oligomers leads to memory impairment and depressive-like behavior in mice (Ledo et al. 2013).

Therefore, it can be difficult to differentiate and consequently diagnose the depressive symptoms of dementia, because a symptom from one condition can overlap the other (Bystad et al. 2014). There are mechanisms involved in the depressive process which are characterized by increases in the production of glucocorticoids and in cerebral vascular disease, leading to atrophy of hippocampal ischemia, and ultimately resulting

in the cognitive decline seen in AD or dementia (Butters et al. 2008). Therefore, this relationship makes it difficult to determine whether depression is a risk factor for AD or a prodromal symptom (Koenig et al. 2014).

For example, when assessing 211 elderly women for depression, these patients showed a cognitive deficit in all of the tests performed in the study (Yaffe et al. 1999), yet another current study which evaluated 1,299 women with mean age of 88 years, found that in 41% of participants there were significant features of cognitive decline, and in those of more than 90 years of age, the association with dementia was more prevalent (Yaffe et al. 2011).

A separate study investigating the prevalence of neuropsychiatric symptoms which assessed 1,799 patients with mild cognitive impairment, found that impairments in executive functions, i.e. cognitive symptoms, were more severe in patients suffering with depression and anxiety (Rosenberg et al. 2011). More recently, they evaluated 527 people who had features of depressive symptoms also associated with mild cognitive impairment. Their findings showed that in this group there was an increased risk for the development of AD (Rosenberg et al. 2013).

These studies suggest that depression might not only be a risk factor for dementia or AD, but may also be a feature symptom of the early stages of cognitive decline or dementia. The main findings and conclusions are presented in Table I.

SCHIZOPHRENIA AND ALZHEIMER'S DISEASE

Schizophrenia is a severe mental disorder with a prevalence of nearly 1% of the world's population, and is estimated to have an incidence of 15 per 100,000 people (Rossler et al. 2005). The nature of this disorder is heterogeneous, which makes its treatment and investigation much more difficult (Casey et al. 2013).

The diagnosis of schizophrenia is essentially based on the description of signs and symptoms

presented by the patient. To date, there have been no pathophysiological parameters with sufficient sensitivity or specificity to provide a positive diagnosis (Bagdy and Juhasz 2013). According to the DSM-V (Diagnostic and Statistical Manual of Mental Disorders), the signs must have been present for at least six months, and must also include a minimum of one month of active symptoms to confirm the diagnosis (APA 2013). Schizophrenia is a mental disorder characterized by positive, negative and cognitive symptoms. The positive symptoms may be expressed as delirium, hallucinations and delusions (Penzes et al. 2011), (Howes and Murray 2014), (Murray et al. 2014). The negative symptoms involve the blunting of affect. The cognitive symptoms are characterized by problems with working memory (APA 2013).

The mechanisms of this disease are still poorly understood. Dysfunction of the dopaminergic system has been postulated to be a contributing factor. This is in part, on the functional roles of dopamine with respect to physiology, and to the decline of cognitive performance, especially in working memory and in reward circuitry (Arnsten 2011). In addition, there are alterations in the function of one or more neurotransmitter systems, involving the dopaminergic, glutamatergic, serotonergic and adenosinergic systems (Carter 2006). A study comparing the prospective memory of 42 healthy people with 42 people suffering with schizophrenia, showed a deficit in the group of patients with schizophrenia. This reinforces the hypothesis that there is a cognitive impairment in schizophrenia (Kumar et al. 2008).

There are several lines of study that have associated cognitive decline and schizophrenia, and this decline can be related to changes in the frontoparietal neural networks and disorders of the hippocampus (Joyce 2013), which are also associated with AD (Nelson et al. 1998), (Wright et al. 2000). Changes in the white matter within the ventrolateral and dorsolateral regions of the left prefrontal cortex (Quan et al. 2013), and decreased myelination in the temporal and occipital regions

have been found in patients with schizophrenia and cognitive decline (Palaniyappan et al. 2013). Spatial working memory abilities are impaired in those individuals with a high risk of psychosis (Wood et al. 2003), and this memory alteration is related to AD (Serino et al. 2014).

The cognitive profile of subjects with late-onset schizophrenia differs from those of patients with AD and depression (Ting et al. 2009), (Etkin et al. 2013). Individuals with schizophrenia show cognitive decline at all stages of the disease (Rajji et al. 2014). This cognitive decline can be easily observed by testing for changes in the episodic memory response of people with schizophrenia (Schaefer et al. 2013), (Barch and Sheffield 2014). It can also be observed in the speed at which they process information (Schaefer et al. 2013), (Woodward et al. 2013), as well as in changes to their verbal memory, which is one of the most prevalent cognitive symptoms of schizophrenia (Lepage et al. 2014).

Similarly, psychotic symptoms, delusions and hallucinations are frequent in AD, which is currently the second most prevalent psychotic disorder (second only to schizophrenia) in the USA, and it may become the most prevalent (Murray et al. 2014). The onset of psychotic symptoms in AD is strongly associated with a hastening cognitive decline (Ropacki and Jeste 2005).

There are few conclusive epidemiological studies relating the development of schizophrenia with the onset of AD. This is mainly because diagnosing elderly patients with schizophrenia is challenging, since various stages of cognitive tests are necessary, and also because AD is only diagnosable in patients through psychiatric assessment. Nicolas et al. (2014) identified 14 schizophrenic patients with dementia amongst 96 elderly patients that were under study, and of these, only two were diagnosed with likely AD. Other studies have shown that the cognitive decline typical in schizophrenic patients in later life is not as consistent or as fast as that which is evident

neurodegenerative diseases such as AD (Harvey et al. 1995), (Friedman et al. 2001).

However, a recent study has led to discussions on the subject. After adjustment for several known medical risk factors, schizophrenia in mid-life was associated with dementia at ages 65-79 (Zilkens et al. 2014). In addition, Douaud et al. (2014) showed that some brain regions develop relatively late during adolescence, and degenerate rapidly during aging in patients with schizophrenia and AD. These regions are also associated with intellectual ability and episodic memory, with deficiencies in these areas directly contributing to the main symptoms of schizophrenia and AD. Thus, the study suggests that there is a common pattern of brain abnormalities in these two disorders.

Some other common findings are seen in the diseases in question. In a comprehensive genomic analysis studying 108 genes from schizophrenic patients, gene associations were found. These were specifically related to the main assumptions of the etiology and treatment of schizophrenia. Many other genes involved in glutamatergic neurotransmission and synaptic plasticity, in addition to the *CACNA1C*, *CACNB2* and *CACNA1I* genes, which encode subunits of voltage-dependent calcium channels, are implicated in the schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). AD is also closely related to calcium signaling, and the upregulation of calcium in neuronal signaling may induce an initial decline in memory. This subsequently progresses into a later phase of apoptosis by excessively activating calcium receptors, and ultimately leads to excitotoxic neuronal death (Berridge 2013). Although the concept of glutamatergic excitotoxicity by calcium signaling is an underlying mechanism in various diseases, this newly discovered link between AD and schizophrenia should be considered.

There are also other findings which are common to both conditions in question, such as a reduction in neurotrophic factors, mainly in the levels of brain-derived neurotrophic factor

(BDNF) in schizophrenia (Ikeda et al. 2008), and in AD (Alvarez et al. 2014), which is important for neurogenesis. There are also increases in interleukin-1, interleukin-6 and tumor necrosis factor (TNF) in schizophrenia (Potvin et al. 2008), and in AD (Heneka et al. 2014), indicating neuroinflammation and decreased hippocampal volume in both diseases (Mondelli et al. 2011), (Voevodskaya et al. 2014). Therefore, despite being different diseases, AD and schizophrenia are linked; however, there is some disagreement as to how close this link actually is. The main findings and conclusions are presented in Table I.

CONCLUSIONS

Although no causal relationship has been proven between AD and the psychiatric disorders in this study, certainly, there is a close relationship between psychiatric comorbidities such as depression, schizophrenia and bipolar disorder and this dementia. Considering that there is still enormous difficulty in identifying AD at earlier stages, understanding of the mechanisms underlying the psychiatric comorbidities and AD, can be useful. The psychiatric comorbidities could be related to an earlier detection of a possible predisposition to development of AD. In turn, the occurrence of depression, schizophrenia and bipolar disorder could be considered a prodromic stage of AD. In particular, this will allow earlier treatment of patients. Moreover, the use of classical drugs for treating these psychiatric comorbidities may possibly have beneficial therapeutic effects in AD.

RESUMO

A doença de Alzheimer (DA) é a causa mais comum de demência e tornou-se um grave problema de saúde pública. Estima-se que, globalmente, 35,6% das pessoas têm alguma forma de demência. Este número deverá duplicar até 2030 e, possivelmente, até mesmo triplicar até 2050. A doença está associada com déficits na cognição / memória e uma redução da capacidade em lidar com a vida cotidiana. Além disso, os pacientes

podem experimentar alterações comportamentais, tais como alterações de humor, depressão e alucinações. Portanto, é comum encontrar a presença de comorbidades neuropsiquiátricas tais como depressão, esquizofrenia e transtorno bipolar durante o curso do desenvolvimento da DA. Estes distúrbios podem tornar-se graves o suficiente para interferir com o funcionamento diário dos pacientes, e podem piorar o curso da doença. No entanto, pouco se conhece sobre a relação causal entre comorbidades psiquiátricas e a DA, ou as razões para a predisposição de alguns indivíduos a tais transtornos. Portanto, o objetivo desta revisão é esclarecer a relação causal entre depressão, esquizofrenia e transtorno bipolar com a DA.

Palavras-chave: doença de Alzheimer, transtorno bipolar, depressão, esquizofrenia.

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