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Role of Stress, Immune System and Well-being in Patients with Alzheimer's Disease

Garcia-Pardo MP¹, Julian Rochina M³ and De La Rubia JE²

¹Department of Psychology, European University of Valencia, Spain

²Faculty of Dentistry, European University of Valencia, Spain

³Faculty of Nursing and Podology, University of Valencia, Spain

Corresponding author: Maria Pilar Garcia Pardo, PhD Professor, Faculty of Psychology, European University of Valencia, C/General Elio, 8. 46010. Valencia, Spain, Tel: +34 660 58 83 90; E-mail: m.pilar.garcia-pardo@uv.es

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Abstract

Alzheimer's disease (AD) is a progressive and neurodegenerative disorder that induces neuropsychiatric symptoms, disability, caregiver burden, and premature death in patients who suffer from it. It represents the most prevalent cause of dementia in our society and its incidence rates exponentially increase with age. Currently, this disorder does not have any cure and it is essential to know all the variables and factors involved in the development of this disorder. Among these factors, there are different categories such as biological and environmental aspects. It seems that the immune system (IS) and the stress system are some of them and the knowledge about their role in this disorder is an important question in this area. Moreover, it has been demonstrated that both systems are related and this relationship can also be influenced by the emotional system. In fact, the levels of the IS biomarker (immunoglobulin A) and the stress system (cortisol) are different in people with and without AD and IgA is higher in patients with high wellbeing. Therefore, the new therapies in AD should be focused on the influence of these systems and on postulating new alternative perspectives like non-pharmacological therapies.

All this is essential for the study of AD in order to improve the quality of life in these patients, as well as knowing all the variables involved, so as to generate new therapeutic targets in AD.

Keywords: Alzheimer disease; Stress; Immune system; Non-pharmacological therapies; Well-being

Introduction

In the last few years, along with a longer life expectancy, new disorders have appeared. Among these diseases, Alzheimer's disease (AD) is the most common dementia in

elderly population mostly affecting individuals beyond the age of 65 (60% to 70% of the total) and its prevalence increases dramatically with age [1].

From a neurobiological point of view, it is known that this disease is characterized by a chronic and progressive neurodegenerative process resulting from the intracellular and extracellular abnormal accumulation of proteins. The main representatives of these proteins are beta-amyloid and hyperphosphorylated. Overaccumulation of these aggregates leads to synaptic dysfunction and subsequent neuronal loss [2]. On the other hand, different neuroanatomic structures are heavily affected, such as the hippocampus or frontal cortex with serious cognitive, emotional and behavioral consequences. In fact, anxiety, depression or poor wellbeing have been described in these people [3].

The etiology of the disease typically has various causes, for example genetic causes, but in the last few years many authors have shown that other biological and environmental factors can be involved. There are studies which have demonstrated that the immune system (IS) and endocrine disorders, due to external factors such as stress [4,5], can influence the apparition of this disorder.

Unfortunately, this severe, irreversible, chronic and progressive neurodegenerative disease eventually leads to death in many cases and, nowadays, it has no cure. For this reason, it is essential to make progress with the objective to find new targets in the treatment and to study all the behavioral, cognitive and emotional parameters involved. Moreover, the absence of drug treatments and the high prevalence of AD, along with the burden of the disease on patients, their families and society, have led to the evaluation of new alternative therapies in an attempt to improve patient wellbeing [6]. In this line, non-pharmacological therapies (such as physical exercise or music therapy) have been showing positive results.

This review is aimed at providing an update of the studies on the role of stress, immune system, well-being and non-pharmacological therapies in AD. First, we will describe the role of stress in this disorder. Secondly, we will explain the

influence of the immune system by explaining the most important studies in this area. In the third place, we will discuss the result of the studies that determine the role of other associated variables, such as anxiety, depression or wellbeing perceived. Finally, we will present the main alternative therapies to improve symptoms in AD. The main objective of this theoretical study is to propose new priorities for future work in the field.

Stress and AD

Different studies show the role of stress in the appearance and maintenance of several disorders with neurobiological consequences, such as drug addiction [7] or AD [8], and other emotional and cognitive consequences, like poor memory or depressive symptoms.

The physiological stress response is modulated through the hypothalamic-pituitary-adrenal (HPA) axis [9] that stimulates the hypothalamus, which initiates the production of corticotrophin-releasing hormone (CRH). This activates the pituitary gland, which secretes adrenocorticotrophic hormone (ACTH). The ACTH stimulates the adrenal gland cortex where the main stress regulating hormone, cortisol, is located. Cortisol is considered to be the most reliable biomarker for measuring physiological stress levels in any biological sample.

When cortisol is persistently high, the cognitive function is compromised based on changes that occur in various parts of the brain and in levels of certain neurotransmitters. In addition, it induces the suppression of neurogenesis in the hippocampus inducing memory loss. Moreover, relevant authors in AD research have demonstrated that the relationship between cortisol levels and memory performance in the aging process could vary according to the presence or absence of cognitive impairment [10]. Also, a recent study in our laboratory [4] has shown that the level of cortisol in people with and without AD is different.

This substance accumulates in blood, saliva, sweat, hair, and urine. Among these, salivary cortisol is used as the most common biomarker of psychological stress because it is a non-invasive procedure and does not generate anxiety for the patient [11].

Immune System and AD

As we have previously mentioned, the etiology typically has various causes. Between one of them, several disorders of the immune system (IS) are included among the non-genetic risk factors for AD too.

The Immune System (IS) is altered in patients with AD mainly due to the inflammatory component of the disease, being Immunoglobulin A (IgA) one of the components of the IS which is severely altered when there is inflammation.

Moreover, data show that stress system and immune system are related. Chronic stress has been associated with detrimental or maladaptive neuroendocrine and immunological changes [5] and there seems to be a

relationship between IS and stress, which may influence the appearance of AD. Furthermore, it has already been shown that the level of IgA in saliva is adequate to measure the immune response to a psychological intervention and to determine a situation of emotional stress [4]. Microglia and astrocytes are activated and secrete inflammatory cytokines and chemokines via a disturbed blood-brain barrier; peripheral immune cells are activated and recruited towards inflamed brain lesions and amyloid plaques. These cells are not able to control inflammation and the associated detrimental immune responses [12]. The values of immunoglobulin A (IgA) vary rapidly as a result of the immunological alterations, so this immunoglobulin is a good indicator of the immunological system's activity at all times. Quantifying the level of IgA in saliva enables changes in immunocompetence to be determined, which may be one-off or produced by some kind of therapeutic intervention [16]. Also, in the laboratory of Prof. De La Rubia it has been demonstrated that the level of IgA in patients, with and without AD, is different and it supports the idea that patients with AD suffer from an immune alteration, which could partly explain the pathogenesis of the disease which presents with great inflammation [4]. The difference in IS in patients with and without AD is based in a hyperactivity of this system in AD patients. In our study we observed that the levels of IgA in AD patients were 103.97 ± 65.62 versus 23.79 ± 16.1 in patients without AD. Moreover, it was seen that there is a tendency in the group of participants without AD since, when cortisol increases, there is a decrease in IgA in saliva, while in AD participants, when cortisol increases, the IgA level in saliva increases too. All of these changes can be explained due to cellular, molecular and physiological changes in the organism that are also related to the mood of patients [13-15].

Psychological and Emotional State in AD: Well-being Perceived

The most relevant symptoms in AD are cognitive and behavioral disorders, but mood impairments have also been described. In fact, the appearance and development of the disease are associated with anxiety or depression [17]. Moreover, the appearance of these emotional symptoms is associated with the response of cortisol and IS too. There is a close relationship between the systems.

Regarding anxiety, it has been demonstrated, by using animal models, that elevated cortisol in AD subjects prompted the hypothesis that stress and glucocorticoids are involved in the development and/or maintenance of AD, and that an intracerebroventricular injection of amyloid- β peptide in rats induces memory impairment with alteration of anxiety responses [18].

On the other hand, other studies show evidence that high level of chronic stress causes depression basically because of monoaminergic changes that are generated in various brain regions and the suppression of hippocampal neurogenesis [19]. This neuronal degeneration could also affect the limbic

structures associated with emotional regulation, which explains the appearance of anxiety in many patients.

Moreover, it seems that poor well-being may affect the immune response, too. The proficiency of the Immune system is related to the emotional wellbeing. Wellbeing is defined as a combination of positive emotions, engagement, meaningful relationships and a sense of accomplishment [20], reflecting the positive aspects of mental health. Persistent psychological stress has been related to the disruption of and it triggers the onset of neuropsychiatric conditions. It has been shown that psychological stress adversely affects the normal functioning of the contributing to the pathophysiology of some neuropsychiatric disorders. Therefore, it seems that psychological stress due to a lack of wellbeing, and severe mental disorders, affect the immune response and the apparition of diseases mediated by the Immune system.

AD patients have well-being impairment and emotional problems such as depression or anxiety. It has been known for some time that cheerfulness and positive emotions are accompanied by an increase in salivary IgA levels. However, immune system is not the only biological system involved with wellbeing in AD. In the last few years, other biological systems seem to have an influence in mood state, for example, the adrenergic system. It is known that noradrenalin is the sympathetic nervous system's main neurotransmitter and provides information about the patient's emotional symptoms, too. An increase in endogenous noradrenalin is recorded when subjects receive emotional stimuli, and are significantly correlated to the suppression of these stimuli but not to the suppression of emotionally neutral stimuli. Activation of the adrenergic system can be evaluated by quantifying alpha-amylase in parotid gland saliva [21], thus becoming another important biomarker of the emotional state too.

The increase in noradrenalin is related not only to emotions but also to increased memory performance in patients with AD. Consequently, elevations in alpha-amylase may be indirectly associated to improved cognitive function – which is precisely the main function found to be impaired in patients with AD.

Non-Pharmacological Therapies in AD

We know that, at present, AD has no cure and pharmacological treatment only alleviates the symptoms. For this reason, the role of non-pharmacological therapies (NFTs) is important, which are very diverse and are based on brain plasticity. These types of treatments are defined as interventions that aim to improve ill or healthy people's quality of life based on the use of non-chemical agents. In patients with mild AD, it has been demonstrated that such therapies improve neuroplasticity, produce improved psychological and physical well-being, optimize the quality of life and encourage social integration [22].

For example, it has been shown that aerobic exercise reduces the risk of dementia, AD and cognitive impairment [23], besides reducing the risk of suffering from psychological and emotional disorders such as anxiety and depression. New

technologies are becoming more popular in the field of physical exercise due to the information and communication technologies (ICTs), based on the use of software on computers, game consoles, tablets, smart phones and so on, with the aim of training or stimulating cognition and memory. In this line, studies in our laboratory have demonstrated that exercise based on ICTs reduces anxiety, depression and cortisol levels in AD patients. [24].

However, there is a multitude of therapies which produce improved psychological and physical wellbeing in AD patients. Within these therapies, music has been shown to have benefits on the patients' quality of life, preserving the skills of expression and socialization, improving anxiety, depression, irritability and social isolation [25]. Therefore, this therapy is being used in the field of dementia as a possible alternative for alleviating various conditions. It induces brain plasticity in the early stages of the disorder, suggesting that it may be a good alternative. Concerning stress levels, music therapy, widely used for stress release in all areas of medicine, tends to be a reliable and efficacious treatment for critically ill patients. It can lessen stress response, decrease anxiety during mechanical ventilation and induce an overall relaxation response without the use of medication. For all this, music therapy has been shown to have benefits in the patients' quality of life, preserving the skills of expression and socialization while improving (i.e., decreasing) anxiety, depression, irritability and social isolation and becoming a new target to treatment in AD [25,26].

Conclusions

Over the last years, the increase of advanced age people in our society has created the need to research on new ways of therapy and on new disorders. AD is the most important disorder in western societies associated with the longevity of individuals and nowadays it has no cure. For this reason, it is important to generate new developments and make progress in this area in order to maintain quality of life.

Regarding that, it seems that stress and IS can be new targets to understand this disorder and to ascertain factors involved in the progression of symptoms. It has been shown that stress can affect several neurobiological disorders, among which AD is found, which helps us to work towards determining new diagnostic and treatment tools. Moreover, the IS changes in individuals suffering from AD, being stress levels and IgA different in patients with and without AD. Furthermore, it seems that both systems are connected, this being an important aim for our future work.

On the other hand, it is known that patients with AD have changes in their emotions and this can induce pathologies, such as anxiety and depression, or poor wellbeing that can influence the development of the disorder. Moreover, the main contribution of this manuscript is that all the systems described are involved at the same time (stress system, immune system and emotional system) and, as a consequence, the therapeutic interventions must be multifactorial. For this reason, new non-pharmacological therapies, unknown until

now in the treatment of this disorder, can be a good option to treat AD.

All in all, the study of the role of stress, emotions and IS can increase the knowledge about the variables involved in AD in order to contribute to future therapies and create new pharmacological and psychological goals in the treatment of AD.

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