Stress, the Immune System and Neurodegenerative Diseases: Alzheimer’s and Parkinsonism

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Abstract
Alzheimer and Parkinson disease are the most common neurodegenerative illnesses in our society. At the moment, no drug is totally effective to delete these disorders and there only exists some to palliate the symptoms. In this regard, it is essential to know possible biomarkers and systems involved of the prognostic, initiation and progression of these illnesses. Different studies show that the stress and the immune system (IS) are related with both disorders and that different molecules can serve as prognostic biomarkers of these illnesses. Concretely, it has been demonstrated that differences exist in cortisol and immunoglobulin A (IgA) levels in Alzheimer disease (AD) patients and people without the illness and that these differences are relational with the progression of the disease. On the other hand, it has been observed that the stress and the immune system are altered in Parkinson disease (PD) too. The data showed that in PD patients the levels of cortisol are increased and that the glucocorticoids can be an important factor on the inflammatory brain response. With respect to the (IS) it has been observed that there is an overactivity of the immune cells in these patients and neuroinflammation on the negre substance. For all this, to contribute to the knowledge of the possible systems involved in these neurodegenerative disorders there is a relevant question in order that we can advance in the cure of AD and PD and improve the quality of life to the patients.

Keywords: Alzheimer, Parkinson, Stress, Immune System, Neurodegenerative Disorder

Introduction
In the last decades neurodegenerative disorders have increased in our society. Between them, the most popular are Alzheimer disease (AD) and Parkinson disease (PD) [1,2].

AD is an irreversible and incurable disorder that produces serious cognitive problems, such as, language, memory, executive functions and social deterioration [3]. Moreover, it induces a progressive decline and an impaired wellbeing in the patients [4,5]. On the other hand, after Alzheimer’s, today Parkinson’s is the most significant neurodegenerative disease in society [6]. Clinically it presents us with a series of symptoms, mostly of motor origin, such as tremor when resting, rigidity and gait alterations [7]. However, this disease has also been related to other signs of an emotional nature such as depression, sleep disorders or anxiety [8].

As happens with several neurodegenerative disorders, there are no medicines to cure AD or PD, there are only some to improve the symptoms. In order to tackle this disease, we must emphasise not only the search for medicines that may help to halt or slow down the progress of the pathologies, but also the search for new molecules that may provide us with a prognosis of the risk of developing the dementia or a diagnosis of its onset, so that we may anticipate therapy in advance. Therefore, an early diagnosis of this illness, systems involved and the biomarkers used as a prognostic of these neurodegenerative disorders are essential to find effective treatment.

In this vein, it is important to know the main risk factors for the disease in order to look more deeply into the knowledge of the different pathogenic mechanisms. Among the causes that bring on dementia, there is the level of chronic stress suffered by patients some years before the dementia starts [9], as well as immunological alterations [10].

As for the level of stress, a long-term excess of cortisol damages neurons, so that it is closely related to the neurodegenerative illness [11]. As regards to the immune system, overstimulation of this related to the fight against the disease may generate an inflammation [12], with immunoglobulin A (IgA) one of the most altered components when the inflammation grows, and specifically in dementia [13].

For all of this, the aim of this work is to provide an update of studies on the involved different systems and biomarkers that can help to predict the initiation and progression of AD and
PD. First, we will describe the relationship between AD, stress and the immune system. Later, we will expose the role of both systems but with the implication in PD. Finally, we will draw some general conclusions and propose a future perspective to continue research in this area.

**Alzheimer Disease, Stress and Immune System**

It is known that the emotional and psychosocial stress induces the activation of the hypothalamic-pituitary-adrenal gland axis, which leads to an increase in the production of glucocorticoid hormones, highlighting cortisol among all of them [9]. There is a relationship between the production of cortisol and the development of the disease a few years later [9]. These elevated levels of stress are associated with the massive production of pro-inflammatory cytokines, related with memory loss [14]. This levels of cytokines, have a role in the appearance and chronicity of the pathology [15]. In fact, it has been observed that for a different pattern to exist on the expression of ARNm of genes as interleukin (IL) -1β and IL-6 being able to observe profiles of maximum expression of these cytokines in the first phases of the illness [16]. Moreover, a long-term excess of cortisol damages neurons producing different brain damage, such as a decrease in brain volume [17,18], related to the AD too. In this sense, the altered production of cortisol in urine over 24 hours can predict the disease in 2.9 years before its onset, thus being a good preclinical marker [19]. Thus, it is evident that the deregulation of cortisol production can be considered as a prognostic marker of the risk of developing the disease, although it is not exactly known how this link affects the development of the disease, so more studies in this area are necessary. However, cortisol in saliva not only is it shown as a good prognostic marker of disease development (since the secretion in this biological sample is different between mildly ill patients and healthy people of the same age) [20], but also as diagnosis of the degree of severity of the same because there are differences in their production depending on the state in which the patient is located [21].

On the other hand, recent studies have shown that the immune system may also be altered in patients with AD [20,21] and that it may be associated with the psychological well-being of patients with Alzheimer’s disease [22]. Thus, both systems (stress system and immune system) would be related [23, 24]. Specifically in AD, IgA is secreted differently in Alzheimer’s patients in a mild degree and healthy volunteers, and among patients in moderate to profound mild stage [20,21]. In our laboratory, we have observed that in patients with a mild state AD, IgA is secreted in high quantity but later, when the patient is in moderate and severity state the production of IgA lowers drastically. Moreover, data showed that there is a correlation between the production of IgA and the production of cortisol but this correlation is different depending on the stage [21]. Also, a remarkable date is that this secretion follows the same pattern observed for the pro-inflammatory cytokines since in the beginning of the disease they are secreted in large quantities, and in later stages production decreases drastically [16,21].

**Parkinson Disease, Stress and Immune System**

Chronic fatigue, life exhaustion and chronic stress syndrome can be found in up to 70% of patients with PD [25]. High levels of cortisol and ACTH, caused by a dysfunctional axis of HPA, have been associated with different disease [26]. It has been shown that in patients with PD, the HHA axis is unbalanced and cortisol levels are significantly increased, which implies a deregulation of glucocorticoid receptor (GR) function. Studies have shown that stress-related glucocorticoids may be an important contributor to modulate long-term inflammatory brain response, including the occurrence of neurotoxic microglia [27], so the impact of chronic stress on the etiology and course of PD is very important [28].

Thus, in patients affected by this disease, the evidence reports that cortisol levels are higher compared to healthy subjects [29]. As we have already explained, it could be due to the fact that corticosteroids are used to fight inflammation, so its main function is to regulate the proinflammatory stimuli that may arise in our central nervous system over time. As we have said, the axis that regulates corticosterone secretion has been affected in patients with Parkinson’s disease, which allows us to explain that neuroinflammation is maintained over time [27,30].

On the other hand, the immune system also seems to be altered in this type of patients [31,32]. Overactivity of the immune cells can be found in these patients [33]. Neuroinflammation is not only due to reactions produced by the different inflammatory pathways, but also due to immunological alterations in the brain that lead to an activation of the glia thus producing a positive feedback and finally, leading to an increase in the number of cytokines proinflammatory [34]. After the activation of the microglia and the subsequent cellular degradation, the resulting products of this process would be mainly pro-inflammatory factors, among which cytokines stand out, which triggers an exacerbation of neurodegeneration [35]. Cytokines, which are the main inflammatory signaling molecules, have been identified in the blood and cerebrospinal fluid of patients with PD [34].

From all of this, it can be concluded that the fact of chronically having a constant release of inflammatory mediators triggers a brain tissue degeneration [29]. In patients with Parkinson’s, neuroinflammation has been observed with an increase in the components of the immune system in the substantia nigra, where the typical neurodegeneration of the disease occurs and in the cerebrospinal fluid [34].

On the other hand, recent studies suggest that Parkinson’s Disease could be based on a viral infection, something that has not been corroborated at present, since the responsible virus has not been identified.

**Conclusion**

As described throughout this review, neurodegenerative disorders, specially AD and PD are increasing in our society and the advance in the knowledge of different systems involved
in the initiation, progression or prediction of these illnesses is a relevant question. We have focused on the stress and immune system because the alteration of the both systems seem to induce different brain problems that can cause neurodegeneration. It seems that different biomarkers related with these systems, such as, cortisol or IgA can help to detect the prognostic and progression of these disorders. Concretely, it has been shown that different levels of cortisol exist in mild AD patients or participants without AD. The data showed that mild AD patients have less level of cortisol [20] than healthy volunteers. With respect to the immune system, dates showed contrary results.

In our laboratory, we have demonstrated that AD patients have a hyperactive immune system compared with voluntaries without AD and that it can be a cause of neuroinflammation [20]. Moreover, recent studies have demonstrated that during the progression of the AD the response to stress and immune systems is variable. It seems that the cortisol level in participants with mild AD is lower and the IgA is much higher according with previous studies cited. However, when the progression of the illness is heavier (participants with moderate and several AD state) the progression of these biomarkers is different. We can observe that in participants with moderate and severe AD the levels of cortisol increase significantly compared with the mild state patients, but the levels of IgA decrease significantly. Hair cortisol and saliva IgA concentrations, as well as the relationship that may be established between them, clearly vary from the mild to the moderate/severe stages of AD [21]. This allows the proposal that these parameters could be used as possible tools in AD. On the other hand, regarding with PD, we have exposure that the stress system and immune system are involved too. In this case, it has been demonstrated that HHA axis are unbalanced and that the levels and its increase in the level of cortisol are related with brain damage and the appearance of PD. Also, overactivity of the immune cells can be found in these patients and higher levels of proinflammatory cytokines that can induce a neural degeneration [35].

Thus, the increase in the knowledge of systems involved in AD and PD can be effective tools to palliate these illnesses. In order to tackle this disease, we must emphasise not only the search for medicines that may help to halt or slow down the progress of the pathology, but also the search for new molecules that may provide us with a prognosis of the risk of developing the dementia or a diagnosis of its onset, so that we may anticipate therapy in advance. Although further studies into the mechanisms of stress and the levels of the different stress markers and of the immune system are needed, this work contributes to the research of different cellular and molecular bases of these neurodegenerative disorders and confirms the importance of the relationship between emotional stress - inflammation in AD and PD indicating that the relationship between both markers could be a tool to diagnose the onset of dementia or predict the risk of these disorders.

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Conflict of Interest Statement

No conflict of interest has been declared by the author(s).

References


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