Biomarkers in Neurodegenerative Diseases: Cortisol

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Abstract
Neurodegenerative diseases are characterized by progressive loss of cognitive function, dementia, and problems with movements. Identification of biomarkers during disease process, induce to an effective and early diagnostic test for neurodegenerative diseases. These biomarkers would allow presymptomatic disease detection of disease and would be valuable for monitoring the efficacy of disease.

Cortisol is a biomarker used for stress evaluation and a potential neurodegenerative disease biomarker.

Objective: The aim of this paper is to review systematically the scientific literature about evaluation to cortisol biomarker in neurodegenerative diseases.

Methods: Systematic literature review on Pubmed, Medline and Scopus database with the keywords "cortisol biomarkers" and "neurodegenerative diseases". It was analyzed all existing articles (between 1988 and 2015). PRISMA criteria reporting of systematic reviews and meta-analyses were applied. The inclusion criteria were: cortisol biomarkers in neurodegenerative diseases diagnosis, presenting quantitative or qualitative results. It was excluded articles outside the scope of the subject and articles with unavailable information.

Results: After applying the methodology, 14 scientific articles were included in the study. So, these studies were analyzed.

Conclusions: This paper review based on the contribution of cortisol biomarkers to diagnose and treat neurodegenerative diseases.

Keywords: Biomarkers; Cortisol; Salivary cortisol; Neurodegenerative diseases

Introduction
Neurodegenerative diseases, such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Amyotrophic Lateral Sclerosis (ALS); Multiple Sclerosis (MS); Huntington’s disease (HD); Machado-Joseph disease; Amyloid Polyneuropathy Family are characterized by a progressive loss of anatomically or physiologically related neuronal systems (cognitive function, dementia, and problems with movements) [1-5]. With extended life expectancy worldwide, patients suffering from these pathologies will increase in the coming years.

Nowadays, symptomatic treatments exist, but there are currently no effective drugs to reverse or halt the progression of the diseases. Improving the early and predictive diagnosis of neurodegenerative diseases is the paramount importance and enormous efforts are under way [6-8].

Therefore, it is required a tool to aid physicians, epidemiologists, and scientists in the study of human diseases by confirming a diagnosis and tracking disease progression, which may help to identify specific therapeutic targets.

So, development of biomarkers may measure disease risk, presence, and progression is one of the main goals and challenges in research in neurodegenerative diseases [8,9].

For National Institutes of Health (NIH) a biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention” (2001).

Advances in biochemistry (neurochemistry, proteomics, genomics) have increased our understanding of the central nervous system at the molecular level and applied us to screen for new biomarkers specific for neurodegenerative processes [1,10]. There is a need for additional and more sensitive biomarkers for the early and differential diagnosis of different neurodegenerative disease [6]. Identification of preclinical biomarkers for neurodegenerative diseases has led to new insights concerning disease pathophysiology and time course and has disclosed some interesting parallels in these common neurodegenerative diseases.

Body fluids, such as cerebrospinal fluid (CSF), serum, saliva, blood or urine, offer an attractive medium to biomarker analysis [5,10-15].

The firsts biochemical biomarkers of neurodegenerative diseases were: the proteins beta-amyloid (Aβ), total tau and its phosphorylated forms (p-tau) measured in cerebrospinal fluid (CSF), but, these markers are dependent upon invasive lumbar puncture and therefore appear less amenable for high through screening of patients [11,13,15]. There is a pressing need for new biomarkers in more easily accessible body fluids such as peripheral blood [6,8,13].

Nowadays, recent studies prove that blood-based testing would be widely available, non-invasive, easy, economic and rapid to perform.

In this review, we analyzed the paper of cortisol biomarker in neurodegenerative disease.

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Copyright: © 2016 Batista P, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cortisol is a steroid hormone and the most important human glucocorticoid, and regulates a variety of important cardiovascular, metabolic, immunological, homeostatic, and brain functions (brain metabolism, gene expression, and memory) [3,16-18]. Cortisol levels are known to increase within minutes of a stressful event, and high cortisol levels increase activity of the hypothalamus-pituitary-adrenal (HPA) axis [4,5,17,18]. Therefore, the aim of this paper is to systematically review the scientific literature about evaluation to cortisol biomarker in neurodegenerative diseases.

Methods

We conducted a study of a reflective systematic literature review. Between 1998 and 2015, we identified scientific papers published in international journals, using a search of the databases in digital format, MedLine and PubMed, and a second phase to Scopus. The descriptors used in the research were: ["biomarkers" and "neurodegenerative diseases"]. Time later, because of the high number of matches (11843 publications), the research was refined to ["cortisol biomarkers" and "neurodegenerative diseases"], having been obtained 34 publications. The study was restricted to English articles published. The research with the final descriptors ["cortisol biomarkers" and "neurodegenerative diseases"] resulted in 34 publications in Pubmed database, 16 publications in MedLine and 16 publications in Scopus. Analyzed 34 publications obtained in the Pubmed database, form excluded 20 publications; 16 publications were outside the scope of the study and 4 articles with unavailable information.

The inclusion and exclusion criteria of the studies are described:

- Inclusion: cortisol biomarkers in neurodegenerative diseases diagnosis, presenting quantitative or qualitative results.
- Exclusion: other biomarkers in neurodegenerative diseases, no presenting quantitative or qualitative results and articles with unavailable information.

PRISMA criteria for preferred reporting items for systematic reviews and meta-analyses (Prisma) were applied. The information collected was compiled and analyzed with respect to the year of publication, authors, sample and country, type of study/methodology, results and aim.

The cataloguing and identification of repeated references were made through the computer program EndNote bibliographic referencing (Figure 1).

Analysis of Results and Discussion

For a better understanding of the systematic literature review, studies analyzed were compiled in a summary table (Table 1). In this table there are several items: year of publication/authors, sample, country, methodology, instruments, results and aims.

It was analyzed fourteen complete articles which met the inclusion criteria.

A total of 4361 adults from four different countries (United States, Canada, Germany, Poland, Australia, France, Switzerland, Sweden and Japan) were analyzed. Different dimensions to evaluate biochemical parameters, physical, neurological and psychiatric dimensions. Similarly, many instruments were used to measure different dimensions were analyzed.

Cross-sectional and longitudinal studies methodology were present in this review.
<table>
<thead>
<tr>
<th>Citation</th>
<th>N</th>
<th>USA/Canada</th>
<th>Data obtained from Alzheimer’s Disease Neuroimaging Initiative (ADNI) database.</th>
<th>SPARE-AD (Spatial Pattern of Abnormality for Recognition of Early Alzheimer’s disease), Cognitive Test, Biomarker Collection and Analysis, Magnetic resonance imaging (MRI) Processing and Analysis, Position emission tomography (PET), Biological markers, Clinical and neuropsychological assessment</th>
<th>Morphological brain, Blood-based biochemical biomarkers</th>
<th>- Association between AD-like patterns of brain atrophy, quantified by the SPARE-AD index, and plasma cortisol, CgA, IGFBP-2 and MIP-1α levels. - Stress and insulin responses and cytokines associated with recruitment of inflammatory cells in MCI-AD are associated with its characteristic AD-like brain atrophy pattern and correlate with clinical changes or CSF biomarkers.</th>
<th>Relationship between a panel of plasma biomarkers and presence of AD-like brain atrophy patterns defined by a previously published index (SPARE-AD) at baseline in subjects of the ADNI cohort. Test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.</th>
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<tbody>
<tr>
<td>Toledo et al. [20]</td>
<td>N=181 adult subjects (396 MCI, 193 probable AD, 229 cognitively normal)</td>
<td>USA and Canada</td>
<td>Data were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database.</td>
<td>SPARE-AD (Spatial Pattern of Abnormality for Recognition of Early Alzheimer’s disease), Cognitive Test, Biomarker Collection and Analysis, Magnetic resonance imaging (MRI) Processing and Analysis, Position emission tomography (PET), Biological markers, Clinical and neuropsychological assessment</td>
<td>Morphological brain, Blood-based biochemical biomarkers</td>
<td>- Suggest that dysregulation of cortisol concentrations may be involved in the decline of verbal learning and memory recall ability in HD (but no causal relationship). - Not find relations between recognition memory performance and cortisol levels. - Cortisol neurotoxicity hypothesis (more relevant). Suggestive correlations showing that heightened stress was present in HD expansion carriers, and was related to evening salivary cortisol levels, as well as learning and memory performance. Suggest hypercortisolism and the underlying pathological changes may begin many years before a clinical diagnosis is made, but the memory decline associated with HPA axis disturbance may only become detectable once motor signs become pronounced.</td>
<td>To identify whether there is an association between cortisol levels and verbal learning and memory in the early stages of HD.</td>
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<td>Shirbin et al. [4]</td>
<td>N=59 (19 early-HD, 20 pre-HD, and 20 HD CAG normal controls)</td>
<td>Australia</td>
<td>Preliminary study</td>
<td>Wechsler Adult Reading (WTAR), Inventory of Depressive Symptomatology—Self Report, Perceived Stress Scale, Pittsburgh Sleep Quality Index (PSQI), California Verbal Learning Test, Saliva collection</td>
<td>Assessment of learning and memory, Diagnostic status on salivary cortisol concentration.</td>
<td>- Significant changes in the metabolite profile of AD patients compared to healthy controls have been identified. - Increased cortisol levels related to the progression of AD and detected AD. - Several combinations of three to five metabolites, including cortisol and various amino acids, in addition to cysteine and uridine.</td>
<td>To identify the metabolic changes resulting from the disease phenotype by a thorough and systematic metabolite profiling approach.</td>
</tr>
<tr>
<td>Czech et al. [12]</td>
<td>N= 130 (59 AD, 51 healthy Controls)</td>
<td>Germany, France, Switzerland, Sweden</td>
<td>Cross-sectional</td>
<td>NINCDS-ADRDA and DSM IV criteria, MRI examination or PET, mass spectrometry analysis</td>
<td>Metabolite profiling</td>
<td>- Biomarker panel was identified in AD: a) markers significantly increased (cortisol, pancreatic polypeptide, insulinlike growth factor binding protein 2, β2 microglobulin, vascular cell adhesion molecule 1, carcinoembryonic antigen, matrix metalloprotein 2, CD40, macrophage inflammatory protein 1α, superoxide dismutase, and homocysteine) b) markers significantly decreased (apolipoprotein E, epidermal growth factor receptor, hemoglobin, calcium, zinc, interleukin 17, and albumin).</td>
<td>To identify plasma biomarkers for the diagnosis of AD.</td>
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<tr>
<td>Doecke et al. [13]</td>
<td>N=961 (754 health adult, 207 AD).</td>
<td>Australia</td>
<td>Longitudinal Data where obtained from Australian Imaging Biomarker and Lifestyle study (AIBL)</td>
<td>151-analyte multiplex panel (Human Discovery/MAP, version 1.0; RBM)</td>
<td>Blood pathology testing</td>
<td>- Biomarker panel was identified in AD: a) markers significantly increased (cortisol, pancreatic polypeptide, insulinlike growth factor binding protein 2, β2 microglobulin, vascular cell adhesion molecule 1, carcinoembryonic antigen, matrix metalloprotein 2, CD40, macrophage inflammatory protein 1α, superoxide dismutase, and homocysteine) b) markers significantly decreased (apolipoprotein E, epidermal growth factor receptor, hemoglobin, calcium, zinc, interleukin 17, and albumin).</td>
<td>To identify plasma biomarkers for the diagnosis of AD.</td>
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<tr>
<td>Reference</td>
<td>N</td>
<td>Country</td>
<td>Study Design</td>
<td>Biomarker Measurement</td>
<td>Findings</td>
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<td>Roosendaal et al., [3]</td>
<td>N=29 ALS patients</td>
<td>Republic of Korea</td>
<td>Cross-sectional nature</td>
<td>ALs functional rating scale (ALSFRS), Manual muscle test (MMT), Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS)</td>
<td>- CAR was significantly smaller in ALS patients than in caregiver controls. - A smaller CAR in ALS patients was significantly correlated to poorer clinical status (as assessed with both the ALSFRS and MMT rating instruments) and a more severe depressive mood status. - No correlations were observed between total cortisol outputs during the first 45 min post awakening and clinical or depressive status.</td>
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<td>Soares et al., [14]</td>
<td>N=566 (396 mild cognitive impairment, 112 AD, 58 healthy control)</td>
<td>USA and Canada</td>
<td>Longitudinal</td>
<td>Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort, Plasma sample collection, Laboratory tests</td>
<td>- All participants with Apo ε3/ε4 or ε4/ε4 alleles showed a distinct biochemical profile characterized by low C-reactive protein and ApoE levels and by high Cortisol, interleukin 13, apolipoprotein B, and gamma interferon levels. - Plasma biomarkers improved specificity in differentiating patients with AD from controls, and ApoE plasma levels were lowest in patients whose mild cognitive impairment had progressed to dementia. - Incorporation of plasma biomarkers yielded high sensitivity with improved specificity.</td>
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<td>Toledo et al., 2012</td>
<td>N= 819 adult subjects (229 cognitively normal (CN), 398 mild cognitive impairment (MCI), 192 AD)</td>
<td>USA</td>
<td>Cross-sectional</td>
<td>Pittsburgh Compound B-positron emission tomography (PiB-PET) studies, Mini- Mental State Examination.</td>
<td>- Association between Aβ brain burden measured in vivo and diastolic blood pressure and cortisol, indicating a possible link between these cardiovascular risk factors and Aβ burden measured by PiB-PET. - Identified a panel of three blood markers, which allowed support vector machine (SVM)-based distinguishing of AD patients from healthy controls. - Blood-based biomarkers might have utility in AD diagnostics.</td>
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<td>Laske et al., [18]</td>
<td>N=310 (170 AD, 140 healthy controls)</td>
<td>Germany</td>
<td>Longitudinal</td>
<td>Mini-Mental State Examination (MMSE)</td>
<td>Blood sampling</td>
<td>- Higher cortisol serum but not CSF levels are associated with minor signs of AD pathology. - Neuroprotective effect of moderately elevated cortisol serum levels in patients with mild AD dementia.</td>
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The current review revealed many studies about biomarkers in neurodegenerative diseases, but few studies about "Cortisol biomarkers in Neurodegenerative diseases". Development of biomarkers that may measure disease risk, presence, and progression is one of the main goals and challenges in research in neurodegenerative diseases.

The availability of neuroimaging and biomolecular biomarkers to monitor and control brain changes structures, inflammatory processes and other biochemical pathways enable investigation of pathways that may be related to neurodegenerative disease [5,19,20].

Biomarkers for these pathologies are of great value as diagnostic aids (especially early in the course of the disease, when the clinical symptoms are vague and diagnosis are difficult), therefore, these biomarkers should reflect the central pathogenic processes of the diseases.

Laske et al., identified three blood markers, involved in several biological pathways including cardiovascular, metabolic, immunological, homeostatic, and brain functions (cortisol), oxidative stress and antioxidant response (OLAB), and endothelial dysfunction (vWF), which have been associated with the pathogenesis of AD [18]. Soares describe a list of biomarkers identified within the Alzheimer Disease Neuroimaging Initiative (ADNI) cohort and Doecke present biomarkers identified (cortisol, IGFBP2, and PPY) within the Australian Imaging, Biomarkers and Lifestyle (AIBL) study [13,14]. These data indicate that further research validating cortisol levels across different neurologic diseases is required to determine its specificity [13].

Other studies about cortisol, indicate that it might independently cause brain atrophy and the increase (peripheral and central) of the AD related biological alterations, hippocampal atrophy and reduced glucose metabolism, and CSF biomarker changes occur early in the course of AD and can be demonstrated already in subjects with MCI, not known, whether HPA axis dysfunction also occurs in pre-dementia AD, CSF cortisol concentrations in MCI and in cognitively healthy controls indicates that a marked cortisol increase does not arise early in AD.

To investigate whether CSF cortisol levels are elevated in AD. To determine if the increase of CSF cortisol represents an early event in the course of AD and can be detected already in MCI.

To investigate the plasma cortisol levels at a fasting state in elderly female Alzheimer’s disease (AD), vascular dementia (VD), and non-demented subjects.

<table>
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<tr>
<th>Popp et al., [17]</th>
<th>N=133 subjects (66 AD, 33 with mild cognitive impairment (MCI) and 34 cognitively normal participants).</th>
<th>Germany</th>
<th>Longitudinal</th>
<th>Diagnostic lumbar punctures; Serum cortisol RIA</th>
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<td></td>
<td>- Higher CSF cortisol levels in AD compared to control subjects after controlling for the APOE genotype effect.</td>
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<td>- AD and vascular dementia subjects had higher levels of plasma cortisol than ND subjects.</td>
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<td>- Normal cortisol level in MCI subjects compared to cognitively healthy controls.</td>
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<td>- Cortisol levels in AD subjects did not change significantly.</td>
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<td></td>
<td>- Several AD related biological alterations, hippocampal atrophy and reduced glucose metabolism, and CSF biomarker changes occur early in the course of AD and can be demonstrated already in subjects with MCI.</td>
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<td>- Significant correlation between cortisol or DHEA levels and non-cognitive measures.</td>
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<td>- Not known, whether HPA axis dysfunction also occurs in pre-dementia AD.</td>
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<td>- Significant correlation between both the initial MMSE and ADAS cognitive measures and initial DHEA level, with lower DHEA levels unexpectedly being associated with better performance on these measures.</td>
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<td>- CSF cortisol concentrations in MCI and in cognitively healthy controls indicates that a marked cortisol increase does not arise early in AD.</td>
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<td>- Potential usefulness of DHEA as a therapeutic agent.</td>
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<tr>
<th>Umejaki et al., [23]</th>
<th>N=115 (66 AD, 28 with vascular dementia and 21 non-demented controls). Japan</th>
<th>Cross-sectional</th>
<th>Mini-Mental State Examination</th>
<th>Basal plasma cortisol levels, Radioimmunoassay</th>
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<td>- Cortisol and dehydroepiandrosterone (DHEA) were determined using conventional radioimmunoassay procedures.</td>
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<td></td>
<td>- Not document relationship between cortisol or DHEA levels and non-cognitive measures.</td>
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<td></td>
<td>- Not document relationship between basal cortisol and dehydroepiandrosterone levels and impairment in different cognitive and non-cognitive measures and the possible interaction of dehydroepiandrosterone with hypercortisolism in dementia.</td>
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<td>- Significant correlation between both the initial MMSE and ADAS cognitive measures and initial DHEA level, with lower DHEA levels unexpectedly being associated with better performance on these measures.</td>
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<table>
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<tr>
<th>Miller et al., [16]</th>
<th>N=27 patients with diagnosis of probable AD California</th>
<th>Longitudinal</th>
<th>Alzheimer’s disease assessment scale</th>
<th>Complete medical, psychiatric, neurologic, neuroimaging and neuropsychological assessment</th>
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<td>- AD and vascular dementia subjects had higher levels of plasma cortisol than ND subjects.</td>
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Table 1: Summary of information from fourteen relevant articles met our inclusion criteria in the study of “Cortisol biomarkers and neurodegenerative diseases”.

The availability of neuroimaging and biomolecular biomarkers to monitor and control brain changes structures, inflammatory processes and other biochemical pathways enable investigation of pathways that may be related to neurodegenerative disease [5,19,20].
The cortisol awakening response in ALS is blunted, and Roozenendaal et al. analyze this problem [3]. They concluded, as previous findings indicates, that particularly the rise in cortisol levels immediately after awakening, the cortisol awakening response (CAR), is associated with indices of physical and emotional well-being. Their data indicates that ALS patients show a blunted CAR, correlated with disease (poorer clinical status) and severe depressive status. Thus, ALS patients may be a consequence of the emotional or physical distress and associated symptoms of chronic fatigue and depression. These results suggest a reduced responsivity of the HPA-axis in ALS [3].

Beyond the depression, epidemiological evidence that cardiovascular risk factors (CVRF) are risk factors for Alzheimer's disease, but there is limited information on this from neuropathological studies. Cortisol has been related to Aβ deposition and memory deficits in normal transgenic mice and to hippocampal atrophy in human brain magnetic resonance imaging studies [15]. Therefore, we examined the relationship between CVRF and amyloid-β (Aβ) brain burden measured by Pittsburgh Compound B-positron emission tomography (PiB-PET) studies in the Alzheimer's Disease Neuroimaging Initiative [15]. This study confirms the relation between cortisol and brain Aβ deposition in human subjects [15].

### Summary of Methodological Limitations

Numerous articles have been developed in the field of biomarkers to the application in neurodegenerative diseases, and search was more restricted.

The selected biomarker can’t be the one with the most reliable results and making the limited study.

The use of a single measuring instrument, would have allowed an easier and more correct comparison of the identified variables.

We found limitations in the analyzed articles: small number the subjects [4,11,24]; longer follow-up in larger samples of participants [5]; difficult to be precise about the interdependence of the parameters [24]; allowing more detailed consideration for the impact of stress, [4]; difficulties in longitudinal epidemiological studies is to discern the underlying pathology or pathologies [15]; small longitudinal studies [14]; little salivary cortisol collections [3], diurnal variability in cortisol levels [18].

### Implications for Practice

Neurodegenerative disorders are a heterogeneous group of disorders characterized by a progressive and selective loss of anatomically or physiologically related neuronal systems that is affecting people of all ages (affects older and some young adults). Although in these diseases, the mechanisms are still far from being clarified. Future studies are needed to investigate the neurological or psychological mechanisms underlying this alteration in HPA responsivity.

In recent years, there has been a growing interest in applying biomarkers to research on prognosis and treatment of neurodegenerative diseases.

This literature review, suggest new studies about biomarkers in neurodegenerative diseases.

More studies are important to understand the mechanism and actuation of biomarkers in diagnosis and treatment of these diseases.

### Conclusion

Neurodegenerative diseases are a growing problem worldwide,
given the rapidly ageing population, the current search for biomarkers is very important.

Biomarkers for neurodegenerative diseases should reflect the central pathogenic processes of the diseases (for example, neuronal degeneration).

There is an urgent need for biomarkers to diagnose neurodegenerative diseases early in their course, to differentiate them from other related diseases or subtypes, and to monitor responses of patients to new therapies.

**Conflict of Interest**

Nothing to declare.

**References**


