Impact of neurobehavioral disorders on quality of life in idiopathic parkinson’s disease without dementia.

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Abstract

Background: Parkinson's Disease (PD) is a multifactorial neurodegenerative pathology, characterized by motor symptoms (tremor, bradykinesia, rigidity and postural instability) and non-motor symptoms (depression, anxiety, apathy, sleep disturbances, dysautonomic symptoms, among others) that affect the worsening of the Quality of Life (QOL) of people with this diagnosis.

Objective: Identify the impact of neurobehavioral alterations in QOL on idiopathic PD without dementia.

Methods: 61 references, 40 research articles, 2 systematic reviews, and 17 review articles were used in the preparation of this study. The literature search was performed in the Pubmed and Scopus databases.

Results: Neurobehavioral disorders such as depression (with a prevalence of 50%) were found to impact on QOL impairment, neurocognitive functioning (attention, memory, executive functions), and impairment in the basic, instrumental and advanced Activities of Daily Living (ADL). Anxiety is another disorder (with a prevalence of more than 40%) that impacts on QOL, especially in motor fluctuations, ADL, working memory and inhibition tasks, followed by apathy that usually occurs in advanced stages of the disease (prevalence of more than 48%) and affects several domains of QOL.

Conclusion: It is necessary to intervene neurobehavioral alterations in earlier phases of the disease, with the aim of generating treatments that get a better QOL.

Keywords: Anxiety, Apathy, Depression, Quality of Life, Idiopathic Parkinson's disease without dementia.

Introduction

Until less than three decades ago, Parkinson's Disease (PD) has been considered a pathology of motor origin. Data obtained from different studies [1-3] indicate that PD is a neurodegenerative pathology characterized by motor and cardinal symptoms such as rest tremor, bradykinesia and rigidity, however, it has been found [1,4] that non-motor symptoms such as depression, anxiety and apathy are highly prevalent, and affect neurocognitive functioning (like executive functions, attention, working memory, immediate verbal memory, visuospatial functioning and visuoconstructive skills), Activities of Daily Living (ADL)
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and deterioration in Quality of Life (QOL) (independence, stigma, communication, neurocognitive functioning, sexual area, among others) in patients with PD. Different studies [5,6] have found that neurobehavioral or emotional disorders such as depression, anxiety and apathy are related to the worsening of QOL, which in turn is related to deterioration at the frontal level, as a possible predictor of dementia due to PD.

QOL is defined as a multifactorial concept that projects the patient's self-perception on his/her life, especially in individual areas, social and family, fields that are altered by neurobehavioral disorders such as depression, anxiety and apathy and clinically correlated with PD, motor exacerbation and neurocognitive impairment.

Depression is one of the most common neurobehavioral disorders in PD, with a prevalence of 50% for clinical pictures of severe depression [6-9] and 17% for signs of mild depression [10]. Other studies [10,11] indicate a prevalence of 35%, which varies according to the incidence and prevalence of the clinical criteria for diagnosis.

Drug symptomatology affects the deterioration of the PD patient's QOL, leading to a point of physical, individual and emotional instability. Currently, depression is considered a predictive factor that is clinically related to the affectation of the primary motor symptoms of PD and the loss of functionality and independence where the subject develops, clinical data that are related to dysfunctions in the frontal lobe, generating a high predisposition to dementia due to PD.

Anxiety is another of the most frequent emotional disorders in PD, with a prevalence of 40% [12,13] and with a significant impact on working memory, executive functions and low learning performance, and a worsening of QOL [1,14,15].

Apathy is another of the neurobehavioral and/or emotional disturbance present in PD, with a prevalence of 40% [16] and acts as a predictor of impaired executive functions and worsening of QOL in advanced stages of the disease.

The aim of this work is to identify the impact of neurobehavioral disturbance such as depression, anxiety and apathy generated in the QOL of the patient with PD.

Materials and Methods

Method

For the elaboration of this study we used 60 references, 40 research articles that aimed to study the impact of emotional disturbances in PD, 2 systematic reviews and 17 review articles and the DSM IV and DSM V criteria for neurobehavioral disturbances such as depression and anxiety. The literature search was performed in the Pubmed and Scopus databases. A number of keywords were used (depression, anxiety, apathy, quality of life, PD) obtaining a total of 150 references. The abstracts of these papers were analyzed and 125 were selected. The articles that met Figure 1. Study selection process.
the criteria indicated in Figure 1 were then selected, for a total of 60 articles (Figure 1).

**Results**

**Results depression in QOL in patients with PD**

Depression in patients with PD occurs even before the diagnosis of the disease [1], and this is a predictive factor used as clinical criteria to determine the onset of PD. This disorder is characterized by sadness, low self-esteem, hopelessness, feelings of guilt, somatoform disorders and disturbances in planning, organizing and directing immediate behavior (executive functions related to the prefrontal cortex of the brain).

Some studies indicate [17] that depression has a prevalence of 50%, for others 30%-40% [18], others 30%-35% [19,20] reporting a high affection in ADL, as well as the impact that depressive symptomatology has on the QOL, directly affecting areas such as stigma, communication, neurocognitive functioning, emotional well-being, sexual activity, especially in aspects of reduced mobility.

The diagnosis of depression in PD tends to be complex, since it often overlaps with mixed clinical pictures of anxiety and apathy (especially apathy in advanced stages of the disease, although the neurological correlation of depression and anxiety is different), for that reason it is necessary that at the time of evaluating depression in patients with PD it is taken into account: First, negative affect; second, mood and third, concerns [21]. That revolve around the immediate context of the patient, his or her family and illness, and how these directly impact on the patient's physical, emotional and mental functioning.

Currently the clinical criteria of the DSM IV and DSM V [22,23] are used to diagnose depression in PD, however, this classification is not specific to PD, since emotional disturbances such as depressive symptoms vary from one patient to another; the aim of the new lines of research and intervention should be to apply and design different scales and corroborate their results with an in-depth interview. The above should be done in order to identify the symptoms of depression that are actually found clinically correlated with pathology. With regard to etiology, some studies [24-27] indicate that depressive symptoms are associated with dysfunctions in the prefrontal cortex, subcortical frontal circuits, anterior cingulate cortex and middle frontal gyrus, brain structures that are related to tasks for planning, organizing and directing immediate behavior, which are also correlated with emotional and motivational tasks and alert states.

Neuroimaging studies [24,28,29] have found alterations in the hippocampus, basal nuclei, prefrontal cortex and orbitofrontal cortex, areas that are involved in depressive symptomatology and information consolidation and storage.

At the biochemical level, depression is associated with an alteration in the dopamine transporter, which causes patients with PD to have fluctuations in their moods. In turn, this deficit will have repercussions on their cardinal motor symptoms, especially bradykinesia and postural instability. Since dopamine is not only related to mood, it
also has to do with complex movements, especially if it is located in the Substantia Nigra pars compacta, exactly in the midbrain, and with projections to frontal areas of your brain [30,31] (Figure 2).

The QOL in PD begins to be affected from the moment of diagnosis; depression acts as a contributory factor in the worsening of stigma, emotional well-being, social, individual, family and sexual support, among others [32-34].

Other studies [35-45] have found that depression directly affects mobility, emotional well-being, stigma, social support, bodily distress and neurocognitive functioning, which supports the findings of other research [44,45] that depressive symptomatology impacts on the domains of QOL. What is clear so far is that depression is a predictive and causal factor in the worsening of QOL in patients with PD, clinically correlated with neurocognitive impairment and overlapping with other neurobehavioral disorders such as anxiety and apathy.

The QOL in the PD patient begins to worsen at the time of diagnosis, at this point, depression becomes a determining factor of causality, and also a factor of association. Since depression affecting QOL will be related to other entities such as insomnia, neurocognitive deficit and alteration of all the dimensions in which the subject develops [39].

It is important that health professionals emphasize the improvement of the patient’s QOL, the intervention processes must be individualized, that is, the interdisciplinary team is aware that they cannot cure the disease (at the moment) but if we can effectively treat depression, if we manage to cure the depressive symptomatology as a neurobehavioral/emotional disorder in PD, we will surely be improving their QOL in each one of its components, and slowing down the disease to later clinical pictures of dementia by PD.

The impact of depression in QOL on idiopathic PD without dementia is reflected in the aspects of mobility and Basic, Instrumental and Advanced Activities of Daily Living (BIAADL) that patients present; depressive symptomatology is clinically correlated with the cardinal motor symptoms of the disease, different studies [33] have found that postural instability, gait and rest tremor are associated with low mood, especially in the morning hours, Communication, receiving a diagnosis of PD disrupts the physical and mental stability of the subject, leading him to have at times a mutated behavior away from his loved ones and his/her immediate context; emotional well-being is another of the dimensions that are affected by depression, the patient is subjected to physical and mental fatigue, becoming obsessive in thought, and with a deficit of strategies to confront his illness, another of the dimensions that depression manages to impact on the QOL of the patient with PD is stigma, the subject feels pointed out and/or judged by others, it is clear that a process of education for patients, families and society in general, is necessary so that stigma or prejudice is less present, especially in the self-perception of health.

Another aspect that impacts on depression in the QOL in patients with PD is the neurocognitive functioning, different works [32,34,44] have found low performance in sustained attention, immediate verbal memory and executive functions, associated with brain dysfunctions in the prefrontal cortex and fronto-subcortical circuits.

In general, depression as the most frequent neurobehavioral/ emotional disturbance in PD impacts on the QOL of
patients with PD.

Figure 3 details the impact that depression has on QOL in patients with PD specifically in aspects such as mobility, communication, emotional well-being, stigma and neurocognitive functioning.

**Anxiety in QOL in patients with PD**

Depression coexists with anxiety, however, the clinical picture of psychosocial stress (anxiety) intervenes independently in each of the states of PD, different studies [12,46] indicate that anxiety correlates and overlaps with ADL, neurocognitive functioning (working memory, executive functions) and QOL, especially correlated with the deterioration and/or increase in motor fluctuations.

Anxiety has a prevalence of 40%; patients report characteristic symptoms such as chest tightness, tachycardia, sweating and psychomotor agitation [12].

Just as depression, its diagnosis is usually complex and imprecise, due to the fact that it usually overlaps with clinical entities such as depressive symptomatology, this overlap generates that diagnoses at a neurobehavioral/emotional level are under-diagnosed and inefficient when generating functional neurorehabilitation plans aimed at evaluating and improving the QOL of subjects with PD.

Currently, the clinical criteria used to diagnose anxiety in PD are those indicated in the DSM IV, DSM IV R and DSM V, [22,23] although there are authors [47] who state that when clinical symptoms of anxiety do not meet the international criteria or standards for diagnosis, this has a negative impact on clinical practice, leading to increased patient disability and increased deterioration in QOL.

The above is also influenced by the lack of specificity and sensitivity of anxiety in PD, then the neurobehavioral disorders such as anxiety and depression have not been specifically defined in the pathology. For this reason, it is necessary that new lines of research focus on generating valid and specific instruments for PD, otherwise the diagnosis will continue to be uncertain; this also applies to lines of treatment, since anxiety is clinically correlated with motor fluctuations, mobility and ADL [12,46].

The scales used to assess anxiety present clinical parameters of the disorder at a general level and are not sensitive for measuring anxiety in PD [48].

With regard to the aetiology of anxiety in PD, it is correlated with an increase in the Gamma aminobutyric acid GABA and a dopaminergic and noradrenergic dysfunction of the functional system [48-51]. A defect has also been found in the serotonin transport gene [48,51-52], a neurotransmitter that is related to mood and the exacerbation of motor symptoms (fluctuations, walking and postural instability).

The data obtained from different studies [53,54] indicate that anxiety does not impact on the neurocognitive functioning of the subjects; however, some studies [55] show that high levels of anxiety have an impact on the deficit that subjects present in operative memory and/or immediate verbal memory [14,15,56], directly affecting the middle frontal gyrus and the sulcus, brain areas related to the consolidation and manipulation of information, other studies [1] indicate that anxiety generates a deficit in executive functions, especially in inhibition and sequentiality tasks.

In relation to QOL, it has been found [55] that anxiety has a direct impact on the emotional well-being of the subjects, ADL, social support, but especially on motor fluctuations, both during the day and at night. It was found [55] that anxiety occurs in the premotor stages of the disease, for that reason it is of great importance to carry out research and intervention studies, with the purpose of designing programs for the improvement of QOL.

Anxiety and QOL are variables of interest to the scientific field, especially in PD, clinical pictures of psychosocial stress have a negative impact on motor fluctuations, break into the functional independence of the subject, generating a greater degree of disability, and dependence on others.

Figure 4 details the impact of anxiety on QOL in PD. Initially, it will be directly correlated with motor fluctuations, this affection will be associated with the difficulties that the subjects will have in emotional well-being, social support and ADL. Domains of great importance in QOL in PD.

![Figure 4. Impact of anxiety on QOL in patients with idiopathic PD is dementia.](image-url)
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**Apathy in QOL in patients with PD**

Depression and anxiety are part of the neurobehavioral or emotional disorders in PD, affecting the functional independence and the QOL of people who suffer from this pathology. However, there is another non-motor alteration that is also related to the neurocognitive deficit, the ADL and the deterioration of the QOL, the apathy.

Apathy, with a prevalence of 16% and 48% [57], affects decision-making and functional activity in subjects with PD.

With regard to diagnosis, apathy often overlaps with depression and clinical and subjective aspects in the patient that make diagnosis difficult, however, different studies [58] have found that apathy often occurs in advanced stages of PD and is clinically correlated with dementia in PD. This leads to the inference that subjects with PD and depression can carry out daily activities of their lives, despite having a clinical picture of depression. The opposite situation is for patients with PD and apathy, since the degree of demotivation and lack of interest in different activities leads the subject to a state of physical prostration, but also emotional and mental.

The etiology of apathy in PD correlates with dysfunctions in the mesocorticollimbic system, dysfunction in the prefrontal cortex, dopaminergic system and dysfunction in fronto-subcortical circuits, biochemical aspects and brain structures that play a role in motivation, mood or expression of affectivity [59,60], however, The loss of interest of the subject in different activities and in advanced stages of the disease, is related to the dysfunction that patients present in the basal ganglia/base nuclei (Figure 5), neuronal structures that play an important role in complex movements, this is surely the reason why patients with PD in advanced stages and with dementia present a decline in their ADL and a worsening in their QOL.

As the disease progresses, the self-perception of health and the relationship between the stages of the pathology greatly deteriorate the QOL of the patient with PD. For this reason, it is necessary to generate research aimed at the evaluation, diagnosis and intervention of apathy as a neurobehavioral disorder that impacts on the QOL of patients with PD.

Specifically, apathy impacts on the functional activities of subjects with PD in the early stages, relating to alterations in mobility, talking and bodily discomfort, but also in the advanced stages of the disease (Figure 6).

**Discussion and Conclusion**

Neurobehavioral and/or emotional disturbances are common in idiopathic PD without dementia, and have been found to correlate with deterioration in QOL in people with this diagnosis.

- Depression is the most prevalent neurobehavioral disorder, worsens QOL and impacts neurocognitive functioning, ADL, and is a strong predictor of dementia in advanced PD.
- Anxiety is another disorder that is related to the worsening of QOL in patients with PD, directly affecting mobility, motor fluctuations, rest tremor and emotional well-being. It also correlates with the deficit that patients present in immediate verbal memory and processes of inhibition of executive functions.
- Apathy associated with advanced stages of PD is considered a predictor of dementia, altering the QOL of people with this diagnosis.

A proposal for the treatment of functional neurorehabilitation for neurobehavioral disorders in PD

1. It is necessary to carry out functional neurorehabilitation plans that aim to improve the QOL in each of the altered dimensions in the patient (emotional well-being, stigma, social support, communication, cognition).
2. The treatment of neurobehavioral disorders such as depression and anxiety will generate an improvement in patients' QOL, and greater performance response in

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**Figure 5. Axial section of the brain representing the following brain structures: 1. Gyrus cinguli, 2. Putamen (part of the base nuclei, related to apathy in advanced stages of PD).**

In relation to QOL, it has been found [16,60] that apathy is a predictor that is correlated with clinical manifestations of dementia in advanced stages of PD, directly altering mobility (walking, rest tremor and postural instability), communication, emotional well-being, neurocognitive functioning, and especially ADL.
different neurocognitive domains.  

3. Treatment of apathy in advanced stages of PD should focus on palliative care of the disease.  

It is necessary that this process of functional neurorehabilitation is implemented in initial phases of the disease, or patients of recent diagnosis, this is going to generate that the deterioration of the QOL can be slowed down, the deficit in different neurocognitive domains and alterations in the ADL, likewise, it is required that the treatment is of multidisciplinary character, this work team, must be confirmed by the  

1. Medical specialist in Neurology (necessary for the diagnosis and the process of evaluation and treatment of motor and non-motor symptoms)  
2. Clinical neuropsychologist (evaluation and treatment of the neurocognitive deficit),  
3. Occupational therapist (strengthening the work of the neuropsychologist),  
4. Physiotherapist (maintenance of physical activity in patients) and  
5. Immediate caretaker (his work goes in two ways: 1) Care the quality of life of the patient. 2) Preventing, above all that he or she does not suffer from Burnout syndrome), this team will aim to improve QOL, and to slow down the process to a clinical picture of dementia due to PD.  

Data Availability  
The statistical data of this review belongs to each of the works that can be consulted in the section of the bibliographic references.  

Ethical Approval  
The proposal for this work was presented to the ethics and research committee of the Faculty of Psychology of the Cooperative University of Colombia, where approval was obtained to carry out the research.  

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