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Review article

Changes in neural circuitry associated with depression at pre-clinical, pre-motor and early motor phases of Parkinson's disease

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ABSTRACT

Although Parkinson's Disease (PD) is mostly considered a motor disorder, it can present at early stages as a non-motor pathology. Among the non-motor clinical manifestations, depression shows a high prevalence and can be one of the first clinical signs to appear, even a decade before the onset of motor symptoms. Here, we review the evidence of early dysfunction in neural circuitry associated with depression in the context of PD, focusing on pre-clinical, pre-motor and early motor phases of the disease. In the pre-clinical phase, structural and functional changes in the substantia nigra, basal ganglia and limbic structures are already observed. Some of these changes are linked to motor compensation mechanisms while others correspond to pathological processes common to PD and depression and thus could underlie the appearance of depressive symptoms during the pre-motor phase. Studies of the early motor phase (less than five years post diagnosis) reveal an association between the extent of damage in different monoaminergic systems and the appearance of emotional disorders. We propose that the limbic loop of the basal ganglia and the lateral habenula play key roles in the early genesis of depression in PD. Alterations in the neural circuitry linked with emotional control might be sensitive markers of the ongoing neurodegenerative process and thus may serve to facilitate an early diagnosis of this disease. To take advantage of this, we need to improve the clinical criteria and develop biomarkers to identify depression, which could be used to determine individuals at risk to develop PD.

1. Introduction

Parkinson's Disease (PD) is a long-term illness that begins quietly with changes in different neuronal circuits. Because these changes are minor or compensatory mechanisms operate, they do not frequently express into clinical symptoms. Symptoms of PD begin as neuronal damage progresses. Non-motor symptoms (NMS) often appear before the onset of the classic motor symptoms, which define the clinical diagnosis of the disease. Thus, the course of PD follows three main phases: (1) pre-clinical, which lack symptoms but can express molecular or imaging markers; (2) pre-motor, characterised by NMS, which however are insufficient to diagnose the disease; and (3) motor, which presents the classical motor symptoms that allow the clinical diagnosis of PD [1].

Depression is one of the first NMS to appear [2] and also has a high prevalence in PD, affecting 31% of patients [3]. Also, subclinical depression, which can be considered a predictor of major depression (MD) [4], is common among PD patients (54.2%) during the early stages of the disease [5]. Different retrospective studies have shown a positive association between depression and the subsequent emergence of PD [6,7]. Depression is three times more common among subjects who develop PD compared to the general population [8]. Notably, a high percentage of individuals carrying mutations related to PD, which represents a risk group to develop the disease, suffer mood disturbances. For example, asymptomatic carriers of the glucocerebrosidase (GBA) mutation show higher depression scores compared to controls, based on the Beck Depression Inventory (BDI) [9]. Similarly, mutations in Parkin

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appear to predispose the occurrence of depression [10], and healthy carriers of the G2019S mutation in the LRRK2 gene develop depression together with other NMS during the prodromal stage [11]. Together, these findings have led to the proposal that depression is a risk factor of PD. However, it is unclear how the neuroanatomical changes and neurochemical imbalance associated with depression could favour the further development of the PD. A more plausible explanation is that, in a significant subgroup of patients, depression is one of the earliest clinical manifestations of the ongoing neurodegenerative process associated with PD.

Other mood disturbances such as anxiety and apathy are also frequent in PD and can occur alone or in combination with depression during the early stages of the disease. For instance, it has been reported that anxiety comorbid with depression at the pre-motor stage of PD [12]. Also, pre-morbid anxious personality and phobic anxiety associate with the later development of PD, suggesting that anxiety could be a risk factor for PD [13,14]. Finally, "pure apathy" has been observed in *de-novo* untreated PD patients [15] and cases of apathy combined with other mood disturbances are described many years before the diagnosis of PD [16].

In this article, we review the data of early neuronal dysfunction related to depression in the context of PD. We include studies where depression comorbid with anxiety and apathy but do not address the "pure apathy" and "pure anxiety" entities due to the reduced number of imaging studies available for these conditions at early stages of PD. In contrast to previous reports that discuss the origin of depression in patients with an established PD condition, here we focus on the pre-clinical, pre-motor and the early motor stages of the disease (period of 5 years or less post-PD diagnosis). In the latter, we also direct our analysis to patients showing minor to mild motor severity (Hoehn and Yahr Scale, H&Y, of 2.5 or less). In this context, we discuss both the clinical features and the changes in brain circuitry, at both structural and functional levels, associated with depressive symptoms.

2. When does depression appear in PD?

Depression can occur throughout the course of PD. The appearance at advanced stages of the disease is possibly a consequence of the widespread neuronal degeneration, a psychological reaction to the physical deterioration and dependence generated by this condition, or both. In contrast, the onset of depression before any clinical sign of PD is not a secondary condition but appears as an integral part of the neurodegenerative process that ultimately trigger the death of dopaminergic (DAergic) neurons.

Diverse studies have demonstrated an early onset of depression in PD. A retrospective cohort analysis of 32,415 individuals from the "Registration Network Family Practices" database (Netherlands) revealed that the first depressive episodes appeared 1–36 years before the diagnosis of PD with an average of 10 years. In this study, the frequency of depression was 9.2% among individuals who later developed PD while it was 4% in the general population [7]. Consistent with these findings, a separate study demonstrated a long-term association (over two decades) between depression and PD [17]. Similarly, a population-based approach involving 371 cases of PD and 402 controls (California) found that depression and anxiety were early symptoms in the prodromal phase but appeared more frequently within five years before the diagnosis of PD [18]. An additional study observed a similar temporality, where the subjects with depression showed this condition at least 4.5 years earlier the diagnosis of PD [19]. Finally, in a case-control study designed to evaluate the pre-diagnostic value of several clinical markers, it was found that depression/anxiety together with some motor and autonomic dysfunctions are present with a high incidence five years before the definitive diagnosis of PD [20]. Altogether, these results indicate that depression is an early manifestation of the ongoing neurodegenerative process and that it may be evident even a decade before the appearance of motor symptoms.

3. Clinical features of depression in PD

One main complication for the assessment of depression in the context of PD is the intrinsic complexity of this affective disorder. Depression is a heterogeneous disease both in etiology and clinical presentation. The diagnosis of depression and its classification in different subtypes rely on a set of subjective aspects involving the personal perception of mental, physical and mood state of the subjects. This problem becomes even harder to solve in patients with PD, where motor disorders mask the neurovegetative symptoms of depression such as fatigue, insomnia, and sleep disturbances. In this sense, the exclusion of the somatic component from the diagnostic scales has been proposed as a solution. Nevertheless, there is still no clear consensus [21], and this generates high variability in the clinical interpretation of depression among PD patients.

Some reports have addressed the clinical features of depression and found differences in the symptoms experienced by patients with PD compared to the rest of the population. A cross-sectional study from the Netherlands and Norway, involving depressed patients with PD and depressed patients without PD, showed that while the cognitive level of patients was similar in both groups, patients with PD had a different depressive profile. PD patients showed less endogenous symptoms such as feelings of guilt and sadness, but more somatic symptoms such as concentration problems [22]. In contrast, a different study found non-significant differences in the psychopathology of depression associated with PD [23]. A meta-analysis that searched for the most prevalent subtypes of depression in PD revealed that this condition associates with minor depression in 22% of cases, major depression (MD) in 17%, and dysthymia in 13% [24]. Additionally, an anxious component was also observed in depression associated with PD. Among 513 patients with PD, 22% had generalised anxiety disorder, 9% depression without significant anxiety, and 8.6% had depressive symptoms coexisting with anxiety and panic [25].

It is important to note that the information presented above derives from studies in patients with an established disease. In contrast, there is little clinical data of the initial phases of PD. Research has been limited to detect the presence or absence of this psychiatric disorder but not distinguishes between subtypes, degrees of severity, or specific clinical profiles. One of the few reports directly addressing this issue was a retrospective case-control study made by Shiba and co-workers, which involved subjects five years before the diagnosis of PD. In this study, they reported an odds ratio of 2.2 for anxiety disorders, 1.9 for depressive disorders and 2.4 for both types of disorders [12].

4. Pathological mechanisms of depression in PD

Since the anatomical and neurochemical changes of depression are highly variable among patients, a clear understanding of the pathophysiology of this disease in PD has been elusive. In spite of this, numerous studies have shown that alterations in neural networks that modulate emotional behaviours might play a role in the process. For example, dysfunctions in the cortico-striato-pallido-thalamic and amygdalo-striato-pallido-thalamic circuits have been associated with the appearance of MD and bipolar disorders [26,27]. In this regard, lesions of the striatum and orbitofrontal cortex, or degenerative processes of the basal ganglia (BG), both increase the risk for major depressive episodes [28]. Also, the

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