

## The behavior of migraine in patients with Parkinson's disease

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### Abstract

Parkinson's disease (PD) is characterized by the degeneration of dopaminergic systems in the central nervous system. In migraine it is supposed to occur hyperactivation of central dopaminergic pathways. We verified the hypothesis of improved migraine in patients who manifest PD. We evaluated 109 patients with PD over 40 years (57 men and 52 women) about the presence throughout the life of migraine, as well as the possibility of improvement in migraine after the onset of motor symptoms of PD. This group was compared to a control group of 152 people (41 men and 152 women) without PD regarding the presence of migraine and its improvement. Twenty-one patients manifested migraine in the group with PD (16 women and 5 men) in which 13 reported improvement in migraine after the onset of symptoms of PD. Among the controls, 37 interviewed had migraine history (32 women and 5 men) among which 20 showed improvement. There was no significant difference when comparing the two groups ( $\chi^2_{1;0,05}=0.337$ ;  $P<0.382$ ). We were unable to relate the improvement of migraine with the emergence of PD motor signs, despite the degeneration of dopaminergic pathways of the central nervous system.

### Introduction

The migraine is among the most frequent diseases at a neurology clinic. In Brazil it is estimated its prevalence of 15 to 20% of population.<sup>1</sup> It is characterized by recurrent

episodes of headache, in most cases, but not exclusively, of pulsatile characteristic, hemi or holocranial, associated with nausea, vomiting, photophobia and phonophobia, hindering the daily activities of an individual. The crisis lasts 4-72 hours if untreated or ineffectively medicated. The diagnosis of migraine is made on clinical basis using the criteria of the international classification of headaches.<sup>2</sup>

Parkinson's disease is the second most common degenerative disease of the central nervous system (CNS) second only to Alzheimer's disease.<sup>3</sup> It is clinically characterized by bradykinesia and at least one of the following three signs: the resting tremor, rigidity, and the later emergence, postural instability (inefficient maintenance mechanisms of posture and balance).<sup>4</sup> In its idiopathic form affects people usually over 55 years of age. In Brazil, it presents an estimated prevalence of 3.3% in the population over 64 years.<sup>5</sup> The diagnosis is made clinically. Usually, the London Parkinson Disease Society Brain Bank Criteria is used for such diagnosis.<sup>4</sup>

Dopamine (DA) is a neurotransmitter with activity in both the CNS and in PNS (peripheral nervous system). In the human brain dopamine acts as a neurotransmitter in areas related to behavior, memory, milk production, modulation response to painful stimuli and harmonization of movements.<sup>6</sup> The DA derives from the amino acid tyrosine and its synthesis begins with the conversion of phenylalanine into tyrosine by phenylalanine hydroxylase. Tyrosine is then transformed into L-DOPA by tyrosine hydroxylase (TH), which is the primary reaction that controls the velocity of formation of DA. The final reaction consists of the conversion of L-DOPA into dopamine by L-DOPA decarboxylase.<sup>7</sup> Five dopamine receptors are recognized in the CNS, divided into two groups whose numbers represent the order in which they were discovered: D<sub>1</sub>(D<sub>1</sub> e D<sub>5</sub>) e D<sub>2</sub> (D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>).<sup>8</sup>

PD is characterized by the degeneration of dopaminergic pathways in the CNS, especially the nigrostriatal pathway. The symptoms occur when there is degeneration of 60 to 70% of dopaminergic neurons of this pathway.<sup>9</sup> Thereafter, with the progression of disease, other symptoms such as mood disorders, behavior and even dementia clinical conditions, possibly relate to the degeneration of dopaminergic pathways in other segments of the CNS.<sup>10</sup>

Among the theories on the pathophysiology of migraine, it is suggested the occurrence of hyperactivation of central and peripheral dopaminergic pathways. This hyperactivation causes prodromal symptoms of crises, such as behavioral changes, appetite, yawning, drowsiness and symptoms of the crisis, such as nausea, vomiting or headache through the trigeminal activation. More rarely, the dopaminergic

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hyperactivation can cause episodes of hypotension or syncope.<sup>7</sup> The DA is involved in migraine mechanisms in many ways.

There is the trigger migraine attack in individuals with migraine headaches, when they use dopamine agonists such as apomorphine, piribedil and the bromocriptine at doses that do not affect healthy controls.<sup>11</sup> Confirming this hypothesis, it is observed the efficacy of DA antagonists in the control of migraine crisis.<sup>12</sup> In fact, the DA seems to be involved in migraine at different stages and in different ways: prodrome (changes in behavior and yawning);<sup>13</sup> activation and pain circuitry awareness (dopamine receptors in the trigeminal sensory nucleus).<sup>14</sup>

Receptor mutations or enzyme linked to the DA metabolism are associated with higher incidence of migraine. Among these we may mention mutations in D2 receptors and COMT (C-O-methyl transferase).<sup>15,16</sup>

Changes in the metabolism of DA, starting at tyrosine, diverting it from the hydroxylation pathway to the decarboxylation pathway can lead to increased production of false neurotransmitters such as octopamine, tyramine and synephrine and these can act through painful modulation during crisis in certain brain areas such as the amygdala and hypothalamus.<sup>17</sup>

In the brainstem the hyperactivity of DA receptors (D2, D3 and D4) in the dorsal nucleus of the vagus and bulbar postrema area are related to nausea and vomiting during crises.<sup>7</sup>

The syncope, sometimes caused by acute

migraine, seems to be due to the dopaminergic dysfunction of the midbrain substantia nigra and ventral tegmental area of the midbrain and its control over the brain microcirculation, causing vasodilation and cerebral hypoperfusion through D1 receptors during a crisis.<sup>18</sup>

In addition, in the peripheral nervous system, hyperexcitation of dopaminergic receptors occurs located in the pre-ganglionic sympathetic nerve endings. This leads to decreased release of noradrenaline (NA) leading to hypotension and it may also cause syncope during an episode of migraine.<sup>11</sup>

Thus, it is hypothesized that individuals with a previous history of migraine show improvement during the rise of PD.<sup>19,20</sup>

## Materials and Methods

### Study design

We conducted a cross-sectional study, in a two-year period (2011-2013) through a questionnaire with closed questions involving 109 patients over 40 years (57 men and 52 women with a mean age of 65 years) with a diagnosis of PD by CPSS, being seen in the unity of the movement disorders at Antônio Pedro University Hospital (HUAP) in Niterói, RJ, Brazil. In this research the frequency of migraine was evaluated over a lifetime, considering the criteria used for the second international classification of headache.<sup>2</sup> The intensity, the duration, the topography, the prodrome, presence and type of aura of crisis were studied. At the end of the interview all participants who had migraine history were asked whether there was an improvement of migraine attacks with senescence and/or after the onset of motor symptoms of Parkinson's disease.

A single author was responsible for the administration of the questionnaire for all subjects. They excluded patients with a history of dementia, the use of prophylactic medication for migraine up to one year before the survey and patients of the headache clinic at HUAP. The study was conducted between August 2011 and August 2013. The study was approved by the Antônio Pedro University Hospital Ethics Committee/UFF (CEP CMM/HUAP No. 056/11)

### Statistical analysis

Statistical analysis was performed using chi-square test, by associating verification of objective and subjective parameters extracted from the interview responses as gender, age, clinical diagnosis of PD, headache and migraine. All calculations and statistics were performed using the SPSS 20.0 software. The significance level in the realization of the associations was  $\alpha=0.05$ .

## Results

Among the 109 patients with PD (mean age 65 years with a minimum of 41 and maximum of 82 years), 35 had recurrent headache history in any period of life and among these, 21 (19%) had a history of migraine. Among the 152 controls (mean age of 61 years with a minimum of 40 and maximum of 87 years), 58 had a history of headache, of which 37 (24%) had history of migraine. When comparing the two groups, the differences in the past existence of migraine were not statistically significant ( $P<0.206$ ) (Table 1).

When comparing patients with migraine in the groups, we observed that among the 21 patients with migraine in the PD group, 13 of these (62%) reported improvement of PD after the onset of motor symptoms of PD (7 women and 4 men), while 8 (38 %) showed no

improvement (six women and one man). Among the controls, 37 patients manifested migraine (32 women and 5 men) among which 20 subjects (54%) noticed improved migraine attacks with senescence (19 women and one man), with no improvement in 17 subjects (46%) (13 women and 4 men). These data did not attribute significant difference in improvement of migraine among patients in the parkinsonian group compared to controls ( $P<0.382$ ) (Table 2).

We also performed the analysis of cases of migraine improvement of all subjects in both groups (58) when divided by age extremes. We consider three groups, as follows.

Group 1: ages ranging from 40-50 years.

Group 2: ages ranging from 50-60 years.

Group 3: age over 70 years.

When compared, in group 1 there were 10

**Table 1. Comparison between the cases of migraine groups.**

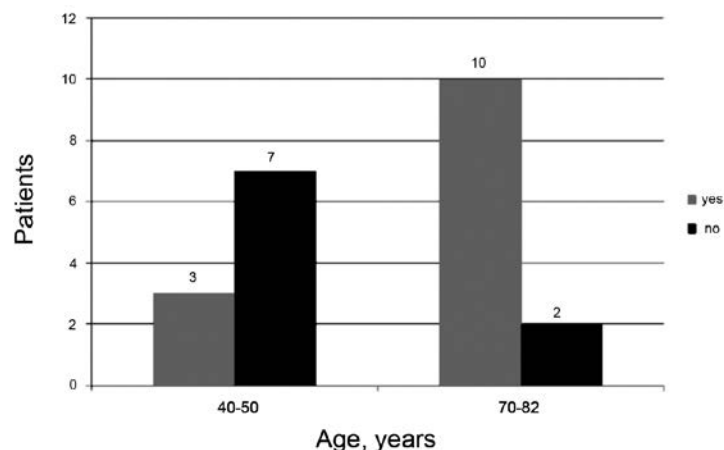
	CG group	PG group	Total
Migraine			
Yes	37 (24%)	21 (19%)	58
No	115 (76%)	88 (81%)	203
Total	152	109	261

CG, control group; PG, group with Parkinson Disease.

**Table 2. Comparative of migraine improvement between groups.**

	CG group	PG group	Total
Improvement in migraine			
Yes	20 (54%)	13 (62%)	33
No	17 (46%)	8 (38%)	25
Total	37	21	58

CG, control group; PG, group with Parkinson Disease.



**Figure 1. Improvement of migraine: comparison between age groups.**

cases of migraine in which 7 patients improved and 3 patients showed no improvement regardless of belonging to the control group or PD. In group 3 there were 12 patients with migraine of which 10 showed improvement. This difference gave significant improvement of migraine in older subjects (Group 3) when compared to the younger group (Group 1) ( $P < 0.017$ ) (Figure 1).

## Discussion

Our work has the advantage of being the first to address the correlation between PD and migraine using the second international classification of headache 2004.<sup>2</sup> The difference between our results and those obtained previously, is that, the lack of improvement of migraine in patients with PD can relate to the difference of migraine diagnostic criteria or the different methods in the selection or exclusion of samples. Although a difference between groups of statistical value does not occur, we question whether the difference of 8% (54% versus 46%) obtained, presents clinical importance. We expected, for example, a higher prevalence of other types of headaches than the PD in the parkinsonians, for these encompass the tension-type headache, the most prevalent in the population.<sup>21</sup> However, we believe that the type of sample, obtained at a tertiary hospital, where migraine is the most prevalent primary headache, has been partly responsible for these results. The fact that the tension-type headache characterized by pain from weak to moderate intensity, which does not disturb the activities of daily living, would lead to recall bias, decreasing its prevalence in our study.<sup>22</sup>

About the limitations of the work performed, we admit that the question of improvement of migraine in groups during the questionnaire application has a high degree of subjectivity and is subject to recall bias. However, we found no validated tools that could provide more reliable data to the research objective of evaluating the behavior of migraine in patients with PD. We believe that the study has minimized most of the factors responsible for recall bias, since it used a questionnaire based on the classification of headache and evaluated a disease as a chronic course and with crises often disabling as migraine, reducing the factors like time and exposure and significance of events such as factors to recall bias.<sup>23</sup>

Although in our sample there were individuals with PD dementia, we do not use tools that would allow exclusion of patients with dysfunction of a single cognitive domain. Thus, we cannot rule out the involvement of other different cognitive mnemonic functions, such as attention deficit, which could interfere in the questionnaire responses.<sup>24,25</sup>

The results of our study indicate that senescence, rather than the presence or absence of PD is related to the improvement of migraine. This may be related to decreased dopamine sensitivity with aging. This fact does not occur with serotonergic system.<sup>20</sup> However we must emphasize that due to the sample size we did not realize the impact assessment of senescence in migraine in each group separately. This fact makes it impossible to rule out the senescence by presenting different impacts in controls and in patients with PD.

Finally, as almost all the studies involving patients with PD, this took into consideration only patients after the onset of motor symptoms of the disease characterizing stage III of pathological studies of Braak.<sup>26</sup> However, early in the early stages I and II, there are changes in dopaminergic pathways, as the nucleus of the solitary tract and motor of the vagus. We theorize the possibility of the occurrence of changes in the behavior of migraine in previous stages to the emergence of motor symptoms. For example, the  $\alpha$ -synuclein accumulation in these topographies would cause changes in vegetative symptoms of migraine crisis as nausea and vomiting.<sup>26,2</sup> The osmophobia that triggers or accompanies migraine crisis could be modified by olfactory alterations that occurs in patients with PD long before the onset of motor symptoms when synucleinopathy has already affected these pathways.<sup>28,29</sup> The same would happen with photophobia as a symptom of migraine, that occurs degeneration in retino-thalamic dopaminergic pathways. This fact would decrease the action of light stimuli as an activator of thalamic pathways linked to trigeminovascular activation during a crisis and allodynia of migraine.<sup>30</sup>

## Conclusions

Our work has not confirmed that Parkinson's disease is an attenuator factor of migraine attacks. The improvement of migraine in patients with PD may be related to senescence, regardless of the presence of PD. Further work involving the relationship between migraine and DP is necessary taking into consideration the already established dopaminergic alterations in both diseases.

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