Regional cerebral blood flow changes in Parkinson's disease: correlation with disease duration

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ABSTRACT

Introduction: Changes in regional cerebral blood flow (rCBF) have been reported in idiopathic Parkinson's disease (PD). Nonetheless, their typical pattern still remains controversial regarding some features, such as basal ganglia involvement and the main cortical regions affected. Functional neuroimaging makes it possible to identify the brain dysfunctions of the neural circuits underlying the disease. Voxel-based analysis methods make it possible to increase the reliability of the results.

Objective: To assess the rCBF changes in patients with PD and their relation with disease duration.

Materials and methods: Thirty PD adult patients without dementia underwent evaluation with $^{99m}$Tc-ECD SPECT. SPM5 was used for statistical comparison with 25 normal controls of similar ages. The disease course duration in years was added as a covariate. Additionally, patients with a 6-year evolution or less and those with more than 6 years were compared separately with normal controls.

Results: Significant hypoperfusion was detected in bilateral premotor and posterior parietal cortex and an increase of perfusion was present in the cerebellum. These changes correlated with the years of evolution of the illness. Patients with longer evolution also presented thalamic, subthalamic and basal ganglia hypoperfusion.

Conclusions: We describe rCBF changes in PD in neural circuits related with control of movements. These changes are more manifest in patients with a longer duration of the disease.

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Introduction

Idiopathic Parkinson’s Disease (PD) is the most frequent neurodegenerative disease following Alzheimer’s disease. It is characterized by extrapyramidal movement disorder (tremor at rest, stiffness, bradykinesia and loss of postural reflexes) with involvement of the cognitive and emotional spheres. Our works have evaluated the regional cerebral blood flow (rCBF) in PD. However, some features continue to be debated. Given that PD is the result of the degeneration of the dopaminergic neurons in the substantia nigra, which indicates a functional alteration of the nigrostriatal system, it could be expected that a decrease would be found in both basal ganglia metabolism and perfusion. However, both reduction and an increase of the basal ganglia activity and absence of changes have been reported with the normal controls. A frequent finding since the first works has been the relatively diffuse decrease of perfusion and metabolism in the cerebral cortex, which would be more accentuated in patients with more advanced stage of Hoehn and Yahr (H&Y). However, there are fewer communications in the literature in regards to the specific cerebral areas that would show the clearest flow disorders. In a very relevant study in this regards, Van Laere et al. studied a group of 81 patients diagnosed of PD, 15 patients with multisystemic atrophy and 44 normal volunteers using SPECT with 99mTc-ECD and SPM (Statistical Parametric Mapping). The patients with PD showed cortical and subcortical symmetric hypoperfusion including the basal ganglia, thalamus, prefrontal cortex and parietal-occipital cortex. Other brain structures would have a tendency for increased blood flow. Standing out among these is the cerebellar dentate nucleus whose hyperactivity has been attributed to a compensatory mechanism due to movement disorders, through this efferent cerebellar projection towards the ventral-lateral thalamus. Current evidence is more categorical in regards to the presence of regional cerebral blood flow (rCBF) disorders related with cognitive deterioration in PD. A significant decrease of the frontal perfusion, possibly linked to disruption or deafferentation of the frontal-striatal circuit, has been detected with the SPECT. A significant reduction of the bilateral posterior temporal-parietal flow has been described in patients with dementia compared to the patients with no cognitive deterioration. This cerebral hypoperfusion pattern is similar to that observed in Alzheimer’s disease and reflects the presence of neuropathological elements common to PD. However, hypoflow or hypometabolism of the posterior cortex has been found in patients having PD without dementia, even when other functional techniques such as the magnetic resonance spectroscopy with P31 are used. This suggests that both the glycolytic and oxidative pathways are involved, raising the question that it could correspond to a primary cortical disease or to deafferentation of the striate-cortical projections. In summary, changes have been communicated in the cortical and subcortical rCBF in PD. Most of the studies coincide on the existence of prefrontal and parietal hypoperfusion, especially in patients having advanced stages of the disease or carriers of significant cognitive disorders. Although basal ganglia dysfunction is a dominant element in the pathophysiology of PD, there are still controversies regarding the presence of changes of the rCBF in these structures, their characteristics and their possible causes. The relationship between the rCBF alterations and the course of the PD has mainly been studied in regards to the presence of cognitive disorders. However, there are few studies in regards to symptom severity and years of evolution of the disease in patients without dementia. These facts reflect the need for new research aimed at going deeper into the understanding of the pathological characteristics of PD.

This study has aimed to evaluate the statistical changes of rCBF in patients with idiopathic PD without dementia using the brain SPECT with 99mTc-ECD and SPMs and to analyze if there are perfusion alterations that are related with the years of disease course.

Material and methods

Patients

In a prospective clinical trial, 30 patients who were carriers of PD without dementia (14 women and 16 men; ages 30-79 years, mean: 57.6 ± 12.1 years) were studied. All were under stable treatment with levodopa analogues. The disease duration ranged from 1 to 26 years (mean: 7.23 ± 5.17 years). One patient presented juvenile PD, 6 early onset PD and 23 late onset (LOP) PD. The presence of dementia was ruled out by means of a neurological clinical examination, using the DSM IVTR criteria. No systematic neuropsychological study was conducted. Presence of cerebrovascular disease, epilepsy, psychiatric disease or other possible causes of rCBF disorders were exclusion criteria. The computed axial tomography (CT scan) showed a normal brain in all of the patients. Symptom intensity was evaluated using the H&Y scale. Twenty-one patients had stage III, and 7 stage II. Only one patient presented stage IV and one stage V.

Normal controls

The patients were compared with a control group of 25 healthy individuals (13 women and 12 men; 32-84 years, mean: 52.2 ± 15 years).

The participants received documentation on the institutional informed consent and freely agreed to it in writing with the guarantee of the Ethics Committee of the “Hospital de Clinicas” of the Medical School.

Brain perfusion SPECT

The patients were studied using a SOPHA DSX rectangular gamma camera equipped with 1994 XT software, with low energy high resolution parallel hole collimator. The images were taken using a 360° circular orbit, with a rotation radius of 11 to 15 cm, in 64 projections of 35 seconds, using the step and shoot modality in a 128 x 128 matrix with zoom 1, one hour after the intravenous administration of 99mTcECD at doses of 25 to 30 mCi (925 to 1.110 MBq) per 70 kg of body weight. The system resolution under these conditions was 10 mm and pixel size 4.46 mm.

For reconstruction, the InterView XP (Mediso, Hungry) v.7.1 of the year 2006 was used. Iterative system OSEM (Ordered Subsets Expectation Maximization) was used, selecting 2 subsets and 5 cycles.

Prefiltering was done with the 10th order Butterworth filter with cutoff frequency of 0.30. Attenuation was corrected, adjusting the ellipse at the height of the brain vault in each cross-sectional cut, using an attenuation coefficient of 0.12 cm⁻¹. Cross-sectional cuts parallel to the anterior commissure - posterior commissure line were obtained and the vertical and horizontal axes of the brain were realigned.

A software zoom of 2.2 was applied and the final pixel size was 2.03 mm, the closest possible to that selected in the statistical analysis (2 mm).

The reconstructed images were exported in DICOM format and then converted to the Analyze 7.5 format using MRicro software (Chris Rorden; www.mrc-cbu.cam.ac.uk/ ~chris.rorden/micro. htm).
Statistical analysis of the images

The Statistical Parametric Mapping version 2005 software was used (SPM5. Friston et al. Wellcome Department of Cognitive Neuroscience. London. UK. http://www.fil.ion.ucl.ac.uk/spm). 19,20

Before making the voxel statistical comparisons, the images were spatially normalized to the pattern image of the single photon emission computed tomography (SPECT) in the stereotaxic coordinates of Talairach and Tournoux, and then smoothed by applying a Gaussian filter with a 16 mm FWHM, to minimize false positives from the statistical noise and spatial normalization errors.

In the statistical analysis, the Student’s T test for independent samples was used to compare the patient groups with the normal controls.

Furthermore, the presence of changes in the rCBF related with years of disease course was investigated, dividing the patient sample into two groups of 15 based on the 50 percentile (6 years of duration).

Uncorrected p values less than 0.01 for voxel level and 0.05 on the cluster level were considered significant. In selected cases, clusters over 100 voxels (volume similar to the system resolution), close to the statistical significant, were also reported when they were recorded in brain areas relevant for the study disease.

The SigmaStat Version 3.00 (SPSS Inc.) program was used for the conventional statistical analysis of the clinical variables.

Results

Analysis of confounding factors

The possible influence of age, a known determining factor of changes in rCBF, in each one of the comparisons of groups, was evaluated. Patients with PD did not differ in age regarding the normal controls (p = 0.146, Student’s t test). The patients with an evolution equal to or less than 6 years did not vary in age regarding those over 6 years (p = 0.633, Mann Whitney Rank Sum Test).

There was a significant correlation between years of disease evolution and H&Y stage (Pearson’s correlation coefficient = 0.756, p < 0.001). Subgroups with more than 6 years of PD evolution and with 6 years or less showed no statistical variation in the H&Y stage (stage II versus stage III or greater, p = 0.390, Fisher’s exact test).
Comparison of Parkinson’s disease with normal controls

Patients with PD showed significant hypoperfusion in the premotor cortex and bilateral parietal cortex of right predominance (p < 0.004, corrected). Furthermore, hypoperfusion was detected in both thalami, subthalamic region and mesencephalus, when clusters greater than 100 voxels (p = 0.098) were considered.

The areas with greater perfusion in the PD group were found in the cerebellum (p < 0.009, corrected). When clusters larger than 100 voxels were considered, areas of hyperflow in the left insula, left posterior mesial parietal cortex and right anterior cingulate were detected.

These results are shown in figure 1.

Influence of the years of evolution in Parkinson’s disease

In a second analysis, the PD group with normal controls was compared, introducing the years of evolution of the PD (fig. 2) as continuous covariable. Areas of hypoperfusion related with said variable were detected in the left posterior temporal parietal cortex (p < 0.01) and an extensive cluster in the right posterior parietal zone that did not achieve statistical significance (p = 0.18). Furthermore, a significant cluster that involved the left thalamus, mesencephalus and bilateral subthalamic region with extension to the left basal ganglia was detected (p = 0.016).

There was a correlation with areas of hyperperfusion in the cerebellum (p = 0.003; p < 0.029, corrected).

The group with PD less than or equal to 6 years of evolution presented bilateral parietal hypoperfusion with significance in the right side clusters (p = 0.031) (fig. 3). There were no clusters with statistically significant increases of perfusion. The greatest tendency was observed in the right cerebellum (p = 0.080).

The PD group of more than 6 years of evolution showed significant hypoperfusion in right posterior temporal parietal and premotor cortex (p < 0.01, corrected) and left posterior parietal cortex (p = 0.032). Clusters with tendency to significance in the left premotor cortex (p = 0.06), thalamus, and basal ganglia (p = 0.072 and 0.082) were detected. The areas with greater perfusion of this group, in relationship with the control group, were located in the cerebellum (p = 0.005, corrected) and the left insula (p = 0.094). These findings are shown in figure 3.

Figure 2. Statistical changes of brain perfusion related with years of evolution of the symptoms in patients with Parkinson’s disease (p < 0.01). Correlations in areas similar to those observed in the previous comparison are seen and the additional presence of significant hypoperfusion in the clusters (p = 0.05) in the left thalamus, bilateral subthalamic region and left basal ganglia is detected.
Discussion

Our results indicate that the patients with PD without dementia present significant areas of neocortical hypoperfusion in premotor and parietal association regions. These alterations coincide with those reported by Imon, Van Laere and Eckert. The functional involvement of the premotor cortex would be related with the motor disorders characteristic of PD and involvement of the striate-cortical circuit. The alterations of the parietal perfusion could be due to deafferentation of the reciprocal connections existing between the motor and parietal association cortex. This demonstrates that the decrease of dopaminergic transmission not only determines alterations in the motor circuits but also involves other association areas. Some authors have manifested that the involvement of these areas is associated to a higher degree of cognitive deterioration.
The analysis demonstrated decreased perfusion in both thalami when the cluster volume was extended to 100 voxels. Even though it did not reach significant values in the clusters, it could be considered as a relevant finding given the strategic situation of the thalami in the subcortical-cortical circuits that involve the premotor areas and basal ganglia, even receiving direct connections from the substantia nigra and then closing the circuit by efferents to the cerebral cortex. This fact has also been described by other authors.12

The subthalamic and mesencephalic region also demonstrated a flow decrease, consistent with the PD pathophysiology.

The data are discordant in regards to the existence of basal ganglia perfusion alterations in PD.2-6 There are authors who have described hypoperfusion and others who have detected flow increases or absence of changes. Their hemodynamic or metabolic situation is difficult to predict. Even though the involvement of the presynaptic neurotransmission in the striate body is well known, the post-synaptic neuron tends to overexpress receptors to compensate for the lack of dopamine in the synapse in PD. In our global analysis, no significant changes were observed of the basal ganglia flow, not even in clusters of 100 voxels. It could be emphasized that these results disagree with those obtained by other authors.7-11 However, significant clusters of basal ganglia perfusion related with years of disease evolution were detected. In the first stages of the PD, the overexpression of post-synaptic dopaminergic receptors as a compensatory mechanism for the lack of dopamine in the synapse could maintain a relatively conserved flow and metabolism in the striate. The appearance of basal ganglia hypoperfusion in patients with longer evolution of the disease agrees with the decline in post-synaptic activity that appears in the more advanced stages of it.

Participation of the cerebellum in the control of voluntary movement is already known, principally, the neocerebellum, that includes the dentate nucleus and receives afferent projections from the ventrolateral and anterior thalamic nuclei, from where the latter is projected to the cortical areas. Our analysis demonstrated the presence of significant increases of cerebellar perfusion that was described by other authors.11,12 This would be explained by a greater activation of these circuits, that determines a more important participation of the cerebellum in the control of movements, as a compensatory mechanism in response to the nigrostriatal dysfunction.

Furthermore, we have found hyperactive areas in the left insula, left mesial parietal cortex and left posterior and in the right anterior cingulate, close to the significance of the clusters. Imon et al13 also discovered hyperperfusion in the paralimbic structures. It should be stated that these structures have important reciprocal connections with the dopaminergic system.

Regarding the relationship between the perfusion disorders and years of disease evolution, we have found greater hypoperfusion in the thalami than in the initial analysis and decrease of the basal ganglia flow, that are significant in the clusters, and a cortical hypoperfusion that was limited to the bilateral posterior parietal ganglia flow, that are significant in the clusters, and a cortical hypoperfusion that was limited to the bilateral posterior parietal and left posterior temporoparietal one, with significant clusters to the left. The areas of significant hyperflow related with years of evolution were similar to those described in the initial analysis and were mainly registered in the cerebellum, with greater intensity to the right. When the groups of patients with PD with less and more than 6 years of evolution were analyzed separately, it was found that the patients with longer evolution presented more extensive and significant areas of decrease and increase of rCBF, with a similar distribution to that observed in the initial analysis.

Having ruled out age of the patients as a confounding variable that could affect the results, we could conclude that there is a relationship between the perfusion disorders existing in PD and their progression both in the cerebral cortex and on the basal ganglia and thalamic level and in the intensity of the changes in the cerebellum. Usually, patients with a longer duration of the disease tend to have more severe symptoms. Duration of the disease in years and the H&Y stage of our patients presented a positive correlation. However, 70% of the patients of our series stage III and within them, there was a wide range of variations in age (2-14 years) that partially superimposed with the stage II patients (1-8 years). On the other hand, the groups with more than 6 years and 6 or less years of evolution of the PD did not have a statistically significant difference in the clinical stage (p = 0.390), even though the rCBF alterations were noticeably greater in the longer PD group. Several authors have observed a progressive involvement of the presynaptic dopaminergic transmission with the years of PD evolution.23-25 It is reasonable to think that this phenomenon would be accompanied by progressive changes in the function of the cerebral circuits that participate in the control of movement.

The greatest limitation of our study is related with the spatial resolution of our SPECT camera, that is not an equipment especially designed for brain studies. On the other hand, although the number of patients of our sample is not small, more would have been necessary to be able to apply the correction by multiple comparisons in a non-paired statistical analysis in SPM with our SPECT images without losing potentially valid results. However, the findings partially agree with previous studies and are described in regions of known participation in the pathophysiology of the PD. On the other hand, several of the clusters described had significant corrected p values (posterior parietal and premotor hyperperfusion, cerebellar hyperperfusion).

Conclusions

The significant hyperperfusion in the bilateral parietal and premotor cortex in patients with PD shows the cortical involvement of the motor circuit and related association areas and the significant hyperflow in the cerebellum as a compensatory mechanism in the response to nigrostriatal dysfunction.

These alterations of the rCBF had a direct relationship with years of evolution of the disease. In the patients with longer evolution, significant basal ganglia and thalamic was also registered, this suggesting that these changes appear in later stages of the disease.

References