ICTAL SPECT IN THE PARKINSON PREMOTOR PHASE OF STUDY

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1. Project summary

Parkinson disease (PD) has a premotor period of several years, during which neuropathological changes and non-motor symptoms (REM sleep behaviour disorder (RBD), hyposmia, constipation and depression) occur before parkinsonism becomes manifest. RBD is a parasomnia characterized by dream-enacting behaviours (e.g. punching, jumping, falling out of bed) confined to REM sleep that often result in injuries to the patient and bedmate (e.g. haematomas, lacerations, fractures). Polysomnography studies in RBD detect increased electromyographic (EMG) activity associated with abnormally vigorous behaviours in REM sleep. Idiopathic RBD (IRBD) is the most specific clinical feature of the premotor stage of PD since most of the patients are eventually diagnosed clinically with PD and other synucleinopathies like dementia with Lewy bodies (DLB). A recent study in IRBD showed that 33% of the patients converted to a synucleinopathy after 5 years, 74% after 10 years, and 92% after 14 years. Thus, IRBD represents the premotor stage of PD. The study of IRBD provides an opportunity to study early disease events and disease progression in premotor PD, and allows to test novel interventions that could slow or prevent the neurodegenerative process. Also, identification of the abnormal neuronal network and mechanisms involved during REM sleep in subjects with IRBD would provide a unique valuable information of the pathological process mechanisms that is implicated during the premotor stage of PD. This information has not been previously evaluated since patients have always been studied during wakefulness.

Brain perfusion single photon emission computed tomography (SPECT) is a functional neuroimaging technique that allows noninvasive study of physiologic and physiopathological events in the human brain. Brain SPECT with hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) is an exploration that allows us to know the distribution of cerebral blood flow at the moment of tracer injection as ^{99m}Tc-HMPAO is a lipophilic substance that quickly crosses the blood-brain barrier and fixes in brain tissue. Cerebral uptake of this radiotracer is in direct proportion to the quantity of cerebral blood flow and detects brain areas of reduced and increased activity related to the pathologic process. ^{99m}Tc-HMPAO SPECT is widely used in the presurgical detection of the epileptic focus in patients with epilepsy, since abnormal hyperactivity during epileptic discharges and seizures is identified as the key area of the epileptic process.

OBJECTIVE: To assess whether, in subjects with IRBD, ictal 99mTc-HMPAO-SPECT performed during RBD episodes while the subject is in REM sleep identifies brain areas of reduced (hypoperfusion) or increased (hyperperfusion) activity in comparison to healthy controls without RBD.

HYPOTHESIS: In subjects with IRBD, ictal 99mTc-HMPAO-SPECT performed during RBD episodes, while the subject is asleep, identifies brain areas of reduced (hypoperfusion) or increased (hyperperfusion) tracer uptake in comparison to healthy controls without RBD during REM sleep. This novel approach will contribute to expand our knowledge of the pathophysiological process in RBD and in the premotor period of PD, when brain networks and brain areas during REM sleep will be identified. These new results may also help to design new therapeutical strategies to slow or stop the neuropathological process and to reduce the risk of injuries during RBD episodes.

2. Results

The final sample consists of 15 patients with IRBD and 12 controls. To reach this number we studied 35 subjects, but five patients with IRBD and 3 controls were excluded from the study due to significant cerebral atrophy in the magnetic resonance image that could have prevented a correct interpretation of the results of SPECT.

There were no differences between the two groups in terms of gender distribution (73.3% men vs 83.3%, p = 0.535) or age at the time of the examination (69.2 ± 6.6 vs. 68.4 ± 5.7, p=0.749). The average follow-up time between the IRBD diagnosis and SPECT is 2.6 ± 2.7 years, and the mean time from the beginning of the symptoms to SPECT is 17.1 ± 7.1 years.

Cognitive function in the 2 groups was assessed with the MoCA screening test and showed no significant differences. Patients with IRBD obtained a MoCA score of 26.4 ± 1.4 and the control group of 26.5 ± 1.5 (p=0.820).

The score on the UPDRS-III motor scale was 2.2 ± 2.5 in the IRBD group and 0.5 ± 0.8 in the control group (p = 0.041 *). Parkinsonism was not detected in any of the subjects.

In the analysis of SPECT images, several brain areas showed statistically significant regional differences in cerebral perfusion ($p<0.001$ at the voxel level and <0.05 at the cluster level) between the two groups are summarized in table 1.

Table 1. Hypoperfusion zones in patients with IRBD compared to controls.

Cluster size (k)	**Location**	**Hemisphere**	**Brodman Area**	**P value (cluster)**
1257	Upper frontal	Right	9, 10, 32, 46, 48	<0.001 FWE
	Frontal cingulum	Right		
	Upper frontal	Left		
	Frontal cingulum	Left		

Figure 1 shows some of the brain image results:

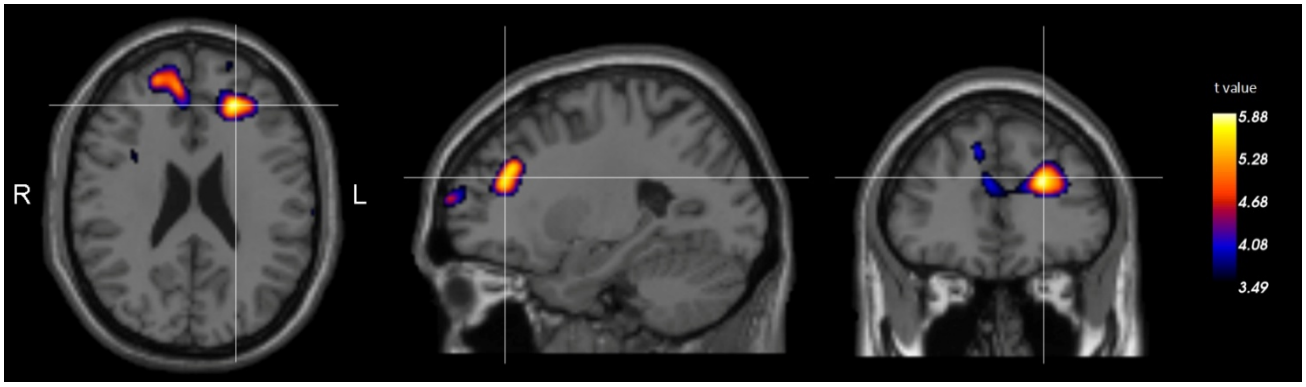

Figure 1. Hypoperfusion zones in patients with IRBD compared to controls.

When compared to the controls, the SPECTs of patients with IRBD show hypoperfusion areas in the upper frontal area and the frontal cingulum in both the left and right hemispheres (BA 9, 10, 32, 46, 48; $p < 0.001$ FWE).

If the comparison is made between each patient with IRBD and the whole group of control subjects ($p<0.001$ at voxel level and <0.05 at cluster level), the regional differences in cerebral perfusion observed in each individual are summarized in table 2.

Table 2. Zones of hyperperfusion and hypoperfusion in the individual comparison of each patient with IRBD and the control group

Subject	Capture	Cluster size (k)	Location	Hemisphere	Brodman Area	p value (cluster)
P01	Hyperperfusion	506	Putamen	Left	48	<0.001
			Pallidus	Left		
P02	Hypoperfusion	151	Upper frontal	Right	9, 10, 32	0.052
P03	Hypoperfusion	267	Middle frontal	Left	9, 45, 46, 48	0.012
	Hypoperfusion	201	Insula	Left	48	0.019
			Putamen	Left		
P04	Hypoperfusion	290	Frontal cingulum	Left	32	0.01
			Frontal cingulum	Right		
P09	Hypoperfusion	306	Putamen	Left	48	0.007
			Pallidus	Left		
	Hypoperfusion	265	Middle frontal	Left	46	0.011
P11	Hypoperfusion	862	Upper frontal	Left	9, 10, 32	<0.001
			Frontal cingulum	Left		
			Frontal cingulum	Right		
P12	Hypoperfusion	193	Angular	Right	7, 40	0.031

Compared to the set of controls, only patient P01 has a hyperperfusion zone located in the left putamen and pallidus (BA 48; p <0.001). P02 shows a hypoperfusion area in the right upper frontal (BA 9, 10, 32; p=0.052). P03 has two areas of hypoperfusion, the first one located in the left middle frontal (BA 9, 45, 46, 48; p=0.012) and the second one is located in the left insula and putamen (BA 48; p=0.019). P04 has an area of hypoperfusion in the frontal cingulum of both hemispheres (BA 32; p=0.01). P09 shows two areas of hypoperfusion, one located in the left putamen and pallidus (BA 48; p=0.007) and a second one located in the left middle frontal (BA 46; p=0.011). P11 presents a hypoperfusion zone between the left upper frontal and the left and right frontal cingulum (BA 9, 10, 32; p<0.001). P12 presents a zone of hypoperfusion in the right angle (BA 7,40; p= 0,031). Finally, the comparison of

patients P05, P06, P07, P08, P10, P13 and P14 with the control group did not show regions with statistically significant differences.

3. Relevance and possible future implications

Our findings imply that the cortex is involved in the physiopathology of the IRBD. Both hemispheres participate equally and the areas involved are the upper frontal and frontal cingulum, where there is a hypofunction. Our findings are new and help to better understand the physiopathological process of the IRBD and the premotor period of the PD, identifying the brain networks and areas of the brain during the REM phase of sleep.

These new results can help develop drugs with target in the frontal lobes to try to avoid RBD symptomatology and stop the neurodegenerative process, preventing the onset of symptoms of Parkinson's disease.

4. Generated literature

We are currently in the process of preparing the manuscript explaining the results obtained for publication in a scientific journal.