HVM BIOFLUX
Human & Veterinary Medicine
International Journal of the Bioflux Society

The relation between cognitive impairment and clinical presentation in early stages of Parkinson's disease

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Abstract. Objective: we studied patients in early stage of Parkinson's disease (PD), after the onset of first motor signs of disease. We evaluated if any cognitive function were affected and if there was a link between such impairment and clinical and imagistic data. Material and Methods: 30 patients previously diagnosed with PD stage I and II were evaluated with COGTEST software. Conclusion: the research concluded that, even if cognitive impairment was detected in patients with tremor, significant deficits of attention, executive function and working memory were found in subjects with excessive rigidity.
Key Words: Parkinson's disease, motor symptoms, COGTEST, cognitive impairment.

Introduction. Parkinson's disease (PD) is a frequent degenerative disease, surpassed in numbers only by Alzheimer's disease. Studies from last decade showed an increasing importance, for PD management, of motor signs and symptoms, especially cognitive deficits. This matter becomes important through the fact that it affects in a major way patients function and quality of life.

The real onset of PD was demonstrated, with the aid of positron emission tomography, to precede the motor impairment by 4 or 5 years. Until the moment of motor symptomatology, about 60% of dopaminergic neurons are already lost and the quantity of dopamine in striatum is reduced by 80%. This time span is known as "prodromal period", in which non-motor symptoms can exist.

Having this fact in mind we studied the prevalence of cognitive impairments that are present in early stages of PD. We tried to define which are the most affected cognitive areas, as well as the relation between clinical presentation (tremor, rigidity, hypo- bradykinesia, postural disturbance) and cognitive impairment.

Material and Method. We studied 30 (17 women, 13 men) patients previously diagnosed with PD stage I and II, after Hoehn & Yahr (1967). All subjects were Caucasians and had a mean age of 64.1 years. Age distribution can be seen in figure 1.

Previous to the inclusion in study the subjects signed an informed consent form, in accordance with the protocol of "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca.

Clinical parameters were noted for every patient. Every subject underwent cerebral magnetic resonance imaging (MRI) or, when MRI was contraindicated, computed tomography (CT). COGTEST was applied to every subject. Description of COGTEST, inclusion and exclusion criteria were described in a previous paper (Căpuşan el at 2011).

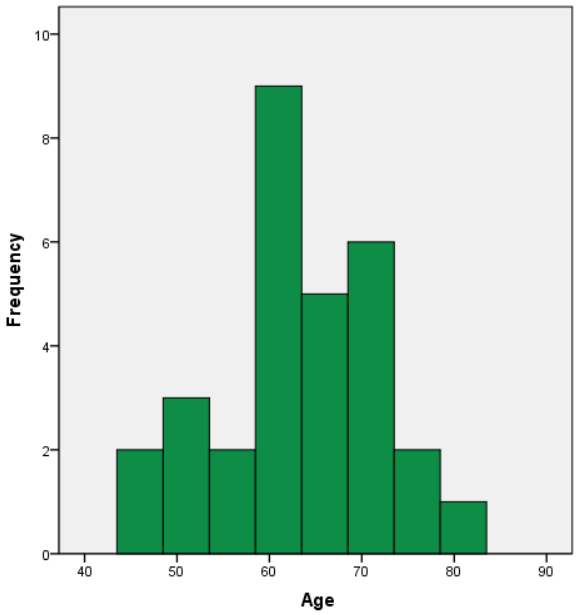

Figure 1. Age distribution for patients with early stages of PD

All obtained data were processed using Statistical Pack for Social Sciences v.15.0 software. Normality was assessed using Kolmogorov-Smirnov test and equality of variances was assessed using Levene test. T test for independent variables and Mann-Whitney test were used when appropriate. Also Spearman's correlations were used. A p value <0.05 was considered to be statistically significant.

Results. We included 13 (43.3%) men and 17 (56.7%) women. Clinical data is presented in table 1.

Table 1

Clinical characteristics of patients

Variables	*Women (17)*	*Man (13)*	*Total*
Age (mean ± standard deviation)	64±8.2	62.38±9.3	-
Limbs tremor	12	10	22
Tremor of cephalic extremity	9	6	15
Hypokinetic-hypertonic syndrome	4	3	7

The presence of limbs tremor was found in 73.3% of patients from our study. At the evaluation of hypokinetic-hypertonic syndrome (HHS), respectively brady/hypokinesia and rigidity, we found that 23.3% of patients displayed this signs. No postural disturbances were recorded in our patients. This fact is in concordance with literature, as postural impairments are present in advanced stages of PD.

Mann-Whitney test was used in order to verify if there is a connection between COGTEST results and presence/absence of tremor. We did not found any statistically significant association between tremor and results of Word List Memory (WLM) Test – evaluation of total number of words that there were not on the list (p=0.84), WLM – total learning capacity (p=0.6) and WLM – trial to transfer (p=0.92).

The presence or absence of tremor did not modify significantly the results of GoNoGo test CorectGo variant (p=0.89). We did not found any significance between presence of tremor and Corect NoGo variant (p=0.34) or GoNoGo reaction time (p=0.18).

There was a statistical significance between presence of tremor and results at emotion discriminating test (PEAT) (mean response rate – p=0.01), but none for PEAT –

reaction time (p=0.67). Association between tremor and mean of correct responses at PEAT can be seen in figure 2.

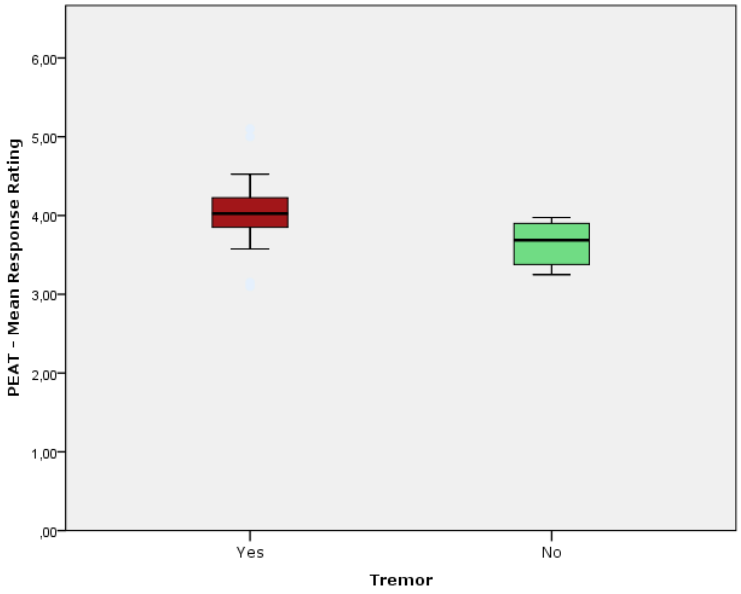

Figure 2. Differences in mean response rating for patients with and without tremor

At Strategic Target Detection test (STDT) we did not found any statistically significant link between tremor and cognitive performances, at Two Shape Mean Reaction Time variable (p=0.66), Two Shape Strategic Efficiency (p=0.48), Two Shape Duration (p=0.51), Four Shape Mean Reaction Time (p=0.97) and at Four Shape Duration (p=0.93).

We found a statistically significant difference between patients with tremor and those without tremor regarding Four Shape Strategic Efficiency variable (p=0.02); figure 3).

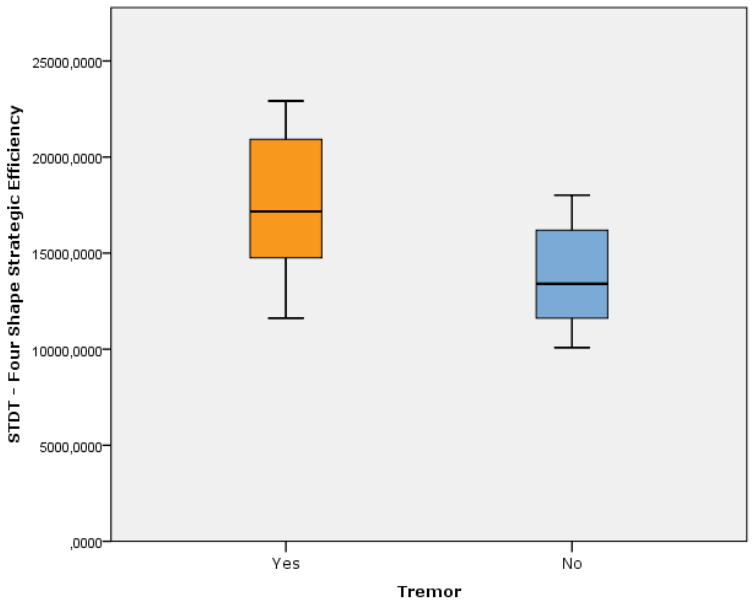

Figure 3. Differences in Four Shape Strategic Efficiency for patients with and without tremor

At STDT Four Shape Proportion of Spatial Repeat Errors evaluation we determined the existence of a significant relation between presence of tremor and repetitive errors (p=0.05).

We applied a Spearman correlation and demonstrated that a medium negative correlation exists between tremor and results at PEAT discrimination of emotions (r=-0.462; p=0.01). When we compared the presence of tremor and STDT test we found a medium negative correlation between them (r=-0.42; p=0.02).

Mann-Whitney test was used in order to verify if there is a association between COGTEST results and presence/absence of HHS. Significant results were obtained for Word Learning Memory, as we determined that total learning capacity is reduced in patients with HHS (p=0.03; figure 4).

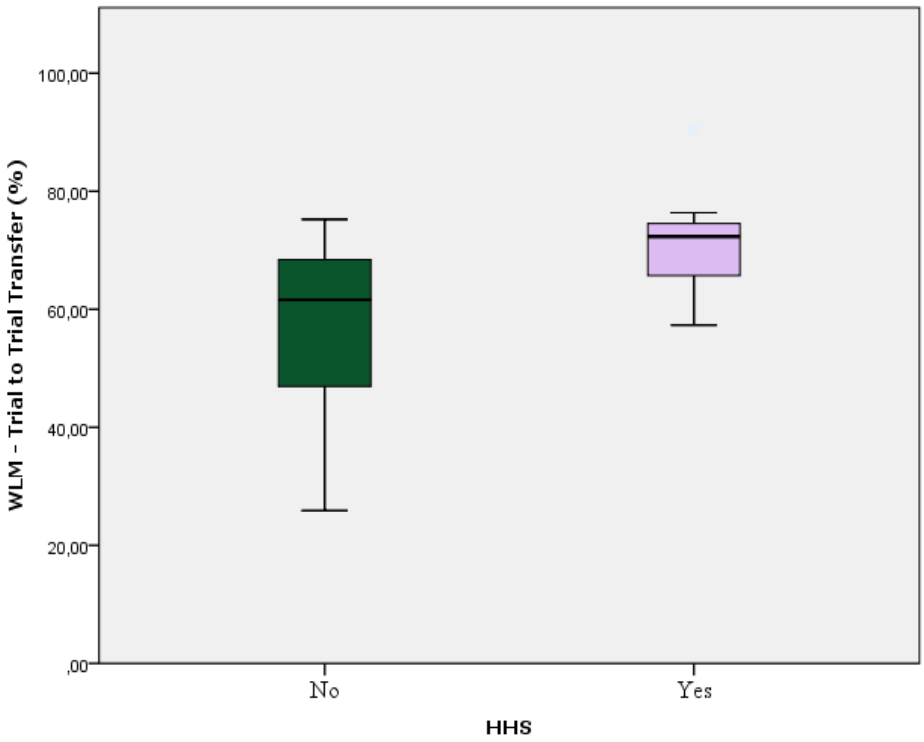

Figure 4. Differences in WLM between patients with HHS and subjects without HHS

Total capacity of accumulating information is lower in the group of patients with HHS, when compared with those without this symptomatology (p=0.05).

When we evaluated GoNoGo test variables we did not found any association between HHS and cognitive performances.

At STDT test, when we analyzed the presence of HHS vs. cognitive performances, we found significant differences between the two groups for a variable named Four Shape Proportion of Non-Perseverative Errors (p=0.05). Also in STDT, patients with HHS needed a longer period of time to solve the test at the stage of identification of two elements (p=0.04).

When we analyzed the relation between presence of HHS and capacity of elaborating efficient strategies, in the stage of detection of four presented forms (STDT - Four Shape Strategic Efficiency), we found a significant association. Patients with HHS recorded weaker results (figure 5).

We applied Spearman correlation in order to see what is the relation between presence of HHS and WLM – Total Learning, and we obtained a medium positive correlation (r=0.392; p=0.03).

Strategic efficiency at stage of identification of four elements, in STDT, is marked by a medium/high negative correlation (r=-0.485; p=0.009).

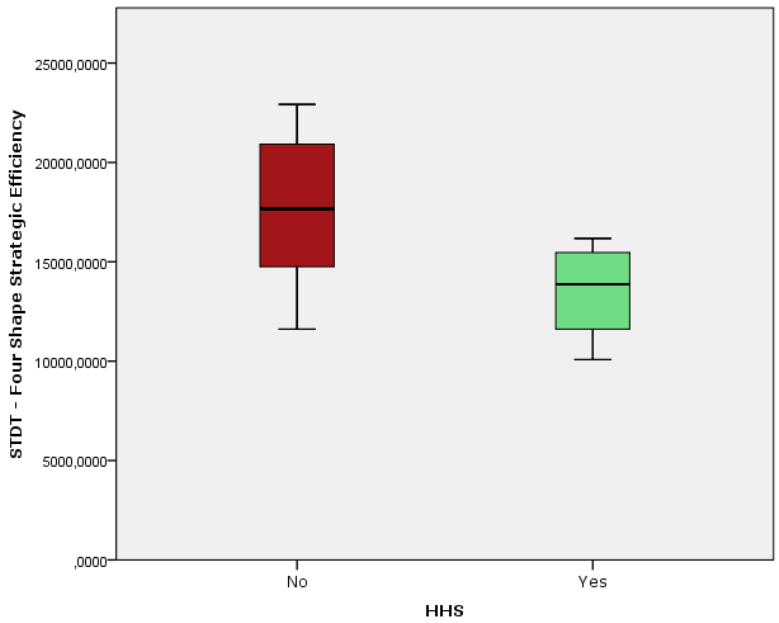

Figure 5. Differences in STDT accounting for HHS presence

Applying a Spearman correlation for STDT - Four Shape Proportion of Non-Perseverative Errors variable, gave us a coefficient equal to 0.366, hence a medium positive correlation (p=0.05).

At SWM test, the application of Spearman correlation for Short Median variable and HHS showed a medium negative correlation (r=-0.351; p=0.05).

At WLM test, Trial to Trial Transfer variable, we found a positive correlation (r=0.351; p=0.05) between this parameter and presence of HHS.

Discussions. In our study we followed the prevalence of some clinical characteristics of PD and we tried to identify their relation with cognitive deficits. Examination of relation between motor function impairment and level of cognitive disturbance was linked to clinical standard of patient approach, in order to determine if the two types of problems are caused by the same neurophysiopathological modifications or there is another anatomo-physiopathological substrate.

By applying statistical comparative tests, in regard to clinical date and cognitive performance, we draw the following conclusions: presence of tremor is associated with smaller total capacity of learning. Also we noted the existence of a relation between tremor and the decrease in efficient strategic thinking. Presence of tremor was associated with weaker results in emotion discriminating test, which means that "social cognition" is influenced, respectively the capacity of community integration (Kawamura & Koyama 2006).

Presence of HHS was associated with a decrease in capacity of efficient strategic thinking. Total capacity of information accumulation at WLM test was lower in patients with HHS, as compared with subjects without HHS. Although we found a cognitive impairment for both groups of patients with tremor as well as for patients with HHS, the scores were smaller for the latter.

In light of our research, we concluded that patients with rigidity, hypo/bradykinesia (HHS) presented a more significant deficit of executive function and working memory. These facts are in accordance with medical literature (Levy et al 2000).

The types of cognitive impairment in PD are very heterogenic, patients presenting disturbances in more than one domain. Different cognitive patterns that were described could be explained by differences between primary neuropathology.

Because we noted heterogeneity of cognitive impairment, we tried to define it. One way to define the subtypes of cognitive impairment in PD considers the profile of motor symptomatology. Patients with a form dominated by tremor seem to present a

smaller risk for development of cognitive decline, than those with a form in which postural and walking disturbance are predominant (Levy et al 2000; Lewis et al 2005). This motor profile, which presents a higher level of postural instability, talking and walking disturbances, reduced tremor seems to be a condition in which executive functions in particular are affected (Lewis et al 2005). Because these motor signs are considered to be caused by lesions localized in other areas than basal ganglions, it is theoreticized that non-dopaminergic mechanisms are responsible for cognitive impairment in this group (Levy et al 2000; Emre 2003).

It seems that when patients in early stages of PD were studied, level of cognitive impairment was not associated with severity of motor symptoms (tremor, bradykinesia and rigidity), which were considered caused by dopaminergic deficit. This fact suggests that cognitive deficit in PD with early onset might reflect neuropathologic dysfunctions other than those responsible for motor disturbances. Another fact that supports this supposition is the lack of association between dopaminergic medication and cognitive dysfunction (Muslimovic et al 2005).

It is possible that these cognitive profiles might have different pathologic substrates, which implies dissimilar prognostics. In many PD patients dysfunctions of frontostriatal circuits are present, which result in specific executive disorders: some hippocampus and temporal lesions, which determine several types of mnesic impairment (Foltynie et al 2004). In other patients modifications of posterior brain can be present. Although executive impairment remains the most important element in degenerative process, the prevalence of deficit in other domains can be also important in determination of cognitive changes progression (Muslimovic et al 2005).

Non-demented PD patients present a specific alteration of free recalling processes, with a relative conservation of recognition capacity, learning and long-term keeping of information, which suggests that storage and consolidation memory is intact, but working memory is somewhat affected. Paradigms of memory necessitate manipulation of some elements, like conditioning-associative learning, or temporal or spatial commands, which also are deficitary in PD (Dubois & Pillon 1997; Emre 2003; Zgarljardic et al 2006).

Identification of phenotypes in PD population can improve our knowledge regarding patients that are more susceptible to develop cognitive decline. They can gain from regulate neuropsychologic evaluations and from implication in support programs.

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Received: 20 September 2011. Accepted: 15 October 2011. Published online: 25 October 2011.
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How to cite this article:
Căpuşan C., Şerban A. M., Cosman D., 2011 The relation between cognitive impairment and clinical presentation in early stages of Parkinson's disease. HVM Bioflux **3**(3):213-219.