Section 1

Original articles

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NON-MOTOR VISUAL DISORDERS IN KAZAKHTAN PATIENTS WITH PARKINSON'S DISEASE

We observed 106 Parkinson's patients in Almaty city to detect non-motor visual disorders.

Among non-motor symptoms in patients with Parkinson's disease (PD), visual symptoms are becoming increasingly important. Visual impairments cause severe disability, reduce compensatory ability and adaptation of the patient to motor impairments and reduce life expectancy. Many neurologists do not take into serious consideration the importance of visual disorders in PD. This type of research has never been carried out in Kazakhstan or indeed the rest of Central Asia.

To study visual non-motor disorders in PD patients in Almaty to help optimize diagnosis and evaluate their correlation with disease duration and severity**.**

The diagnosis included the following elements: patient's complaints and history, a general physical examination, a neurological examination with auxiliary assessment scales.

The study confirmed that non-motor manifestations are common in PD patients. Research to date has confirmed the predictive value of non-motor PD manifestations.

Non-motor visual impairments are important to the overall quality of life of Parkinson's patients as well its motor manifestation, and require a very careful approach and considerable effort for early detection by a physician, medical personnel and caregivers, including relatives.

Key words: Parkinson's Disease, non-motor manifestations, clinical features, MDS(UPDRS), Kazakhstan.

Introduction

According to Global Burden of Disease 2016 6,1 million people in the world suffer with Parkinson's disease, out of which 2,9 million (47,5%) are women and 3,2 million (52,5%) are men [1]. The projected increase in the number of patients over the next 30 years will result in more than 12 million patients worldwide by about 2050 [1,2].

Parkinson's disease (PD) is characterized by a number of classic motor symptoms, including tremor at rest, rigidity and bradykinesia, which occur in the early stages of the disease and are highly dependent on neuronal degeneration of dopaminergic neurons from the substantia nigra pars compacta [3].

However, PD symptoms are now recognized as heterogeneous, with clinically significant non-motor features such as cognitive disorders, autonomic dysfunction, neuropsychological symptoms, sleep disorders, pain, fatigue and olfactory dysfunction, aggravating the disability. There is increasing evidence that non-motor PD symptoms do not only occur at an early stage of the disease, but may also precede motor symptoms by several years [4].

The prevalence of PD patients in Kazakhstan averages 62 cases per 100,000 and increases significantly above 70 years of age, with the averageage of onset being 56.4 ±2.8 for women and 63.3 ±3.5 for men [5,6]. Various studies have shown that the disease manifests when 50% to 70% of substantia

nigra neurons die and dopamine levels in the striatum are reduced by more than 80% [7,8,9,10].

Braak H, et all (2004) have expressed the opinion that long before the characteristic clinical motor symptoms of PD appear, the pathological process begins from the vagus nerve to the brain stem and eventually progresses to the limbicand neocortical regions of the brain [9]. This determines the development of various non-motor and premotor clinical manifestations of PD – sensory, vegetative, dissimilar, affective, etc. The prodromal phase of progressive degeneration of the DA of neurons until symptoms appear, which proves the existence of compensatory mechanisms in the early stages of PD [9,10].

Visual function can be important in predicting dementia in PD. In a prospective study, abnormal color vision at baseline tripled the probabilityof developing dementia [11]. Some non-motor symptoms can be detected early in the disease, at which time affordable treatments can be initiated toprevent progression. Other non-motor symptoms are more resistant and require the introduction of new drugs. Visual impairments in PD can be caused by pathological mechanisms such as retinal dopamine depletion or reduced innervation to the visual cortex. [12]. Most visual impairments are curableor preventable, so early diagnosis is clearly crucial [13]. The presence of visual and visual impairmentsin PD patients remains grossly underestimated by neurologists and general practitioners. The preservation of the eye organ function is particularlyimportant for patients with PD due to their need to compensate for locomotor automaticity disorders, including unstable postures [14]. Visually-spatial disorders, one of the life-threatening manifestations of the disease, have been insufficiently studied so far [15]. These include double vision, a change in contrast sensitivity and color vision, a feeling of sand in the eyes, as well as psychotic syndromes associated with visual impairment: illusions and hallucinations [16,17,18].

The Objective

To study visual non-motor disorders in PD patients in Almaty for optimization of diagnosis and correlation with the duration and severity of disease.

Materials and Methods

This is a prospective study of ambulatory patients observed in various polyclinics of Almaty, which is the major city of Kazakhstan.

Symptoms were rated in a group of 106 patients with PD (64 women and 42 men) using the Movement Disorder-Unified Parkinson's Disease Rating Scale (MDS-UPDRS; alpha-Kronbach =0,979). A total of 61.9% of the subjects were Asian, and 38.4% were European; all of them were eligible. All patients were diagnosed with PD by the British Brain Bank.

The control group consisted of 54 neurologically healthy individuals of the relevant age and sex, from the database of polyclinics in Almaty, regardlessof nationality. The total number of people studied, including the control group, was 160. Personal information was encoded by unique identifiers. All patients or their legal representatives have given informed written consent to participate in our study. Prior to the start of the study, all PD patients filled out a form for visual impairment in Parkinson's Visual impairment in Parkinson's Disease Questionnaire (VIPD-Q) (available in the public domain).

The questionnaire also assesses the effects of eye symptoms on everyday activities. Patients with significant concomitant and ocular pathology that may increase the unreliability of the results were excluded from the study.

The research paper defined the main demographic and clinical characteristics, including age at the time of the study, age and duration of the disease, Parkinson's history, Levodopa response, UPDRS score (unified Parkinson's scale) and the clinical subtype of PD. The severity of the disease and stage was estimated by the Hoehn & Yahr Scale (1967). Motor disability was evaluated with the help of the revised MDS-UPDRS, Parts II and III.

For the determination of cognitive function, the Montreal Cognitive Assessment (MoCA), the Non-Motor Symptoms Questionnaire (NMSQ; 2006), and the Hospital Anxiety Scale and Depression (HADS; 1983) were used; early and late visual symptoms were evaluated with the Popelreiter test and the Yerkes test; the Mirror letters and test numbers were used to determine visual andspatial impairments. Test with an assessment of theposition of the hands on the clock), Rupp's Test, noise images, and Raven's Progressive Matriceswere also used.

The questionnaires were filled in by the patients themselves or their relatives, or by a doctor when the patients did not fully understand the question orhad pronounced motor disorders. Data processing was done using IBM SPSS Statistics version 27.0 for Windows and Data wrapper.

The highest number of patients was in the group over 60-80 years of age. The age of patients ranged

from 40 to 90 years; the average age of patients with PD was 69.72+0.732 (female-64, male-42) and in the control group was 67.54+0.561 (female-38, male-16) (Figure 1).

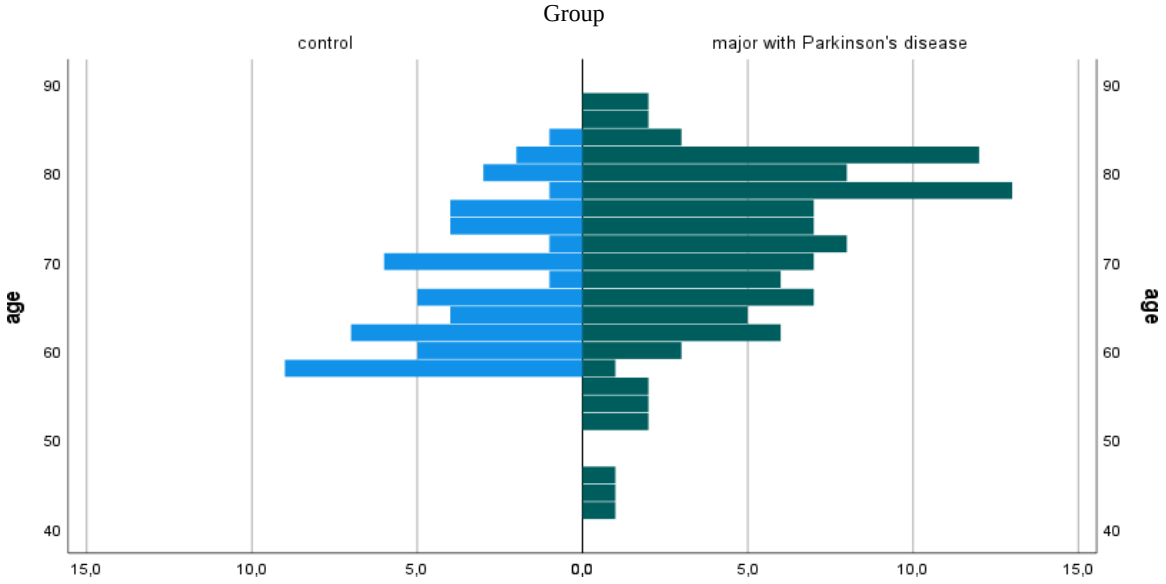

Figure 1 – Pareto diagram comparing PD patients and controls according to age

The average duration of the PD was 15.04+0.74 years (women 14.52+0.6 years, men 16.24+0.4 years; no significant difference; p>0.05). The average age at the time (onset of symptoms) of illness was 58.23+0.652 years (men 61.25 ±1.45 years, women 56.13 ±2.57 years) (Figure 2).

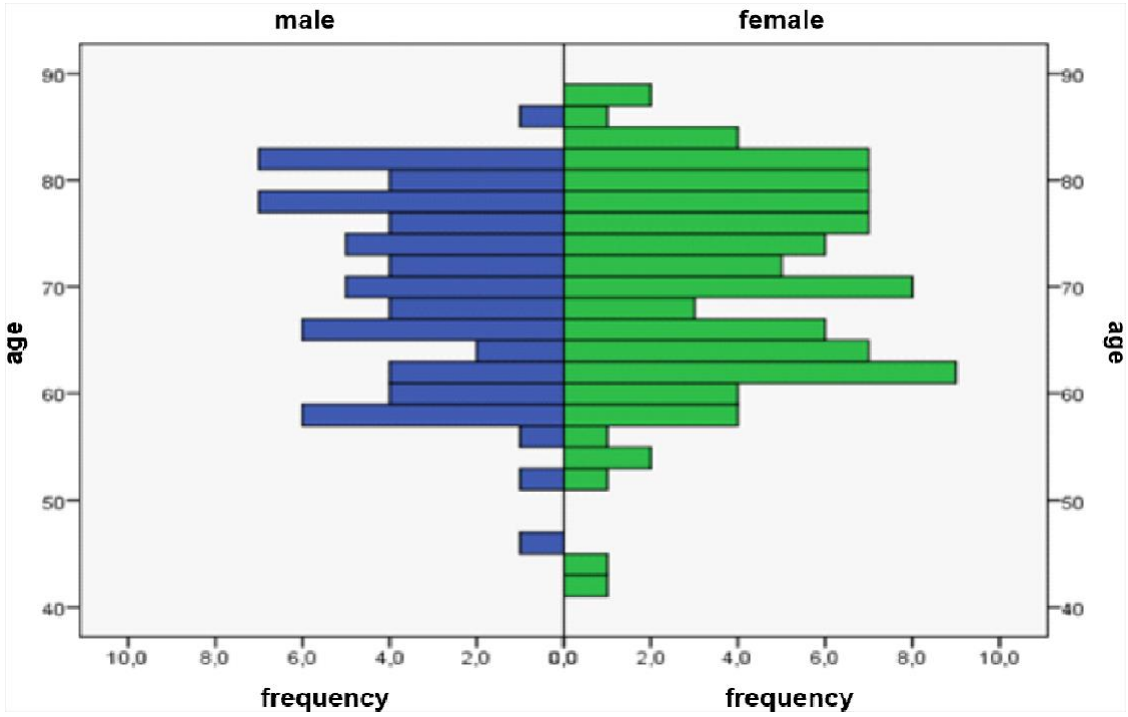

Figure 2 – Pareto diagram in comparison of PD patients by gender and age

Results and Discussion

The majority of PD patients presented with the akinetic-rigid form of PD (55,6%; n=59 patients), followed by the tremor dominant form (23,25%; n=25) and the mixed form (20,7%; n=22) (Table 1).

Table 1 – Demographics and Disease Characteristics

Parameters		PD patients		Controls	
Total number of observed patients		(n =106)	%	(n =54)	%
male		42	37,7%	16	29.63%
female		64	62,26%	38	70,37%
Level of education					
Graduate		65	61,32%	32	59,26%
Undergraduate		10	9,43%	9	16,67%
Secondary		17	16,04%	8	14,81%
8 and less grades		14	13,21%	5	9,26%
Average age at time of study		69,72±0,732		67,54±0,561	
Average age at the diagnosis, female male		58,23±0,652 56,13±2,57 61,25±1,45		-	-
Average duration of illness, years female male		15,04±0,74 14,52±0,6 16,24±0,4		-	-
MDI duration PD (years)		from 0 to 29		-	-
The form of disease				-	-
· Tremor		25	23,5%	-	-
· Akinetic-rigid		59	55,6%	-	-
· Mixed		22	20,7%	-	-
Stage of disease on Hoehn and Yahr scale				-	-
PD	Stage 1	10	9,4 %	-	-
	Stage 1.5	3	2,8%	-	-
	Stage 2	25	23,6%	-	-
	Stage 2.5	8	7,5%	-	-
Control	Stage 3	44	41,5%	-	-
	Stage 4	14	13,2%	-	-
	Stage 5	2	1,8%	-	-
Parameters		PD patients		Controls	
Total number of observed		(n =106)	%	(n =54)	%
Male		42	37,7%	16	29.63%
Female		64	62,26%	38	70,37%
Level of education					
Graduate		65	61,32%	32	59,26%
Undergraduate		10	9,43%	9	16,67%
Secondary		17	16,04%	8	14,81%
8 and less grades		14	13,21%	5	9,26%
Average age at the moment of study,		69,72±0,732		67,54±0,561	
Average age at the moment of illness, female male		58,23±0,652 56,13±2,57 61,25±1,45		-	-

Average duration of illness, years female male		 15,04±0,74 14,52±0,6 16,24±0,4		-	-
MDI duration PD (years)		from 0 to 29		-	-
The form of disease				-	-
· Trembling		25	23,5%	-	-
· Akinetic-rigid		59	55,6%	-	-
· Mixed		22	20,7%	-	-
Stage of disease on Hoehn and Yahr scale				-	-
1 group	Stage 1	10	9,4 %	-	-
	Stage 1.5	3	2,8%	-	-
	Stage 2	25	23,6%	-	-
	Stage 2.5	8	7,5%	-	-
2 group	Stage 3	44	41,5%	-	-
	Stage 4	14	13,2%	-	-
	Stage 5	2	1,8%	-	-

Some authors note the importance of pathophysiological differences between motor symptoms, although both are usually associated with changes in the motor cortex and basalganglia. According to literature, akinetic-rigid syndrome is more closely associated with the anatomical functional changes of the motor hinges of basal ganglia, especially in theprojections of globus pallidus, with external and internal parts, thalamus and eventually the motor cortex [16]. In contrast, the symptoms of tremor (Dirkx, M. F. et al. 2016) are associated with pathological interactions between the globuspallidus and cerebellar pathways [17].

Many authors point out that motor akinetic-rigid syndrome correlates with a worse prognosis and an increased risk of dementia compared to the shaking subtype of PD [19]. Our results also show that the more severe cases were statistically more frequent ($p<0.001$) in the group with akinetic-rigid syndrome.

The severity of the disease in the patients we examined corresponded on the Hoehn and Yahr scale mainly to 1-2-3-4 stages; on average 2.75 ±0.148. (Figure 3).

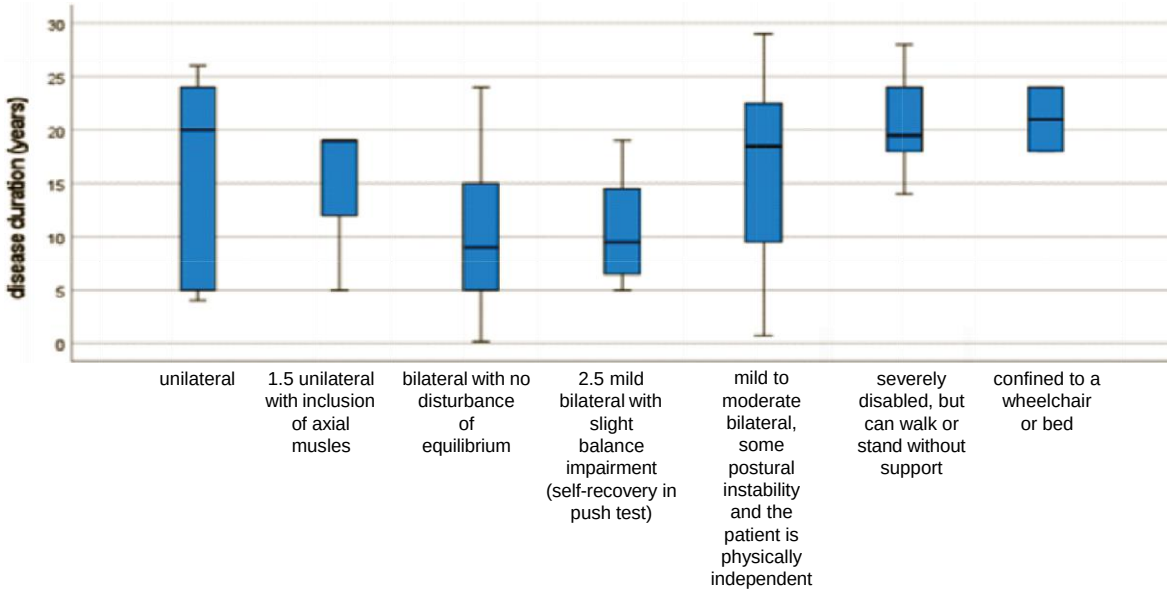

Figure 3 – Box diagram of PD patients' distribution according to Hoehn и Yahr scale on duration of disease

The results show that patients with mild or moderate two-way symptoms with 41.5% (44) already having visual and cognitive impairments are more prevalent among PD patients and they remain independent at home, but cannot overcome the retropulsive-pull test.

Patients with bilateral manifestations without postural instability accounted for 23.6% (n=25). In third place, patients with severe disability, with a number of motor symptoms, could get up and walk unaided on «good» days or hours 13.2% (n=14) (Figure 4).

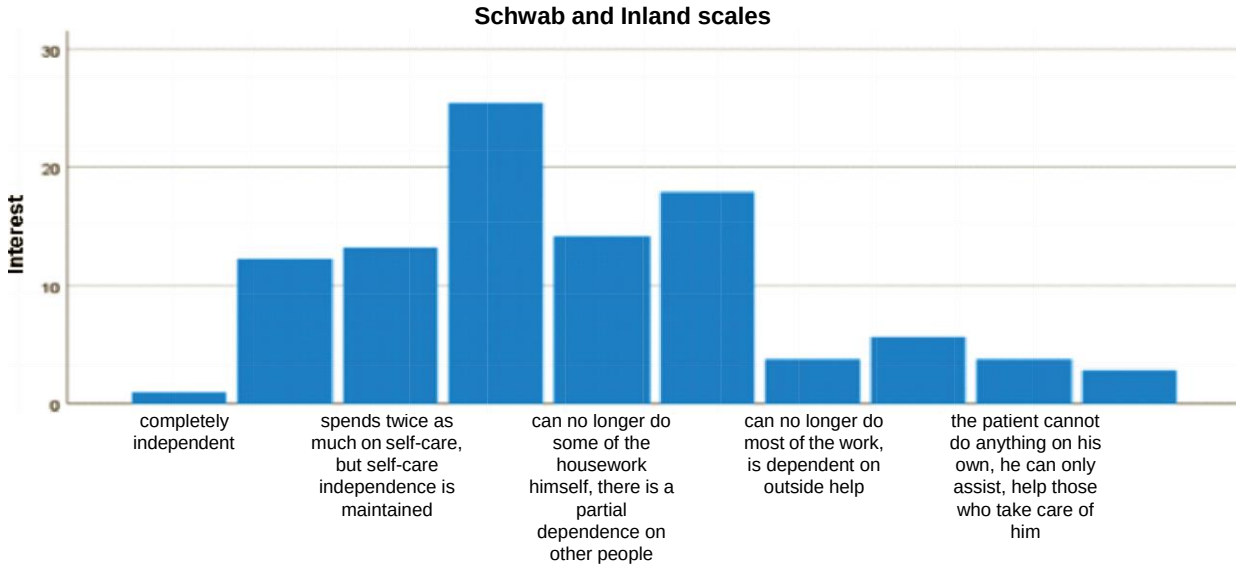

Figure 4 – Histogram of PD patients according to Schwab and England Activity scale in %.

A total of 51,89% (n=55) patients experienced a slow course of the disease, characterized by stage changes for 5 years or more; 33.96% (n=36) had a moderate progression rate, with stages changing over 2-5 years. About 14.15% (n=15) of patients had a rapid progression of the disease, with stages progressing over two years or less.

The majority of PD patients (87.74%; n=93) had visual impairments. Seventeen (18.28%) of them had symptoms in the early months and years prior to diagnosis of PD. Most frequently, patients complained of weak and fatigued eyes, dry eyes, vague (reading or working with a computer for a while), difficulty in reading, poor orientation at twilight or poor lighting (often encountered with objects or people), visual hallucinations, and color impairment (colors appear paler than before).

Screening of cognitive functions (using the MMSE scale) is important, allowing early detection of initial impairments and preventing or correcting significant declines in the quality of life of patients and caregivers. According to Aarsland et al. (2007), dementia affects on average up to 40% of patients; it is likely that almost 80% of patients in the final stage of the disease will have dementia [20]. Cognitive decline among our patients was 61.32% (n=65) in the core group, taking into account the criteria for excluding patients with severe dementia from the Short-Term Mental Assessment (MMSE) study below 21. Clinical dementia in PD is characterized primarily as a syndrome of executive dysfunction, action planning, spatial-visual impairment and only later memory impairment.

Patients often complained of elementary and subject-specific hallucinations, a sense of thepresence of an outsider in the apartment, photopsiasand spots in their eyes. In some patients, visual hallucinations occurred while falling asleep or waking up. Three patients described movement hallucinations that developed in the early stagesof the disease prior to the initiation of Parkinson's therapy. Our study found that visual hallucinations were more often combined with cognitive deficits, and longer-term illness. The most difficult patients to treat were long-term patients with both PD and visual hallucinations. Most (81.25%) visual

hallucinations in patients with PD were combined with cognitive deficits, with duration of over 20 years. Of these, 37 patients had pre-dementia cognitive impairments with MMSE scores ranging from 22 to 27; 28 patients had mild dementia scores of 20-23 on the MMSE scale (Figure 5).

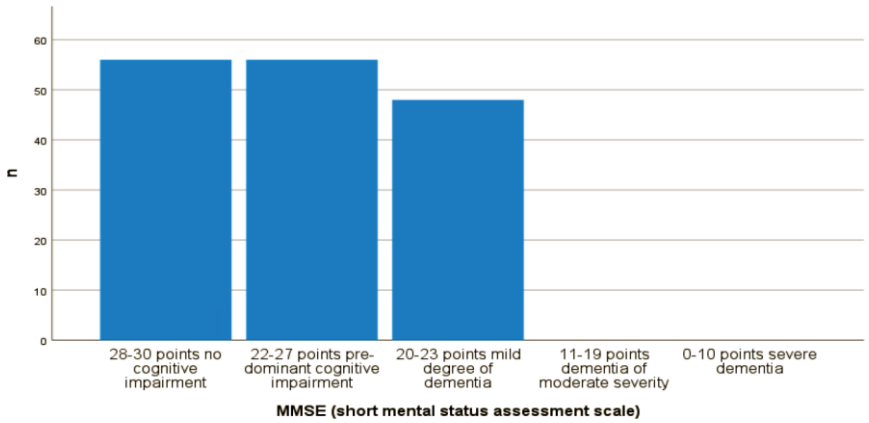

Figure 5 – Tables of concordance of visual hallucinations in PD patients according to the MMSE (brief mental status assessment scale)

We have analyzed correlations between visual impairment parameters and MMSE, MoCA, anxiety, cognitive test, PD group watch test and control group (Table 2).

Table 2 – Pearson correlation of visual impairment and MMSE, MoCA, NMSQ, anxiety, cognitive test, and clock test scales(n=159)

	MMSE	MOCa	anxiety scale	cognitive test	clock test
dry eye	**-,508****	**-,508****	**-,535****	**-,542****	**-,617****
weakness and eye fatigue	-,397**	-,397**	-,464**	-,438**	**-,543****
blurred vision (do you have blurred vision, for example, when reading or working with a computer for a while?)	-,462**	-,462**	-,484**	**-,508****	**-,543****
difficulty reading	-,452**	-,452**	**-,544****	**-,528****	**-,528****
poor orientation at dusk or in low light (do you bump into objects or people?)	-,476**	-,476**	-,497**	**-,536****	**-,557****
visual hallucinations	-,386**	-,386**	-,401**	-,421**	-,487**
color vision impairment (colors seem paler than before?)	-,415**	-,415**	**-,522****	-,471**	**-,523****

We found statistically significant correlations between visual impairment and cognitive function in both MMSE and MoCA, as well as anxiety test scores ($p<0.01$); visual hallucinations were not statistically significant across all cognitive parameters. Note that dry eye was significantly correlated with almost all parameters: MMSE and MoCA (-,508*), anxiety (-,535*), cognitive test (-,542**), and clock test

(-,617**). The extent of cognitive disorders in PD patients ranged from lack of cognitive impairment to mild dementia according to the MMSE scaleand is also one of the three main predictors of PD and dementia risk. Both groups were tested using the NMSQ questionnaire. Most PD patients are diagnosed with one or more NMS during their illness.

The average number NMS per patient with PD was 10 as compared to 4 in the control group (p< 0.001). The total number of NMS in PD ranged from 1 to 28, with the highest incidence of 10 or more symptoms per patient in 66.98% (n=71) patients and less than 10 NMS in 33.02% (n=35)of patients (Figure 6.)

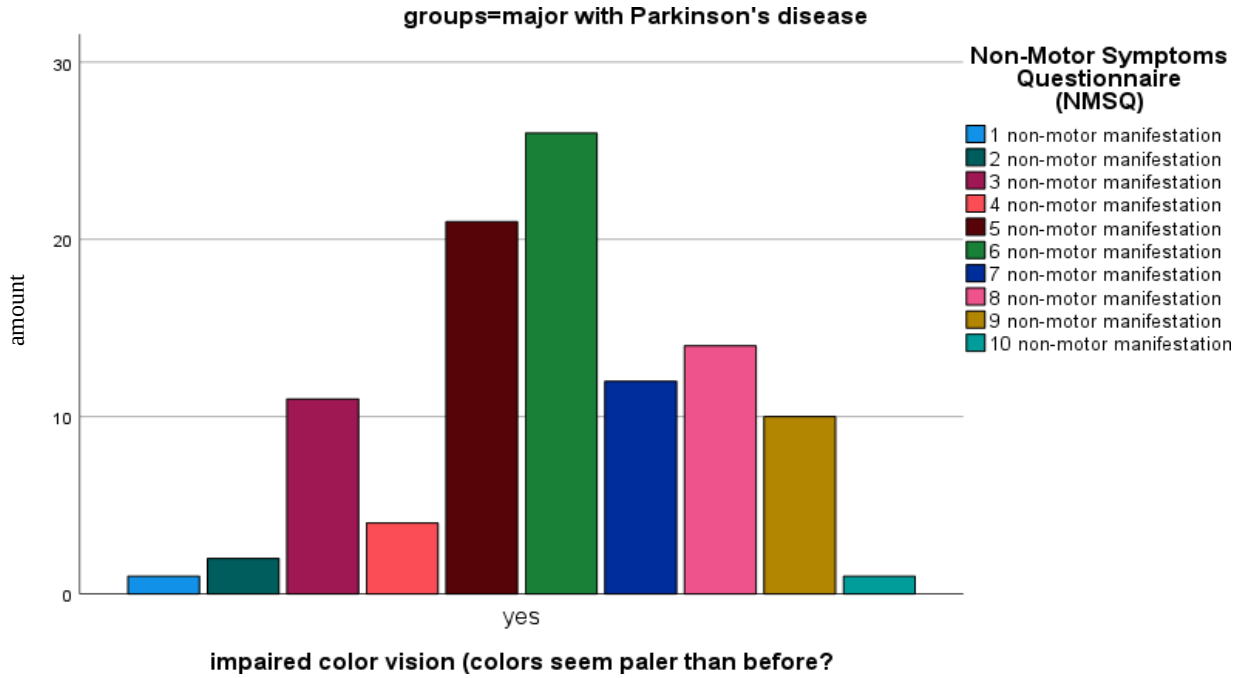

Figure 6 – Results of the non-motor symptom questionnaire (NMSQ) in the group of patients with PD and visual disorders.

The following symptoms were significantly more frequent in the PD group than the control group: hypersalivation, hyposmia, dysphagia, difficulty in concentrating and maintaining attention, intense and vivid or frightening dreams, anxiety, fear, panic, nausea, vomiting, constipation,and increased sweating (all p<0.001). NMSs often occurred early in the disease, and in 11.32% (n=12) patients pre-motor, doctors did not pay sufficient attention to these symptoms, so there was no proper correction. In the later stages ofPD, non-motor manifestations begin to dominateas factors which affect the patient's quality of life and become more important and disabling at certain moments by motor fluctuations, causing insurmountable difficulties for the patients and their caregivers. The diagnosis of PD was basedon the detection and identification of specific motor manifestations that are direct consequence of insufficient dopaminergic transmission in the nigrostriatal system.

The set of non- motor symptoms we have identified from the NMSQ questionnaire turns out to be equallycharacteristic of the disease, most of which are non-dopaminergic in nature.

According to the literature, visual impairments are common in PD, but their exact frequency and severity are unknown. Good visual function is crucial for patients with PD as they need to compensate the loss of automatic motor control and unstable posture, forcing patients to direct their movements visually [21]. Awareness and early recognition of eye and visual problems in PD can lead to timely individualized treatments leading to safer patients, greater independence and better quality of life. Non-motor visual impairments in PD can be detected early [22]. Figure 7 shows visual impairments depending on the duration of the disease indescending order: dry eyes, color impairments and visual hallucinations, etc.

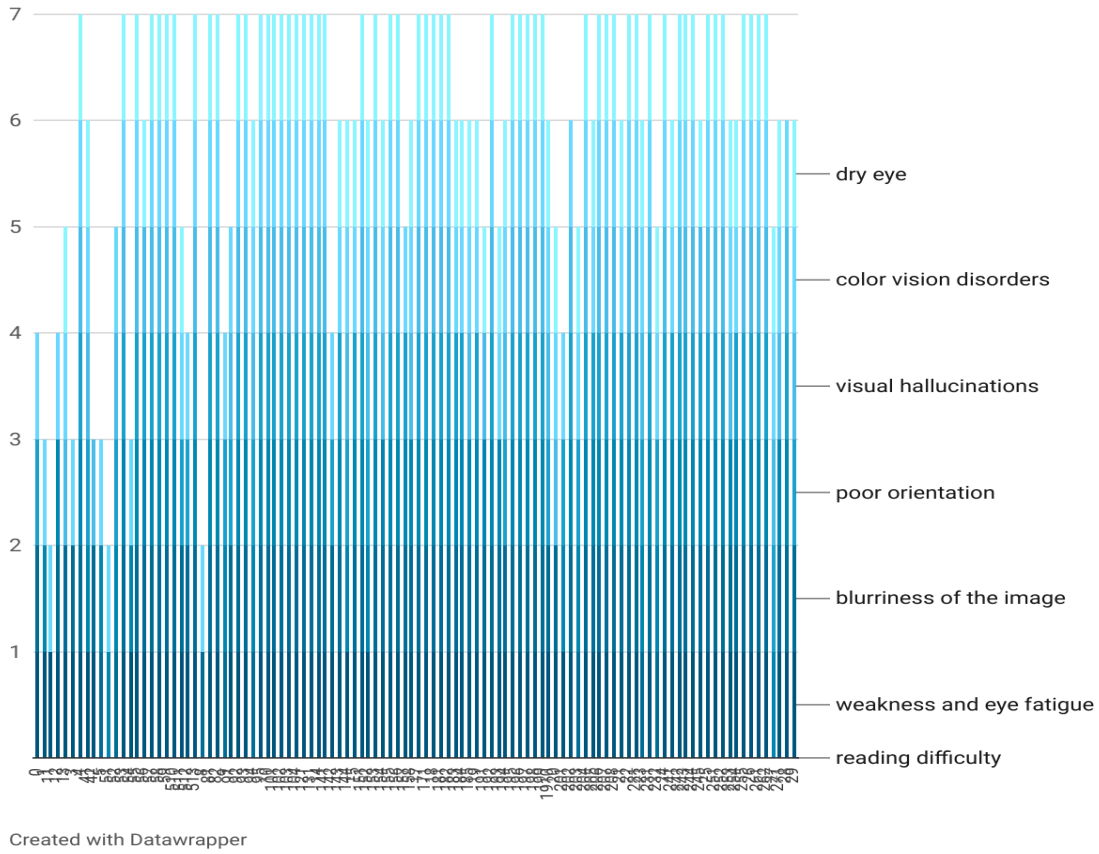

Figure 7 – Bar chart with the accumulation of visual impairment as a function of the duration of PD (Datawrapper)

Conclusion

The early detection of visual non-motor symptoms greatly expands our understanding of the disease by demonstrating its complex nature, which goes far beyond conventional knowledge. When planning therapeutic strategies for PD in clinical practice, doctors tend to focus primarily on motor symptoms, and non-motor symptoms are often unrecognized and underestimated. Special measures to improve visual non-motor disorders will lead to increased patient safety, greater autonomy, better quality of life and better medical care. Vision problems may precede the onset of the disease itself and may serve as an early marker for PD.

In our study, 18.28% (n=17) of cases had visual problems in the early period. Moreover, vision problems can also help predict the progression of cognitive impairment, dementia, and PD itself. Currently, we are actively searching for biomarkers of PD and cerebrovascular diseases capable of predicting the development of the disease, determining the rate of progression of the disease, evaluating the effectiveness of the therapy conductedat the molecular level [23,24,25].

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