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Clinical and Genetic Aspects in Patients with Idiopathic Parkinson Disease

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1. Introduction

Parkinson syndrome is one of the most often neurodegenerative diseases, which affects the Central Nervous system. James Parkinson was the first who described the clinical symptoms of factor complex, a complex which can be present as a combination of six cardinal signs: tremor, rigor, bradikinesia-hypokinesia, curve pose, lose of postural reflexes and freezing phenomena. To get to the final diagnose, the clinicians usually use the Brain Bank Criteria of UKPDS [9].

Generally, there are four categories of Parkinsonism: Idiopathic Parkinson Disease; Secondary Parkinsonism; Parkinson plus syndrome and other neurodegenerative diseases in which Parkinsonism is main clinical manifestation [7].

Idiopathic Parkinson disease is the most represented type of Parkinsonism and it is maintained in almost 80 percents of the patients with movement disorders. Mostly with unilateral presentation, well responds on Dopamine-agonists and Levodopa, characterized with general slowness and typical tremor, from 4 to 6 Herz.

The basic patho-anatomical findings in patients with Idiopathic Parkinson Disease, is loss of neurons which contain neuromelanin. These neurons are located in particular parts of the brain, such as substantia nigra and locus ceruleus. Dopamine level is reduced for almost 80 percents under normal level, especially in striatum [7].

Hystopatological findings direct to presence of intracellular inclusions called Lewy-body, primary in substantia nigra, and they contain alpha-synuclein.

Alpha-synuclein is present in many parts of the brain, but mostly in substantia nigra, and it is the only synuclein included in Parkinson disease. It was found that two non-sence mutations in gene of alpha-synuclein, A53T and A30P, are closely related with early appearance of Idiopathic Parkinson Disease between populations in Europe. Accumulation of this protein in dopaminergic neurons is responsible for the process of neurodegeneration [20].

2. Aims

1. To determinate age, sex and difficulty of clinical manifestations in patients with Idiopathic Parkinson Disease, using UPDRS scale.
2. To compare the findings of genetic researches, by age and sex in patients with Idiopathic Parkison's Disease, with those in control group.

3. Materials and methodes

This is a prospective study, clinical and genetic, approved by the Ethical Committee, at Medical Faculty of Skopje. The clinical part of the study was made at University Clinic of Neurology in Skopje. Laboratory and genetic part of the study was made at the laboratory of molecular biology at Faculty of Math and Natural sciences at University of “St. Cyril and Methodius” in Skopje.

In the study were included and were analyzed 30 patients. At each of them, Idiopathic Parkinson Disease was diagnosed, by using many diagnostic criteria such as: History of the patient’s disease; Neurological examination; Neurophysiologic examinations such as EEG, ENMG, EP (VEP, SEP, BAEP); Neuroimaging methods, such as CT scan and MRI of brain; Neuropsychological tests.

4. Genetic analysis: Detection of mutations in gene of alpha-synuclein (SNCA)

DNA Isolation: under aseptic conditions, from each one of the patients, blood sample was taken, with the function of a vein. Each of those blood samples are kept invacuum pots (Vacutainer), and anticoagulant EDTA Na₂ is added in each of the pots.

Amplification: amplification of regions of SNCA gene was made with polymerase chain reaction.

Detection of mutations: to detect the mutations in selected regions of SNCA gene, polymerase chain reaction- Restriction Fragment Length Polymorphism, was used.

Amplification of the region of egzon 3 of SNCA gene was made, using the primers 5'- GTC TCA CAC TTT GGA GGG TTT C-3' and 5' CAC CTA CCT ACA CAT ACC TCT GAC and TC-3'.

PCR amplification of region of egzon 4 of SNCA gene was made by using the primers 5' GCT AAT CAG CAA TTT AAG GCT AG-3' and 5' GAT ATG TTC TTA GAT GCT and CAG-3'. All of these amplifications have length of 215 bp.

Amplificated products were digested with appropriate restrictive endonuclease under the optimal conditions.

G88C mutation in egzon 3 of SNCA gene was detected with restricted digestion with enzyme Mval.

G209A mutation in egzon 4 of SNCA gene was detected with enzyme Mael.

5. Results

In this part of the article, we have a presentation of the results gained with processing, in other words, a statistic data analysis, needed for fulfilling the research aims set.

As respondents in the research, we’ve included 32 patients with clinically confirmed Idiopathic Parkinson’s disease (IPD), diagnosed to Brain Bank Criteria, treated in the University Clinic of Neurology in Skopje – ward for extra pyramidal diseases.

The gender structure of the respondents is presented with 18 (56.25%) males and 14 (43.75%) females, table 1 and picture 1.

The average age of the respondents is 52, 7+10.3 years. The youngest respondent is 30 years and the oldest is 78 years. The median value with value of 50 years shows that 16 of the respondents (50%) are in the age group of 50-59 years, and even 23 of the patients are older than 50 years, table 2 and picture 2.

Gender	N	%
Males	18	56.25
Females	14	43.75
Total	32	100

Table 1. Respondents distribution by gender

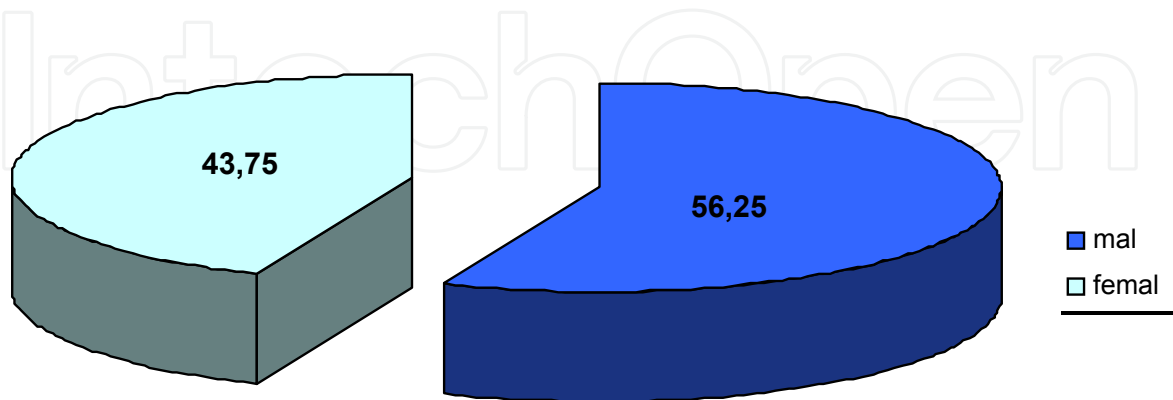


Fig. 1. Respondents distribution by gender

Years	N	%
30-39	4	12.5
40-49	5	15.62
50-59	16	50.0
60-69	5	15.62
70 >	2	6.26
Total	32	100
Mean = 52.75±10.3 Median = 50	Min=30	Max=78

Table 2. Respondents distribution by age

In table 3 and picture 3, the representation of neurological symptoms with extra pyramidal origin, typical for diagnosed with IPD, is presented.

The objective neurological finding, confirmed the presence of rigidity and hypertonia with extrapyramidal origin, to all 32 respondents. This also happened with tremor, which is one of the key symptoms of IPD.

Dyskinesia, as a symptom of long-lasting usage of substitution therapy (levodopa), is found in 15 patients (46.9%) and lack of these symptoms is seen in 17 patients (53.1%).

Symptoms	Rigidity		Tremor		Dyskinesia	
	Number	%	Number	%	Number	%
Present	32	100	32	100	15	46.88
Absent	/	/	/	/	17	53.12
Total	32	100	32	100	32	100

Table 3. Rigidity, tremor and dyskinesia distribution

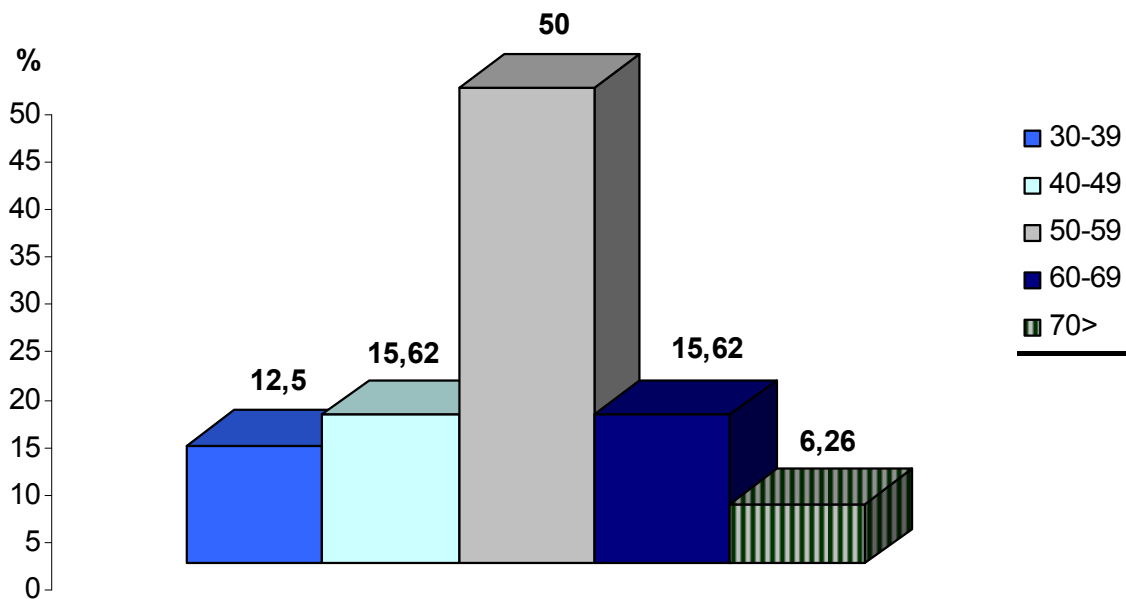


Fig. 2. Respondents distribution by age

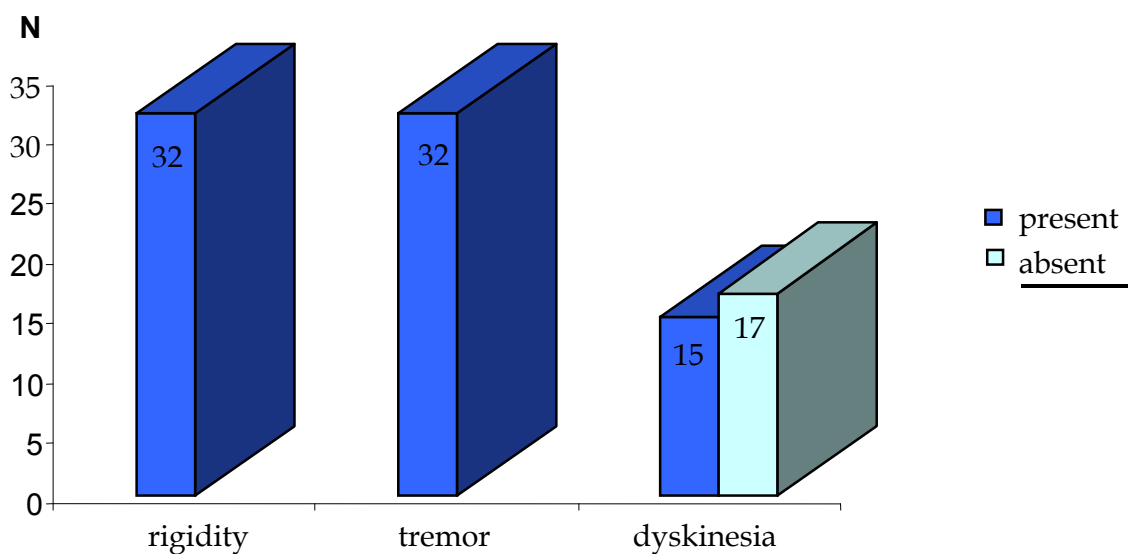


Fig. 3. Rigidity, tremor and dyskinesia distribution

Bradykinesia or stutment in movements, as main of the list of cardinal symptoms, according to Brain Bank Criteria of UK Parkinson's Disease, was found present in all respondents.

Reduced postural reflexes are positive in dominant number of respondents, 31 (96.6%).

Bradydilalia or the changes in speech (stunt and monotonous speech), is found in 28 patients (87.5 %) and in 4 of our patients (12.5%) a fully normal speech is present, table 4 and picture 4.

Dominant patients with bradydilalia are those with minimal changes in speech, estimated by UPDRS scale, with 1 are 16 patients(50%), with 2, 8 patients (25%), with 3 and 4, 2

patients(6.25%) and in 4 patients(12.5%) a fully normal speech is present and the speech itself is estimated with 0, according to UPDRS scale.

Symptoms	Bradykinesia		Reduced postural reflexes		Bradylalia	
	Number	%	Number	%	Number	%
Present	32	100	31	96.87	28	87.5
Absent	/	/	1	3.13	4	12.5
Total	32	100	32	100	32	100

Table 4. Bradykinesia, reduced postural reflexes and bradydilalia distribution

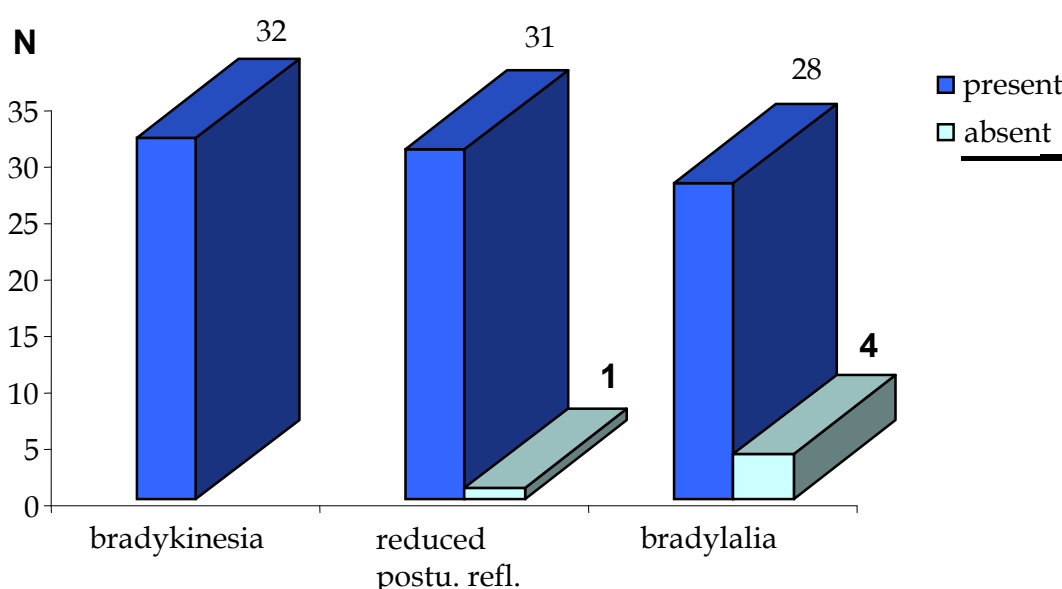


Fig. 4. Bradykinesia, reduced postural reflexes and bradydilalia distribution

The respondents gained the following neurophysiologic examinations: visual evoked potentials (VEP), somatosensory evoked potentials (SSEP), acoustic evoked potentials (BAEP) and electroencephalography (EEG).

The VEP is with proper finding in 29 respondents (90.6%), 2 of them (6.3%) have prolonged latency and the finding of one respondent shows low-volted response, table 5 and picture 5.

VEP	N	%
Proper finding	29	90.62
Low-volted response	1	3.12
Prolonged latency	2	6.26
Total	32	100

Table 5. Visual evoked potentials (VEP) in patients with IPD

30 of the respondents have proper finding of somatosensory potentials SSEP and in 2 of them (6.2%), those potentials show low-volted responses, table 6 and picture 6.

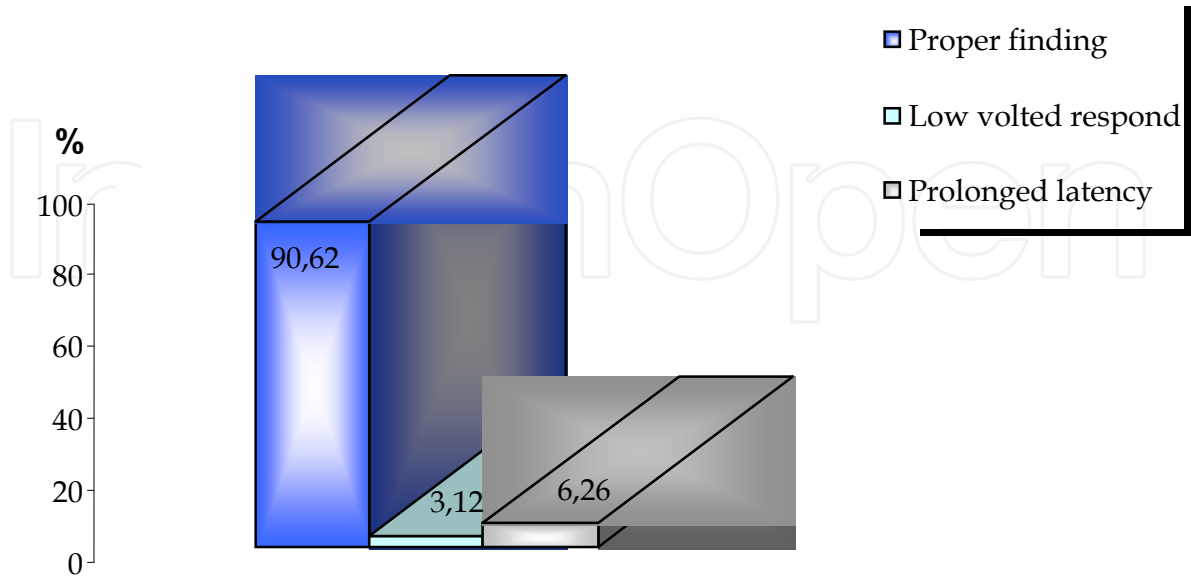


Fig. 5. Visual evoked potentials (VEP) in patients with IPD

SSEP	N	%
Proper finding	30	93.75
Low-volted responses	2	6.25
Total	32	100

Table 6. Somatosensor evoked potentials in patients with IPD

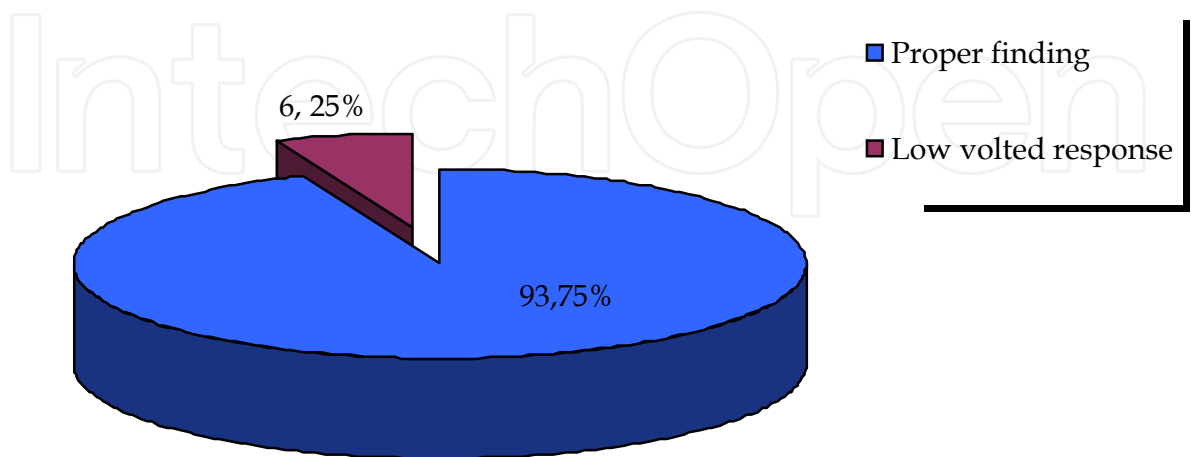


Fig. 6. Somatosensory evoked potentials in patients with IPD

22 of the respondents (68.7%) have proper finding of caustic evoked potentials BAEP and 10 of them (31.2%) are with low-volted responses, table 7 and picture 7.

BAEP	N	%
Proper finding	22	68.75
Low-volted responses	10	31.25
Total	32	100

Table 7. Caustic evoked potentials BAEP in patients with IPD

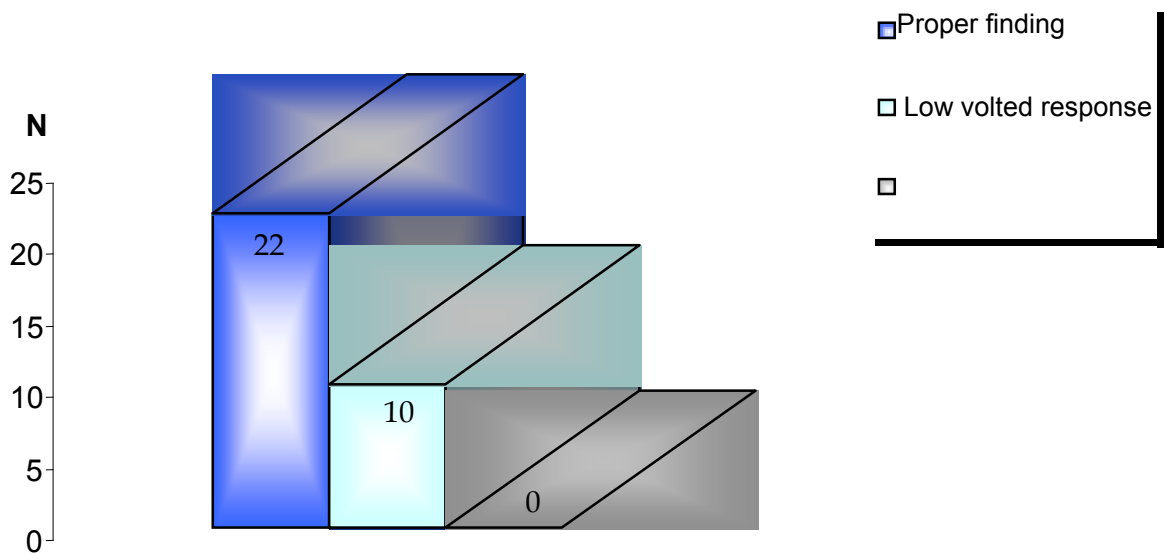


Fig. 7. Caustic evoked potentials BAEP in patients with IPD

19 of the responders (59.4%) have proper finding of electroencephalography; the finding of 12 of them (37.5%) shows unstable basic brain activity, without pathological graph elements and in only one patient, unstable brain activity with presence of different types of pathological graph elements is found, table 8 and picture 8.

EEG findings	N	%
Proper finding	19	59.37
Unstable basic brain activity without pathological graph elements	12	37.5
Unstable basic brain activity, with presence of pathological graph elements	1	3.13
Total	32	100

Table 8. EEG in patients with IPD

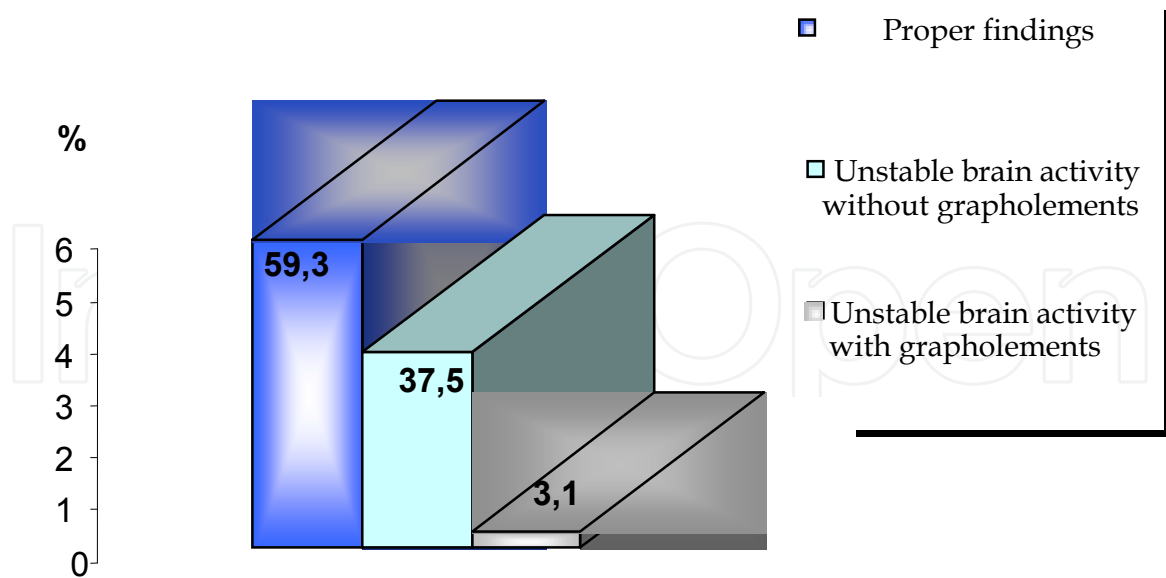


Fig. 8. EEG in patients with IPD

CT and MRI of brain findings	N	%
Proper finding	12	37.5
Discrete cortical reductive changes	11	34.37
Global cortical reductive changes	9	28.13
Total	32	100

Table 9. CT and MRI of brain in patients with IPD

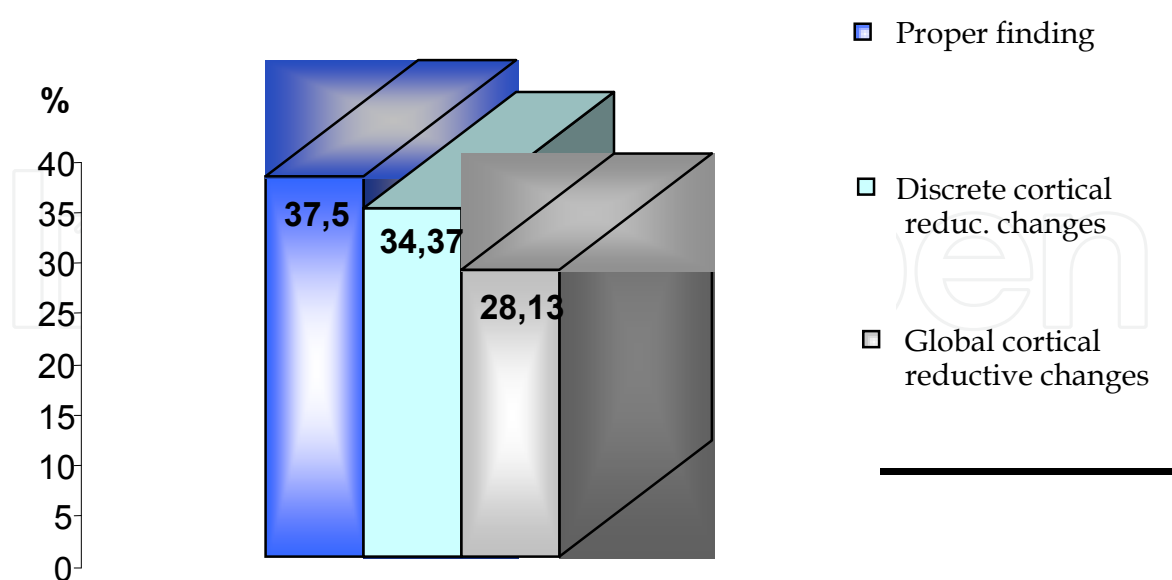


Fig. 9. CT and MRI of brain in patients with IPD

All patients gained neuroimaging examinations (CT and MRI of brain) and the examination results are presented in table 9 and picture 9.

In 12 patients (37.5%), the results of CT and MRI of brain are normal; 11 (34.4%) have discrete cortical reductive changes and 9 (28, 1 %) have global cortical changes. Doppler color sonography of the extra cranial blood vessels is with proper finding in 20 respondents (62.5%), 7 (21.9%) are with lightly expressed intimacy and proper hemodynamic parameters; 5(15.6%) have expressed arteriosclerosical changes of carotidal blood vessels, table 10 and picture 10.

Doppler color sonography of the carotid system	N	%
Normal finding	20	62.5
Lightly expressed intimacy with proper chemo dynamic parameters	7	21.87
Expressed arteriosclerotic changes of the blood vessels of the carotid system	5	15.63
Total	32	100

Table 10. Doppler color sonography of the carotid system in patients with IPD

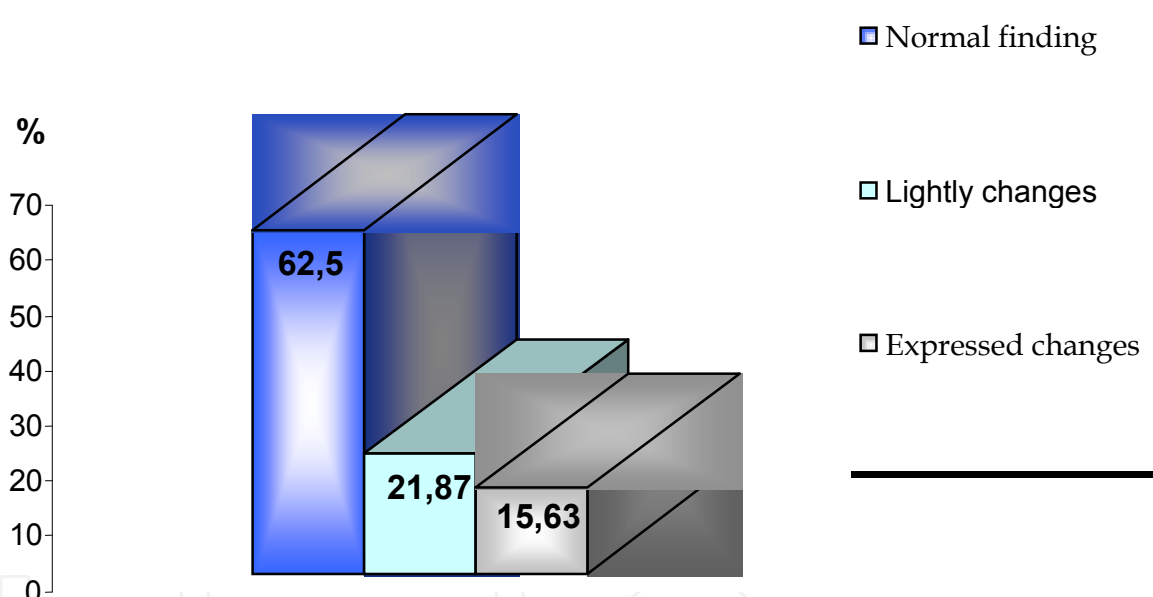


Fig. 10. Doppler color sonography of the carotid system in patients with IPD

In tables 11a and 11b, the results of the neuropsychological testing are shown. It's visible that only 3 patients (9.4%) have proper cognitive capacities. In table 11a all neuropsychological findings are examined individually, with percentage representation in our 32 respondents. Depression is found in 24 patients (84.4%); anxiety in 3 patients (9.4%); in 13 patients (40.6%), initial or global cognitive and mnesitic reduced changes are found. In table 11b, a statistic analysis of different combinations of findings from neuropsychological testing is presented, so between the patients dominant are those with depression and initial reduced cognitive capacities, as well as global reduced cognitive capacities. According to the frequency of occurrence, next is the finding of depression and global reduced cognitive and mnestical capacities, found in 3 respondents (9.4%). The rest findings from the neuropsychological testing: depression, anxiety, initial reduced cognitive capacities, depression and anxiety together, as well as the mutual presence of

depression and anxiety, joined with initial reduced cognitive and mnestic capacities, are found only in one of the respondents.

Neuropsychological testing	N	%
Proper finding	3	9.37
Depression	27	84.37
Anxiety	3	9.37
Initial reduced cognitive and mnestic capacities	13	40.62
Global reduced cognitive and mnestic capacities	13	40.62

Table 11.a. Neuropsychological testing of respondents with IPD

Neuropsychological testing	N	%
Proper finding	3	9.37
Depression	1	3.12
Anxiety	1	3.12
Global reduced cognitive and mnestic capacities	10	31.25
Initial reduced cognitive and mnestic capacities	1	3.12
Depression and anxiety	1	3.12
Depression and global reduced cognitive and mnestic capacities	3	9.37
Depression and initial reduced cognitive and mnestic capacities	11	34.37
Depression and anxiety and initial reduced cognitive and mnestic capacities	1	3.12
Total	32	100

Table 11.b. Neuropsychological testing of respondents with IPD

UPDRS	Gender		Total
	Males	Females	
Minimal signs	2 11.11%	9 64.29%	11
Light signs	9 50.00%	4 28.57%	13
Expressed symptoms	3 16.67%	1 7.14%	4
Extremely expressed symptoms	4 22.22%	0	4
Total	18	14	32
% of total number	56.25%	43.75%	

Table 12. The immensity of the clinical state, according to the respondents' gender Mann-Whitney $U=47,5$ $Z=2,98$ $p=0,0029$

The immensity of the clinical state of Parkinson's disease in our respondents, of different gender, is presented in table 12 and picture 11. The male respondents have significantly tougher clinical state comparing to female respondents. This statistic comment is a result of

the distribution shown in the table. It is noticeable that half of the male respondents (9.50%), have light disease symptoms; 2 (11.1%) have minimal signs or symptoms according to UPDRS scale; 4 (22.2%) are with extremely visible symptoms. In the female respondents, the disease is often manifested with minimal symptoms; 9(64.3%) and 4(28.6%) have light symptoms and there aren't any female respondents with extremely visible symptoms.

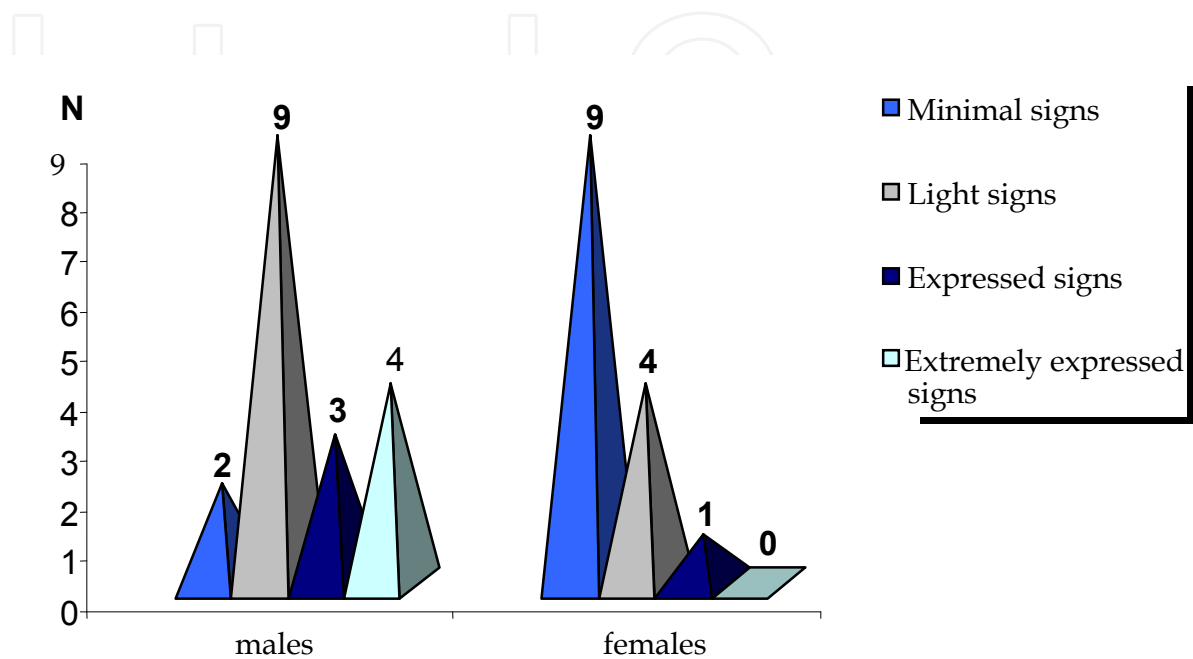


Fig. 11. The immensity of the clinical state, according to the respondents gender

The average age of the respondents, which according to UPDRS scale, have minimal symptoms of Parkinson’s disease, is 53, 6+10.3 years.

The respondents with light signs have average age of 52.8+8.1 years; the respondents with extremely expressed symptoms have average age of 45+15.3 years, table 13 and picture 12.

UPDRS	N	Age (Mean)	Age (SD)
Minimal signs	11	53.63	10.28
Light signs	13	52.85	8.10
Expressed signs	4	57.75	11.73
Extremely expressed symptom	4	45.00	15.30

Table 13. The immensity of the clinical state (UPDRS), according to the patient’s age

The connection between the age and the immensity of the clinical state of the respondents, estimated by UPDRS scale is presented in picture 13. That correlation has value for Spearmanov’s correlation coefficient, $R=0.039$, which indicates indirect or negative correlation. Parkinson’s disease has more difficult clinical state in younger patients and vice versa lighter symptoms in older patients. But, considering the value of the coefficient, we can conclude that the correlation between these two parameters is weak and statistically insignificant ($p>0.05$).

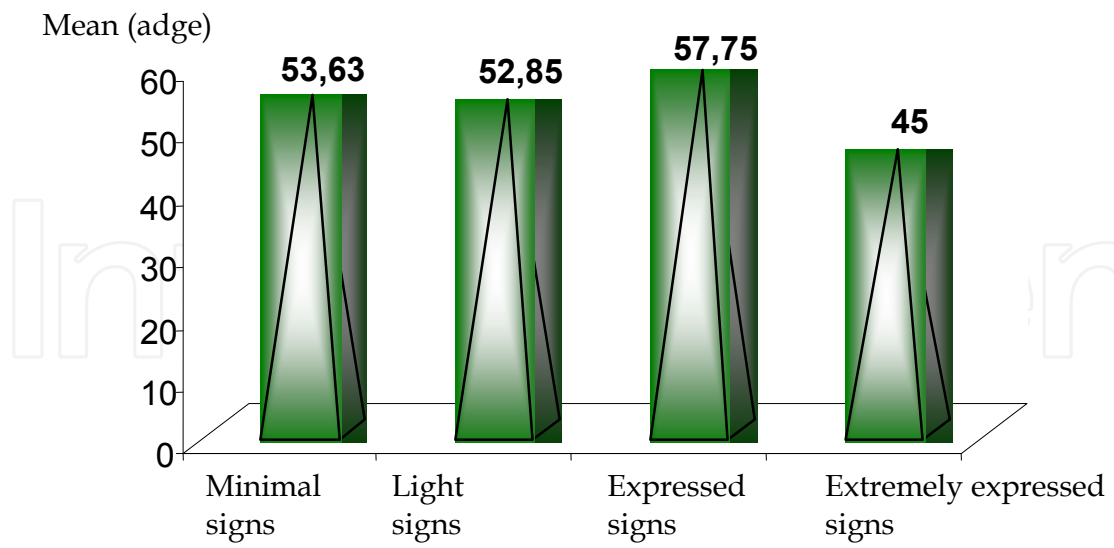


Fig. 12. The immensity of the clinical state (UPDRS), according to the patient’s age

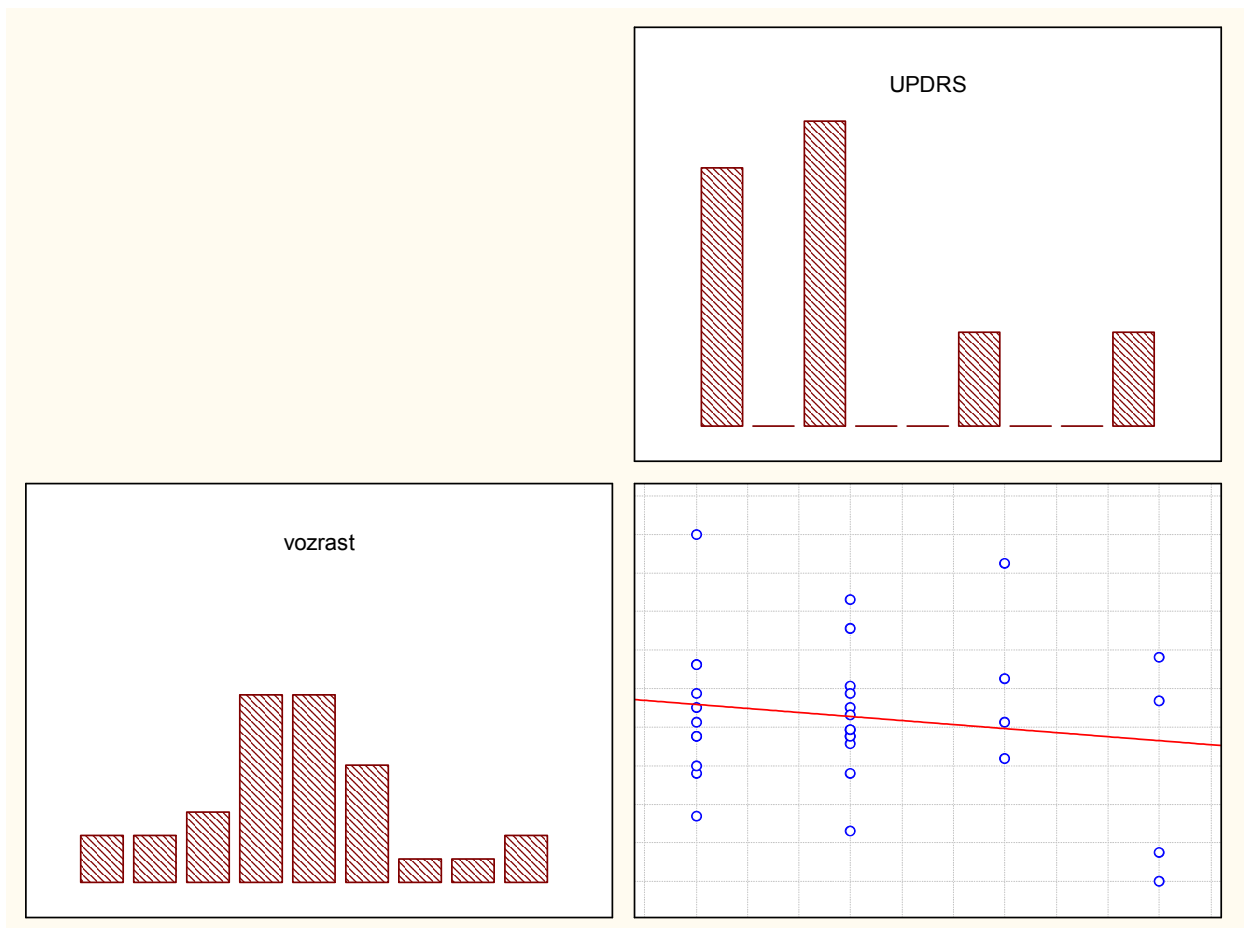


Fig. 13. Correlation between the immensity of the clinical state, according to UPDRS and the age of the respondents with IPD

6. Spearman rank order correlations $R=-0.039$ $p>0.05$

In our research, we've concluded that direct or positive statistic significant correlation between the number of hospitalizations and the immensity of the clinical state, according to UPDRS, indeed exists.

The value of the Spermen's coefficient ($r=0.48$), shows that these two parameters are proportionally connected, in other words, patients with IPD difficult manifestations of the disease, according to UPDRS scale, have more hospitalizations in the University clinic of Neurology in Skopje.

Table 14 and picture 14, show the results from the crostabulation between the CT finding and MRI of brain and the immensity of the clinical state, determined according UPDRS scale. In the respondents group with light disease symptoms, according to UPDRS scale, dominant are the findings with normal level, previously determined with CT and MRI of brain, present in 5 patients (45.4%), from this group. Between the respondents with light disease symptoms, the finding from CT and MRI of the brain shows discrete cortical reduced changes in 6 patients (46.1%). In half of the respondents, the finding from CT and MRI of brain, shows presence of discrete cortical reduced changes.75% of the respondents with highly expressed disease symptoms, have global cortical reduced changes, proved on CT and MRI of brain.

CT and MRI of brain	Immensity of the clinical state (UPDRS)				Total
	Minimal signs	Light signs	Expressed signs	Extremely expressed signs	
Normal finding	5 45.45%	5 38.46%	1 25.00%	1 25.00%	12
Discrete cortical reductive changes	3 27.27%	6 46.15%	2 50.00%	0	11
Global cortical reductive changes	3 27.27%	2 15.38%	1 25.00%	3 75.00%	9
Total	11	13	4	4	32

Table 14. Immensity of the clinical state (UPDRS) in relation to CT and MRI of brain

The connection or the correlation between the immensity of the clinical state, determined by UPDRS scale and brain CT/MRI finding, is also proved with the usage of Spearsmen's correlation coefficient. Its value ($r=0.2$) shows presence of direct, positive correlation between these two parameters, in other words, there is a match between the brain CT/MRI finding and the results from the UPDRS scale. In patients with difficult clinical forms of IPD, most often the brain CT/MRI finding shows global cortical reduced changes. But, the confirmed correlation is statistically insignificant, ($p>0.05$), picture 15.

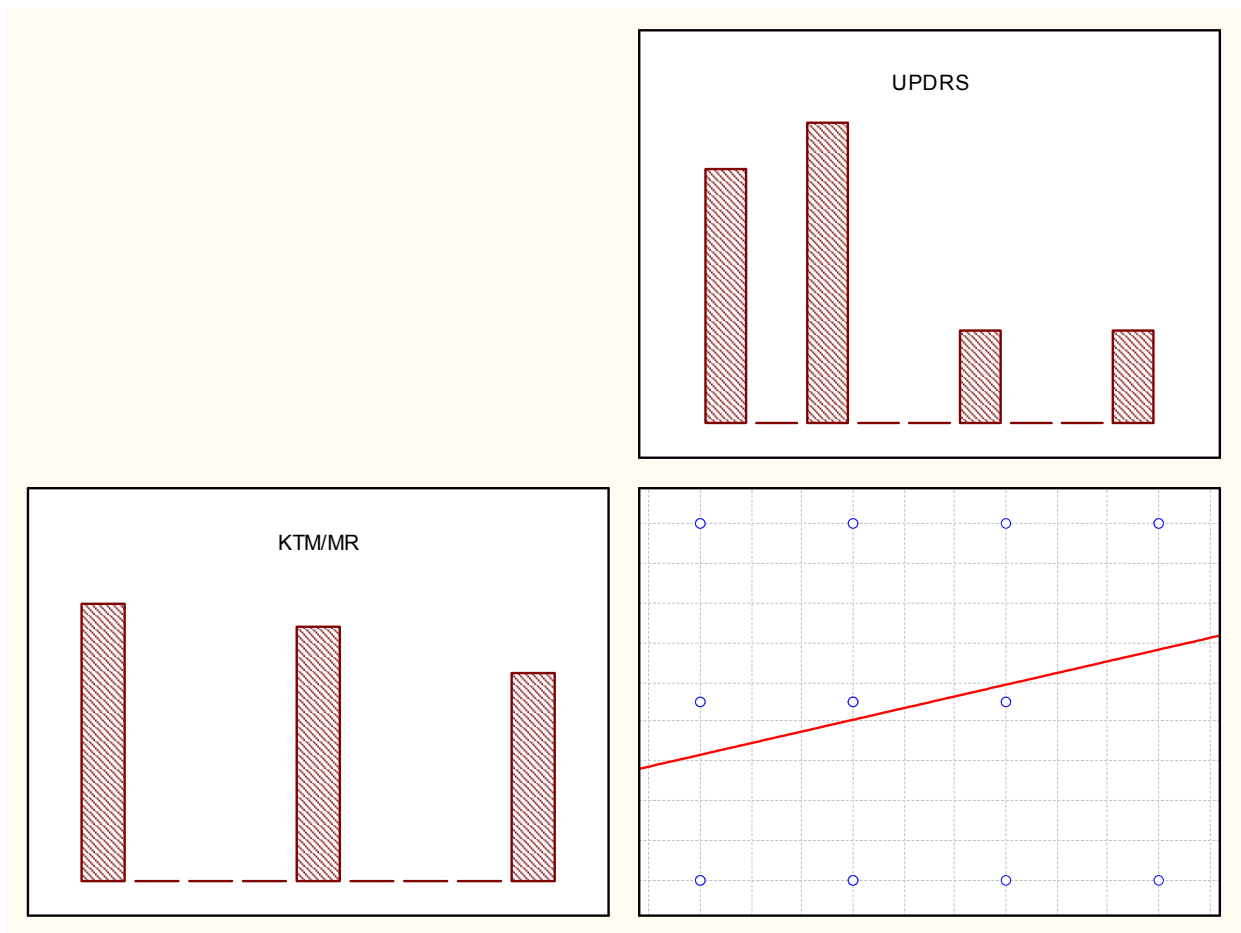
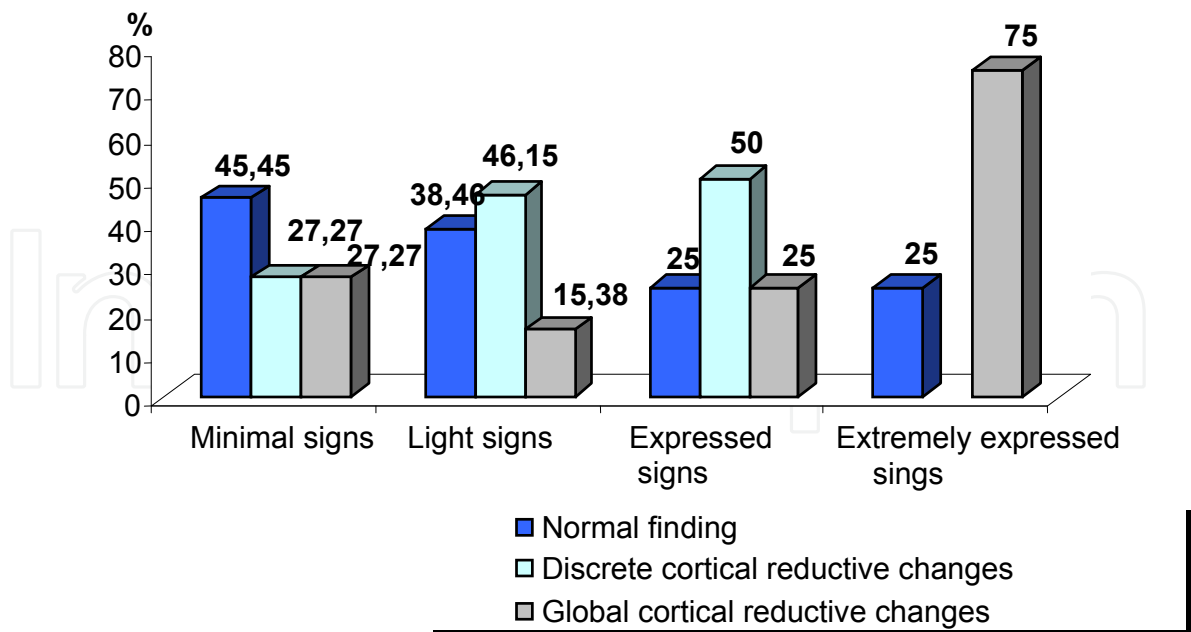


Fig. 15. Correlation between the immensity of the clinical state (UPDRS) and brain CT/MRI finding Spearman Rank Order Correlations $R=0,2$ $p>0.05$

7. Mutation detection

After amplification of a region from egzon 3 of SNCA gene, with usage of the following primers: 5'-GTC TCA CAC TTT GGA GGG TTT C-3 and 5'-CAC CTA CCT ACA CAT ACC TCT GAC TC-3', the result was an amplified product with length of 395 base pairs (bp). PCR amplification of a region from egzon 4 of SNCA gene, was performed with these primers 5'-GTC AAT CAG CAA TTT AAG GCT AG-3' and 5'-GAT ATG TTC TTA GAT GCT CAG-3', and the amplifications have length of 215 bp. The amplified products were digested with proper restrictive endonuclease under optimal conditions (puferian solutions suitable for each enzyme separately on temperature of 37 c). With that, no mutated sequence in the PCR product is found.

G88C mutation in egzon 3 of SNCA gene isn't detected in our 32 respondents with IPD. No mutations were found in the G209A in the enzonz 4 from SNCA gene, also.

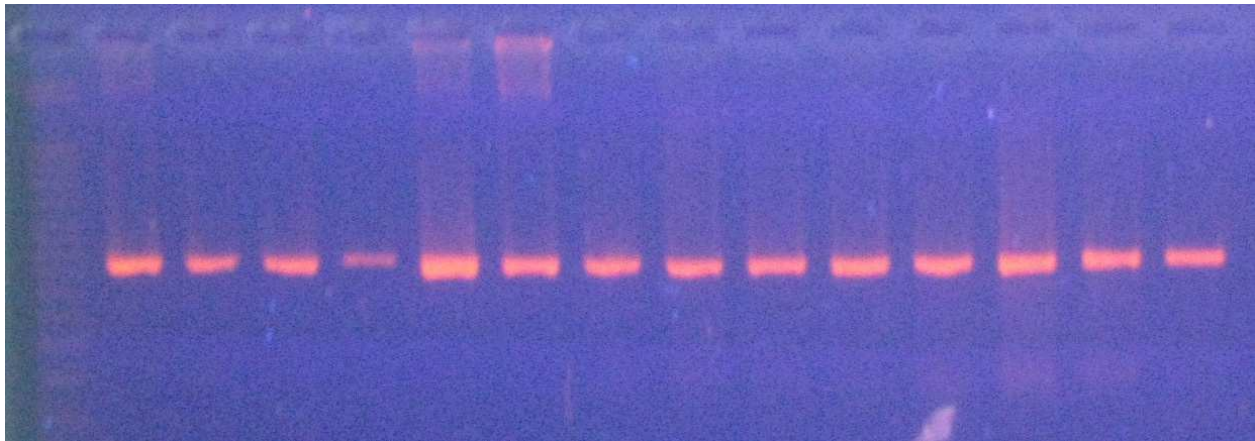


Fig. 16. Electroforetogram from PCR-RELP analysis (agaros gels colored with etidium bromide and photographed on ultraviolet light).

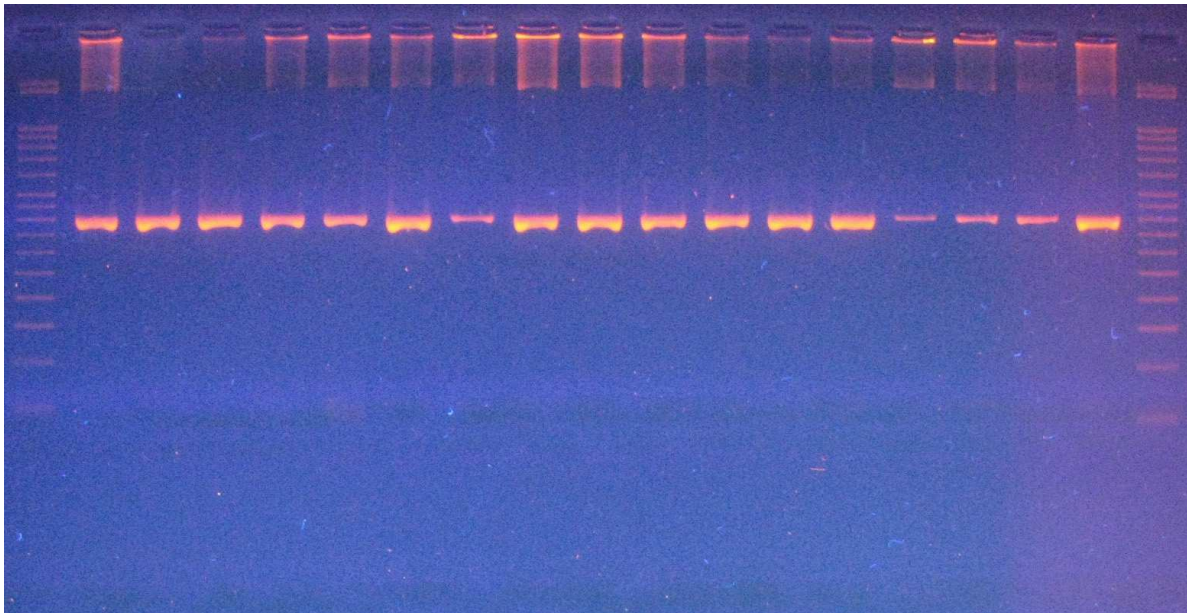


Fig. 17. Electroforetogram from PCR-RELP analysis (agaros gels colored with etidium bromide and photographed on ultraviolet light)

8. Discussion

IPB is found in both genders, with discretely higher representation in males. Our study shows that the gender representation for 32 patients with clinically confirmed diagnosis of JPB, by Brain Bank Criteria, is 18 males (56.25%) and females (43.75%). In most studies, as those of Haksma and all. (2007), Lions and all (2009); Linder and all. (2010), conducted in different periods and different populations, the results have big similarity with ours (8, 17, and 12).

In our study the average age of the respondents is 52.7 years. The youngest is only 30 years and the oldest is 78 years. The median value (50 years) shows that 16 respondents (50%) are in the age group of 50-59 years, and even 23 patients (71.87%) are older than 50 years (table 2, picture 2 from the results).

From the analyzed articles about the average beginning of IPD, dominant are those where the average beginning is in the sixth decade from life [21, 16, and 1].

Alves and all. (2009) in their epidemiological study in Norway, conducted on 554 patients with IPD, noted that the average age for beginning of symptoms manifestation of IPD is 54.3 years (this fits perfectly with the average age of our 32 respondents) [1].

Bradykinesia or the of stutment in movements, as main from the list of cardinal symptoms according to Brain Bank Criteria of UK Parkinson's Disease (BBC-UKPCD), was present in all respondents. According to BBC-UKPCD criteria, to set the JPD diagnosis, the patient should have bradykinesia plus one of the rest cardinal symptoms such as tremor, rigidity or reduced postural reflexes. With the presence of only 2 symptoms (from which one must be bradykinesia) IPD can be confirmed.

Bradykinesia as cardinal symptom according to UPRDS, was estimated in the following way: 15 patients (47.87%) with 1; 10 (31.25%) with 2; 5 (15.62%) with 3 and only 2 respondents (6.25%) with 4 according to UPRDS scale.

Stefanie Lui and all. (2009) in their study make analysis of the development of bradykinesia as symptom in different disease stadiums. According to them, the disease progression is influenced from the bradykinesia as main cardinal symptom [19].

When our respondents are in question, in only one of them (3.12%), the lack of symptom reduced postural reflexes was confirmed and its value was 0, according to UPDRS scale. In our respondents, 75% had reduced postural reflexes, estimated with 1; 5 (15.62 %) with 2 and 1 (3.12%) were with values of 3 and 4.

Spildoren I and all. (2010), in their article described the postural instability as common and very important symptoms in IPD. In their patients, this instability is seen through partial walking instability in the initial disease stadium and as freezing phenomena in the advanced disease stadiums. According to them, the freezing phenomena are often expressed in simultaneous double activities and in the act of turning after short walking [13].

Kerstin Ziegler and all. (2010), describe festination and freezing in all 33 patients with more advanced stadium of IPD. The way they estimated festination and freezing in walking, was with 12 episodes walking capturing, in which motor block was seemed in 4 situations with 3 levels of double activities. Practically, these phenomenas are reflected in parameters expressed by measuring the number of steps of those patients, walking on special stripe and analysis on walking on distance of 10 meters. This is how you make assessment on expression of the postural instability [14].

Besides bradykinesia, as main cardinal symptom, as symptoms od IPD, are also found tremor and rigidity. We've found their presence in all our respondents (100%).

Tremor is estimated with 2, according to UPDRS scale in 18 respondents (56.25%); 10 (31.25%) with 1; 3 (9.4%) with 3 and only one patient (3.1%) we've found tremor estimated with 4.

Petra Vingensuh and all (2010) conducted examination on 25 respondents in initial stadium of IPD. In all of them, unilateral tremor pointed with bradykinesia was found, and it was possible to make diagnosis. Additionally, all these patients gained SPECT testing and in only 10% a proper finding of SPEKT was found. Lately, a number of articles are published, which through examination of cardinal secondary symptoms in patients with IPD, make analysis on their life quality. In our article, the estimation of the immensity of the clinical state was made using the UPDRS scale, which is generally accepted and applied in most scientific articles for Parkinson's disease [6].

The correlation between respondents' age and the immensity of the clinical state, estimated according to UPDRS scale, is shown in picture 26 in our results. This relation points the existence or negative correlation. Parkinson's disease has fairly difficult clinical state in younger patients and vice versa; the disease is manifested with lighter symptoms in elder patients. But, considering the coefficient value, we can conclude the correlation between these two parameters is statistically insignificant ($p > 0.05$).

Barone P and all. (2009), this multicentric article shows the frequency of the nonmotor signs and symptoms such as hyposmia, mood, sleeping, tiredness, perception difficulties, attention, memory capacity, erectil disfunction [3].

All these signs are examined in patients on different disease stadiums, and than analyzed to present their influence on the life of these patients.

The authors monitor 524 patients with Parkinson's disease, and they register their nonmotor symptoms and their influence on patients' life in different disease stadiums. They stated, that in younger patients the clinical state is tougher according to UPDRS, comparing to elder patients. Also, the study witnessed that disease progression is much faster in younger patients comparing to elder patients [3].

Keush SH and all. (2009), conducted their clinical examination of motor and nonmotor symptoms of Parkinson's disease in Holland. The authors developed a specific scale through which, the possibilities and capabilities for daily activities were analyzed, and according to which the degree of disease progression can be determined.

According to them, in younger patients we have faster symptoms progression, comparing to patients where the clinical state is manifested later [15].

The immensity of the clinical state of Parkinson's disease in our respondents of different gender, show that male patients have significantly tougher clinical state comparing to female patients.

Ivi Miler and Golomb AC (2010) made interesting, clinical-epidemiological study, in which is clearly shown that the disease is nearly equally manifested in two genders, but specific symptoms are more frequent in females and others in males. Motor symptoms which appear as a consequence of reduced function of dopaminergic system, those which we often examine, are dominant in males, and only rigidity as motor symptoms and nonmotor signs are dominant in females [11].

It is assumed that this difference in manifestation by gender, most likely, is influenced by unknown hormonal mechanisms.

From the list of the neuropsychological examinations, the respondents gained: visual evoked potentials (VEP); somatosesoral evoked potentials (SSEP); caustic evoked potentials (BAEP) and electroencephalography (EEG). Generally in our 32 respondents, the most

findings for evoked potentials (VEP, SSEP and BAEP) are proper. Proper VEP is found in 29 respondents (90.6%); prolonged latencies and low-volted responses are found in 2 (6.3%) and only in 1 respondent (3.1%), the finding is with low-volted response.

SSEP is with proper finding in 30 respondents (93.8%) and low-volted responses are found in 2 (6.2%). Proper BAEP finding is found in 22 (68.72%) and low-volted different components are found in 10 (31.25%).

In our patients, neuroimaging examination (CT and MRI of brain) are made; 37.5% have proper results; in 34.4% of them discrete cortical reduced changes are found and in 28.1% the pathological process is manifested with global cortical reduced changes.

Doppler color sonography on extra cranial blood vessels, shows proper finding in 62.5% of the respondents; in 21.9% lightly expressed intimacy and proper chemo dynamic parameters are found; in 15.6% of our patients have arteriosclerotic changes of the carotid blood vessels.

Lio CH and all. (2010) made a study on 84 patients with IPD, without dementia signs. They made several short capturing with MRI of brain, examining the regions which are most often damaged in these patients. Patients with medium developed clinical state were selected. They also had plenty symptoms and the exact regions which influenced the domination on specific motor and nonmotor symptoms, were determined. Dementia as a symptom was excluded [4].

Table 11a and 11b from our results, presents the results from the neuropsychological testing. Proper cognitive capacities of testing were found only in 3 patients with IPD. Between the patients dominant are those with depression and initial reduced cognitive capacities (34.4%), as well as 31.2% with global reduced cognitive capacities.

According to the frequency of occurrence, next is the finding of depression and global reduced cognitive capacities, found in 9.4% of our respondents.

The rest findings of the neuropsychological testing: depression in behavior, anxiety in behavior, initial reduced cognitive capacities; depression and anxiety in behavior, as well as the mutual presence of depression and anxiety in behavior and initial reduced cognitive capacities are found only in 1 patient with IPD.

Lately, in different magazines and congresses, scientists try to prove the correlation between the IPD and depression as secondary symptom, as well as, dementia, found in high percent of patients with Parkinson's disease.

Ivi N Miler and Golumb AC (2010) made interesting clinical and epidemiological study, where they proved that the disease is nearly equally manifested in both genders. But, certain symptoms more often appear in females and other in males. Etiopathogenetical mechanisms for these symptoms division, is still unknown, but it is assumed that the hormonal status influences on manifestation of these symptoms. Consequently, the nonvoter symptoms (mood, hyposmia, sleeping, attention, memory, perception difficulties and depression) are dominant in females [11].

Huijuan Li and all. (2010), made a study on 82 Chinese patients, 46 males and 36 females with IPD, which lasted 18 months. Patients were on average age of 65 years. Generally, they examined the motor signs such as: mood, sleeping, depression, attention, memory capacity and perception disorder. To determine the degree of disease, the authors used UPDRS scale. Then using a special scale for determination of nonmotor symptoms development, they determined the degree of these symptoms. They concluded that there is a positive correlation between the development of the nonmotor and psychological symptoms in relation to the development of motor signs of the disease, according to UPDRS. Actually, all

these symptoms, nonmotor and motor, develop parallel, meaning that in the early disease stadiums, all symptoms are lightly developed, no matter what they are like, while in the more advanced stadiums, all symptoms are expressed and visible [10].

Ajlin Juxel and all. (2010) in their study of 28 patients with IPD, conducted in Turkey, made multiple capturing with nuclear magnetic resonance on brain (MRI), measuring the thickness of brain callus in different brain regions. A correlation between the immensity of the clinical state, determined by UPDRS scale and the finding from MRI (measurement of the brain callus thickness), was set. The authors concluded that the thinner brain callus is, the more developed the clinical state of patients with IPD is [2].

In our study, G88C mutation in egzon 3 form SNCA genes isn't detected in our 32 respondents with IPD. The same happens with G209A in egzon 4 form SNCA gene.

Sutherland GT and all (2009) in their immense study conducted on Australian population, of 331 patients with scattered form and family form of Parkinson's disease and 296 healthy people. The authors examined 11 known genes and all kinds of combinations of these genes correlations with symptoms manifestations of Parkinson's disease. They concluded that only LRRK2 gene has hardly any influence only in the family form of Parkinson's disease, while the rest genes, between which SNCA, have no influence at all in scattered Parkinson's disease manifestation in Australians, a result which fits the findings of our research [20].

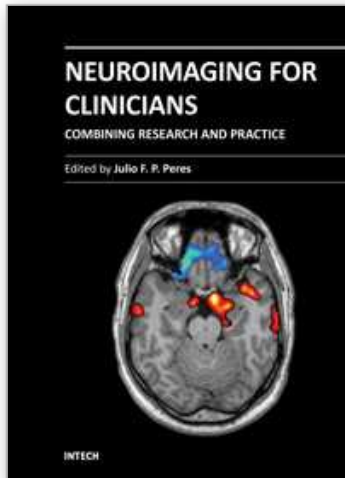
Sarah Kamargos and all. (2009) made a study to evaluate the frequency and the phenotypical and genotypical manifestation in family and scattered forms of Parkinson's disease in Brazilian population. The examination was conducted on 575 patients with Parkinsonism, where the ones with IPD are 428. Mutations and polymorphisms on many different genes, typical for Parkinson's disease, such as alpha synuclein and LRRK2 gene, were examined. In the end, they concluded that there wasn't any mutation on alpha synuclein in all respondents and in only one patient with initial symptoms of IPD, a slight mutation of LRRK2 gene, was found [18].

Kristian Vajder and all. (2009), made immense study on 1262 patients with IPD and control group of 1881 patient. They checked the correlations between the fibroblastic growing factor 20 and alpha synuclein in patients with Parkinson's disease. They examined their correlations on 9 brains on deceased patients, which were previously diagnosed with IPD. The authors concluded that the role of alpha synuclein in Parkinson's disease is undisputable, but the changes in sequences in this gene, were negative [5].

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Neuroimaging for clinicians sourced 19 chapters from some of the world's top brain-imaging researchers and clinicians to provide a timely review of the state of the art in neuroimaging, covering radiology, neurology, psychiatry, psychology, and geriatrics. Contributors from China, Brazil, France, Germany, Italy, Japan, Macedonia, Poland, Spain, South Africa, and the United States of America have collaborated enthusiastically and efficiently to create this reader-friendly but comprehensive work covering the diagnosis, pathophysiology, and effective treatment of several common health conditions, with many explanatory figures, tables and boxes to enhance legibility and make the book clinically useful. Countless hours have gone into writing these chapters, and our profound appreciation is in order for their consistent advice on the use of neuroimaging in diagnostic work-ups for conditions such as acute stroke, cell biology, ciliopathies, cognitive integration, dementia and other amnesic disorders, Post-Traumatic Stress Disorder, and many more

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