CLINICAL STUDY

Clinical, neurophysiologic, neuropsychological findings and short genetic analysis in patients with idiopathic Parkinson’s disease

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Abstract: The aim of this paper is to analyze the results of correlation of clinical symptoms and their characteristics with the results of neurophysiologic, neuropsychologic investigations and short genetic analyses in patients with Idiopathic Parkinson’s disease (IPD).

Material and methods: The paper is a prospective and retrospective study of 15 IPD patients and 25 patients with different forms of parkinsonism.

Results: Patients with idiopathic Parkinson’s disease had all cardinal symptoms characteristic for the disease: tremor, rigidity and reduced postural reflexes in 100 %. Conclusion: Clinical, neurophysiologic, neuropsychologic and neuroimaging methods of investigations showed changes that are nonspecific in proportions corresponding to those in available literature (Tab. 3, Fig. 2, Ref. 11). Full Text (Free, PDF) www.brnj.sk.

Key words: clinical, neurophysiologic, genetic, Idiopathic Parkinson’s Disease.

Idiopathic Parkinson’s Disease (IPD) is a syndrome that responds to favourable clinical results in treatment with dopamine agonists or levo-dopa preparations, manifests a characteristic clinical picture and typical tremor resembling the counting of money. The crucial change in IPD was the impaired dopaminergic transmission in basal ganglia. Idiopathic parkinsonism was represented in 80 % of the patients with parkinsonism. Apart from the fact that dopamine cell apoptosis is the primary neurologic deficit in idiopathic Parkinson’s disease, its cause remains unknown (1).

Gait disturbances in PD correspond to sensory disturbances that affect the sensomotor integration. They point out the possible contribution of the neurophysiologic technique in evaluating the functionality of sensomotor integration mechanism in PD. SEP is a corresponding method of evaluating the sensory processes in the brain. They indicate that especially in the early stage of their diseases, the IPD patients show a strongly impaired frontal response to sensory stimuli tested through SEP. Neurophysiological methods used showed that there was a functional disturbance in some parts of the central nervous system (CNS). In IPD, the EEG finding was positive in some patients.

Szargel, Engelender et al (2), identified a protein, synphilin-1 that interacts with alpha synuclein, and it is possible that the latter interaction indirectly causes familial Parkinson’s disease (PD). Their results suggest a novel function for synphilin-1A as a regulator of SIAH activity and formation of Lewy body-like inclusions.

Karz et al (3) proved the role of genetic factor in the development of PD. The first association between alpha-synuclein and neurodegenerative diseases was reported by Ueda et al (4). These authors showed that the short amyloids, referred to as a non-amyloid components (NAC), present in cleaned amyloid plaques in patients with Alzheimer disease, originated from greater protein precursors that are today known as alpha-synuclein (then they were referred to as non-amyloid component precursors or NACP).

Two nonsense mutations in alpha-synuclein gene, namely A53T and A3OP, started to relate with rare cases of IPD presenting early in families with European descent. Aggregation and accumulation of this abnormal α-synuclein protein in dopaminergic neurons was postulated as being responsible for the consequence of neurodegeneration (5).

Material and methods

This article represents a prospective retrospective study in 15 patients with IPD and 25 patients with different forms of parkinsonism.

Materials used in this study came from the University Clinic of Neurology in Skopje, the Unit for Extrapyramidal Diseases.

Clinical and neurophysiological materials were analyzed within one year (2008 to 2009), while the genetic and epidemiologic observations within a 10-year period (1993–2002).
The interviewees were 15 patients with idiopathic Parkinson’s disease, with a mean age of 50.13 years, ten of whom were men (66.6 %) and five were women (33.3 %).

At the same Neurology Clinic, the patients underwent detailed anamnesis, detailed clinical neurologic examinations and investigations as follows:
- neurophysiologic investigations: EEG, EMG, EP (SEP, VEP, BAEP);
- neuroimaging investigations (CT, MRI);
- Doppler of extracranial and intracranial blood vessels and
- neuropsychological investigations.

EEG was made on 18-channel “Galileo” apparatus in four standard montages where the electrodes were placed on the skull according to 10–20 International System. EMG was performed on “Kantata” apparatus with needle electrode of conduction. VEP (visual evoked potentials) were made by means of the apparatus for evoked potentials “TÖNNIS” with visual “Heiziff-shift” stimulation according to standardized technique. SEP (somatosensory evoked potentials) was made on the same apparatus for EP when median and tibial nerves were stimulated. BAEP was stimulated with a clicking sound of minimal strength to one ear while the other was masked with noise. EPs were received by means of electrodes placed on vertex and mastoid.

Doppler of the blood vessels was made on Colour duplex sonograph “TOSHIBA”, at the University Clinic of Neurology in Skopje.

From neuropsychological tests, the following were used: mini-mental test, Wechsler intelligence test, Ray test, Ray-Osterit complex figure, Huger test for visual orientation, Boston test and Minnesota Multiphasic Personality Inventory.

Genetic investigation was a retrospective-observational analysis of genealogical trees in families with positive anamneses (epidemiologic and statistical analyses).

**Results**

In all 15 patients with IPD, i.e. in 100 % of the examinees, the following cardinal symptoms for this disease were present: tremor, rigor and reduced postural reflexes in 100 %. Bradykinesia as a cardinal symptom was present in 12 (80 %) of 15 patients and bradylalia as a symptom was present in 8 (53.3 %) of all 15 patients.

As to neurophysiologic methods, the EEG was nonspecifically changed in 4 (26.6 %) of 15 patients with IPD. EEG was in normal boundaries in other 11 patients.

VEP, BAEP and SEP were low-volted in 5 (33.3 %) of the patients; other neurophysiologic findings were normal.

Cortical reduction changes shown on CT and MRI of the brain were recorded in 10 (66.6 %) of all 15 patients.

Slightly thickened blood vessels intima of carotid system were recorded in 4 patients (26.6 %). When neuropsychologically investigated, elements of depression were recorded in 6 (40 %), while in other 3 (20 %) of the 15 IPD patients, global cognitive mnestic deficit was recorded.

Concerning the existence of heredity in patients with IPD, positive familiar anamnesis was present in 25 (10.5 %) of the total of 239 interviewed persons (Fig. 1).

Of 25 interviewees with positive familial anamnesis, 14, i.e. more than a half, gave evidence that his/her father was a carrier of such a type of disease in the family, only in 3 (12 %), the mother was diseased with parkinsonism (Tab. 1, Fig. 2).

The question as to whether anyone in his/her close family suffered from parkinsonism, was affirmatively responded by 25 (10.46 %) of the examinees. However, the anamnesis was positive in 18 (7.5 %) of IPD patients, 5 (2.1 %) with secondary parkinsonism and 2 (084 %) with Parkinson plus syndrome.

The number of examinees with idiopathic parkinsonism, without such disease in the family, namely 170 (71.13 %), made the statistically significant difference among the three groups

**Tab. 1. Familial anamnesis – distribution.**

<table>
<thead>
<tr>
<th>FA</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brother</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Father</td>
<td>14</td>
<td>56</td>
</tr>
<tr>
<td>Sister</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Mother</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

**Fig. 1.** Familial anamnesis in patients with PD and SP.

**Fig. 2.** Positive familial anamnesis for PD distribution.
Tab. 2. Representation of patients with a positive familial anamnensis of parkinsonism.

<table>
<thead>
<tr>
<th>FA</th>
<th>IP</th>
<th>SP</th>
<th>PPS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>170</td>
<td>25</td>
<td>19</td>
<td>214</td>
</tr>
<tr>
<td>%</td>
<td>71.13</td>
<td>10.46</td>
<td>7.95</td>
<td>89.54</td>
</tr>
<tr>
<td>Yes</td>
<td>18</td>
<td>5</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>%</td>
<td>7.3</td>
<td>2.09</td>
<td>0.84</td>
<td>10.46</td>
</tr>
</tbody>
</table>

Total: No | 188 | 30 | 21 | 239 |
| % | 78.66 | 12.55 | 8.79 | 100 |

Tab. 3. Distribution of patients with familial parkinsonism.

<table>
<thead>
<tr>
<th>FA</th>
<th>IP</th>
<th>SP</th>
<th>PPS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brother</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>%</td>
<td>4.0</td>
<td>8.0</td>
<td>0</td>
<td>12.0</td>
</tr>
<tr>
<td>Father</td>
<td>No</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>%</td>
<td>40.0</td>
<td>8.0</td>
<td>8.0</td>
<td>56.0</td>
</tr>
<tr>
<td>Sister</td>
<td>No</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>%</td>
<td>16.0</td>
<td>4.0</td>
<td>0</td>
<td>20.0</td>
</tr>
<tr>
<td>Mother</td>
<td>No</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>%</td>
<td>12.0</td>
<td>0</td>
<td>0</td>
<td>12.0</td>
</tr>
</tbody>
</table>

Total: No | 18 | 5 | 2 | 25 |
| % | 72.0 | 20.0 | 8.0 | 100 |

of examinées, and in relation to positive/negative familial anamnensis (U=0.0, p=0.049) (Tab. 2).

By Kruskal-Wallis test, the difference among the examinées with idiopathic, secondary and Parkinson plus syndrome was tested in relation to the fact as to which member in their family was ill with parkinsonism.

The obtained results indicated that it was the father, who suffered most frequently from this disease. The latter evidence was given by ten patients (40 %) with idiopathic parkinsonism, 2 (8 %) with secondary and 2 (8 %) with Parkinson plus syndrome. The incidence of positive familial anamnese was due to diseased brothers, sisters and mothers of the examinées was less significant. The difference tested was significant for the test value of H=5.48 and p=0.06 (Tab. 3).

Discussion

In order to complete the “mosaic” of diagnosis and to explain the ethiology of this syndrome, it is necessary to complement clinical and neurological examination methods together with other morphologic and psychologic investigations.

Namely the clinical investigations showed the neurologic symptoms and the engaged parts of the extrapyramidal system in patients with parkinsonism, while the neurophysiological methods provide objective and relevant information for the functioning abnormalities of adequate systems in CNS. Combined usage of various neurophysiological techniques (EEG, ENG, VEP, SEP, BAEP) could assist the diagnosis, and together with the morphological and psychological methods and the etiology of the disease, the correct classification and differentiation from other diagnosis with similar clinical presentation.

The usage of neurophysiological methods of examination showed that some parts of the CNS were functionally disturbed. In IPD, the EEG finding has been positive in a number of patients, especially in those of younger age. Takeuchi and Osawa [6], stated that unstable background activity was recorded in about 17 % of the patients with early manifestation of IPD with non-specific changes on EEG. Also in our row of 15 patients with IPD, we found nonspecific EEG changes in 4 patients (26.6 %) who actually were the youngest patients in this group.

Uday et al. (7), described changes in low-voltaged evoked potentials (sensory and auditory) in 23 patients with early manifestation of IPD. In their study, they did not show any significant difference in the changes in evoked potentials between the younger and more adult patients. These findings are compatible with the findings of our study, where the changes in evoked potentials were recorded in 5 patients (33.3 %) out of the total of 15 patients with IPD. The changes in evoked potentials in our patients, as well as in the above mentioned study, were low-volted and with no other more specific changes.

Pauletti and Tosco (8) report the results of neuropsycho logical and CT investigations they made in 30 patients with IPD. They found that deficits in cognitive functions were recorded in almost one third of the patients. Almost similar results were obtained also in our patients, namely two thirds of the patients or 10 (66.6 %) were found to suffer from a global cognitive deficit.

Ross OA et al. (9) in their study stated that heredity as an etiologic factor was most frequently expressed in idiopathic parkinsonism. In this study they also described the role of polymorphisms in alpha-synuclein gene in correlation with sporadic and idiopathic forms of parkinsonism.

According to the results of investigation of the possible genetic defect in patients with idiopathic parkinsonism done by Shushant Jain, Nicholas Wood and Daniel Healy from the Institute for Neurology in Queen Square in London (10), the same defect has not been present in all persons suffering from this type of parkinsonism. In addition to the latter finding, on the basis of various genetic analyses, they found out that some genetic changes similar to those found in patients with parkinsonism were detected also in their symptomless relatives. This led the latter scientists to state that in some people, the genetic factor gives a predisposition for the development of parkinsonism, however without the parallel influence of other factors they do not manifest the symptoms and signs for this disease at all. The statement of the British Parkinsonism Institute is that one of the etiologic factors for the development of parkinsonism is the genetic factor, however it is not the leading and decisive cause inducing the occurrence of this syndrome.

Gloeckner CJ et al. (11) present evidence of a new class of molecular targets for mutant LRRK2 that links neurotoxicity, cellular stress, cytoskeletal dynamics and vesicular transport. Despite this, the evidence that G2019S and I2020T mutations show definitely Idiopathic Parkinson disease is not unambiguous.
Up to now, it has been thought that IPD occurs in mutual action of age and external factors, and that the genetic factor plays a minimum role. But the results of extended origin and family aggregation studies of genetic predisposition to sporadic parkinsonism show that the genetic component is still a valuable factor in assuming whether parkinsonism is going to be manifested at older age. As already mentioned, using the widened family nuclei and the analysis of their connection, some of genetic components for PD were found. Because these mutations were very dangerous for families and their members, they gave the science the possibility to penetrate the pathogenesis of this disease. Meanwhile, this does not still help us discover definitely the role of the genetic factor in the usual sporadic form of IPD. In fact, it could serve as an argument that there actually was no irrefutable genetic factor associated with the increase in the risk of manifestation of sporadic PD.

References


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