Correlation Between the Age, Motor Subtypes and the Necessity of Advanced Therapy in Parkinson Disease

OANA CRICIUTOIU1, DIANA IULIA STANCA2*, SIMONA BONDARI1, RAMONA- DENISE MALIN3, MIRCEA-SORIN CILOFAN4, MICHAEL SCHENKER1, MIOARA DESDEMONA STEFAN5, FLORENCI MARIUS ROMANESCU6, OVIDIU STEFAN GEORGESCU7, LUCIAN PAUL DRAGOMIR1, VICTOR GHEORGMAN8, VERONICA GHEORGMAN9, DAN IONUT GHEONEA11

1University of Medicine and Pharmacy of Craiova, Doctoral School, 2 Petru Rares Str., 200349, Craiova, Romania
2 University of Medicine and Pharmacy of Craiova, Faculty of Medicine, Department of Neurology, 2 Petru Rares Str., 200349, Craiova, Romania
3University of Medicine and Pharmacy of Craiova, Department of Radiology and Medical Imaging, County Hospital of Craiova, 1 Tabaci Str., 200642, Craiova, Romania
4University of Medicine and Pharmacy of Craiova, Faculty of Medicine, Department of ORL, 2 Petru Rares Str., 200349, Craiova, Romania
5University of Medicine and Pharmacy of Craiova, Oncology Department, 2 Petru Rares Str., 200349, Craiova, Romania
6University of Medicine and Pharmacy of Craiova, Department of Pediatrics, 2 Petru Rares Str., 200349, Craiova, Romania
7University of Medicine and Pharmacy of Craiova, Department of Physiology, 2 Petru Rares Str., 200349, Craiova, Romania
8University of Medicine and Pharmacy of Craiova, Department of Radiology and Medical Imaging, County Hospital of Craiova, 1 Tabaci Str., 200642, Craiova, Romania
9University of Medicine and Pharmacy of Craiova, Psychiatry Department, Neuropsychiatry Hospital of Craiova, 24 Aleea Potelu Str., 200473, Craiova, Romania
10 University of Medicine and Pharmacy of Craiova, Faculty of Medicine, Department of Neurology, 2 Petru Rares Str., 200349, Craiova, Romania
11University of Medicine and Pharmacy of Craiova, FEU of Medicine, 1 Tabaci Str., 200642, Craiova, Romania

Levodopa (L-dopa), a precursor of dopamine, remained the gold standard among antiparkinsonian drugs and virtually, in different stages, all patients will require the more powerful symptomatic effect of L-dopa. In addition, continuous Levodopa/Carbidopa intestinal gel (LCIG) infusion therapy, via a percutaneous endoscopic gastrostomy (PEG) and a portable infusion pump, is well established for the treatment of advanced Parkinson’s disease (PD), substantially improving motor symptoms and quality of life in these patients. This study aimed to evaluate the necessity of LCIG depending the PD motor subtypes and age at onset of the disease. Seventy patients diagnosed with PD were included in our study. The Unified Parkinson’s Disease Rating Scale (UPDRS) was performed in on state. The patients were classified as tremor-dominant type (TDT), akinetic-rigid type (ART) and mixed type (MT). Depending on form of levodopa, thirty-six patients were on L-dopa orally and thirty-four patients were on LCIG. The results of our study showed that there was a statistically significant correlation between the age at onset of PD and the motor subtype of the disease. Also, we observed that the lower the age at diagnosis, the more our patients have reached the need for LCIG. Regarding the motor subtype, our study showed that the mixed typed request more frequent LCIG. Our data show that age and motor profile at onset can predict the necessity of advanced therapy.

Keywords: levodopa, oral administration, intrajejunal gel, Parkinson disease, age

Correlation Between the Age, Motor Subtypes and the Necessity of Advanced Therapy in Parkinson Disease

Levodopa (L-dopa), a precursor of dopamine, remained the gold standard among antiparkinsonian drugs and virtually, in different stages, all patients will require the more powerful symptomatic effect of L-dopa. In addition, continuous Levodopa/Carbidopa intestinal gel (LCIG) infusion therapy, via a percutaneous endoscopic gastrostomy (PEG) and a portable infusion pump, is well established for the treatment of advanced Parkinson’s disease (PD), substantially improving motor symptoms and quality of life in these patients. This study aimed to evaluate the necessity of LCIG depending the PD motor subtypes and age at onset of the disease. Seventy patients diagnosed with PD were included in our study. The Unified Parkinson’s Disease Rating Scale (UPDRS) was performed in on state. The patients were classified as tremor-dominant type (TDT), akinetic-rigid type (ART) and mixed type (MT). Depending on form of levodopa, thirty-six patients were on L-dopa orally and thirty-four patients were on LCIG. The results of our study showed that there was a statistically significant correlation between the age at onset of PD and the motor subtype of the disease. Also, we observed that the lower the age at diagnosis, the more our patients have reached the need for LCIG. Regarding the motor subtype, our study showed that the mixed typed request more frequent LCIG. Our data show that age and motor profile at onset can predict the necessity of advanced therapy.

Keywords: levodopa, oral administration, intrajejunal gel, Parkinson disease, age

Correlation Between the Age, Motor Subtypes and the Necessity of Advanced Therapy in Parkinson Disease

Levodopa (L-dopa), a precursor of dopamine, remained the gold standard among antiparkinsonian drugs and virtually, in different stages, all patients will require the more powerful symptomatic effect of L-dopa. In addition, continuous Levodopa/Carbidopa intestinal gel (LCIG) infusion therapy, via a percutaneous endoscopic gastrostomy (PEG) and a portable infusion pump, is well established for the treatment of advanced Parkinson’s disease (PD), substantially improving motor symptoms and quality of life in these patients. This study aimed to evaluate the necessity of LCIG depending the PD motor subtypes and age at onset of the disease. Seventy patients diagnosed with PD were included in our study. The Unified Parkinson’s Disease Rating Scale (UPDRS) was performed in on state. The patients were classified as tremor-dominant type (TDT), akinetic-rigid type (ART) and mixed type (MT). Depending on form of levodopa, thirty-six patients were on L-dopa orally and thirty-four patients were on LCIG. The results of our study showed that there was a statistically significant correlation between the age at onset of PD and the motor subtype of the disease. Also, we observed that the lower the age at diagnosis, the more our patients have reached the need for LCIG. Regarding the motor subtype, our study showed that the mixed typed request more frequent LCIG. Our data show that age and motor profile at onset can predict the necessity of advanced therapy.

Keywords: levodopa, oral administration, intrajejunal gel, Parkinson disease, age

Parkinson disease is a neurodegenerative disorder caused by substantia nigra neuronal loss and Lewy body inclusions and presented in a variety of ways[1].

The classical triad of motor symptoms includes resting tremor, akinesia and rigidity. However, the expression of these cardinal motor symptoms varies markedly between patients. PD, a heterogeneous condition, can be classified into different subtypes: tremor-dominant type (TDT), akinetic-rigid type (ART) and mixed type (MT) [2].

Many studies support the idea that akinesia-rigidity phenotype and tremor-dominant phenotype reflect different pathophysiological phenomena in the basal ganglia [3-4].

Also, clinical observations suggest that distinct subtypes of PD have a different clinical course. It has been shown that patients with ART develop a faster clinical progression with more severe cognitive deficits[5]. These data were confirmed in pathological studies, which showed that the more favorable course of TDT was related with a less widespread pallidal and striatal reduced dopamine level in comparison with ART [6].

Levodopa/carbidopa intestinal gel is an advance therapy first established in Scandinavian countries and then extended to other European countries. With this treatment, although invasive and expensive and requiring special experiences, the patients with refractory fluctuations and dyskinesias can achieve marked and sustained improvement[7-8].

In our study we want to evaluate the necessity of advanced therapy depending of motor subtype of Parkinson’s disease and, also, if there is a possible correlation between the patient’s age at diagnosis and motor subtype of this disease.

Experimental part

Methods and Materials

We studied 70 cases (28 females and 42 males), mean age 67.79 ± 7.77 years, diagnosed with PD according with widespread pallidal and striatal reduced dopamine level in comparison with ART [6].

Levodopa/carbidopa intestinal gel is an advance therapy first established in Scandinavian countries and then extended to other European countries. With this treatment, although invasive and expensive and requiring special experiences, the patients with refractory fluctuations and dyskinesias can achieve marked and sustained improvement[7-8].

In our study we want to evaluate the necessity of advanced therapy depending of motor subtype of Parkinson’s disease and, also, if there is a possible correlation between the patient’s age at diagnosis and motor subtype of this disease.

Experimental part

Methods and Materials

We studied 70 cases (28 females and 42 males), mean age 67.79 ± 7.77 years, diagnosed with PD according with widespread pallidal and striatal reduced dopamine level in comparison with ART [6].

Levodopa/carbidopa intestinal gel is an advance therapy first established in Scandinavian countries and then extended to other European countries. With this treatment, although invasive and expensive and requiring special experiences, the patients with refractory fluctuations and dyskinesias can achieve marked and sustained improvement[7-8].

In our study we want to evaluate the necessity of advanced therapy depending of motor subtype of Parkinson’s disease and, also, if there is a possible correlation between the patient’s age at diagnosis and motor subtype of this disease.

Experimental part

Methods and Materials

We studied 70 cases (28 females and 42 males), mean age 67.79 ± 7.77 years, diagnosed with PD according with widespread pallidal and striatal reduced dopamine level in comparison with ART [6].

Levodopa/carbidopa intestinal gel is an advance therapy first established in Scandinavian countries and then extended to other European countries. With this treatment, although invasive and expensive and requiring special experiences, the patients with refractory fluctuations and dyskinesias can achieve marked and sustained improvement[7-8].

In our study we want to evaluate the necessity of advanced therapy depending of motor subtype of Parkinson’s disease and, also, if there is a possible correlation between the patient’s age at diagnosis and motor subtype of this disease.

Experimental part

Methods and Materials

We studied 70 cases (28 females and 42 males), mean age 67.79 ± 7.77 years, diagnosed with PD according with widespread pallidal and striatal reduced dopamine level in comparison with ART [6].

Levodopa/carbidopa intestinal gel is an advance therapy first established in Scandinavian countries and then extended to other European countries. With this treatment, although invasive and expensive and requiring special experiences, the patients with refractory fluctuations and dyskinesias can achieve marked and sustained improvement[7-8].

In our study we want to evaluate the necessity of advanced therapy depending of motor subtype of Parkinson’s disease and, also, if there is a possible correlation between the patient’s age at diagnosis and motor subtype of this disease.
United Kingdom Parkinson’s Disease Society Brain Bank criteria[9]. For each patient details of demographic data, age at onset, disease duration, symptoms at onset, medications, motor fluctuations, L-dopa induced dyskinesia and family history were recorded. The patients were assessed using United Parkinson’s Disease Rating Scale - motor section (UPDRS part III) [10]. The Hoehn and Yahr Scale was used for disease staging. Both scale (UPDRS and Hoehn and Yahr scale) were evaluated while the patients were in on state, all patients receiving L-dopa (either orally, or intrajejunal)[11].

The subgroups of PD that include TDT, ART and MT were classified by means of UPDRS part III, using a method similar with Lewis at all [12]. First, we calculated a tremor score from the sum of item 20 of UPDRS (tremor at rest) and 21 (action and postural tremor) divided at 7 (the number of single subitems). Then, we calculated a non-tremor score from the sum of UPDRS item 18 (speech), 19 (facial expression), 22 (arising from chair), 28 (posture), 29 (gait), 30 (postural instability) and 31 (body bradykinesia and hypokinesia), divided by 12 (the number by single subitems).

For the non-motor symptoms we used Non-motor Symptoms Questionnaire for Parkinson’s Disease (NMSQ). It is an questionnaire with 30 items and different non-motor domain like memory, sleep, gastrointestinal and others[13].

The patients were classified as TDT if the tremor score was at least twice the non-tremor score, or ART if the non-tremor score was at least twice the tremor score. The remaining patients, in whom the tremor score and non-tremor score differing by less than a factor 2, were classified as MT.

The statistical analysis was performed using IBM SPSS Statistics V20. We made descriptive and exploratory data analysis. For comparison we used Pearson R correlation - test, the statistical significance was established when p<0.05.

Results and discussions:

We included in this study 70 patients with PD, 28 females and 42 males. When analyzing the provenience there were 32 form rural areas and 38 from urban areas. The disease stage was between 1 and 5 with an average of 3.21 and a standard deviation of 0.99. Age of onset was between 38 and 76 years with an average of 58.2 years. After we analyzed the motor type of the disease using UPDRS part III there were 24 patients in the tremor dominant type, 26 in the akinetic-rigid type and 30 in the mixed type (table 1).

This study revealed statistically significant correlation with p<0.001 between the motor subtype of PD and the administration form of L-dopa. Therefore, it seems that the mixed type is treated especially with LCGI infusion therapy (table 2, fig. 1).

Our study analysis showed that the patient age at diagnosis could have an important meaning. In the group we have studied there was a statistically significant correlation with p=0.007 between the age at onset and the motor subtype of the disease. This shows that the tremor-dominant form of the disease is more likely diagnosed at an older age then the other forms. Also, it seems that our younger PD patients at diagnosis presented predominantly a mixed form (fig. 3,table 2)

| Variable          | N/a Patients(N=70) |
|-------------------|--------------------|
| Sex               |                    |
| Male              | 42                 |
| Female            | 28                 |
| Average age (years)| 67.69              |
| Disease duration  | 9.49               |
| Hoehn & Yahr Stage| 3.21               |
| Sex UPDRS motor   | 49.83              |

Fig. 1. Correlations between administration form and motor subtype

![Table 2](image)

**This table shows the correlations between administration form and motor subtype.**

**Table 2**

| Administration form | Pearson Correlation | Sig (2-tailed) | N |
|---------------------|---------------------|----------------|---|
| LCGI                | -0.27               | 0.03           | 70|
| Oral                | 0.06                | 0.60           | 60|

**Correlations between age of onset and motor subtype**

![Table 3](image)

**Table 3**

| Age_of_Onset | Pearson Correlation | Sig (2-tailed) | N |
|--------------|---------------------|----------------|---|
| LCGI         | -0.32               | 0.007          | 70|
| Oral         | 0.04                | 0.59           | 60|

Fig. 2. Correlations between age of onset and motor subtype
There was a statistically significant correlation between the age of onset and the form of L-dopa administration with p < 0.001 (table 4).

In the figure above we can observe that there was a link between the age of onset and the form of L-dopa administration. It seems that while the age at diagnosis decrease it is more likely that those patients need for intrajejunal L-dopa/carbidopa administration (fig. 3).

Parkinson’s disease is a disorder with a variate symptomatology divided in motor and non-motor type. Akinetic-rigid and tremorogenic type has different performance once the disease progressed [6].

Currently, there is no cure for Parkinson’s disease. The therapy include oral medication (L-dopa, dopamine agonists, monoamine oxidase-B inhibitors, catechol O-methyltransferase inhibitors, anticholinergics), continuous Levodopa/Carbidopa intestinal gel (LCIG) infusion therapy and deep brain stimulation[14]. It is very important that patients receive the right therapy for their type and stage of the disease[15-19]. In our study the mixed type correlated with a frequent need advanced therapy.

Even if the presentation is the same regardless of the age group, there is a difference when we study the age at onset. In our study the mixed type presented a younger age at onset but in other studies the akinetic-rigid form has a higher prevalence on those patients[20].

Our study headlights the importance of the age of onset in PD and its importance on diagnosis and clinical management.

Conclusions
This study indicates that the age and motor subtype can be a predictor for the necessity of advanced therapy in Parkinson’s disease. The younger patients with a mixed form of the disease are the type that request more LCGI.

References
1. MATSUMOTO, H., SENGOKU, R., SAITO, Y., KAKUTA, Y., MURAYAMA, S., IMAFUKU, I., Sudden death in Parkinson’s disease: A retrospective autopsy study, Journal of the Neurological Sciences, vol. 343, 2014, pp. 149-152.
2. ZHANG, J., WEI, L., HU, X., XIE, B., ZHANG, Y., WU, G.-R., WANG, J., Akinetic-rigid and tremor-dominant Parkinson’s disease patients show different patterns of intrinsic brain activity. Parkinsonism & Related Disorders, vol. 21, 2015, pp. 23-30.
3. GOLDMAN, J. G., POSTUMA, R., Premotor and nonmotor features of Parkinson’s disease, Current Opinion in Neurology, vol. 27, 2014, p. 434-441.
4. HODOROG, D. N., SZALONTAY, A. S., Dopaminergic Centers Neurodegeneration Biochemical and radiologic approach, 2018, pp. 2015-2018.
5. SHALASH, A. S., HAMID, E., ELRASSAS, H. H., BEDAIR, A. S., ABUSHOUK, A. I., KHAMIS, M., HASHIM, M., AHMED, N. S.-E., ASHOUR, S., ELBALKIMY, M., Non-Motor Symptoms as Predictors of Quality of Life in Egyptian Patients With Parkinson’s Disease: A Cross-Sectional Study Using a Culturally Adapted 39-Item Parkinson’s Disease Questionnaire, Frontiers in Neurology, vol. 9, 2018, p. 357.
6. PEREIRA, M. P., PELICIONI, P. H. S., AND GOBBI, L. T. B., Parkinson’s disease severity and motor subtype influence physical capacity components, Motriz: Revista de Educacao Física, vol. 19, 2013, pp. 605-613.
7. LOPIANO, L., ISAIAS, I. U., PEZZOLI, G., ANTONINI, A., CANESI, M., DAL FANTE, M., ZIBETTI, M., MANCINI, F., AND MANFREDI, L., Duodenal levodopa infusion for advanced Parkinson’s disease: 12-month treatment outcome, Movement Disorders, vol. 22, 2007, pp. 1145-1149.
8. LEDETI, A., VLASE, G., CIRCIOBAN, D., LEDETI, I., STELEA, L., AND VLASE, T., Comparative Stability of Levodopa Under Thermal Stress in both Oxidative and Inert Media, Rev. Chim.(Bucharest), 67, 2016, p. 2649-2650.
9. POSTUMA, R. B., BERG, D., STERN, M., POEWE, W., OLANOW, C. W., OERTEL, W., OBESO, J., MAREK, K., LITVAN, I., LANG, A. E., HALLIDAY, G., GOETZ, C. G., GASSET, T., DOUBIS, B., CHAN, P., BLOEM, B. R., ADLER, C. H., AND DEUSCHL, G., MDS clinical diagnostic criteria for Parkinson’s disease, Movement Disorders, vol. 30, 2015, pp. 1591-1601.
10. Ba, F., Obaid, M., Wielar, M., Camicioli, R., and Martin, W. R. W., Parkinson Disease: The Relationship Between Non-motor Symptoms and Motor Phenotype. The Canadian Journal of Neurological Sciences, 261, Can J Neurol Sci, vol. 43, 2019, pp. 261–267.

11. Schrag, A., Jahanshahi, M., and Quinn, N. What contributes to quality of life in patients with Parkinson’s disease? Journal of Neurology Neurosurgery and Psychiatry, vol. 69, 2000, pp. 308–312.

12. Egggers, C., Pedrosa, D. J., Kahrman, D., Maier, F., Lewis, C. J., Fink, G. R., Schmidt, M., and Timmermann, L. Parkinson Subtypes Progress Differently in Clinical Course and Imaging Pattern. PLoS ONE, vol. 7, 2012, p. e46813.

13. Todorova, A., Jenner, P., and Ray Chaudhuri, K. Non-motor Parkinson’s: integral to motor Parkinson’s, yet often neglected. Practical neurology, vol. 14, 2014, pp. 310-22.

14. Bogdanici, C., Bogdanici, T., Moraru, A., Costin, D., and Feraru, C., Levodopa as Treatment for Adults with Amblyopia. Rev. Chim. (Bucharest), 68, no. 2017, p. 1595–1597.

15. Oertel, W. H., Recent advances in treating Parkinson’s disease. F1000 Research, vol. 6, 2017, p. 260.

16. Bleaga, C. V., Vere, C. C., Patrascu, P. A. M., Moraru, E., Crafciuc, A. V., Foarfă, M. C., Mogolăntă, S. S., Strebă, C. T., Bondari, S., Paitici, S., Mirea, C. S., and Vilcea, I. D., Severe upper gastrointestinal bleeding determined by a gastric lymphoma associated with helicobacter pyloripositive atrophic gastritis. Romanian Journal of Morphology and Embryology, vol. 58, 2017, pp. 611-617.

17. Calborean, V., Gheorman, V., Constantin, C. Istratoaie, O. Venous Thromboembolism Secondary to Adult-Onset Still’s Disease: A Case Report. Journal of Cardiovascular Emergencies, 2018, 4, nr.2, p.101-105.

18. Calborean, V., Ciobanu, D., Mirea, S.C., Galceava, O., Gheorman, V., Padureanu, V., Fortofoiu, C.M., Fortofoiu, M., Mita, A., Dinescu, S.N., Miscoci, S.A., Dinescu, V.C. Benefit of Cardiac Resynchronization Therapy in Patients with Heart Failure. Rev. Chim. (Bucharest), 69, no. 9, 2018, p.2461-2464.

19. Calborean, V., Gheorman, V., Dinescu, S.N., Stanca, D., Galceava, O., Fortofoiu, M., Mita, A., Mihailevici, A.R., Miscoci, V.S.A., Baleanu, V.D., Dinescu, V.C., Arrhythmia Risk in Patients with Chronic Hepatic Disease. Rev. Chim (Bucharest) 69, no. 11, 2018, p. 4237-4240.

20. Pagano, G., Ferrara, N., Brooks, D. J., and Paveze, N., Age at onset and Parkinson disease phenotype. Neurology, vol. 86, 2016, pp. 1400-1407.

Manuscript received: 30.10.2018