Impact of neuroprotective therapy on cognition and oxidative stress in the early stages of Parkinson’s disease

A. V. Demchenko, V. V. Biriuk

Zaporizhzhia State Medical University, Ukraine

The aim of this study was to investigate the clinical and biochemical efficiency of citicoline in cognitive improvement and changes of glutathione peroxidase (GPx) blood plasma levels in patients at early stages of Parkinson’s disease (PD).

Materials and methods. We recruited 42 patients at I–II Hoehn and Yahr PD stages and 20 controls. The Montreal Cognitive Assessment test (MoCA) was used to assess several cognitive domains in PD patients (before citicoline treatment, after intravenous therapy and after pills therapy) and controls (once). Plasma was collected once in controls and twice in PD patients (on the first and the last days of observation). Citicoline was administrated to 23 of 42 PD patients in addition to basic antiparkinsonian therapy intravenously during 10 days and with pills during next 30 days. The rest 19 of 42 PD patients had been taking basic antiparkinsonian treatment only (comparison group).

Results. We observed significant improvement of MoCA scores in PD patients with citicoline course (PD-Cs) in each check day. But in spite of such an improvement in PD patients, who were left on the basic antiparkinsonian treatment (PD-Bs), on the 10th day of observation, patients of this group did not keep it to the last day of the research (P < 0.001). After the treatment the GPx level in plasma of PD-Cs was significantly higher than in PD-Bs (P < 0.001). Furthermore, the activity of GPx plasma level after citicoline course was significantly higher than before additional neuroprotective therapy, which wasn’t observed in PD patients on basic treatment only.

Conclusions. The cognition of PD patients (according to MoCA scores) at the early stages of the disease was significantly improved after citicoline treatment. Citicoline treatment had significant positive influence on the increasing antioxidant GPx plasma activity in PD patients at the early stages of the disease.
Materials and methods. In the study, we included 42 patients with PD (I–II stages) and 20 healthy controls. For the assessment of cognitive functions, we used the Montreal Cognitive Assessment (MoCA) test. The patients were divided into two groups: one group received citicoline (1000 mg per day) intravenously for 10 days and then orally (500 mg twice per day) for 10 days, while the other group received basic antiparkinsonian therapy (levodopa, dopamine agonists, amantadine, MAO-B inhibitors). The MoCA scores were assessed at the beginning of the study, after intravenous therapy, and at the end of the study.

Aim. The aim of this study was to investigate the clinical and biochemical efficiency of citicoline in cognitive improvement and changes of GPx blood plasma levels in patients at early stages of PD.

Key words: Parkinson's disease, cognitive impairment, antioxidant, glutathione peroxidase.

Materials and methods. This study was conducted in the Medical Educational and Scientific Center “University Clinic” (Zaporizhzhia State Medical University, Ukraine). We recruited 42 patients (10 males and 32 females) at I–II Hoehn and Yahr (H&Y) PD stages (9 patients at the I H&Y PD stage and 33 patients at the II H&Y PD stage, respectively) and 20 controls (5 males and 15 females). The Movement Disorder Society Clinical Diagnostic Criteria for PD were used to establish the diagnosis [10]. The mean age of all PD patients and controls was 66.86 ± 5.32 and 64.35 ± 5.45 years, respectively.

The exclusion criteria were: III–V H&Y PD stages, secondary parkinsonism, other extrapyramidal disorders; inflammatory, autoimmune, oncological and mental diseases; decompensated stages of somatic diseases.

All our PD patients had been taking basic antiparkinsonian treatment (levodopa, dopamine agonists, amantadine, MAO-B inhibitors) and were divided into two groups. Citicoline (1000 mg per day) was administered intravenously to 23 of 42 PD patients (mean age – 66.74 ± 4.96 years; 4 patients at the I H&Y PD stage and 19 patients at the II H&Y PD stage) in addition to basic antiparkinsonian therapy during 10 days and with pills (500 mg 2 times per day) during next 30 days (PD-Cs group). The rest 19 of 43 PD patients (mean age – 67.00 ± 5.87 years; 5 patients at the I H&Y PD stage and 14 patients at the II H&Y PD stage) had been taking basic antiparkinsonian treatment only (comparison group, PD-Bs).

The Montreal Cognitive Assessment test (MoCA) was used to assess several cognitive domains in PD patients (before citicoline treatment, after intravenous therapy and after pills therapy) and controls. We defined patients with MoCA scores of <26 as PD with mild cognitive impairment (PD-MCI) (minimal MoCA score in our PD patients was 19 points) [11]. MoCA scores were checked on the 1st day (the 1st visit), the 10th day (the 2nd visit) and the 40th day (the 3rd visit) of PD patients’ observation and once in controls.

Plasma was collected once in controls and twice (on the first and the last days of observation) in PD patients at a fixed time interval between 7:00–9:00 AM using a 10 ml K2-EDTA tubes (BD Vacutainer). Samples were centrifuged for 15 min at 1000 × g at 2–8 °C within 30 min of collection. Then 0.5 ml of supernatant plasma was removed from each tube and transferred into a
There were no significant differences between age in PD patients and HCs (P = 0.09), as well as PD-Cs and PD-Bs (P = 0.87), last groups did not differ in duration of the disease (age medians – 2.0 (1.5–2.0) and 2.0 (1.5–2.0), P = 0.74). PD-Cs and PD-Bs groups did not differ on the percentage of patients with I and II H&Y PD stages (P = 0.71).

None of adverse effects of citicoline administration were observed. There were 34 PD-MCI patients (20 in PD-Cs group and 14 in PD-Bs group) and 8 out of 20 controls with MCI according to MoCA test scores on the 1st day of observation. The cognitive functions initially were significantly worse in PD patients than in controls (MoCA scores medians – 23.0 (22.0–25.0) and 28.0 (26.0–30.0), respectively, P < 0.001). The MoCA scores did not differ between PD-Cs and PD-Bs groups on the 1st day of observation (P = 0.724), but were significantly higher in PD-CS group on the 10th (P = 0.006) and 40th (P < 0.001) days of observation by 17.4 % (P < 0.001) and 21.7 % (P < 0.001), respectively.

We observed significant improvement of MoCA scores in PD-Cs in each check day. But in spite of such an improvement in PD-Bs, on the 10th day of observation, patients of this group did not keep it to the last day of the research (Table 1).

Plasma GPx level in controls (371.70 (332.52–406.99) pg/mL) was significantly higher than in PD-Cs (314.51 (289.64–339.76) pg/mL, P < 0.001) and PD-Bs (310.44 (278.73–328.41) pg/mL, P < 0.001) initially before treatment. The level of GPx in PD-Cs did not differ from the one in PD-Bs initially as well (P > 0.05). But after the treatment the GPx level in plasma of PD-Cs (364.56 (340.34–390.94) pg/mL) was significantly higher than in PD-Bs (313.03 (259.10–348.21) pg/mL, P < 0.001). Furthermore, the activity of GPx plasma level after citicoline course was higher by 15.9 % (P < 0.001) than before additional neuroprotective therapy, which wasn’t observed in PD patients on basic treatment only (Table 2). But after citicoline course plasma GPx concentrations in PD-Cs did not differ significantly from controls (P = 0.503).

Discussion

The search of evidence-based neuroprotective therapy in PD has still been continuing. Some antioxidants and neuroprotectors are being studied nowadays in the context of possible improvement of non-motor symptoms of PD. But in general, the results of such researches are quite controversial. This controversy in neuroprotection was found even in antiparkinsonian drugs, such as levodopa, dopamine receptor agonists (pramipexole, bromocriptine, R-aperomorphine, ropinirole), NMDA receptor antagonists (amantadine), MAO-B inhibitors (rasagiline) in spite of their positive effect on PD in the early stages [12,13]. Other drugs identified as antioxidants (coenzyme Q10, creatine), apoptotic inhibitory factors, neurotrophic factors, iron chelators, calcium channel blockers, kynurenines and alpha-synuclein immunotherapy showed controversial results as well [12,13]. There were some researches, devoted to GPx activity in PD patients [13–15] and citicoline effect on cognition in different diseases [16,17] with different results. Patryk Jasiecki mentioned in his review many researches with both positive and uncertain effects of citicoline during acute stroke, mild vascular dementia, after traumatic brain injury [16]. There was an interesting CITIMEM study represented by Pietro Gareri et al. in

<table>
<thead>
<tr>
<th>PD patients</th>
<th>GPx levels before treatment, pg/mL</th>
<th>GPx levels after treatment, pg/mL</th>
<th>P (Wilcoxon–test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-Cs, n = 23</td>
<td>314.51 (289.64–339.76)</td>
<td>364.56 (340.34–390.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PD-Bs, n = 19</td>
<td>310.44 (278.73–328.41)</td>
<td>313.03 (259.10–348.21)</td>
<td>0.765</td>
</tr>
</tbody>
</table>

**Table 1.** MoCA scores dynamic in PD patients depending on therapy, Me (Q1–Q3)

<table>
<thead>
<tr>
<th>Patients</th>
<th>MoCA score</th>
<th>P (Wilcoxon–test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-Cs, n = 23</td>
<td>24.0 (21.0–26.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>PD-Bs, n = 19</td>
<td>27.0 (25.0–27.0)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

**Table 2.** Dynamic of plasma GPx levels in PD patients before and after treatment, Me (Q1–Q3)

<table>
<thead>
<tr>
<th>PD patients</th>
<th>gp levels before treatment, pg/mL</th>
<th>gp levels after treatment, pg/mL</th>
<th>P (Wilcoxon–test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-Cs, n = 23</td>
<td>314.51 (289.64–339.76)</td>
<td>364.56 (340.34–390.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PD-Bs, n = 19</td>
<td>310.44 (278.73–328.41)</td>
<td>313.03 (259.10–348.21)</td>
<td>0.765</td>
</tr>
</tbody>
</table>

**PD-Cs:** patients who underwent citicoline course in addition to basic antiparkinsonian therapy; **PD-Bs:** patients who took only basic antiparkinsonian therapy.

1.5 ml Eppendorf tubes. All the plasma samples were frozen at -80 °C. Samples were prepared for evaluating GPx concentrations with Elabscience® Enzyme linked immunosorbent assay kit in clinical and diagnostic laboratory of the Medical Educational and Scientific Center “University Clinic” (Zaporizhzhia State Medical University, Ukraine). GPx levels were checked with Microplate Reader Immunochem-2100 (USA) on the 1st and 40th days of observation (the 1st and the 3rd visits). The Shapiro–Wilk test was used as a test of normality. Numerical variables were expressed as the mean ± standard deviation (SD) or median with interquartile range (Q1–Q3). For variables not following a normal distribution, data was compared using the Mann–Whitney test. The Wilcoxon signed-rank test was used to compare two related samples, on the first and the last days of observation. The Friedman test was used to compare multiple dependent samples. The Fisher exact test was used to find the differences between percentage of PD H&Y stages in groups. We performed all analyses using the Statistica® for Windows 13.0 (No. JPZB041382130ARCHN10–J). A P-value of <0.05 was considered significant.

The study protocol was approved by ethics committee of Zaporizhzhia State Medical University, according to the current version of The Declaration of Helsinki. Written informed consent was provided by all study participants prior to enrollment in the study.

Discussion

The search of evidence-based neuroprotective therapy in PD has still been continuing. Some antioxidants and neuroprotectors are being studied nowadays in the context of possible improvement of non-motor symptoms of PD. But in general, the results of such researches are quite controversial. This controversy in neuroprotection was found even in antiparkinsonian drugs, such as levodopa, dopamine receptor agonists (pramipexole, bromocriptine, R-aperomorphine, ropinirole), NMDA receptor antagonists (amantadine), MAO-B inhibitors (rasagiline) in spite of their positive effect on PD in the early stages [12,13]. Other drugs identified as antioxidants (coenzyme Q10, creatine), apoptotic inhibitory factors, neurotrophic factors, iron chelators, calcium channel blockers, kynurenines and alpha-synuclein immunotherapy showed controversial results as well [12,13]. There were some researches, devoted to GPx activity in PD patients [13–15] and citicoline effect on cognition in different diseases [16,17] with different results. Patryk Jasiecki mentioned in his review many researches with both positive and uncertain effects of citicoline during acute stroke, mild vascular dementia, after traumatic brain injury [16]. There was an interesting CITIMEM study represented by Pietro Gareri et al. in...
2020, in which researchers confirmed the hypothesis that combined use of citicoline and memantine could have an enhanced action in patients affected with Alzheimer's disease and mixed dementia [17]. Antioxidant activity was studied in all these neurological diseases as well, but there are not so many researches of citicoline impact on it. For example, there was a study by Demchenko et al. (2016) in which citicoline positively affected cognitive functions and GPx activity in blood plasma and erythrocyte hemolysate of patients with chronic cerebral ischemia [18]. Due to results of this research we demonstrated that citicoline was able to increase the activity of antioxidant GPx and to improve the cognition on long term period in PD patients at I–II stages. Although our research has some limitations in number of participants and large clinical trials are needed, these results show that citicoline administration may influence the important pathogenetic chain in PD and helps patients to improve the quality of life even in the early stages of the disease due to cognitive functions improvement.

Conclusions

1. Citicoline administration had positive influence on cognitive improvement in PD patients at the early stages of the disease, according to the MoCA scores.

2. Citicoline treatment had significant positive influence on the increasing antioxidant GPx activity in PD patients at the early stages of the disease.

Perspectives of the future researches

are in large clinical trials for confirming citicoline benefits in treatment of PD in the early stages.

Conflicts of Interest: authors have no conflict of interest to declare.

Information about authors:
Demchenko A. V., MD, PhD, Dsc, Associate Professor of the Department of Family Medicine, Therapy, Cardiology and Neurology of FFE, Zaporizhzhia State Medical University, Ukraine. ORCID ID: 0000-0001-4296-0502

Biruk V. V., MD, PhD student of the Department of Family Medicine, Therapy, Cardiology and Neurology of FFE, Zaporizhzhia State Medical University, Ukraine. ORCID ID: 0000-0001-8826-1536

Vідмітності про авторів:
Демченко А. В., д.м. нав., доцент каф. сімейної медицини, терапії, кардіології та неврології ФПО, Запорізький державний медичний університет, Україна. Бірук В. В., очній аспірант каф. сімейної медицини, терапії, кардіології та неврології ФПО, Запорізький державний медичний університет, Україна.

Сведення об авторах:
Демченко А. В., д.м. нав., доцент каф. семейной медицины, терапии, кардиологии и неврологии ФПО, Запорожский государственный медицинский университет, Украина. Бирюк В. В., очный аспирант каф. семейной медицины, терапии, кардиологии и неврологии ФПО, Запорожский государственный медицинский университет, Украина.

References


ISSN 2306-8027 http://pat.zsmu.edu.ua 355