UDC 616.858-092-085.21
DOI: 10.14739/2310-1237.2021.3.247142

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

**A. V. Demchenko**[A,F], **V. V. Biriuk***[B,C,D,E]

Zaporizhzhia State Medical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

**Key words:** Parkinson's disease, early stages, neuroprotector, cognitive impairment, glutathione peroxidase.

**Pathologia 2021; 18 (3), 352-355**

***E-mail:** varvarabiryuk@gmail.com

**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 10$^{th}$ 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.

**Ключові слова:** хвороба Паркінсона, ранні стадії, нейропротектор, когнітивний розлад, глутатіон-пероксидаза.

**Патологія. 2021. Т. 18, № 3(53). С. 352-355**

## Вплив нейропротективної терапії на стан когнітивних функцій та оксидативний стрес на ранніх стадіях хвороби Паркінсона

**А. В. Демченко, В. В. Бірюк**

**Мета роботи –** визначення клінічної та біохімічної ефективності цитиколіну в корекції когнітивних розладів і рівня глутатіонпероксидази (ГПО) плазми крові в пацієнтів на ранніх стадіях хвороби Паркінсона (ХП).

**Матеріали та методи.** У дослідженні взяли участь 42 пацієнти з I–II стадіями ХП за Хен–Яром і 20 осіб групи контролю. Для оцінювання когнітивних функцій (КФ) використали Монреальську шкалу когнітивного оцінювання (МоСА) в пацієнтів із ХП до початку терапії цитиколіном, після завершення парентерального курсу та перорального приймання препарату, а також в осіб групи контролю (один раз). Плазму крові брали для дослідження один раз у осіб групи контролю та двічі (на перший та останній день спостереження) в пацієнтів із ХП. Цитиколін призначали 23 із 42 пацієнтів із ХП на додаток до базисної протипаркінсонічної терапії внутрішньовенно протягом 10 днів і в таблетках протягом наступних 30 днів. Решта 19 із 42 пацієнтів із ХП отримували тільки базисну протипаркінсонічну терапію (група порівняння).

**Результати.** Спостерігали вірогідне покращення КФ за балами шкали МоСА в пацієнтів із ХП, які отримували цитиколін (ХП-Ц) кожного контрольного дня. Незважаючи на покращення КФ на 10 день спостереження у пацієнтів з ХП, яким призначили тільки базисну протипаркінсонічну терапію (ХП-Б), вони не змогли утримати позитивний результат до останнього дня дослідження ($p < 0,001$). Після лікування рівень ГПО плазми в пацієнтів групи ХП-Ц суттєво вищий, ніж у хворих групи ХП-Б ($p < 0,001$). Активність ГПО у плазмі після курсу цитиколіну вірогідно вища, ніж до призначення додаткової нейропротективної терапії; це не спостерігали в пацієнтів групи ХП-Б.

**Висновки.** Когнітивні функції (відповідно до показників шкали МоСА) пацієнтів на ранніх стадіях ХП суттєво поліпшилися після терапії цитиколіном. Курс цитиколіну вірогідно вплинув на підвищення активності антиоксиданта ГПО в пацієнтів на ранніх стадіях ХП.

## Влияние нейропротекторной терапии на состояние когнитивных функций и оксидативный стресс на ранних стадиях болезни Паркинсона

**А. В. Демченко, В. В. Бирюк**

**Цель работы –** определение клинической и биохимической эффективности цитиколина в коррекции когнитивных расстройств и уровня глутатионпероксидазы (ГПО) плазмы крови у пациентов на ранних стадиях болезни Паркинсона (БП).

**Материалы и методы.** В исследование включили 42 пациента с I–II стадиями БП по Хен–Яру и 20 лиц группы контроля. Для оценки когнитивных функций (КФ) использовали Монреальскую шкалу когнитивного оценивания (МоСА) у пациентов с БП до начала терапии цитиколином, после завершения парентерального курса и перорального приёма препарата, а также у лиц группы контроля (один раз). Плазму крови брали для исследования один раз у лиц группы контроля и дважды (на первый и последний день наблюдения) у пациентов с БП. Цитиколин назначали 23 из 42 пациентов с БП в дополнение к базисной противопаркинсонической терапии внутривенно в течение 10 дней и в таблетках на протяжении следующих 30 дней. Остальные 19 из 42 пациентов с БП принимали только базисную противопаркинсоническую терапию (группа сравнения).

**Результаты.** Отмечено достоверное улучшение КФ по баллам шкалы МоСА у пациентов с БП, которые принимали цитиколин (БП-Ц), на каждый контрольный день. Несмотря на улучшение КФ на 10 день наблюдения у пациентов с БП, которые принимали только базисную противопаркинсоническую терапию (БП-Б), они не смогли удержать положительный результат до последнего дня исследования ($p < 0,001$). После лечения уровень ГПО плазмы у пациентов группы БП-Ц существенно выше, чем у пациентов группы БП-Б ($p < 0,001$). Более того, активность ГПО в плазме после курса цитиколина достоверно выше, чем до назначения дополнительной нейропротекторной терапии; это не наблюдали у пациентов группы БП-Б.

**Выводы.** Когнитивные функции (соответственно показателям шкалы МоСА) пациентов на ранних стадиях БП существенно улучшились после терапии цитиколином. Курс цитиколина достоверно повлиял на повышение активности антиоксиданта ГПО у пациентов на ранних стадиях БП.

**Ключевые слова:** болезнь Паркинсона, ранние стадии, нейропротектор, когнитивное расстройство, глутатион-пероксидаза.

**Патология. 2021. Т. 18, № 3(53). С. 352-355**

Parkinson's disease (PD) remains one of the most widespread neurodegenerative diseases of our time [1]. The pathogenesis of PD is quite complicated [2], which is why researches, that may lead to its understanding and influencing on it, are still relevant. It is known that PD belongs to synucleopathies as α-synuclein takes the central place in its pathogenesis [3]. But the oxidative stress influences α-synuclein aggregation, which leads to exacerbation of oxidative stress itself and forms "vicious circle" in PD's pathogenesis [4]. As this part of PD's complex pathogenesis is obligate, it may play sufficient role in motor and non-motor PD symptoms development.

Citicoline is known as a natural precursor of phospholipid synthesis and serves as a source of choline in the metabolic pathways for biosynthesis of acetylcholine [5]. Researchers observed the positive effect of citicoline in increasing brain dopamine levels and inhibiting dopamine reuptake [5]. It is also known that choline liberated from citicoline can be metabolized to glutathione, one of the most important endogenous antioxidant defense systems in the brain, which has a neuroprotective role by decreasing lipid peroxidation [6]. And glutathione peroxidase (GPx) catalyzes detoxification of hydrogen peroxide and lipid peroxides by reduced glutathione [7]. The complex of these facts allows us to be interested in studying of citicoline influence on GPx levels in patients at early stages of PD. Moreover, the positive effect of citicoline on cognitive functions in PD patients was found [8]. The GPx activity in patients with vascular cognitive impairment-no dementia was studied as well [9], but we did not find in open access similar researches in PD patients.

## 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.

## Materials and methods

This study was conducted in 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 administrated 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 1$^{st}$ day (the 1$^{st}$ visit), the 10$^{th}$ day (the 2$^{nd}$ visit) and the 40$^{th}$ day (the 3$^{rd}$ 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

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

| Patients | 1st day | 10th day | 40th day | P1-2-3 | P1-2 | P1-3 |
|---|---|---|---|---|---|---|
| PD-Cs, n = 23 | 23.0 (22.0–25.0) | 27.0 (25.0–27.0) | 28.0 (27.0–28.0) | <0.001 | <0.001 | <0.001 |
| PD-Bs, n = 19 | 24.0 (21.0–26.0) | 25.0 (23.0–26.0) | 24.0 (23.0–25.0) | 0.005 | 0.029 | 0.272 |

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

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

| PD patients | GPx levels before treatment, pg/mL | GPx levels after treatment, pg/mL | P (Wilcoxon–test) |
|---|---|---|---|
| PD-Cs, n = 23 | 314.51 (289.64–339.76) | 364.56 (340.34–390.94) | <0.001 |
| PD-Bs, n = 19 | 310.44 (278.73–328.41) | 313.03 (259.10–348.21) | 0.765 |

**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. JPZ8041382130ARCN10-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.

## Results

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-apomorphine, 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 Jasielski 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 plasma 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.
**Конфлікт інтересів:** відсутній.

Надійшла до редакції / Received: 15.07.2021
Після доопрацювання / Revised: 02.11.2021
Прийнято до друку / Accepted: 12.11.2021

**Information about authors:**
Demchenko A. V., MD, PhD, DSc, Associate Professor of the Department of Family Medicine, Therapy, Cardiology and Neurology of FPE, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0002-4296-0902
Biriuk V. V., MD, PhD-student of the Department of Family Medicine, Therapy, Cardiology and Neurology of FPE, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: 0000-0001-8826-1536

**Відомості про авторів:**
Демченко А. В., д-р мед. наук, доцент каф. сімейної медицини, терапії, кардіології та неврології ФПО, Запорізький державний медичний університет, Україна.
Бірюк В. В., очна аспірантка каф. сімейної медицини, терапії, кардіології та неврології ФПО, Запорізький державний медичний університет, Україна.

**Сведения об авторах:**
Демченко А. В., д-р мед. наук, 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.

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