MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

2, Rymskogo-Korsakova st., Sumy 40007, Ukraine
e-mail: EUMJ@med.sumdu.edu.ua
eumj.med.sumdu.edu.ua
ISSN: 2663-5909 (print)

DOI: https://doi.org/10.21272/eumj.2021;9(3):247-255

Abstract

Olha S. Chyniak
ORCID: 0000-0002-6008-1039
Department of Neurosurgery and Neurology, Medical institute, Sumy State University, Sumy , Ukraine;
Olga Ye. Dubenko
ORCID: 0000-0002-4911-5613
Department of Neurology and Neurosurgery, Kharkiv Medical Academy of Postgraduate Education, Kharkiv, Ukraine;
Olexander O. Potapov
ORCID: 0000-0002-9683-3685
Department of Neurosurgery and Neurology, Medical institute, Sumy State University, Sumy , Ukraine

THE RELATIONSHIP BETWEEN DECREASED COGNITIVE FUNCTIONS AND THE LEVEL OF PROINFLAMMATORY CYTOKINES IN PATIENTS WITH ALZHEIMER'S DISEASE, VASCULAR DEMENTIA, AND MILD COGNITIVE DISORDER

Introduction. Alzheimer's disease (AD) is a degenerative disease that leads to dementia symptoms [1, 2]. Histopathological signs of AD are amyloid plaques in the brain, mainly consisting of fibrillary forms of amyloid β-peptide-40 (Aβ-40) and amyloid β-peptide-42 (Aβ-42). Neutrophils are the main targets for IL-17 in the central nervous system (CNS) that promote inflammation and damage to CNS tissues, and may play an important role in the development of AD pathology. Interleukin 23 (IL-23) synergizes with IL-6, IL-1 and is involved in the differentiation of Th17 cells in a pro-inflammatory context.

The aim of the study was to analyze the relationship between interleukin levels of IL-17, IL-23 and neurocognitive scales in patients with AD, vascular dementia (VD) and mild cognitive disorder (MCD).

Materials and methods: The study involved 89 patients, of which 59 patients had cognitive impairment (32 men and 27 women, mean age 66.8±8.4 years); among them, 29 had major neurocognitive impairment (NCD), including 15 patients with AD, 14 – with VD, 30 patients – with MCD and 30 people in the control group had no cognitive deficit.

All patients were tested with comprehensive neuropsychological examination using the following tests and scales: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Alzheimer Disease Assessment Scale-cognitive (ADAScog).

Serum levels of cytokines of IL-17 and IL-23 were assayed using sandwich ELISA on «Chem Well 2900» immunoanalyzer (Awareness Technology, USA). Test systems using Bender Medsystems, Australia (IL-17 and IL-23) were used in accordance with the manufactures instructions.

Discussion. Levels of detectable interleukins (IL-17 and IL-23) were significantly higher in patients with AD vs. patients with VD and MCD. The correlations between the two cytokines and the MMSE scales, MoCA, ADAS-cog and FAB were examined. Our results showed a significant positive correlation between the serum concentration of IL-23 and neurocognitive scales in all patients with AD. The most relevant correlations in the AD group were linked with the scales: ADAS-cog ($r = 0.760$; $p = 0.001$), namely with the sections «tasks for repeating words» ($r = 0.775$; $p < 0.001$), «constructive praxis» ($r = 0.651$; $p = 0.010$), «orientation» ($r = 0.684$; $p = 0.01$), as well as «word recognition tasks» ($r = 0.616$; $p = 0.020$); and

with MoCA scale (r = −0.592; p = 0.020), namely with the section «delayed recall» (r = −0.641; p = 0.010). A significant positive correlation was established between IL-23 and individual sections of the ADAS-cog scale in patients with MCD (r = 0.423; p = 0.020), namely with «word recognition tasks» (r = 0.466; p = 0.030), «understanding» (r = 0.306; p = 0.059) as well as «strike out numbers» (r = 0.301; p = 0.061). A weak positive correlation was found between the serum concentration of IL-23 and ADAS-cog scores in patients with VD (r = 0.497; p = 0.045). Moderate positive correlation was observed for IL-23 with «concentration and distraction» (r = 0.558; p = 0.040). An inverse correlation was established between the serum levels of IL-23 and MoCA scores in patients with VD (r = −0.510; p = 0.060), especially with «language» (r = −0.538; p = 0.047) and «executive functioning» (r = −0.485; p = 0.079). However, no other significant correlations were found between the serum concentration of IL-17 and neurocognitive domains in patients with MCD and VD.

Correlation analysis confirmed the relationship between the severity of cognitive impairment and the level of proinflammatory markers, suggesting that inflammation can lead to cognitive decline in AD patients. The results of the study indicated that IL-23 may have a more complex relationship with the progression of this disease which gives reason to consider IL-23 as a marker of inflammatory activity.

Levels of detectable proinflammatory cytokines (IL-17 and IL-23) were significantly higher in patients with AD vs. patients with VD and MCD. Such more pronounced changes in the production of interleukin 23 in patients with AD may indicate the activity of the inflammatory process. The level of IL-23 in all examined patients with Alzheimer's disease had high correlations with indicators of neurocognitive scales, which indicated its important role in the pathogenesis of this disease. There were no other significant correlations between the serum concentration of IL-17 and neurocognitive domains in patients with MCD and VD.

Key words: Alzheimer’s disease, vascular dementia, mild cognitive disorder, neurocognitive domains, interleukins 17 and 23.

Corresponding author:
Olha S. Chyniak, Department of Neurosurgery and Neurology, Medical institute, Sumy State University, Sumy, Ukraine
e-mail: o.chinyak@med.sumdu.edu.ua

Резюме

Ольга С. Чиняк
ORCID: 0000-0002-6008-1039
кафедра нейрохірургії та неврології, Медичний інститут, Сумський державний університет, м. Суми, Україна;
Ольга Є. Дубенко
ORCID: 0000-0002-4911-5613
кафедра невропатології та нейрохірургії, Харківська медична академія післядипломної освіти, м. Харків, Україна;

ВЗАЄМОЗВ’ЯЗОК МІЖ ЗНИЖЕННЯМ КОГНІТИВНИХ ФУНКЦІЙ ТА РІВНЕМ ПРОЗАПАЛЬНИХ ЦИТОКІНІВ У ПАЦІЄНТІВ З ХВОРОБОЮ АЛЬЦГЕЙМЕРА, СУДИННОЮ ДЕМЕНЦІЄЮ ТА МАЛИМ КОГНІТИВНИМ РОЗЛАДОМ

Актуальність. Хвороба Альцгеймера (ХА) – це дегенеративне захворювання, яке призводить до симптомів деменції. Гістопатологічними ознаками ХА є амілоїдні бляшки в мозку, переважно що складаються з фібрилярних форм амілоїду β-пептиду-40 (Аβ-40) та амілоїду β-пептиду-42 (Аβ-42). Нейтрофіли є головними мішенями для інтерлейкіну 17 (IL-17), сприяють запаленню та пошкодженню тканин ЦНС і можуть відігравати важливу роль у розвитку патології ХА. Інтерлейкін 23 (IL-23) синергується з IL-6, IL-1 та приймає участь в диференціюванні Th17-клітин в прозапальному контексті.

Олександр О. Потапов
ORCID: 0000-0002-9683-3685
кафедра нейрохірургії та неврології, Медичний інститут, Сумський державний університет, м. Суми, Україна

Мета дослідження – проаналізувати взаємозв'язок між рівнями ІЛ-17, ІЛ-23 та нейрокогнітивними шкалами у пацієнтів з ХА, судинною деменцією (СД) та малим когнітивним розладом (МКР).

Матеріали та методи: У дослідженні взяли участь 89 пацієнтів, з яких 59 хворих з когнітивними порушеннями (32 чоловіки і 27 жінок, середній вік 66,8 ± 8,4 роки), з яких 29 – з великим когнітивним розладом (ВКР), з них 15 хворих з ХА, 14 – з СД, 30 пацієнтів з МКР та 30 осіб контрольної групи.

Всім пацієнтам провели нейропсихологічне обстеження за допомогою тестів та шкал: коротка шкала дослідження психічного статусу (MMSE), Монреальска шкала оцінки когнітивних функцій (MoCA), батарея лобної дисфункції (FAB), шкала оцінки хвороби Альцгеймера – когнітивна субшкала (ADAS-cog).

Рівні цитокінів ІЛ-17 та ІЛ-23 у сироватці крові аналізували за допомогою ІФА методом «сендвіч» на імуноаналізаторі «Chem Well 2900» (Awareness Technology, США). Тестові системи з використанням Bender Medsystems, Австралія (ІЛ-17 та ІЛ-23) аналізували згідно з інструкціями виробників.

Результати. Рівні прозапальних цитокінів (ІЛ-17 та ІЛ-23) були значно вищі у пацієнтів з ХА, у порівнянні з СД та МКР. Були досліджені кореляційні зв'язки між двома цитокінами та шкалами MMSE, MoCA, ADAS-cog та FAB. Отримані нами результати показали значну позитивну кореляцію між сироватковою концентрацією ІЛ-23 та нейрокогнітивними шкалами у всіх хворих на ХА. Найбільш релевантними кореляціями в групі ХА виявилися зв'язки із шкалами: ADAS-cog ($r = 0{,}760$; $p = 0.001$), а саме за розділами підтестів «завдання для повторення слів» ($r = 0{,}775$; $p < 0{,}001$), «конструктивний праксис» ($r = 0{,}651$; $p = 0{,}010$), «орієнтація» ($r = 0{,}684$; $p = 0{,}010$), а також «завдання на впізнавання слів» ($r = 0{,}616$; $p = 0{,}020$) та шкалою MoCA ($r = -0{,}592$; $p = 0{,}020$), а саме в домені «відстроченого відтворення» ($r = -0{,}641$; $p = 0{,}010$). Встановлено значну позитивну кореляцію між ІЛ-23 та окремими доменами шкали ADAS-cog у пацієнтів з МКР ($r = 0{,}423$; $p = 0{,}020$), а саме із «завданнями на впізнавання слів» ($r = 0{,}466$; $p = 0{,}030$), з «розумінням» ($r = 0{,}306$; $p = 0{,}059$), а також з «закреслюванням цифр» ($r = 0{,}301$; $p = 0{,}061$). Виявлено слабку позитивну кореляцію між сироватковою концентрацією ІЛ-23 та оцінками ADAS-cog у пацієнтів із СД ($r = 0{,}497$; $p = 0{,}045$). Помірна позитивна кореляція спостерігалася для ІЛ-23 з «концентрацією та відволіканням уваги» ($r = 0{,}558$; $p = 0{,}040$). Була встановлена зворотна кореляція між сироватковими рівнями ІЛ-23 та показниками MoCA у пацієнтів з СД ($r = -0{,}510$; $p = 0{,}060$), особливо з «мовою» ($r = -0{,}538$; $p = 0{,}047$) та з «виконавчими функціями» ($r = -0{,}485$; $p = 0{,}079$). Однак значущих кореляційних зв'язків між концентрацією ІЛ-17 у сироватці крові та нейрокогнітивними доменами у хворих з малим когнітивним розладом та судинною деменцією не було виявлено.

Кореляційний аналіз дозволив підтвердити взаємозв'язки між тяжкістю когнітивних порушень та рівнем прозапальних маркерів, припускаючи, що запалення може спричинити когнітивний спад у пацієнтів з ХА. Результати дослідження свідчать про те, що ІЛ-23 може мати більш складний взаємозв'язок із прогресуванням даного захворювання та дає підстави розглядати ІЛ-23 як маркер запальної активності.

Висновки. Рівні прозапальних цитокінів (ІЛ-17 та ІЛ-23) у сироватці крові були значно вищі у пацієнтів з ХА, у порівнянні з СД та МКР. Такі більш виражені зміни продукції інтерлейкінів (особливо ІЛ-23) підкреслює роль запального процесу при ХА, на відміну від СД та МКР. Рівень інтерлейкіну 23 у всіх обстежених пацієнтів з ХА мав найвищі кореляційні зв'язки з показниками нейрокогнітивних шкал, що вказувало на його важливу роль у патогенезі даного захворювання. Не було знайдено значущих кореляційних зв'язків між сироватковою концентрацією ІЛ-17 та нейрокогнітивними доменами у пацієнтів з МКР та СД.

Ключові слова: хвороба Альцгеймера, судинна деменція, малий когнітивний розлад, нейрокогнітивні домени, інтерлейкіни 17 та 23.

Автор, відповідальний за листування:
Ольга С. Чиняк, кафедра нейрохірургії та неврології, Медичний інститут, Сумський державний університет, м. Суми, Україна
e-mail: o.chinyak@med.sumdu.edu.ua

How to cite/ Як цитувати статтю: Chyniak OS, Dubenko OYe, Potapov OO**.** The relationship between decreased cognitive functions and the level of proinflammatory cytokines in patients with Alzheimer's disease, vascular dementia, and mild cognitive disorder**.** *EUMJ*. 2021;9(3):247-255
DOI: https://doi.org/10.21272/eumj. 2021;9(3):247-255

Introduction/Вступ

Alzheimer's disease (AD) is a degenerative disease that leads to dementia symptoms [1, 2]. Histopathological signs of AD are amyloid plaques in the brain, mainly consisting of fibrillary forms of amyloid β-peptide-40 (Aβ-40) and amyloid β-peptide-42 (Aβ-42). Insoluble Aβ peptides formed in the central nervous system (CNS) play a decisive role in the pathogenesis of AD, activating the complement pathway, stimulating microglia to produce pro-inflammatory cytokines and chemokines. This pro-inflammatory process mediated by microglia leads to neurodegeneration [3]. Aβ peptides also increase the production of reactive nitrogen and oxygen species by microglial cells, which leads to the development of oxidative stress, stimulation of Th17 cells, and production of interleukin (IL-17) [4]. Apparently, the main role of IL-17 in the pathogenesis of AD is the recruitment of neutrophils and the stimulation of their function. Neutrophils are the main targets for IL-17 in the CNS, promote inflammation and damage to CNS tissues, and may play an important role in the development of AD [5]. Since several studies [6, 7] indicate an important role for IL-17 and IL-23 in the pathogenesis of AD and VD, the aim of the study was to investigate the relationship between IL-17 and IL-23 levels and neurocognitive scales in patients with AD, VD and mild cognitive disorder (MCD).

Materials and methods

In accordance with the set goal on the basis of the neurological department of Municipal non-commercial organization «Clinical Hospital № 4» of Sumy city council, 89 patients were examined, of which 59 had cognitive impairment (32 men and 27 women, the average age was 66.8 ± 8.4 years); among them 29 persons had major NCD (neurocognitive disorder) and 30 persons had MCD, while 30 people in the control group had no cognitive deficit. The criteria of clinical practice proposed for the diagnosis of AD in the Alzheimer's Association of the National Institute on Aging were met by 15 patients with AD [8], 14 persons met the criteria for probable VD according to the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et Enseignement en Neurosciences (NINDS-AIREN) [9].

Inclusion criteria were: the objective confirmation of cognitive impairment according to clinical and neuropsychological tests based on criteria of probable AD, probable VD and MCD, signs of cerebrovascular and neurodegenerative brain damage according to clinical and neuroimaging methods.

Exclusion criteria were: severe somatic pathology, other diseases of the nervous system

(Parkinson's disease, fronto-temporal degeneration, dysmetabolic encephalopathies, demyelinating diseases, traumatic brain injury, tumors of the brain and its membranes, neuroinfections, intoxications, alcohol abuse, severe post-stroke deficit, drugs use (neuroleptics, benzodiazepines, antidepressants, barbiturates, antiepileptic), inability to have sufficient verbal contact.

All patients were tested with a comprehensive neuropsychological examination using the following tests and scales: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Alzheimer Disease Assessment Scale-cognitive (ADAS-cog). Neuroimaging (CT or MRI) was performed in all patients. Serum levels of cytokines of IL-17 and IL-23 were assayed using sandwich ELISA on «Chem Well 2900» immunoanalyzer (Awareness Technology, USA). Test systems using Bender Medsystems, Australia (IL-17 and IL-23) were used in accordance with the manufactures instructions.

The work was performed in accordance with the principles of the World Health Association Helsinki Declaration «Ethical Principles of Medical Research with Human Involvement as Object of Study» and the Order of the Ministry of Health of Ukraine No. 690 (dated September 23, 2009). Before inclusion in the study, patients and their relatives were informed of the study protocol and signed written informed consent.

Statistical analysis was performed using Microsoft Excel 2016 software. Comparisons of categorical variables for demographic and clinical characteristics were made using the χ^2 test, and Student's t-test was applied for continuous variables. The Mann–Whitney U-test and the Kruskal–Wallis test were used to compare the concentrations between groups. The Spearman correlation test was used to ascertain the associations between the cytokines concentrations and the score for the MMSE, MoCA, FAB and ADAS-cog. The differences were considered statistically significant at $p < 0.05$.

Results

Comparison of the results of neurocognitive scales (Table 1) showed that the mean scores of MMSE were significantly lower in patients with AD vs. patients with VD and MCD ($p_1 < 0.0001$), ($p_3 = 0.0028$).

MoCA total score test also was significantly lower in patients with AD vs. patients with VD and MCD ($p_1 < 0.0001$), ($p_3 = 0.0005$). The mean scores of ADAS-cog test was significantly higher in patients with AD vs. patients with VD and MCD ($p_1 < 0.0001$), ($p_3 = 0.0063$). Levels of detectable interleukins (IL-17 and IL-23) were significantly higher in patients with AD vs. patients with VD ($p_3 = 0.0481$), ($p_3 = 0.0027$),) and MCD ($p_1 = 0.0003$), ($p_1 = 0.0065$). We detected higher serum concentrations of IL-23 in patients with higher ADAS-cog scores (ADAS-cog >30), as well as the predomination of pro-inflammatory IL-23 over IL-17 in the peripheral blood of patients with AD.

The use of correlation analysis revealed statistical association between the serum concentration of IL-17, IL-23 and neurocognitive scales in patients with AD, VD and MCD (Table 2). The level of proinflammatory interleukins (IL-17, IL-23) in the control group was within normal limits.

Our results revealed a significant positive correlation between the serum concentrations of IL-17 and IL-23 for all patients with AD and MCD ($r = 0.723$; $p = 0.002$), ($r = 0.432$; $p = 0.017$). An examination of the possible connection between the serum concentration of IL-23 and ADAS-cog scores in patients with MCD revealed the following results: positive correlation was established between IL-23 and individual domains of the ADAS-cog scale ($r = 0.423$; $p = 0.020$). There was a positive relationship between IL-23 and sections «word recognition tasks» ($r = 0.466$; $p = 0.030$), «understanding» ($r = 0.306$; $p = 0.059$) and «strike out numbers» ($r = 0.301$; $p = 0.061$).

A negative moderate interdependence was found between the serum concentration of IL-23 and MMSE scores in patients with AD ($r = -0.553$; $p = 0.032$). The average inverse correlation was detected between IL-23 and sections «memory» ($r = -0.566$; $p = 0.030$) and «orientation» ($r = -0.596$; $p = 0.040$).

A significantly inverse correlation was found in patients with AD between the serum concentration of IL-23 and individual domains of the MoCA ($r = -0.592$; $p = 0.020$). The average inverse correlation was observed between IL-23 and «delayed recall» ($r = -0.641$; $p = 0.010$) and «orientation» ($r = -0.566$; $p = 0.030$).

Table 1 – Comparison of characteristics between Alzheimer's disease, vascular dementia and mild cognitive disorder

Characteristic	MCD (n=30)	AD (n=15)	VD (n=14)	P value
Males/female, n	18/12	5/10	9/5	p=0.5150
Mean age, years	65.6± 0.8	67.9±0.8	67.0±0.3	p_1=0.0766 p_2=0.2483 p_3=0.3145
Education level, n (%)				
• secondary-level	6 (20)	6 (40)	4 (28.6)	p=0.7790
• vocational secondary	17 (56.7)	7 (46.7)	8 (57.1)	p=0.0580
• higher	7 (23.3)	2 (13.3)	2 (14.3)	p=0.1030
Mean MMSE score	25.2±0.85	18.8±0.56	21.7±0.69	p_1<0.0001 p_2=0.0122 p_3=0.0028
Mean MoCA test	24.2±0.86	16.6±0.50	19.7±0.61	p_1<0.0001 p_2=0.0016 p_3=0.0005
Mean FAB score	14.3±0.9	12.4±0.50	11.1±0.36	p_1=0.1594 p_2=0.0222 p_3=0.0468
Mean ADAS –cog test	12.9±2.3	38.9±1.93	30.4±2.13	p_1<0.0001 p_2<0.0001 p_3=0.0063
Mean HIS score	-	2.4±0.50	9.1±0.77	p_3<0.0001
Mean IL-17, pg/ml	4.04±1.10	22.44±8.92	3.11±1.35	p_1=0.0065 p_2=0.6194 p_3=0.0481
Mean IL-23, pg/ml	1.84±0.38	64.33±22.41	5.14±1.62	p_1=0.0003 p_2=0.0102 p_3=0.0027

Note: p_1 – differences between MCD and AD; p_2 – differences between MCD and VD; p_3 – differences between AD and VD

A close connection was observed with the serum concentration of IL-23 and ADAS-cog scores in patients with AD (r = 0.760; p = 0.001). In particular, these sections are: «tasks for repeating words» (r = 0.775; p < 0.001), «word recognition tasks» (r = 0.616; p = 0.020), «constructive praxis» (r = 0.651; p = 0.010), «orientation» (r = 0.684; p = 0.010) and «name of objects and fingers» (r = 0.585; p = 0.030). The level of IL-23 was positively correlated with ADAS-cog scores in patients with VD (r = 0.497; p = 0.045). Moderate positive correlation was observed for IL-23 with «concentration and distraction» (r = 0.558; p = 0.040). In addition, an inverse correlation was found between the serum levels of IL-23 and MoCA scores (r = −0.510; p = 0.060), especially with «language» (r = −0.538; p = 0.047) and «executive functioning» (r = −0.485; p = 0.079).

However, no other significant correlations were found between the serum concentration of IL-17 and FAB score, between the serum concentration of IL-23 and FAB score in patients with AD (r = −0.1084; p = 0.702), (r = −0.110; p = 0.697), with VD (r = −0.195; p = 0.503), (r = −0.158; p = 0.590) and with MCD (r = −0.013; p = 0.947), (r = −0.160; p = 0.399).

Discussion

Numerous recent studies demonstrated a correlation between proinflammatory cytokines (such as IL-2, IL-8, IL-9, IL-10, TNF-α, IL-17, IL-18, IL-21) and cognitive deficits, especially with AD and MCD [10, 11, 12, 13]. In patients with Alzheimer's disease, elevated levels of IL-6 were moderately correlated with decreased cognitive function, lower memory, and lower verbal velocity on the MMSE scale [14].

Table 2 – Correlations among IL-17, IL-23 in patients with Alzheimer's disease, vascular dementia and mild cognitive disorder

Cytokine	MCD (n=30)		AD (n=15)		VD (n=14)	
	r	p	r	p	r	p
IL-17 vs. IL-23	0.432	0.017	0.723	0.002	0.322	0.261
IL-17 vs. MMSE	-0.602	0.099	-0.384	0.157	-0.212	0.467
IL-17 vs. MoCA	-0.127	0.504	-0.116	0.680	-0.182	0.534
IL-17 vs. FAB	-0.013	0.947	-0.108	0.702	-0.195	0.503
IL-17 vs. ADAS-cog	0.125	0.510	0.141	0.617	0.335	0.241
IL-23 vs. MMSE	-0.276	0.140	-0.553	0.032	-0.146	0.620
IL-23 vs. MoCA	-0.111	0.633	-0.592	0.020	-0.510	0.060
IL-23 vs. FAB	-0.160	0.399	-0.110	0.697	-0.158	0.590
IL-23vs. ADAS-cog	0.423	0.020	0.760	0.001	0.497	0.045

Note: r – Spearman correlation criterion; p – statistical significance of the difference

Subsequently, several researchers confirmed that under inflammatory conditions, excessive IL-6 through activation of neuronal NADPH-oxidase induced by inflammation impair cognitive processes, such as spatial learning and memory [14, 15, 16]. Saresella et al. found that IL-23 was significantly increased in the brain, but that IL-17 was not augmented in AD, MCD and did not correlate with measures of progression or dementia severity [17]. Other studies showed that level of IL-17 was significantly increased in the brain and in the cerebrospinal fluid of individuals with AD and correlated with cognitive impairment [18].

We investigated for the first time the peripheral cytokine profile in AD, VD, and MCD. In particular, it was noted that the concentrations of IL-17 and IL-23 are interrelated, and the content of each of them increased linearly with the progression of the disease. In our study, IL-23 correlated with cognitive functions in patients with AD. This study found an association between severity of cognitive impairment and the level of pro-inflammatory markers, suggesting that inflammation may cause cognitive decline in patients with AD. Recent studies confirmed that improved cognitive performance was seen after blocking IL-23 signaling p40 subunit by antibody [19]. These findings suggest that IL-23 may show a more complex relationship with disease progression. In conclusion, this gives grounds to consider the level of IL-23 in the serum as marker of inflammatory activity. However, understanding the complete interaction process of the two cytokines in the pathogenesis of AD requires further studies.

Conclusions/Висновки

Our results showed that levels of detectable pro-inflammatory cytokines (IL-17 and IL-23) were significantly higher in patients with AD as compared with VD and MCD. Such more pronounced changes in the production of IL-23 in patients with AD may indicate the activity of the inflammatory process. The level of interleukin 23 in all examined patients with AD had the highest correlations with the neurocognitive scales, which indicated its important role in the pathogenesis of this disease. There were no significant correlations between the serum concentration of IL-17 and neurocognitive domains in patients with MCD and VD.

Prospects for future research/Перспективи подальших досліджень

Future investigation may elucidate a potential role of interleukin 23 as additional biomarker for early predicting of MCD progression in AD.

References/Список літератури

1. Lai P, Liu S, Rau A, Lanctôt L, Köhler A, Pakosh M, et al. Peripheral inflammatory markers in Alzheimer's disease: a systematic review and meta-analysis of 175 studies. *J. Neurol. Neurosurg. Psychiatry*. 2017;88:876-882. Doi: 10.1136/jnnp-2017-316201
2. Kinney J, Bemiller S, Murtishaw A, Leisgang A, Salazar A, Lamb B. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement (N Y).* 2018;4:575-590. Doi: 10.1016/j.trci.2018.06.014
3. Ahmad, M, Fatima, M, Mondal, A. Influence of microglia and astrocyte activation in the neuroinflammatory pathogenesis of Alzheimer's disease: Rational insights for the therapeutic approaches. *Journal Of Clinical Neuroscience*. 2019;59:6-11. Doi: 10.1016/j.jocn.2018.10.034
4. Tahmasebinia F, Pourgholaminejad A. The role of Th17 cells in auto-inflammatory neurological disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;3(79):408-416. Doi: 10.1016/j.pnpbp.2017.07.023
5. Milovanovic J, Arsenijevic A, Stojanovic B, Kanjevac T, Arsenijevic D, Radosavljevic G, Milovanovic M, Arsenijevic N. Interleukin-17 in Chronic Inflammatory Neurological Diseases. *Front. Immunol.* 2020;11:947. Doi: 10.3389/fimmu.2020.00947
6. Park JC, Han SH, Mook-Jung I. Peripheral inflammatory biomarkers in Alzheimer's disease: a brief review. *BMB Reports.* 2020;53(1):10-19. Doi: 10.5483/BMBRep.2020.53.1.309
7. Chen J, Jiang G, Li Q, Zhou Z, Cheng Q. Increased Serum Levels of Interleukin-18, -23 and -17 in Chinese Patients with Alzheimer's Disease. *Dement Geriatr Cogn Disord.* 2014;38:321-329. Doi: 10.1159/000360606
8. McKhaann M, Knopman, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institue on Aging- Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263-269. Doi: 10.1016/j.jalz.2011.03.005
9. Sachdev P, Lipnicki D, Crawford J, Brodaty H. The Vascular Behavioral and Cognitive Disorders criteria for vascular cognitive disorders: a validation study. *Eur J Neurol*. 2019;9:1161-1167. Doi: 10.1111/ene.13960
10. Shen X, Niu L, Wang Y, Cao X, Liu Q, Tan L, Zhang C, Yu J. Inflammatory markers in Alzheimer's disease and mild cognitive impairment: A meta-analysis and systematic review of 170 studies. *Alzheimer's Dement*. 2020;16(4):e041476. Doi: 10.1002/alz.041476
11. Wang W, Tan M, Yu J, Tan L. Role of pro-inflammatory cytokines released from microg lia in Alzheimer's disease. *Ann Transl Med.* 2015; 3(10)136. Doi: 10.3978/j.issn.2305-5839.2015.03.49
12. Domingues, C, da Cruz E Silva, O, Henriques G. Impact of Cytokines and Chemokines on Alzheimer's Disease Neuropathological Hallmarks. *Current Alzheimer research*. 2017;14(8):870-882. Doi: 10.2174/1567205014666170317113606
13. Zhu Y , Chai Y , Hilal S. Serum IL-8 is a marker of white-matter hyperintensities in patients with Alzheimer's disease. *Alzheimers Dement.* 2017;**7**:41–7. Doi: 10.1016/j.dadm.2017.01.001
14. Wennberg M, Hagen C, Mary M, Machulda M, Knopman D, Petersen R, Michelle M, Mielke M. The Cross-sectional and Longitudinal Associations Between IL-6, IL-10, and TNFα and Cognitive Outcomes in the Mayo Clinic Study of Aging, *The Journals of Gerontology: Series A.* 2019;74(8):1289-1295. Doi: 10.1093/gerona/gly217
15. Balldin VH , Hall JR , Barber RC , et al The Relation between Inflammation and Neuropsychological Test Performance. *Int J Alzheimers Dis.* 2012;2012:1–6. Doi: 10.1155/2012/703871
16. Uslu S , Akarkarasu Z , Ozbabalik D , et al. Levels of amyloid beta-42, interleukin-6 and tumor necrosis factor-alpha in Alzheimer's disease and vascular dementia. *Neurochem Res.*2012;37:1554–9. Doi: 10.1007/s11064-012-0750-0
17. Saresella M, Calabrese E, Marventano I, Piancone F, Gatti A, Alberoni M, Nemni R, Clerici M. Increased activity of Th-17 and Th-9 lymphocytes and a skewing of the post-thymic differentiation pathway are seen in Alzheimer's disease. *Brain Behav Immun.*

2011;25:539-547.
Doi: 10.1016/j.bbi.2010.12.004

18. Chen, J, Liu, X, Zhong, Y. Interleukin-17A: The Key Cytokine in Neurodegenerative Diseases. *Front Aging Neurosci*. 2020;12:307. Doi: 10.3389/fnagi.2020.566922

19. Pastor-Fernández G, Mariblanca IR, Navarro MN. Decoding IL-23 Signaling Cascade for New Therapeutic Opportunities. *Cells.* 2020; 9(9):2044. Doi: 10.3390/cells9092044.

(received 12.07.2021, published online 29.09.2021)

(одержано 12.07.2021, опубліковано 29.09.2021)

Conflict of interest/Конфлікт інтересів

The authors declare no conflict of interest.

Information about the authors/Відомості про авторів

Chyniak Olha Serhiivna, Assistant of Department of Neurosurgery and Neurology, Medical institute, Sumy State University, Sumy, Ukraine.
ORCID: 0000-0002-6008-1039, e-mail: o.chinyak@med.sumdu.edu.ua
Address for correspondence: 2 Rymskogo-Korsakova st., Sumy, Ukraine 40007
Telefone: +38 095 063 01 71 (mobile)

Dubenko Olga Yevhenivna, MD, PhD, Professor of Department of Neurology and Neurosurgery, Kharkiv Medical Academy of Postgraduate Education, Kharkiv, Ukraine.
ORCID: 0000-0002-4911-5613 e-mail: olgadubenko05@gmail.com
Address for correspondence: 58 Amosova str., Kharkiv, Ukraine 61176
Telefone: +38 050 660 14 42 (mobile)

Potapov Olexander Oleksandrovych, MD, PhD, Professor, Head of Department the Neurosurgery and Neurology, Medical institute, Sumy State University, Sumy, Ukraine.
ORSID: 0000-0002-9683-3685 e-mail: neiro@med.sumdu.edu.ua
Address for correspondence: 2 Rymskogo-Korsakova st., Sumy, Ukraine 40007
Telefone: +38 050 577 50 00 (mobile)