Abstract

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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.

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.

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**Резюме**

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ВЗАЄМОЗ'ЯЗОК МІЖ ЗНІЖЕННЯМ 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 ($\text{A} \beta - 40$) та амілоїду β-пептиду-42 ($\text{A} \beta - 42$). Нейтрофіли є головними мішенями для інтерлейкіну 17 (IL-17), сприяють запальному та пошкодженню тканини 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.

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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), Монреальська шкала оцінки когнітивних функцій (МоCA), батерія лобної дисфункції (FAB), шкала оцінки хвороби Альцгеймера – когнітивна субшкала (ADAS-cog).

Рівні цитокінів ІЛ-17 та ІЛ-23 у сироватці крові аналізували за допомогою КФА методом «сендвіч» на імуноаналізаторі «Chem Well 2900» (Awareness Technology, США). Тестові системи з використанням Bener Medsystems, Австралія (ІЛ-17 та ІЛ-23) аналізували згідно із 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, МоCA, 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; р = 0.001), а саме за розділами підтестів «завдання для повторення слів» (r = 0.775; р < 0.001), «конструктивний праксис» (r = 0.651; р = 0.010), «орієнтація» (r = 0.684; р = 0.010), а також «завдання на впізнання слів» (r = 0.616; р = 0.020) та шкалою МоCA (r = −0.592; р = 0.020), а саме в домені «відстороненого відтворення» (r = −0.641; р = 0.010). Встановлено значну позитивну кореляцію між ІЛ-23 та окремими доменами шкали ADAS-cog у пацієнтів з МКР (r = 0.423; р = 0.020), а саме із «завданнями на впізнання слів» (r = 0.466; р = 0.030), з «розуміння» (r = 0.306; р = 0.059), а також з «закреслюванням цифр» (r = 0.301; р = 0.061). Виявлено слабку позитивну кореляцію між сироватковою концентрацією ІЛ-23 та оцінками ADAS-cog у пацієнтів із СД (r = 0.497; р = 0.045). Помірна позитивна кореляція спостерігалась для ІЛ-23 з «концентрацією та відволіканням уваги» (r = 0.558; р = 0.040). Була встановлена зворотна кореляція між сироватковими рівнями ІЛ-23 та показниками МоCA у пацієнтів з СД (r = −0.510; р = 0.060), особливо з «мовою» (r = −0.538; р = 0.047) та з «виконавчими функціями» (r = −0.485; р = 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’язок між тяжкістю когнітивних порушень та рівнем прозапальних маркерів, припускаючи, що запалення може спричиняти 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.
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**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
elation was found.

Awareness Technology, USA).

positive correlation was
lic encephalopathies, frontal Assessment Battery
(ADAS) were
scales (Table 1) showed that the
statistically significant at р.<0.05).

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 χ² 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 р.<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 (р₁ < 0.0001),
(p₂ = 0.0028).

MoCA total score test also was significantly
lower in patients with AD vs. patients with VD
and MCD (р₁ < 0.0001), (р₁ = 0.0005). The mean
scores of ADAS-cog test was significantly higher
in patients with AD vs. patients with VD and
MCD (р₁ < 0.0001), (р₁ = 0.0063). Levels of
detectable interleukins (IL-17 and IL-23) were
significantly higher in patients with AD vs.
patients with VD (р₁ = 0.0481), (р₁ = 0.0027),) and
MCD (р₁ = 0.0003), (р₁ = 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; р = 0.002), (r = 0.432; р =
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; р = 0.020).

There was a positive relationship between IL-23
and sections «word recognition tasks» (r = 0.466;
р = 0.030), «understanding» (r = 0.306; р = 0.059)
and «strike out numbers» (r = 0.301; р = 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; р = 0.032). The average inverse
correlation was detected between IL-23 and
sections «memory» (r = −0.566; р = 0.030) and
«orientation» (r = −0.596; р = 0.040).

A significantly inverse correlation was found
in patients with AD between the serum
congration of IL-23 and individual domains
of the MoCA (r = −0.592; р = 0.020). The average
inverse correlation was observed between IL-23
and «delayed recall» (r = −0.641; р = 0.010) and
«orientation» (r = −0.566; р = 0.030).
Table 1 – Comparison of characteristics between Alzheimer’s disease, vascular dementia and mild cognitive disorder

| Characteristic          | MCD 1 (n=30) | AD 2 (n=15) | VD 3 (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    | p1=0.0766 p2=0.2483 p3=0.3145 |
| Education level, n (%) | 6 (20)       | 6 (40)      | 4 (28.6)    | p=0.7790 |
| • secondary-level      |              |             |             |         |
| • 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   | p1<0.0001 p2=0.0122 p3=0.0028 |
| Mean MoCA test         | 24.2±0.86    | 16.6±0.50   | 19.7±0.61   | p1<0.0001 p2=0.0016 p3=0.0005 |
| Mean FAB score         | 14.3±0.9     | 12.4±0.50   | 11.1±0.36   | p1=0.1594 p2=0.0222 p3=0.0468 |
| Mean ADAS –cog test    | 12.9±2.3     | 38.9±1.93   | 30.4±2.13   | p1<0.0001 p2<0.0001 p3=0.0063 |
| Mean HIS score         | -            | 2.4±0.50    | 9.1±0.77    | p1<0.0001 |
| Mean IL-17, pg/ml      | 4.04±1.10    | 22.44±8.92  | 3.11±1.35   | p1=0.0065 p2=0.6194 p3=0.0481 |
| Mean IL-23, pg/ml      | 1.84±0.38    | 64.33±22.41 | 5.14±1.62   | p1=0.0003 p2=0.0102 p3=0.0027 |

Note: p1 – differences between MCD and AD; p2 – differences between MCD and VD; p3 – 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].
Recent studies confirmed that inflammatory measures of progression or dementia severity have increased in patients with AD, VD, and MCD. The concentration of IL-17 was significantly increased in the brain, but that IL-23 was not augmented in AD, MCD and did not significantly increase in VD 

| 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-23 vs. 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 литературы

1. Lai P, Liu S, Rau A, Lancetö 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, Murtsishaw 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. McKhaan M, Knopman, Chertkow H, et al. The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute 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 Neuro. 2019;9:1161-1167. Doi: 10.1111/ejne.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 microglia 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. Baldin 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 , Ozbalikli 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, Nemri 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.
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.

Conflict of interest/Конфлікт інтересів
The authors declare no conflict of interest.

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