NEUROLOGIA I NEUROCHIRURGIA POLSKA 51 (2017) 24–32

Available online at www.sciencedirect.com

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journal homepage: http://www.elsevier.com/locate/pjnns

Original research article

Cognitive impairment and BDNF serum levels

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ARTICLE INFO

Article history:
Received 20 June 2016
Accepted 4 October 2016
Available online 21 October 2016

Keywords:
Brain-derived neurotrophic factor
Serum brain-derived neurotrophic factor level
Cognitive impairment
Dementia
Alzheimer's disease

ABSTRACT

Background/aims: To investigate the alterations of brain-derived neurotrophic factor (BNDF) serum levels in subjects with different intensity of cognitive impairment and different neurodegenerative processes.

Material and methods: Serum BDNF levels were analyzed by ELISA kit in 378 subjects: 134 Alzheimer's disease (AD) patients, 115 amnestic mild cognitive impairment (MCI) patients, and 129 controls divided into two groups: neurodegenerative control group (ND), consisting of 49 Parkinson's disease patients without any cognitive complaints, and cognitively normal control group (CN), consisting of 80 subjects without any neurological disorders.

Results: AD patients had significantly lower ($p < 0.001$) BDNF serum levels compared to MCI, CN and ND controls. Age and education had significant influence on BDNF serum levels regardless the diagnosis or group assignment. We have found no influence of depression on BDNF serum levels either in our group as a whole, or in each group assessed separately. We found significant correlation between BDNF serum levels and cognitive impairments. After multiple comparisons between the groups, we found that, after adjustment for confounding factors (age, gender, education, depression, cognitive impairment), BDNF serum levels were the lowest in AD group ($p = 0.05$).

Conclusions: Advanced age and low educational level are associated with decreased BDNF serum levels. Decreased BDNF serum levels correspond to the severity of cognitive impairment. There is no correlation between BDNF serum levels and depressive symptoms.

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http://dx.doi.org/10.1016/j.pjnns.2016.10.001
0028-3843/

1. Introduction

The most common form of neurodegenerative disorders is Alzheimer's disease (AD) affecting over 20 million people all over the world [1,2]. Dementia in AD is related to progressive neurodegeneration, which is characterized by synaptic injury and neuronal loss associated with the formation of senile plaques composed of amyloid-β (Aβ) oligomers and intracellular neurofibrillary tangles (NFT) composed of hyperphosphorylated tau protein [3–5]. The earliest pathological changes usually occur in medial temporal lobe structures, interrupting the neural network critical for episodic memory function (e.g., free recall, recognition, paired-associate learning). Mildly demented AD patients are also impaired on tests of object naming and semantic categorization, that reflect deterioration in the structure and content of semantic memory (i.e., general knowledge of facts, the meanings of words) that supports language. Knowledge for particular items or concepts and the associations between them may be disrupted as the neuropathology of AD spreads throughout the temporal, frontal, and parietal association cortices in which they are thought to be diffusely stored. Deficits in executive functions, responsible for the mental manipulation of information, concept formation, and problem solving can occur early in the course of AD, and in addition to difficulties with delayed memory recall may predict disease progression. Deficits in executive functioning have been hypothesized to reflect AD pathology, especially neurofibrillary tangle burden in prefrontal cortex [2–4,6]. Recently, there has been increasing evidence that alterations in the brain neurotrophic support and in particular in the brain-derived neurotrophic factor (BDNF) expression and signaling might contribute to neurodegeneration [7,8]. The BDNF is a member of the neurotrophin family of proteins that is not only important for the normal development of the peripheral and central nervous system, but also plays a key role in neuronal survival, synaptic plasticity, axonal guidance, cell morphology, memory formation and cognition in the adult brain [8–11]. The BDNF is highly concentrated in the nervous system. The BDNF produced in brain neurons acts locally at synapses, and is not released and transported from the brain to periphery [12]. Circulating BDNF in platelets is produced from megacaryocytes and stored in α-granules, which do not receive their content from external sources [13]. It is speculated that, the variance of circulating BDNF may partly reflect the variance of BDNF secretion in the human brain, and reduced brain BDNF levels could be associated with lower circulating BDNF levels [14]. The reduction of BDNF concentration in hippocampus and cerebral cortex may induce a neurodegenerative process in the human brain [15].

BDNF serum concentration was reported to be significantly reduced in patients with severe dementia comparing to control subjects [15,16]. Additionally, higher BDNF serum levels were associated with better neuropsychological functioning in healthy elderly subjects [17,18]. The correlation between the BDNF serum levels and dementia has been analyzed in AD patients with mixed results. While some researchers found a decrease in BDNF serum concentrations in AD [15], others reported increased BDNF levels in patients in the early as well as in advanced stages of AD [19,20]. The BDNF levels were found to be significantly negatively associated with the scores on immediate and delayed verbal memory and immediate visual memory [21]. Other studies showed that BDNF serum levels correlate positively with performance on neuropsychological tests investigating executive functioning and attention [22]. Moreover, BDNF was recognized as a potent inhibitor of apoptosis-mediated cell death and neurotoxin-induced degeneration of dopaminergic neurons. The decrease of BDNF was detected in the substantia nigra in PD [23]. Lower BDNF serum levels were reported in early stages of Parkinson's disease, and the increase of BDNF levels was reported with the disease progression suggesting a compensatory mechanism involved in more advanced stages of Parkinson's disease [24,25].

The current study aims to contribute to the discussion on the involvement of BDNF in neurodegenerative diseases by assessing alterations of peripheral BDNF levels. It replicates and extends previous findings by comparing BDNF serum levels in a group of patients with the Alzheimer's dementia and with patients diagnosed with the mild cognitive impairment (MCI), which is a clinical concept proposed by the Mayo Clinic Group in 1999 [26]. MCI is placed between normal aging and dementia with 5–8% annual progression rate to AD [27]. Patients were compared with two types of controls: a subgroup of cognitively normal subjects without any known neurological disorders and a subgroup of subjects with the idiopathic Parkinson's disease with a normal cognitive status. We decided to include PD patients as an additional control group to examine if BDNF serum levels would depend on a type of a neurodegenerative process.

2. Materials and methods

2.1. *Study population*

The subjects in the study were: 134 Alzheimer's disease patients (81 females and 53 males with the mean age of 72.2 ± 9.4 years), 115 amnestic MCI patients (67 females and 48 males with the mean age of 71.1 ± 9.6 years), and 129 controls subdivided into two groups: a neurodegenerative control group (ND), consisting of 49 Parkinson's disease patients without any cognitive deficits (22 females and 27 males with the mean age of 63.3 ± 10.5 years), and a cognitively-normal control group (CN), consisting of 80 subjects without any neurological disorders (44 females and 36 males with the mean age of 65.6 ± 11.9 years) (Table 1). Patients and ND controls were recruited from the outpatient clinic at the Department of Neurology. The subjects in the CN control group were independently functioning community dwellers without any subjective complaints on cognitive impairment and without any movement disorder symptoms. All patients and control subjects were right-handed. A written informed consent to participate in the study was obtained from each participant. The study was approved of by the Local Ethics Committee for Medical Research.

All the patients were examined by neurologists with expertise in neurodegenerative diseases (dementia and movement disorders) and met the internationally accepted

Table 1 – Demographic, clinical and BDNF serum levels of different studied groups.

Diagnosis	Controls CN	Controls ND	MCI	AD	*p*-Value
Sample size *N* (100%)	80 (21.2%)	49 (13.0%)	115 (30.4%)	134 (35.4%)	<0.001
Demographic variables					
Age (years ± SD)	65.6 ± 11.9	63.3 ± 10.5	71.1 ± 9.6	72.2 ± 9.4	0.8
Gender F/M (M%)	44/36 (45.0%)	22/27 (55.1%)	67/48 (41.7%)	81/53 (39.5%)	0.1
Education (years ± SD)	13.5 ± 2.5	12.5 ± 2.7	12.2 ± 3.6	10.7 ± 2.7	0.9
Disease duration (years ± SD)	NA	8.41 ± 5.8	1.77 ± 1.3	3.02 ± 2.0	NA
Clinical variables					
MMSE (pts ± SD)	28.8 ± 1.4	27.2 ± 2.4	26.5 ± 2.4	16.1 ± 6.4	<0.001
BDI (pts ± SD)	14.17 ± 7.2	10.8 ± 9.9	11.7 ± 7.5	7.84 ± 6.7	<0.05
CDT (pts ± SD)	9.64 ± 1.1	8.69 ± 2.4	7.9 ± 2.7	3.4 ± 3.7	<0.001
Hoehn-Yahr (stage ± SD)	NA	2.7 ± 0.7	NA	NA	NA
Treatment					
AChEI (+/−)	NA	(0/49)	(0/115)	(134/0)	NA
L-dopa (+/−)	NA	(49/0)	NA	(0/134)	NA
LEDD (mg ± SD)	NA	940.2 ± 493.8	NA	NA	NA
BDNF					
ng/ml ± SD	10.0 ± 4.0	9.2 ± 4.7	8.7 ± 6.1	4.8 ± 4.7	<0.001
Median (IQR)	9.3 (5.3)	8.0 (7.3)	7.1 (12.2)	2.4 (4.3)	

Controls CN, cognitively normal controls; Controls ND, neurodegenerative controls with Parkinson's disease without cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory; CDT, Clock Drawing Test, BDNF, brain-derived neurotrophic factor; IQR, Interquartile range; NA, not applicable; AChEI, acetylocholin esterase inhibitors; LEDD, L-dopa equivalent daily dose; (+/−), treated/not treated.

criteria for the mild cognitive impairment [26,27], Alzheimer's disease [2,3] or Parkinson's disease [28,29].

All the subjects underwent clinical evaluation that included previous medical history, followed by physical, neurological and neuropsychological examination. Prior to the study, each individual underwent laboratory tests and structural imaging scanning of the brain for the exclusion of secondary causes of cognitive deficit and movement disorders.

All subjects with medical, psychiatric or neurological disorders (other than MCI, AD, PD) that could interfere with cognitive performance or could cause parkinsonism, were excluded from the study.

2.2. *Cognitive assessment*

All the patients and controls were examined in the morning hours. The Parkinson's disease patients were evaluated in ON state, to avoid the influence of movement disorder symptoms on tests results. The general cognitive status was assessed with the Mini-Mental State Examination (MMSE) [30] and the Clock Drawing Test (CDT) scored by the Sunderland method [31,32]. A battery of detailed cognitive tests, performed by a clinical psychologist, was used to assess the cognitive status of every subject [33,34]. Episodic memory was assessed with the Rey Auditory Verbal Learning Test (AVLT). The language abilities were assessed with categorial and phonetic verbal fluency tests. Executive functions and attention were evaluated with the Trail Making Test (TMT parts A and B). The Beck Depression Inventory (BDI) was used to evaluate depressive symptoms [35]. The final diagnosis of cognitive status was made individually as a consensus of a neurologist's and neuropsychologist's opinion. Additionally the data obtained from the patient's informant (caregiver) were taken into consideration. The subjects were classified as cognitively normal if they had no subjective complaints and there was no objective memory impairment in the clinical assessment. The diagnosis of MCI was made according to the Mayo Clinic Group criteria [27]. The dementia diagnosis was made according to DSM IV and the Alzheimer's disease was diagnosed according to the NINCDS-ADRDA criteria [2,3].

2.3. *Measurements*

Blood samples were collected after overnight fasting. Venous blood (5 ml) from the upper arm of each subject was collected into anticoagulant free tubes. The samples were incubated at a temperature of 4 degree Celsius (°C) for half an hour before the serum was isolated. The samples were then centrifuged at 2000 × *g* for 10 min. The supernatants were transferred to an Eppendorff tube and stored at −70 °C before testing. The concentration of BDNF in the serum was measured by a standard protocol using the RayBio® Human BDNF Enzyme-Linked Immunosorbent Assay (ELISA) kit [36].

2.4. *Statistical analysis*

Statistical analyses were performed using the R 3.1.2 software on GNU GPL license and the STATISTICA 10.0 Stat Soft Polska software. The measurable data analyses were done using mean values and standard deviations (±SD) in the case of normal distribution, and the median with interquartile range (IQR) for skewed distribution. Testing for normality of distribution was performed with the Shapiro–Wilk test. The *t*-test or the *U* Mann–Whitney test, depending on the distribution of normality, were used to assess the significance of differences in values of BDNF in two groups (taking into account a dichotomous variable: gender – female/male). The Kruskal–Wallis test by ranks was used to compare three or

more groups for statistical differences in distribution (taking into account ordinal variables: age (years); education (years); cognitive impairment – no dementia/mild dementia/moderate dementia/severe dementia; depressive disorders – no depression/mild symptoms/moderate symptoms/severe symptoms). Spearman's rank correlation coefficients with 95% confidence intervals (95% CI) were used to measure statistical dependence between variables. A two-way Permutational Multivariate Analysis of Variance (ANOVA) was used to analyze the influence of confounding factors, e.g., age, gender or education on the differences in BDNF serum levels between groups. Statistical significance was assessed by permutational pairwise comparisons between group levels. The significance level was established at $p < 0.05$.

3. Results

Demographic information for controls and patients is reported in Table 1. Differences in BDNF serum levels in controls and patients with different neurodegenerative disorders are presented in Fig. 1. AD patients had significantly lower ($p < 0.001$) BDNF serum levels compared to MCI, CN and ND controls. MCI patients had significantly lower ($p < 0.05$) BDNF serum levels compared to CN controls, but not to ND controls ($p > 0.05$). CN and ND controls did not different significantly in BDNF serum levels ($p > 0.05$). The significant effects of age, education and cognitive impairment variables on BDNF serum levels were observed in our sample. There was a significant association between BDNF serum levels and the number of years of schooling ($p < 0.01$) (Table 2).

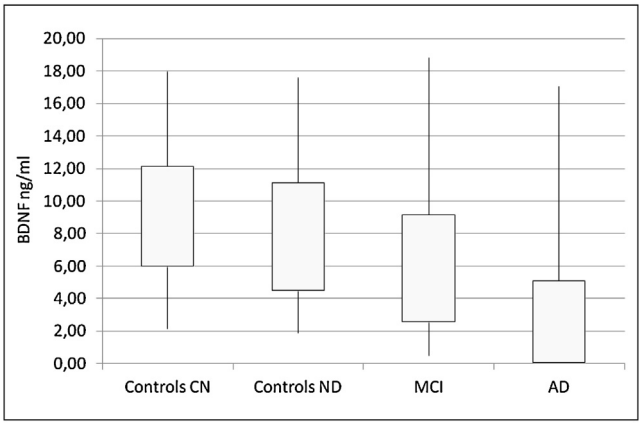

Fig. 1 – BDNF serum levels in all studied groups. Controls CN, cognitively normal control group; Controls ND, neurodegenerative control group (Parkinson's disease patients without cognitive impairment); MCI, mild cognitive impairment; AD, Alzheimer's disease; rectangle, mean value of BDNF ± SD; vertical line, range of BDNF (from lowest to highest value).

Next, we analyzed each group separately (Online Resource – Suppl. Figure 1, Suppl. Tables 1 and 2). The two-way analysis of variance (ANOVA) confirmed that age and education had significant influence on BDNF serum levels regardless of the diagnosis or group assignment. Interestingly, in the MCI group the BDNF serum levels were higher in older population, but this difference did not reach significance ($p > 0.05$).

Table 2 – BDNF serum levels in cases and controls with regard to gender, age, education, cognitive impairment, and depressive symptoms – total.

	N (%)	BDNF ng/ml ± SD	Median (IQR)	p-Value
Gender				
Female	214 (56.7%)	7.4 ± 5.4	6.0 (8.7)	0.4
Male	164 (43.3%)	8.0 ± 5.6	6.7 (10.3)	
Age (years)				
≤65	97 (25.7%)	8.5 ± 5.6	7.4 (10.2)	<0.05
65+	281 (74.3%)	7.2 ± 5.4	6.1 (8.8)	
Education (years)				
General (≤8)	59 (15.6%)	5.7 ± 5.2	2.9 (6.2)	<0.01
Vocational (9–10)	80 (21.1%)	8.6 ± 6.1	7.2 (11.2)	
High school (11–12)	136 (35.9%)	8.0 ± 5.6	7.0 (10.2)	
Higher education (≥13)	103 (27.4%)	8.6 ± 4.8	8.6 (7.6)	
Cognitive impairment				
No dementia	242 (64.1%)	9.1 ± 5.3	8.3 (9.3)	<0.001
Mild symptoms	49 (12.9%)	5.4 ± 5.4	2.4 (6.5)	
Moderate symptoms	63 (16.6%)	5.3 ± 4.6	3.1 (5.8)	
Severe symptoms	24 (6.4%)	3.7 ± 3.9	2.1 (3.3)	
Depressive disorders				
No depression	229 (60.6%)	6.6 ± 5.1	5.3 (8.8)	0.5
Depressive symptoms	149 (39.4%)	7.4 ± 5.8	5.7 (10.2)	
Mild symptoms	128 (33.8%)	7.3 ± 5.7	5.7 (10.2)	
Moderate symptoms	14 (3.7%)	6.4 ± 5.4	3.9 (9.2)	
Severe symptoms	7 (1.9%)	9.9 ± 7.1	9.9 (13.8)	

BDNF, brain-derived neurotrophic factor; IQR, interquartile range.

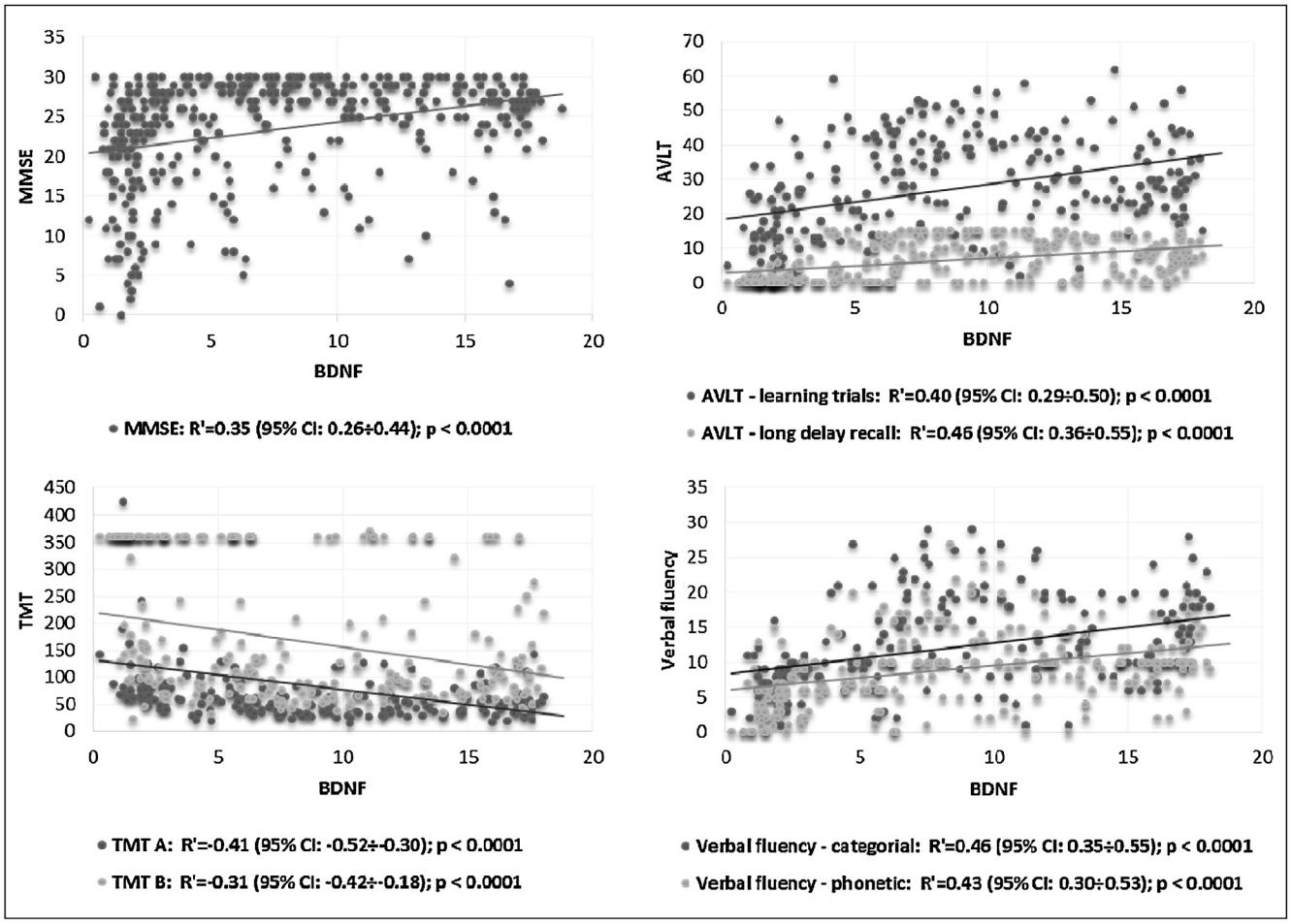

Fig. 2 – Spearman's correlation coefficient between BDNF serum levels and neuropsychological tests results – total. MMSE, Mini Mental State Examination; AVLT, auditory verbal learning test; TMT A&B, trail making test parts A&B.

Gender had no influence on the BDNF serum levels in AD, MCI and cognitively normal control group, but we found significantly lower BDNF serum levels in males compared to females in the neurodegenerative control group of subjects with Parkinson's disease.

The depressive symptoms were present in the one-third of the studied group (Table 2). We have found no influence of the severity of depressive symptoms on variability in BDNF serum levels either in the whole tested population or in each group separately (Online Resource – Suppl. Table 2). After multiple comparisons between the groups, we found that, affiliation to the Alzheimer's disease group was the strongest factor influencing the BDNF serum levels.

A significant correlation between BDNF serum levels and cognitive impairments, as measured by scores on the MMSE, was observed in the tested sample (Table 2, Fig. 2). Analogously, the following significant correlations were found between BDNF serum levels and different domains of cognitive impairment measured by the neuropsychological tests. A positive correlation was found between BDNF serum levels and episodic memory, as measured by the number of words memorized and recalled after the delay in AVLT, and the number of words in verbal fluency tests. A negative correlation was found between BDNF serum levels and the time to complete tasks in TMT A&B used to assess executive function impairment ($R' = -0.41$ and $R' = -0.31$ respectively, $p < 0.001$). None of the tests turned out to be specific, but all tests showed significant correlation coefficients with BDNF serum levels (Online Resource – Suppl. Table 3).

4. Discussion

The main goal of our study was to evaluate alteration of BNDF serum levels in subjects with different intensity of cognitive impairment caused by neurodegenerative processes.

Significantly lower BDNF serum levels were detected in our sample of patients with AD, which is in accordance with the previous results [7,37]. The decreased level of peripheral BDNF concentration was previously reported in patients with AD, depending on the severity of the disease [15,38,39]. Most of our AD patients were already in more severe stages of the disease, with the mean MMSE score of 16.6 pts., reflecting the moderate dementia syndrome. The AD patients had the lowest BDNF serum levels out of all the examined subjects with neurodegenerative disorders. However, it should be pointed out that neither dementia nor mild cognitive impairment was present in our neurodegenerative control group of PD patients. Other

data on BDNF serum levels had been reported in AD patients as well. Significantly increased BDNF serum levels were found in the early stages compared to low BDNF serum levels in the severe stages of AD, which may be explained by a compensatory increase in BDNF in early dementia [19]. To confirm the hypothesis that there is a link between the severity of cognitive deficit and BNDF serum levels, we assessed MCI patients separately and found decreased BDNF serum levels in this group. Nonetheless, BDNF serum levels were significantly lower in the AD group than in the MCI group confirming a correlation between BDNF serum levels and cognitive impairment severity. Decreased serum BDNF levels in the preclinical stage of AD suggest that BDNF deficiency with lack of trophic support may play a pivotal role in a neurodegenerative process [39]. Inconsistent results regarding BDNF serum levels in dementia syndrome reported in the literature may, at least partially, be explained by differences in the criteria of patient recruitment, inclusion and exclusion used in the previous studies, and differences in methodology used to classify MCI group. Similarly, low BDNF serum levels in our MCI group may be explained by the fact that this group was not representative of the whole population. The patients were recruited in a neurodegenerative disorders clinic located in a tertiary care hospital, where strict criteria are used to recognize MCI subjects with high probability of future dementia development.

The three demographic variables: gender, age and education level, were previously found to be possible confounding factors determining the BDNF serum levels [39]. Some data suggest that women have higher BDNF serum levels than men [39], but other reports give contrasting results [40]. The differences in BDNF serum levels in men and women might be related to sex hormone differences. Most female subjects in our population were postmenopausal, resulting in the insignificant effect of gender on BDNF serum levels in our sample. Despite the diagnosis, a significant effect of age and education on BDNF serum levels was observed in our sample. Elderly patients had lower BDNF serum levels than younger patients, which is in concordance with the results from previous studies [39,18,41]. Interestingly, in the MCI group the BDNF serum levels were higher in older population, but this difference did not reach significance.

Most of our subjects had finished high school, and there were no significant differences in the educational level between the investigated groups, however a low level of education indicated lower BDNF serum levels. Opposite results were found in the MCI group, where highly educated patients had lower BDNF serum levels. MCI usually has multifactorial etiology, where cardiovascular pathology coexists with a neurodegenerative process [27]. Well-educated adults are more likely to seek medical help, therefore, appropriate prevention and treatment of modifiable risk factors of dementia is more often and earlier conducted in this group. Consequently, in this group, mild cognitive impairment is more often caused by the neurodegenerative process and Alzheimer's disease is more likely to develop [42].

The results of the battery of neuropsychological tests correlated with the BDNF serum levels. The observed relationship between lower BDNF serum levels and impaired episodic memory, and between executive functions and processing speed is consistent with previous studies [38,39]. We found no differences favoring a single cognitive domain by comparing BDNF serum levels and different tests assessing episodic memory, verbal fluency and executive functions.

Depressive disorders are common in subjects with cognitive impairment. Depression may precede, accompany or follow dementia [43]. Some studies indicated that peripheral BDNF can be used as a biomarker of mood state and disease progression for mood disorders, including major depressive disorder [40,44,45]. In our studied group there were no patients with severe depression as diagnosed by a consulting psychiatrist. We found no correlation between BDNF serum levels and depressive symptoms in our sample. Our results are in line with the studies of Bus et al., who found that, the severity of depressive symptoms is not significantly associated with BDNF serum levels, and with Curto et al., who assessed BDNF serum levels in Alzheimer's disease patients with and without depression, and found no significant correlation between Geriatric Depression Scale score and BDNF serum levels [46,47]. We are aware that the presence of some depressive symptoms found in self-reported inventory such as Beck Depression Inventory cannot be recognized as synonymous with depression diagnosis. This may explain why our results stand in contrast to the previous reports regarding full blown depressive disorder [44,45,48].

Some limitations of our investigation should be discussed. No data on cardiovascular risk factors of dementia were gathered in our study to be available for statistical evaluation. However, in a recent studies, the importance of BDNF was suggested in high cardiovascular risk conditions, such as obesity, metabolic syndrome, and coronary atherosclerosis [49,50]. In a study by Ejiri et al., patients with unstable angina have been reported to have increased BDNF levels in the coronary circulation compared with individuals with stable angina, suggesting that BDNF may detrimentally influence atherosclerotic plaque stability [51]. Conversely, Manni et al. reported lower BDNF plasma levels in the acute coronary syndrome cases compared with the controls, suggesting a protective role of BDNF [49]. Studies by Krabbe and Kaess have also shown, that higher BDNF levels is associated with lower risk of cardiovascular disease events and death, independently of standard risk factors [52,53]. In a study of Nemcsik et al., BDNF serum levels were elevated in a chronic hypertensive patients, and authors suggested that BDNF could play a role in a compensatory mechanism targeting peripheral neurons and vascular cells [54]. Moreover, decreased BDNF serum level was found to be associated with increased risk of incident stroke [55]. Circulating BDNF was reported to be increased in obese women, and high BDNF levels were observed in subjects with metabolic syndrome [56], while other studies shown low BDNF concentrations in subjects with obesity [52]. On the other hand, serum BDNF was not associated with fat components of the body in a study of Lee et al., and no correlation between BDNF serum levels and obesity was found by Gajewska et al. [57,58]. Alterations in BDNF serum levels in patients with type 2 diabetes (T2DM) have also been studied, but the conclusions are inconsistent. Some researchers reported decreased circulating BDNF levels in T2DM patients [50], while other studies shown increased serum BDNF levels in these patients [59].

In conclusion, our results suggest that the BDNF serum level is probably dependent on a neurodegenerative process as in Alzheimer's disease. At present, since there is no cure for neurodegenerative diseases, physical activity, rehabilitation and motor function training that improve health status of patients and elderly adults should be recommended, because research findings suggest it positively influences the BNDF levels [60]. Modulating BDNF signaling may be a future promising therapeutic concept for reducing the risk of neurodegenerative diseases and future investigations are warranted.

5. Conclusions/highlights

Advanced age and low educational level are associated with decreased BDNF serum levels. Decreased BDNF serum levels correspond to the severity of cognitive impairment. No correlation was found between BDNF serum levels and depressive symptoms.

Conflict of interest

None declared.

Acknowledgement and financial support

We would like to thank all the patients for the participation in the study. This research was supported by the grant (KNW-1-105/N/3/0) from the Medical University of Silesia. JS was partially supported by the Stowarzyszenie na Rzecz Rozwoju Neurologii Wieku Podeszłego grant.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved of by the Local Ethics Committee for Medical Research.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.pjnns.2016.10.001.

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