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CAROTID ATHEROSCLEROSIS AND DEMENTIA – INFLAMMATORY MARKERS AND MARKER OF MACROPHAGE ACTIVATION

MIAŻDŻYCA TĘTNIC SZYJNYCH A OTĘPIENIE – CZYNNIKI ZAPALNE I WSKAŹNIK AKTYWACJI MAKROFAGÓW

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Abstract

Purpose: To assess the relationship between serum inflammatory markers (interleukin 6, high sensitivity C-reactive protein [hsCRP] and chitotriosidase activity) and the extent of carotid atherosclerotic lesions in subjects with various types of dementia.

Methods: Four hundreds persons with dementia (166 diagnosed as probable Alzheimer's disease, 85 as vascular dementia [VaD], 149 as mixed dementia [MD] and 180 controls) were observed. In all persons carotid intima-media thickness (IMT) was measured and all were subjected to a general medical and neurological evaluation, neuroimaging examination (computed tomography and magnetic resonance) and comprehensive neuropsychological examination. The pro-inflammatory markers interleukin-6 (IL-6) and hsCRP, and anti-inflammatory markers (paraoxonase-1 activity and HDL cholesterol level), were determined in blood serum. Chitotriosidase activity – an indicator of chronic macrophage activation – was also determined.

Results: A higher frequency of carotid atherosclerosis was observed in the whole group of dementia and in the VaD and MD groups as compared to the controls. A significant positive correlation of IMT with the inflammatory indicators IL-6 and hsCRP was found. A negative correlation of IMT with inflammatory markers (paraoxonase-1 activity and HDL cholesterol level) was observed. Chitotriosidase activity was significantly elevated, as compared with the controls, in the whole group with dementia and in the MD group, and depended on the degree of carotid stenosis.

Conclusions: Serum IL-6, hsCRP and chitotriosidase activity can be considered as markers of the extent of carotid arteriosclerosis in dementia, especially in patients with dementia with vascular lesions. High chitotriosidase activity may indicate chronic macrophage activation in the course of dementia development.

Key words: dementia, inflammatory markers, carotid atherosclerosis, chitotriosidase activity.

INTRODUCTION

A link between various types of dementia and carotid atherosclerosis has been observed by several authors [1-3].

Of the several types of dementia Alzheimer's disease (AD) is the most widespread. Its main mechanism is neurodegeneration, although vascular factors also play an important role in it.

In the development of the type called vascular dementia (VaD), vascular factors play the most important role though neurodegeneration is also present. When cognitive decline is caused in a similar degree by neurodegeneration and cerebrovascular lesions the type of dementia is called mixed dementia (MD).

In various studies, as well as in our own observations, it has been observed that metabolic syndrome and particular metabolic syndrome traits plays an important role in the development of carotid atherosclerosis and dementia [4-7]. Inflammation and carbohydrate metabolism disturbances such as insulin resistance are important factors. It has been shown that inflammatory markers (high sensitivity C-reactive protein [hsCRP] and interleukin-6 [IL-6]) are positively correlated and could be used as markers of the progression of carotid atherosclerosis and dementia [8, 9].

Yet an additional marker, namely the activity of the enzyme chitotriosidase, could be used in cerebrovascular disease dynamics. Chitotriosidase is considered to be a marker of chronic macrophage activation. Macrophages are important in the immune system and chitotriosidase has a role in their differentiation and may reflect the induction of an immunological response [10].

Chitotriosidase activity has been used as a marker in atherosclerosis [11] and various other diseases [12, 13]. It has been shown to be a good marker of inflammatory processes in neurological diseases [14-17] and is useful in monitoring treatment effects in Gaucher disease [18]. A positive correlation between chitotriosidase activity and age has also been observed [19].

Chitotriosidase activity is high in cerebrovascular diseases [11, 20]. It does not behave as an acute reactive protein but rather as a marker of chronic inflammation. No correlation between chitotriosidase and hsCRP has been found [11].

In our study we wanted to compare serum chitotriosidase activity with typical inflammatory markers in patients with carotid atherosclerosis in various types of dementia.

One has to consider, however, that about 30% to 40% of individuals in the white population are carriers of a recessively inherited deficiency in the chitotriosidase gene and that approximately 6% are homozygous for this mutation [11]. In these individuals an extremely low level of chitotriosidase activity is observed and they must be excluded from the analysis.

METHODS

Subjects

The total group consisted of 400 patients diagnosed as having dementia on the basis of the ICD-10 and DSM-IV criteria. A Mini Mental State Examination (MMSE) and a Clock Drawing Test were used as screening tests for existing dementia. 180 persons without dementia and in a good general health served as a control group.

The type of dementia was identified on the basis of the NINCDS-ADRDA scale for AD and NINDS-AIREN for VaD. The Hachinski Ischemic Scale for differential diagnosis of AD, VaD and MD was used. Significant ischemic changes diagnosed by computer tomography (CT) or magnetic resonance imaging (MRI) were the basis the assignment of patients to the VaD or MD groups.

Methods

All persons were subjected to a general medical and neurological evaluation, CT and MRI neuroimaging examinations and comprehensive neuropsychological tests [21].

IMT was assessed by a EsaoteMyLab 25 Gold duplex Doppler scanner with a 7.5-12 MHz linear transducer. An automated radiofrequency method (QIMT software; Esaote, Maastricht, Holland) was applied. IMT was measured at the posterior wall of the right and left CCA, 10 mm from the carotid bifurcation. The assessment was done in a 15 mm part of the wall (Region of Interest [ROI]). Patients were placed in the supine position. CCA were identified in B mode in a transverse view and then imaged in a longitudinal view from a lateral approach. The software calculated the mean and SD of the IMT values from six cardiac cycles. The measurement was qualified as reliable when SD was < 20 micrometers. The extent of carotid atherosclerosis was expressed as a stenosis grade on the scale 0% to 100%. Carotid atherosclerosis was defined as significant when it was equal to or exceeded 50% (≥ 50%).

Blood was taken after an overnight fast, serum was isolated, frozen and kept in –70°C if necessary.

IL-6 (high sensitivity method – hsIL-6) was determined using an ELISA kit (R&D Systems).

C-reactive protein (high sensitivity method – hsCRP) and insulin were determined using ELISA kits (DRG Medtek).

IL-6 and hsCRP were determined in 224 of the 400 dementia patients and in 109 of the 180 controls.

Paraoxonase-1 (PON1) activity was determined spectrophotometrically on the basis of the Kitchen method [22], using phenylacetate as the substrate. One unit of activity was 1 mmol of phenol liberated per minute per 1 ml of serum.

HDL cholesterol (HDL C) was determined in fresh serum by the enzymatic method.

Glucose was determined using the enzymatic method.

HOMA-IR (homeostatic model assessment index) was calculated as follows: fasting glucose [mmol/l] × fasting insulin [ml]/22.5.

Chitotriosidase activity (CHIT) was measured using the spectrofluorimetric method according to Hollak [23], using the synthetic substrate 4-methylumbelliferyl beta-N-N',N"-triacetylchitotrioside (Sigma Chemical Co, St.Louis, MO). Fluorimetric measurements were made at excitation wave λ = 365 nm and emission λ = 445 nm.

DNA was isolated by phenol extraction.

Apolipoprotein E polymorphism was investigated using Hixson and Vernier procedure [24].

The Chitotriosidase gene (*CHIT1*) variant namely 24 bp duplication was identified by duplication mutation analysis using specific primers (Chs9, 5'AGCTATCTGAAGCAGAAG-3'; and Chas8,GGAGAAGCCGGCAAGTC-3'). Fragments of 75 and 99 bp are amplified from the normal and mutant chitotriosidase gene alleles, respectively. Electrophoresis in 3% agarose gel allows for the detection of both fragments [25]. In the case of carriers for the duplication, the mixture of both fragments is detected. Homozygotes of the mutant form display an extremely low activity; heterozygotes show medium activity. Homozygotes for *CHIT1* 24-bp duplication were excluded from statistical analyses concerning chitotriosidase activity.

Statistical analyses were performed using Statistica version 12 (StatSoft, Poland). The Shapiro and Wilk test was carried out to ascertain the normality of the distribution of continuous variables. Normally distributed variables were presented as means ± SD. Non-normally-distributed variables were presented as median values and interquartile ranges because these variables had skewed distributions. Between-group differences were tested using the nonparametric Mann-Whitney test or Kruskal-Wallis analysis of variance (ANOVA), followed by a post-hoc test for multiple comparisons. Statistical significance of the differences in the frequencies of qualitative variables was evaluated using Pearson's χ^2 test. The associations between various types of dementia and carotid IMT and plasma inflammatory markers were tested using univariate and multiple logistic regression analysis with age, sex, level of education, family history of dementia and the *APOE* genotype as confounding factors and presented as odds ratios (OR) with 95% confidence intervals (CI). Pearson correlation coefficients were calculated to describe the associations of chitotriosidase activity and carotid atherosclerosis parameters with various inflammatory and metabolic indices, as well as with age and MMSE score among the dementia and control subjects (univariate analysis).

P values lower than 0.05 were considered as statistically significant.

The study was approved by the Ethics Committee of the Institute of Psychiatry and Neurology (Warsaw, Poland).

RESULTS

AD was diagnosed in 166 patients 46-86 years old, mean age 72.4 ± 8.39 years, 43 men and 123 women; VaD in 85 persons 48-86 years old, mean age 73.9 ± 7.93 years, 39 men and 46 women and MD in 149 persons 50-92 years old, mean age 76.7 ± 6.46 years, 62 men and 87 women. The control group consisted of 180 persons 45-89 years old, mean age 71.1 ± 7.37 years, 65 men and 115 women. There were more women than men in the AD group (74.1% vs. 25.9%), in contrast to the VaD (45.9% vs. 56.1%) and MD (41.6% vs. 58.4%) groups. In the control group there were 36.1% men vs. 63.9% women. The differences were statistically significant ($p < 0.005$).

As shown in Table 1, significantly higher mean carotid IMT values were stated in the whole dementia group as compared to the controls. Particularly high values were found in the mixed dementia group.

IL-6 level was significantly higher in the whole dementia group and in the VaD and MD groups as compared with controls. Mean hsCRP showed the highest levels in the VaD group.

Analysis of the 24 bp dup variant in the chitotriosidase (*CHIT1*) gene revealed a similar distribution as that reported in the literature, as in Artieda 2003 [11]. Genotype examination revealed that in 56 persons from the control group and in 139 patients with dementia a 24-bp duplication of the genotype has been found. Among these, 25 were diagnosed as homozygotes, 7 in the control group (4%) and 18 in the dementia group patients (4.6%).

Significant elevation of chitotriosidase activity was observed in individuals with VaD and MD but not in AD patients. It concerned only individuals homozygous for the wild type (WT) allele of the *CHIT1* gene and was not homozygotes for CHIT1 24-bp duplication. This is shown in Figure I.

To test whether carotid IMT and plasma inflammatory markers (the levels of IL-6 and hsCRP) and chitotriosidase activity are independently associated with the presence of various types of dementia, we performed univariate and multivariate logistic regression analyses including known dementia risk factors such as age, gender, level of education, family history of dementia and *APOE* polymorphism as confounding variables. The results are shown in Table 2. The odds ratios show an increased risk of dementia associated with the presence of carotid atherosclerosis and the risk caused by a high chitotriosidase activity level. The crude odds ratios (ORs) indicate that higher carotid IMT values (≥ 0.9 mm) were significantly associated with an increased (over 2 times greater) risk

Table 1. Carotid intima-media thickness and serum inflammatory markers and in various types of dementia and control group

Factor	Dementia	p^A	AD	VaD	MD	Controls	p^B
	n = 400		*n* = 166	*n* = 85	*n* = 149	*n* = 180	
IMT mean (mm)	0.80 (0.675-0.92)	0.00001	0.775 (0.66-0.905)#	0.785 (0.655-0.905)#	0.83 (0.70-0.94)***	0.73 (0.645-0.825)	< 0.00001
IMT mean ≥ 0.9 mm (%)	31.3	0.00002	29.8***	25.6*	36.4***	14.4	0.00009
Maximal carotid stenosis	30 (0-50)	0.002	28 (0-40)	35 (0-50)**	40 (0-50)***	25 (0-40)	< 0.00001
Carotid atherosclerosis (%)	25.3	0.008	14.1	29.4**	35.1***	15.3	< 0.00001
IL-6 (pg/ml)	1.87 (1.17-3.08)	0.004	1.34 (0.78-2.61)	2.10 (1.50-4.83)**	2.00 (1.22-3.35)**	1.41 (0.93-2.29)	0.0001
hsCRP (mg/l)	1.515 (0.575-4.19)	0.565	1.005 (0.36-2.52)	2.69 (1.02-4.63)*	1.79 (0.76-4.37)	1.49 (0.78-3.02)	0.0008
Chitotriosidase activity (nmol/ml/h) non-carriers of *CHIT*1 24-bp dup	92 (65-128) (*n* = 235)	0.006	81 (56-116) (*n* = 97)	94.5 (67-134.5)# (*n* = 48)	94.25 (70-128)** (*n* = 90)	80 (54-105) (*n* = 119)	0.003
Chitotriosidase activity > 150 nmol/ml/h (%)	10.0	0.082	9.1	6.0	13.4*	5.6	0.071

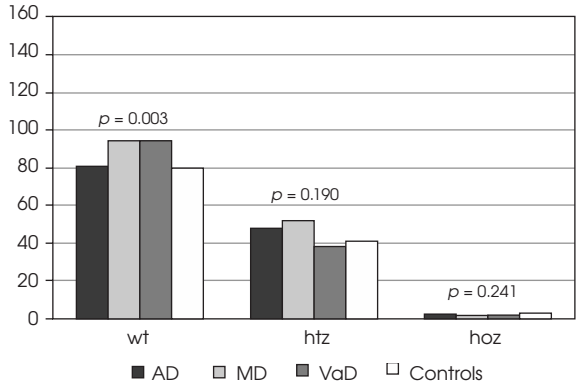
Continuous variables are presented from the median and interquartile range, from first to third quartile.

[A] – Mann-Whitney test or $\chi 2$ test, [B] – Kruskal-Wallis ANOVA or $\chi 2$ test

**p < 0.05, **p < 0.01, ***p < 0.001 vs. controls, # – borderline significant (0.1 > p > 0.05) vs. controls*

AD – Alzheimer's disease, IMT – intima-media thickness, MD – mixed dementia, VaD – vascular dementia

Carotid atherosclerosis defined as maximal carotid stenosis ≥ 50%



CHIT1 24-bp duplication genotype: wt – wild type, htz – 24-bp duplication heterozygote, hoz – 24-bp duplication homozygote

AD – Alzheimer's disease, MD – mixed dementia, VaD – vascular dementia

Figure I. Serum chitotriosidase activity in various types of dementia and controls according to CHIT1 genotype

of all-cause dementia (OR = 2.72), AD (OR = 2.52), VaD (OR = 2.05) and MD (OR = 3.41). In the case of VaD this association was no longer statistically significant after taking into consideration the other risk factors (age, sex, *APOE* genotype, education and family history of dementia). In WT homozygotes, high serum chitotriosidase activity (> 150 nmol/ml/h) was associated with over twice as great a risk of all-cause dementia (OR = 2.99), AD (OR = 2.70) and 4 times greater risk of MD (OR = 4.00). Only in MD did the association remain statistically significant after controlling for the other risk factors.

In Table 3 the correlation between carotid atherosclerosis and chitotriosidase activity and selected inflammatory and metabolic indices is shown. In the patients with dementia, a significant positive correlation between carotid IMT and maximal carotid stenosis and the inflammation indicators hsCRP and IL-6 (with carotid stenosis only) was observed. A negative correlation of IMT with paraoxonase-1 activity and with HDL cholesterol was observed.

Figure II shows the results of IL-6, hsCRP, chitotriosidase activity and HOMA-IR determinations depending on the grade of carotid stenosis and demonstrates a statistically significant degree of this dependence in patients with dementia but not in the control group.

DISCUSSION

In the whole group with dementia, a significant positive correlation between carotid IMT and inflammation indicators – IL-6 and hsCRP – is shown; as are a negative correlation with negative inflammation indicators (paraoxonase-1 activity and HDL cholesterol) and a positive correlation with chitotriosidase activity.

Chitotriosidase is a nonspecific marker of chronic macrophage activation.

In the study of Ariteda *et al.* [11], comparison of the results of chitotriosidase determination in cerebrovascular disease with the results of its determination in coronary atherosclerosis showed that subjects of the first group showed a higher activity of the enzyme. In the authors' opinion this could be caused by the fact that in cerebrovascular disease the process is more widespread as compared with the coronary disease. There was no correlation between chitotriosidase and hsCRP in both groups; therefore, the authors have con-

Table 2. Odds ratios and 95% confidence intervals for carotid atherosclerosis and chitotriosidase with various types of dementia

Factor	Dementia *n* = 400		AD n = 166		VaD *n* = 85		MD *n* = 149	
	OR (95% CI)	OR (95% CI)#	OR (95% CI)#	OR (95% CI)#	OR (95% CI)#	OR (95% CI)#	OR (95% CI)#	OR (95% CI)#
IMT mean ≥ 0.9 mm	2.72 (1.69-4.38) *p* = 0.00004	2.15 (1.24-3.73) *p* = 0.006	2.52 (1.46-4.36) *p* = 0.0009	2.13 (1.09-4.19) *p* = 0.027	2.05 (1.07-3.95) *p* = 0.031	1.51 (0.66-3.42) *p* = 0.326	3.41 (1.97-5.88) *p* = 0.00001	2.62 (1.34-5.11) *p* = 0.005
Carotid atherosclerosis (maximal carotid stenosis ≥ 50%)	1.88 (1.17-3.00) *p* = 0.008	1.46 (0.85-2.51) *p* = 0.170	0.91 (0.50-1.67) *p* = 0.766	0.76 (0.36-1.59) *p* = 0.460	2.31 (1.24-4.32) *p* = 0.008	1.63 (0.78-3.41) *p* = 0.193	3.01 (1.77-5.13) *p* = 0.00005	1.86 (0.97-3.57) *p* = 0.062
Chitotriosidase activity > 150 nmol/ml/h (non-carriers of *CHIT1* 24-bp dup)	2.99 (1.29-6.95) *p* = 0.011	2.55 (0.99-6.54) *p* = 0.051	2.70 (1.04-7.02) *p* = 0.041	2.55 (0.81-7.98) *p* = 0.107	1.86 (0.56-6.23) *p* = 0.311	1.56 (0.38-6.37) *p* = 0.535	4.00 (1.58-10.11) *p* = 0.003	5.13 (1.58-16.63) *p* = 0.006

AD – Alzheimer's disease, IMT – intima-media thickness, MD – mixed dementia, VaD – vascular dementia

#Values adjusted for age, sex, APOE genotype, education and family history of dementia

Table 3. Spearman's correlation coefficients (R) of carotid IMT and chitotriosidase and selected inflammatory and metabolic indices in dementia and control groups

Factor		Dementia (*n* = 400)			Controls (*n* = 180)		
		IMT mean	Carotid stenosis	Chitotriosidase[A]	IMT mean	Carotid stenosis	Chitotriosidase[A]
Age	R *p*-value	**0.207** 0.00004	**0.218** 0.00001	**0.211** 0.00005	**0.346** 0.000003	**0.321** 0.00001	0.113 0.140
MMSE	R *p*-value	–0.033 0.526	0.018 0.714	0.006 0.911	–0.071 0.353	–0.111 0.141	–0.007 0.928
HOMA-IR	R *p*-value	–0.087 0.090	0.068 0.177	–0.060 0.257	0.066 0.390	0.038 0.613	0.003 0.967
IL-6	R *p*-value	0.112 0.107	**0.182** 0.007	**0.240** 0.0004	0.076 0.443	0.130 0.183	0.051 0.611
hsCRP	R *p*-value	**0.200** 0.004	**0.174** 0.010	**0.173** 0.011	–0.010 0.921	–0.036 0.714	–0.055 0.578
PON1	R *p*-value	**–0.145** 0.004	**–0.201** 0.00006	0.004 0.945	–0.260 0.0005	**–0.150** 0.046	–0.072 0.347
HDL-C	R *p*-value	**–0.147** 0.004	**–0.211** 0.00006	–0.091 0.086	**–0.193** 0.011	–0.137 0.068	–0.074 0.334
Chitotriosidase[A]	R *p*-value	0.035 0.512	0.103 0.051	–	0.043 0.584	0.065 0.400	–

CRP – C-reactive protein, HDL-C – high density lipoprotein cholesterol, HOMA-IR – homeostatic model assessment index, IL-6 – interleukin 6, IMT – intima-media thickness, MMSE – mini mental state examination, PON1 – paraoxonase-1

IL-6 and hsCRP were determined in 333 of 580 of the whole group subjects, in 224 out of 400 dementia patients and in 109 out of 180 controls.

[A] – Homozygotes for CHIT1 24-bp duplication were excluded from statistical analyses

cluded that these markers seem to be regulated by different mechanisms [11].

Di Rosa *et al.* [10] tried to clarify the mechanism and the possible role of chitotriosidase in cerebrovascular disease. They hypothesize that it is a local and self-sustaining immune and inflammatory response within cerebrovascular disorders. In the future it should be clarified whether it is only the marker or whether it contributes to the progression of the disease. In our study we have compared the level of the inflammatory markers IL-6 and hsCRP and the marker of chronic macrophage activation, i.e. chitotriosidase activity in patients with carotid atherosclerosis suffering from various types of dementia. The question arises of whether chitotriosidase determination could be a useful marker of chronic macrophage activation in carotid atherosclerosis. The positive correlation of serum chitotriosidase activity with the grade of carotid stenosis, but not with the mean carotid IMT observed in our study in dementia group, indicates the role of chitotriosidase activity as a potential marker of chronic inflammation in the later steps of the atherosclerotic process in the vascular walls of carotid arteries rather than in preclinical atherosclerosis.

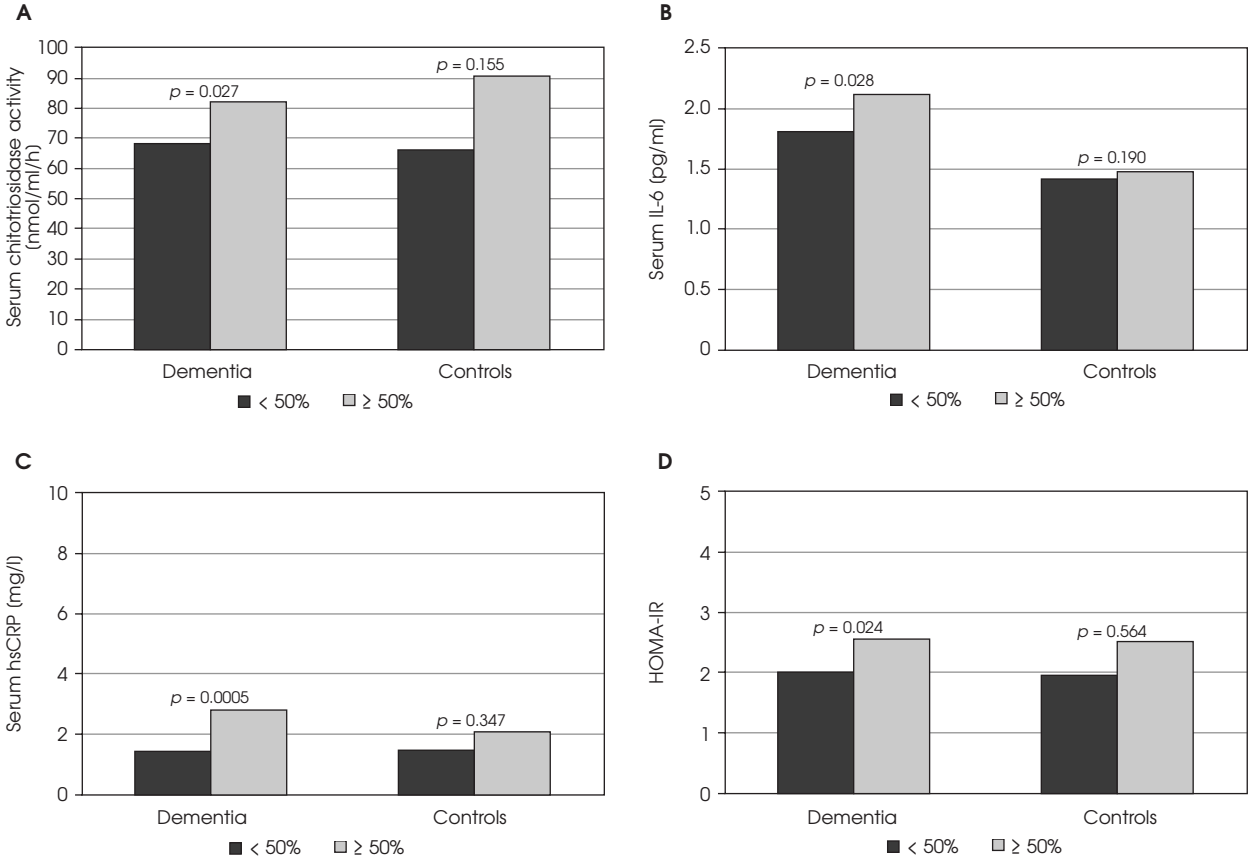


Figure II. The results of chitotriosidase, IL-6, hsCRP and HOMA-IR determinations depending on the grade of carotid stenosis. Homozygotes CHIT1 24-bp duplication were excluded from analyses of chitotriosidase

CONCLUSIONS

IL-6, hsCRP and chitotriosidase activity may serve as biomarkers of carotid arteriosclerosis in dementia, especially in patients with vascular changes. High chitotriosidase activity may indicate chronic macrophage activation in the course of the development of dementia and suggests that immunological processes are involved. This finding contributes new information concerning the mechanism of the development of dementia in the course of carotid atherosclerosis.

The determination of chitotriosidase activity seems to be less valuable for AD diagnosis.

Conflict of interest/Konflikt interesu

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