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Metabolic syndrome and dementia

Zespół metaboliczny i otępienie

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SUMMARY

Objectives. *Co-occurrence of metabolic syndrome features and dementia was studied.*

Methods. *In 151 demented patients and 64 control individuals the presence of metabolic syndrome was diagnosed according to the modified Grundy et al. criteria (hypertension, obesity, high triglyceride and low high density lipopoprotein (HDL) cholesterol serum levels, as well as hyperglycemia). The serum insulin level was determined and the HOMA-IR index of insulin resistance was calculated. Polymorphic forms of a gene candidating for a role in the insulin signaling pathway – the glycogen-associated regulatory subunit 3 of protein phosphatase 1 (PP1R3), and of the apolipoprotein E gene - ε2, ε 3 and ε 4 alleles – which are well-known strong genetic risk factors for Alzheimer's disease - were identified.*

Results. *Metabolic syndrome was found more often in the group with vascular dementia (VaD) than in the controls. In the former group a tendency for higher HOMA-IR index values was observed. The most frequent characteristic of glucose metabolism differing all the patients from the controls was an increased 2-hour postload glucose level, which is a feature of prediabetes. No differences between the patients and controls were found in the frequency of particular polymorphic forms of the PPP1R3 gene. Low HDL cholesterol levels and glucose intolerance – two important metabolic syndrome features - were significantly more frequent only in the ε4 allele noncarriers, but not in the carriers of this allele.*

Conclusions. *Metabolic syndrome features were observed most often in patients with dementia of vascular origin. Frequency of these characteristics was higher only in noncarriers of the apolipoprotein E ε4 allele.*

STRESZCZENIE

Cel. *Zbadanie jednoczesnego występowania objawów zespołu metabolicznego i otępienia.*

Metody. *U 151 pacjentów z otępieniem i 64 osób grupy kontrolnej rozpoznawano występowanie zespołu metabolicznego według zmodyfikowanych kryteriów Grundy i wsp. (nadciśnienie, otyłość, podwyższony poziom triglicerydów i niski cholesterolu lipoprotein wysokiej gęstości (HDL) surowicy oraz hiperglikemia). Oznaczano również poziom insuliny i obliczano wskaźnik HOMA-IR informujący o oporności na insulinę Identyfikowano polimorfizm genu kandydującego do roli w intensywności szlaku sygnalizacyjnego insuliny – związaną z glikogenem podjednostkę 3 fosfatazy białkowej (PPP1R3). Identyfikowano również polimorficzne warianty genu apolipoproteiny E- ε 2, ε 3 i ε 4 – najsilniejsze znane czynniki genetyczne otępienia.*

Wyniki. *Zespół metaboliczny stwierdzano częściej u osób z otępieniem pochodzenia naczyniowego (VaD) w porównaniu z grupą kontrolną. W tym typie otępienia występowała tendencja do podwyższonego wskaźnika HOMA-IR. Najczęściej obserwowaną różnicą między całą grupą osób z otępieniem a grupą kontrolną był podwyższony poziom glukozy surowicy 2 godz. po obciążeniu glukozą – jest to objaw charakteryzujący stan przedcukrzycowy. Nie stwierdzono różnic w częstości występowania poszczególnych typów polimorficznych genu PPP1R3 między pacjentami i grupą kontrolną. Niski poziom HDL i nietolerancja glukozy – dwa ważne objawy zespołu metabolicznego występowały istotnie częściej tylko u nienosicieli allelu ε4, nie obserwowano tego natomiast u nosicieli tego allelu.*

Wnioski. *Objawy zespołu metabolicznego obserwowano najczęściej u pacjentów z otępieniem pochodzenia naczyniowego. Objawy te występowały ze zwiększoną częstością tylko u nienosicieli allelu ε4 apolipoproteiny E.*

Key words: zespół metaboliczny / otępienie / oporność na insulinę
Słowa kluczowe: metabolic syndrome / dementia / insulin resistance

The incidence of both metabolic syndrome and cognitive disorders increases considerably with age and in view of the increasing longevity of populations worldwide, the prevalence of both diseases is rapidly growing. It seems very important to recognize their associations, since this can help in their prevention and, possibly, treatment.

Metabolic syndrome (MetS) is a well-known cluster of cardiovascular risk factors. Several prospective studies have recently shown associations of the whole

syndrome and/or its particular features with cognitive impairment. Special attention was paid to abnormalities of carbohydrate metabolism. Frisardi et al. [1] proposed a metabolic-cognitive syndrome (MCS) as a pathophysiological model integrating metabolic syndrome disturbances and dementia. Some discrepancies in the reported research findings were noted. Muller et al. found no association between metabolic syndrome and dementia, but an association of cognitive impairment with diabetes and hyperinsulinemia [2]. Raffaitin [3] described a more frequent incidence of VaD but not of AD in individuals with hypertriglyceridaemia. Solfrizzi et al. [4] in the Italian Longitudinal Study found a greater risk for VaD, but only in cases of coexisting inflammation.

In this study we tried to assess whether the metabolic syndrome features traits in individuals with dementia are connected mostly with neurodegeneration (a prevailing mechanism in AD) or rather with pathology of the vascular system, as the metabolic syndrome characteristics are well-known strong vascular risk factors. Therefore, three types of dementia were investigated: Alzheimer's disease (AD), dementia of vascular origin (VaD) and mixed dementia (MD) (the concept of mixed dementia retained in the recent classification covers a wide spectrum of cases involving both neurodegenerative and vascular pathology).

Insulin resistance is considered to be an important detrimental factor in glucose metabolism. It was suggested that insulin resistance could be caused by inefficient functioning of the insulin signaling pathway due to the presence of less active polymorphic variants of its constituents. The glycogen-associated regulatory subunit 3 of protein phosphatase 1 (PPP1R3) is one of the key components of this pathway controlling glycogen synthase activity. Polymorphism of one important candidate gene, i.e. the glycogen-associated regulatory subunit 3 of protein phosphatase 1 (PPP1R3), was analysed in this study [5].

Polymorphic forms of the apolipoprotein E gene – ε2, 3 and 4 alleles, well-known strong genetic risk factors for Alzheimer's disease – were identified.

SUBJECTS

The sample studied consisted of 151 individuals with dementia (48 men and 103 women, mean age 73.7 ± 7.28 years), and 64 controls (27 men and 37 women, mean age 72.6 ± 7.09) with no symptoms of dementia and in a good general health.

The Mini Mental State Examination (MMSE) was used as a screening test for dementia. Dementia was diagnosed by the ICD-10 and DSM-IV criteria. The patients and controls underwent a general medical and neurological evaluation, CT or MR examinations and other neuropsychological tests. The type of dementia was diagnosed according to the NINCDS-ADRDA criteria for AD, and NINDS-AIREN criteria for VaD. When a significant radiological evidence on CT or MRI suggested a coexisting cerebrovascular disease in AD patients, they were included in the MD group.

METHODS

Metabolic syndrome was recognized using the criteria by Grundy et al. [6]. The following criteria were taken into account: elevated blood pressure (BP): systolic BP≥130 mm/Hg or diastolic BP≥85 mm/Hg or drug treatment for hypertension; elevated triglycerides (TG) ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated TG; reduced high density lipoprotein cholesterol (HDL-C) <40 mg/dL (1.03 mmol/L) in men, <50 mg/dL (1.3 mmol/L) in women or drug treatment for reduced HDL; elevated fasting glucose ≥100 mg/dL or drug treatment for elevated glucose. To evaluate obesity, instead of waist circumference, body mass index (BMI) was used, with obesity defined as ≥30kg/m^2 using the criterion proposed by the World Health Organization [7]. Carbohydrate metabolism was evaluated as: NFG – normal fasting glucose – below 5.6 mmol/L (100 mg/dL), IFG – impaired fasting glucose – between 5.6 mmol/L (100 mg/dL) and 7.0 mmol/L (125 mg/dL), NGT – normal glucose tolerance – post-load – below 7.8 mmol/L (140 mg/dL), IGT – impaired glucose tolerance – post-load – between 7.8 mmol/L (140mg/dL) and 11.1 mmol/L (199 mg/dL), type II diabetes mellitus – fasting glucose ≥7.0 mmol/L (126 mg/dL) or post-load ≥11.1 mmol/L (200 mg/dL), or previously diagnosed type II DM currently treated with insulin and/or oral hypoglycemic agents [8]. We also investigated disturbances characterizing an increased risk for diabetes (prediabetes) [9].

2-hour post-load glucose was measured after a 75-gram glucose drink. This test was not performed in subjects diagnosed with diabetes, taking insulin or other hypoglycemic drugs. Other tests including fasting serum glucose and serum insulin were performed after an overnight fast. Glucose was determined using the enzymatic method. Insulin concentration was assayed using the ELISA kit (DRG Instruments GmbH, Germany). HOMA-IR (homeostatic model assessment index) was calculated as follows: [fasting glucose (mmol/L) x fasting insulin (mU/L)]/22.5]. Triglycerides and. HDL cholesterol levels were determined by enzymatic methods.

In order to identify genetic polymorphisms DNA was isolated using phenol extraction. Polymorphism

of the regulatory G-subunit of protein phosphatase (PP1R3) gene was identified by the Hansen method [10]. Apolipoprotein E (*APOE*) ε2, 3 and 4 genotypes were identified by the Hixson and Vernier method [11].

All statistical analyses were performed using the Statistica version 9. Quantitative data (glucose and insulin concentrations and HOMA-IR) were expressed as median values and interquartile ranges (IQR), because these variables had skewed distributions. Between group differences were tested using the non-parametric Kruskal-Wallis analysis of variance (ANOVA) followed by 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 particular variables identified using multiple logistic regression analysis were expressed as odds ratios (OR) with 95% confidence intervals (CI). *P*-values lower than 0.05 were considered as statistically significant. Diabetic patients taking hypoglycemic drugs were not included in the analyses concerning parameters related to glucose and insulin levels.

Informed consent had been obtained from the subjects and the study was approved by the Ethics Committee of the Institute of Psychiatry and Neurology.

RESULTS

In the whole dementia group diabetes was recognized in 19.1% of patients (in 15.7% of AD patients, 25.% of those with VaD, 19.% with MD), and in 15.% of the controls. The differences were not statistically significant.

Significant differences between the patients and controls were found in the frequency of particular metabolic syndrome features. Hypertension was present less often in AD patients than in the controls, while obesity (BMI≥30) and low HDL cholesterol were more frequent in the VaD subgroup. Metabolic syndrome diagnosed according to Grundy's criteria was more frequent in the VaD group than in the controls (Table 1). The most frequent difference in glucose metabolism between patients and controls was an increased 2-hour post-load glucose level resulting from impaired glucose tolerance. A tendency for higher HOMA-IR index was noted in the group with vascular dementia (Table 2).

Table 1. Metabolic syndrome features in various types of dementia. Data are presented as percent of individuals with pathological values, and as odds ratio (OR) with 95% confidence interval (CI).

Tabela 1. *Objawy zespołu metabolicznego w różnych rodzajach otępienia. Wyniki przedstawiono jako odsetek osób z wartościami nieprawidłowymi oraz jako iloraz szans (OR) z 95% przedziałem ufności (CI).*

Variable	Measure	AD (n = 71)	VaD (n = 32)	MD (n = 48)	Controls (n = 64)	p values
1. Obesity BMI≥30	%	4.4	**26.7[c]**	6.7	6.3	**0.002**
1.	OR [95%CI]	0.69 [0.15–3.27]	**5.45 [1.47–20.28][d]**	1.07 [0.22–5.13]		
2. Hypertension	%	**43.7[a]**	59.4	66.7	62.5	**0.049**
1.	OR [95%CI]	**0.47 [0.23–0.93][b]**	0.88 [0.36–2.11]	1.2 [0.54–2.65]		
3. Triglycerides >150mg/dL	%	14.1	25.0	20.8	17.5	ns
1.	OR [95%CI]	0.77 [0.30–1.99]	1.58 [0.55–4.48]	1.24 [0.47–3.26]		
4. HDL-C <40mg/dL M <50mg/dL F	%	23.9	**40.6[e]**	27.1	17.5	0.103
1.	OR [95%CI]	1.49 [0.63–3.51]	**3.23 [1.22–8.55][f]**	1.76 [0.70–4.41]		
5. IFG or antidiabetic treatment	%	32.4	50.0	45.8	37.5	ns
	OR [95%CI]	0.80 [0.39–1.63]	1.67 [0.70–3.98]	1.41 [0.65–3.04]		
Metabolic syndrome >3 out of 5 traits	%	11.4	**37.5[g]**	17.0	17.5	**0.017**
	OR [95%CI]	0.61 [0.23–1.64]	**2.84 [1.06–7.56][h]**	0.97 [0.35–2.67]		

a – p = 0.029 vs. controls (χ2 test)
b – p = 0.031 (logistic regression analysis)
c – p = 0.015 vs. controls (χ2 test)
d – p = 0.012 (logistic regression analysis)
e – p = 0.014 vs. controls ($\chi 2$ test)
f – p = 0.018 (logistic regression analysis)
g – p = 0.031 vs. controls ($\chi 2$ test)
h – p = 0.037 (logistic regression analysis)

BMI – body mass index; HDL-C – low high density lipoprotein cholesterol; M – male; F – female; IFG – impaired fasting glucose (fasting glucose 100mg/dL)
AD – Alzheimer's Disease; VaD – dementia of vascular origin; MD – mixed dementia

Table 2. Abnormalities of glucose metabolism in various types of dementia. Results are presented as median and interquartile ranges (IQR) and odds ratios (OR) with 95% confidence interval (CI).

Tabela 2. *Zaburzenia metabolizmu glukozy w różnych rodzajach otępienia. Wyniki przedstawiono jako odsetek osób z wartościami nieprawidłowymi oraz jako iloraz szans (OR) z 95% przedziałem ufności (CI).*

Variable	Measure	AD (n=65)	VaD (n=23)	MD (n=40)	Controls (n=55)	p-value
Glucose 0h (mg/dL)	Median (IQR)	93.1 (86.8–100.6)	98.2 (91.0–102.7)	96.4 (88.1–110.7)	92.0 (87.0–102.0)	0.318
	OR [95%CI]	1.01 [0.98–1.04]	1.03 [0.98–1.08]	**1.04 [1.002–1.07]**[e]		
Glucose 2h (mg/dL)	Median (IQR)	**127.1 (106.0–157.8)**[a]	125.0 (97.9–186.4)	**129.3 (107.9–158.6)**[f]	105.0 (92.2–141.8)	**0.022**
	OR [95%CI]	**1.01 [1.001–1.02]**[b]	1.01 [0.997–1.02]	**1.01 [1.001–1.02]**[g]		
Insulin (mU/L)	Median (IQR)	7.45 (5.35 – 11.15)	10.05 (4.90 – 11.95)	9.23 (6.59–13.42)	7.96 (5.59 – 11.66)	0.368
	OR [95%CI]	1.01 [0.98–1.04]	0.96 [0.88–1.05]	1.03 [0.97–1.09]		
HOMA-IR	Median (IQR)	1.84 (1.23 – 2.66)	2.37 (1.24 – 2.76)	2.28 (1.53 – 3.69)	1.86 (1.28 – 2.75)	0.322
	OR [95%CI]	1.04 [0.92–1.17]	0.87 [0.61–1.25]	1.17 [0.94–1.45]		
HOMA-IR >2.1	%	42.2	**60.9**[c]	52.5	38.2	0.217
	OR [95%CI]	1.18 [0.56–2.49]	**2.52 [0.91–6.95]**[d]	1.79 [0.78–4.13]		

a – p = 0.045 vs. controls (ANOVA Kruskall-Wallis post-hoc test)
b – p = 0.027 (logistic regression analysis)
c – p = 0.066 vs. controls ($\chi 2$ test)
d – p = 0.074 (logistic regression analysis)
e – p = 0.037 (logistic regression analysis)
f – p = 0.054 vs. controls (ANOVA Kruskall-Wallis post-hoc test)
g – p = 0.037 (logistic regression analysis)
Glucose 0h – fasting plasma glucose; Glucose 2h – 2-hour postload plasma glucose
BMI – body mass index; HDL-C – low high density lipoprotein cholesterol; M – male; F – female; IFG – impaired fasting glucose (fasting glucose 100mg/dL)
AD – Alzheimer's Disease; VaD – dementia of vascular origin; MD – mixed dementia

No differences were found between patients and controls in the frequency of particular polymorphic forms of the G-subunit of protein phosphatase (PPP1R3) gene.

Obviously the ε4 allele was present much more frequently in patients with dementia than in the controls. When the occurrence of such metabolic syndrome features as low HDL cholesterol and impaired glucose tolerance were stratified according to the ε4 allele carriership, these features turned out to be significantly more frequent in dementia only in the ε4 noncarriers, but not in the carriers of this allele. A tendency for higher HOMA-IR in demented noncarriers of the ε4 allele was also observed. When glucose metabolism disturbances were considered jointly (IFG or IGT or DM), a similar tendency towards higher frequency was seen in demented noncarriers (Table 3).

Table 3. Comparison of the unfavorable features in noncarriers (-) and carriers (+) of *APOE* ε4 allele.

Tabela 3. *Porównanie objawów u nienosicieli (-) i nosicieli (+) allelu ε4 genu APOE.*

		APOE ε4 (-)			APOE ε4 (+)		
Variable	Measure	Dementia	Controls	p value	Dementia	Controls	p value
Low HDL-C <40mg/dL M; <50mg/dL F	%	33.8	16.7	**0.029**	23.2	22.2	ns
	OR [95%CI]	2.55 [1.07–6.06]			1.06 [0.19–5.76]		
Glucose 2h (mg/dL)	Median (IQR)	137.4 (108.2–176.0)	105.3 (91.62–140.4)	**0.002**	125.0 (105.1–141.5)	105.0 (99.0–147.9)	ns
	OR [95%CI]	1.01 [1.004–1.022]			1.005 [0.98–1.03]		
Glucose metabolism disturbances (IFG or IGT or DM)	%	57.9	48.1	0.116	49.3	44.4	ns
	OR [95%CI]	1.48 [0.73–3.01]			1.21 [0.29–5.03]		
HOMA-IR>2.1	%	51,6	37,5	0.140	45.2	42.9	ns
	OR [95%CI]	1.78 [0.82–3.86]			1.10 [0.22–5.48]		

M – male; F – female
IFG – impaired fasting glucose; IGT – impaired glucose tolerance; DM – diabetes mellitus

DISCUSSION

The main abnormality in glucose metabolism in the group under study was impaired glucose tolerance (IGT). Fasting glucose was increased in some of our deme-nted patients (IFG), but no significant differences were found between patients and controls. While in a majority of methods to assess metabolic syndrome IFG, and not IGT is used as the diagnostic criterion, it should be emphasized that IGT being an early signal of an incorrect disposal of administered glucose is considered to be an important symptom indicating or preceding insulin resistance [12].

The classic gold standard to evaluate insulin resistance is the Hyperinsulinemic Euglycemic Glucose Clamp. In clinical practice several simpler indices are used. The Homeostasis Model Assessment of Insulin Resistance Index (HOMA-IR) used in our study takes into account both fasting insulin and fasting glucose levels – the index was shown [13] to correlate highly with the Clamp results.

The metabolic syndrome features were observed most often in dementia of vascular origin. This could be expected as they are mostly of vascular character.

In the study by Liolitsa [5] a marginally significant more frequent association of the less active PPP 1 R3 polymorphic form was observed in AD patients and the controls, while in our study no differences were found.

The ε4 carriership of apolipoprotein E gene is a well-known strong genetic risk factor for dementia, especially for AD development. The joint effect of insulin resistance syndrome and apolipoprotein E phenotype was investigated by several authors. In a prospective study of nondiabetic patients Kuusisto [14] found that hyperinsulinemia in individuals without the ε4 allele was associated with increased risk for AD. According to Messier [15], the risk for developing AD in people who have both diabetes and the ε4 allele is more than twice as high as that in non-diabetic carriers. Our observation that the increased frequency of two important metabolic syndrome features, namely, of a low HDL cholesterol level and increased median glucose level after glucose load, (i.e. glucose intolerance), occurred only in the absence of the ε4 carriership shows that the effect of these characteristics traits was weaker than that of apolipoprotein E polymorphism. They could promote dementia development only in the absence of the ε4 allele. This fact is important for clinicians and suggests that special care should be given to ε4 noncarriers so as to avoid metabolic syndrome features predisposing to dementia.

It should be noted that among important metabolic syndrome components hypertension and adiposity in middle age were undoubtedly shown to be risk factors for dementia [16]. However, at the onset of dementia and during its progression a decrease in blood pressure can be observed [17]. Also in our AD group hypertension frequency was found to be lower than in the controls. Weight loss often occurring in preclinical phases of dementia could be its early sign [18]. Such features named "reverse epidemiology related to geriatrics" [19] may influence and complicate the interpretation.

CONCLUSIONS

1. Co-occurrence of metabolic syndrome features and dementia was observed most often in dementia of vascular origin.
2. The frequent abnormality of glucose metabolism in dementia was the 2h post-load glucose level.
3. Low HDL cholesterol and impaired glucose tolerance were significantly more frequent in dementia only in the ε4 noncarriers, but not in the carriers of this allele.

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