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The metabolic syndrome, diabetes, and Alzheimer's disease

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ABSTRACT

Background. The metabolic syndrome (MS) is a cluster of metabolic abnormalities that has been controversially associated with Alzheimer's disease (AD), so the purpose of this report was to investigate the association between these two chronic diseases a sample of older persons. **Methods.** Case-control study of 90 consecutive outpatients with AD and 180 non-demented controls from a dementia clinic at a tertiary care hospital in Mexico City. Probable or possible AD was diagnosed according to the guidelines of the Consortium to Establish a Registry for Alzheimer's Disease, whereas control participants where those classified as normal by the same instrument. MS was defined according to the World Health Organization criteria. Patients were matched 1:2 by age, sex, and years of education. Conditional regression analysis was used to test the association between MS and AD. **Results.** Compared to controls, MS was more frequent among AD patients (72.2% vs. 23.3%; P < 0.01). While all components of MS were more frequent among cases than control patients, only diabetes was statistically significant, whereas hypertriglyceridemia and low HDL cholesterol were marginally associated. Conditional regression analysis showed that among AD participants, the probability of having MS was about sevenfold higher than for their non-demented counterparts (OR 6.72, 95% CI 3.72-12.13; *P* < 0.01). **Conclusions.** The MS is a clinical entity that encompasses a diverse range of chronic diseases, which could be a better risk indicator than any individual MS component for adverse health outcomes, like AD. Our findings underscore the harmful role of MS in the health status of the elderly.

Key words. Cognition. Dementia. Alzheimer's Disease. Metabolic syndrome. Case-Control Study.

El síndrome metabólico, la diabetes y la enfermedad de Alzheimer

RESUMEN

Antecedentes. *El síndrome metabólico (SM) es una constelación de alteraciones metabólicas que, controversialmente, ha sido relacionado con el desarrollo de enfermedad de Alzheimer (EA). El objetivo de este estudio es investigar la asociación entre esas dos enfermedades crónicas en adultos mayores.* ***Métodos.*** *Estudio de casos y controles con 270 pacientes externos de la Clínica de Cognición de un hospital de tercer nivel en la ciudad de México. De ellos, 90 fueron diagnosticados con probable o posible EA según el* Consortium to Establish a Registry for Alzheimer's Disease *y 180 fueron controles. La presencia de SM fue catalogada con base en los criterios de la Organización Mundial de la Salud. Los pacientes fueron pareados 1:2 por edad, sexo y escolaridad. Análisis de regresión logística condicional probaron la asociación entre SM y EA.* ***Resultados.*** *Comparados con los controles, SM fue más frecuente en los pacientes con EA (72.2%* vs. *23.3%; P < 0.01). A pesar de que todos los componentes del SM fueron más frecuentes en los casos que en los controles, sólo la diabetes fue estadísticamente significativa, mientras que la hipertrigliceridemia y el colesterol HDL bajo estuvieron marginalmente asociados. El análisis de regresión logística condicional mostró que entre los pacientes con EA, la probabilidad de tener SM fue casi siete veces más elevada que en los pacientes sin demencia (OR 6.72, 95% CI 3.72-12.13;* P *< 0.01).* ***Conclusiones.*** *El SM es una entidad clínica que involucra distintas enfermedades crónicas, el cual pudiera ser un mejor indicador de riesgo para EA más que sus componentes individuales de forma aislada. Esos resultados destacan el papel nocivo del SM para la salud de los adultos mayores.*

Palabras clave. *Cognoscitivo. Demencia. Enfermedad de Alzheimer. Síndrome metabólico. Estudio de casos y controles.*

INTRODUCTION

Alzheimer's disease (AD), the most widespread form of dementia,[1] is a progressive neurodegenerative disease of epidemic proportions in developing societies, and its cause remains unknown.[2,3] The amyloid hypothesis has been the most prevalent theory to explain the pathophysiology of AD. However, several lines of evidence support a "vascular hypothesis" for the pathology of AD, with the likely principal factor being the metabolic syndrome.[4,5] The metabolic syndrome (MS) is a clinical entity composed of a cluster of metabolic abnormalities that are all associated with an increased risk of coronary heart disease, stroke, and cardiovascular mortality.[6] MS has been shown to be independently associated with cognitive impairment,[7] vascular dementia, and recently with AD.[8] MS is highly prevalent among the Mexican population,[9] a population that seems to differ from others with regard to risk factors for AD. For example, in a Mexican-Mestizos elderly urban population, it was found that APOE ε4 did not increase risk for AD.[10]

To date, no one has tested the hypothesis that an association exists between MS and AD in older Mexican persons. Such an association would have significant implications for the understanding and prevention of this devastating disorder. Therefore, the aim of the present research was to investigate, in a case-control study, whether MS is associated more frequently with AD patients among the Mexican elderly.

METHODS

Study Population

We conducted a case-control study involving 376 consecutive patients followed at the dementia clinic of a tertiary care hospital in Mexico City. Demographic (age, sex, and years of education) and clinical data were obtained from medical records, which contained data prospectively collected from 1997 through 2006.

Case patients were participants who had the diagnosis of probable or possible Alzheimer's disease (AD) according to the standardized instrument developed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).[11] CERAD was established in 1986 to develop a standardized method to evaluate patients with AD based on clinical,[12] neuropsychological,[13] and neuropathological information about this illness.[14] The clinical assessment protocol was designed to provide clinicians with the minimum information necessary to make a confident diagnosis of AD.[15] For each case patient, 2 control subjects who were non-demented were selected and matched by age (± 3 years), sex, and years of education (± 3 years). Control subjects were patients who had a normal performance on the CERAD instrument. Exclusion criteria included patients with dementia other than AD, or with missing clinical or biochemical data.

According to the World Health Organization (WHO),[16] the metabolic syndrome (MS) is defined as: having insulin resistance that includes alterations in fasting plasma glucose (glucose higher than 100 mg/dL), glucose intolerance (defined by a glucose load after 2 h above 140 mg/dL), or diabetes mellitus (DM; glucose higher than 200 mg/dL in a casual test and 2 h post glucose load or fasting glucose above 126 mg/dL plus symptoms), and two or more of the following criteria: obesity (waist circumference greater than 102 cm or 88 cm for men and women, respectively, or a body mass index [BMI] higher than 30 kg/m^2); a serum triglyceride concentration higher than 150 mg/dl; a serum HDL cholesterol concentration lower than 35 mg/dL or 39 mg/dL for men and women, respectively; and a blood pressure of at least 140/90 mm Hg.

Statistical methods

Variables are described using arithmetic mean and standard deviation (SD) or frequency and proportion, where appropriate. The following statistical procedures were used according to the characteristics of each variable: a chi-square test for qualitative data or a Student t-test for continuous variables. To look for possible associations between the metabolic syndrome and Alzheimer's disease, unconditional and conditional logistic regression models were calculated, and odds ratios with 95% confidence intervals (CI) were determined. Because results from the unconditional and conditional models were similar, results from the conditional models are presented according to the matched sampling procedure. In addition, conditional logistic regression analyses based on the maximum likelihood method were used to investigate the association of the metabolic syndrome and each of its components with Alzheimer's disease. All possible combinations of individual components (without the complete metabolic syndrome) and their association with AD were also tested. All statistical tests were performed with $P < 0.05$ considered significant. Statistical

tests were performed using the SPSS software for Windows® (SPSS Inc., Chicago, IL, version 13.0).

RESULTS

The study sample was composed of 90 cases and 180 controls matched by age, sex, and years of education. Mean age and years of education for all participants was 80.8 ± 6.7 years (range 66 to 97 years) and 6.7 ± 5.6 years (range 0 to 25 years), respectively. Thirty percent were males. A comparison of the demographic and health characteristics between cases and controls is shown in Table 1. As expected, cases had lower MMSE scores (20.7 ± 4.3) compared to control subjects (25.1 ± 3.0). AD patients had higher mean plasma glucose compared to controls (126.9 ± 50.2 mg/dL *vs.* 108.9 ± 35.6 mg/dL; $P < 0.01$) but lower cholesterol levels (180.8 ± 51.1 mg/dL *vs.* 196.4 ± 46.4 mg/dL; P = 0.01). In contrast, there were no statistical differences between cases and controls in serum HDL cholesterol, triglycerides, or body mass index.

The frequency of abnormalities in metabolism of glucose (alterations in fasting plasma glucose, glucose intolerance or diabetes mellitus) were significantly higher among participants with AD compared to non-demented subjects (72.2% *vs.* 37.8%, P < 0.01); this difference was marginally significant for hypertriglyceridemia (61.1% *vs.* 48.9%, P = 0.05) and low HDL cholesterol (46.7% *vs.* 34.4%, P = 0.05). Despite the increased frequency of hypertension and obesity among cases compared to control participants, there were no statistically significant differences between the matched groups (Table 1).

Table 1. Characteristics of case and control participants (n = 376).

	Case patients n = 90	Control patients n = 180	*P*-Value	Odds Ratio (95% CI)	*P*-Value
Age, years; mean (SD) (range 66 to 97 yrs)	81.0 ± 6.8	80.8 ± 6.7	0.80	-	-
Sex (%)					
Men	30	30		-	-
Women	70	70		-	
Education, years; mean (SD) (range 0 to 25 yrs)	6.7 ± 5.9	6.6 ± 5.5	0.87	-	-
MMSE; mean (SD) (range 10 to 30)	20.7 ± 4.3	25.1 ± 3.0	< 0.01	0.71 (0.64-0.79)	< 0.01
Glucose, mg/dL; mean (SD) (range 75 to 374)	126.9 ± 50.2	108.9 ± 35.6	< 0.01	1.01 (1.00-1.02)	< 0.01
Cholesterol, mg/dL; mean (SD) (range (54 to 342)	180.8 ± 51.1	196.3 ± 46.4	0.01	0.99 (0.98-0.99)	0.01
Triglycerides, mg/dL; mean (SD) (range 65 to 469)	165.2 ± 73.8	158.2 ± 61.5	0.41	1.00 (0.99-1.01)	0.41
HDL cholesterol, mg/dL; mean (SD) (range 20 to 136)	42.2 ± 15.7	45.1 ± 13.7	0.12	1.66 (0.99-2.80)	0.05
Body mass index, kg/m; mean (SD)	26.0 ± 4.6	25.9 ± 4.0	0.83	1.01 (0.95-1.07)	0.82
Systolic blood pressure; mean (SD) (range 100 to 190)	141.5 ± 22.1	137.1 ± 24.7	0.14	1.01 (0.99-0.01)	0.15
Diastolic blood pressure; mean (SD) (range 57 to 110)	78.7 ± 11.3	81.2 ± 13.7	0.10	0.98 (0.96-1.01)	0.12
Abnormalities in metabolism of glucose (%)					
No	27.8	62.2	< 0.01	1.0	
Yes	72.2	37.8		3.83 (2.21-6.63)	< 0.01
Hypertension (%)					
No	37.8	47.8	0.12	1	
Yes	62.2	52.5		1.55 (0.90-2.65)	0.11
Obesity (%)					
No	85.6	86.1	0.90	1	
Yes	14.4	13.9		1.05 (0.51-2.15)	0.90
Hypertriglyceridemia (%)					
No	38.9	51.1	0.05	1	
Yes	61.1	48.9		1.68 (0.99-2.86)	0.05
Low HDL cholesterol concentration (%)					
No	53.3	65.6	0.05	1.0	
Yes	46.7	34.4		1.66 (0.99-2.79)	0.05
Metabolic syndrome (%)					
No	27.8	76.7		1.0	< 0.01
Yes	72.2	23.3		6.72 (3.72-12.13)	

SD: Standard deviation. CI: Confidence Interval. MMSE: Mini-Mental State Examination.

Conditional regression analysis showed that abnormalities of metabolism of glucose were the only isolated component of MS statistically associated with AD (Odds Ratio [OR] 3.83, 95% CI 2.21-6.63; P < 0.01). Hypertriglyceridemia (P = 0.05) and low HDL cholesterol (P = 0.05) were only marginally associated with AD, and hypertension and obesity were not associated. However, among those with AD, the probability of having MS was about sevenfold higher compared to the control participants (OR 6.72, 95% CI 3.72-12.13; P < 0.01).

In order to explore whether any combination of the isolated MS components had a higher strength of association than MS as a whole, all possible combinations were tested. All combinations that included an abnormality of metabolism of glucose and at least one of the other MS components were significantly associated with AD, excepting for the combination with obesity (Table 2). With respect to other components of MS, only the combination of hypertriglyceridemia and low HDL cholesterol was statistically significant (OR 2.04, 95% CI 1.10-3.79; *P* = 0.02). However, neither diabetes alone nor combination showed an OR greater than 4.00.

DISCUSSION

The main purpose of this research was to describe the association between the metabolic syndrome and Alzheimer's disease in a sample of older Mexican persons. Although the relationship remains controversial,[17,18] these results are consistent with those previously described,[19-21] and show that MS is more frequent among participants with AD than those without a diagnosis of dementia. To our knowledge, the current study is the first to examine this relationship among Latin American older persons. Razay et al. found an association between MS (National Cholesterol Education Program Adult Treatment Panel III criteria, ATP-III) and AD after adjusting for age, sex, and place of residency (OR = 3.2, 95% CI 1.2 to 8.4). However, this association was strengthened when hypertension was excluded from the definition of MS, which suggests an inverse association between hypertension in later life and the risk of AD (OR = 7.0, 95% CI 2.8 to 18.3).[19] On the other hand, Vanhanen et al. examined 959 adults aged 69 years and older, and they reported that the incidence of dementia was higher among participants with MS (ATP-III criteria) compared to subjects without this syndrome (7.2% *vs.* 2.8%, P < 0.01). In addition, multivariate analyses showed that MS was independently associated with AD (OR = 2.46, 95% CI 1.27 to 4.78).[21] Similarly, the longitudinal study of Luchsinger et al. reported that the risk for AD increased 3.4-fold when 3 or more cardiovascular risk factors were added (diabetes, hypertension, heart disease, and smoking) (95% CI 1.8 to 6.3); however, this investigation did not use specific criteria to define MS.[20]

Table 2. Conditional Logistic Regression Analysis for the Metabolic Syndrome and its Individual Components.

	Case patients n = 90	Control patients n = 180	*P*-Value	Odds Ratio (95% CI)	*P*-Value
Diabetes alone (%)					
No	54.4	73.3	< 0.01	1.0	< 0.01
Yes	45.6	26.7		2.33 (1.35-4.02)	
Diabetes and hypertension (%)					
No	52.3	78.3	< 0.01	1.0	
Yes	46.7	21.7		2.95 (1.71-5.08)	< 0.01
Diabetes and hypertriglyceridemia (%)					
No	45.6	76.4	< 0.01	1	
Yes	54.4	23.3		3.55 (2.07-6.08)	< 0.01
Diabetes and Low HDL cholesterol (%)					
No	60.0	85.0	< 0.01	1	
Yes	40.0	15.0		4.00 (2.12-7.54)	< 0.01
Diabetes and obesity (%)					
No	85.6	92.8	0.05	1	
Yes	14.4	7.2		2.23 (0.96-5.17.)	0.06
Hypertriglyceridemia and Low HDL cholesterol (%)					
No	66.7	78.9	0.03	1	
Yes	33.3	21.1		2.04 (1.10-3.79)	0.02

The potential mechanisms through which MS may be associated with AD are not well understood and are the subject of debate. Despite having different pathophysiological mechanisms, the different components of MS could converge at a common pathway leading to the development and clinical manifestations of AD.[1,4] For example, a directly harmful effect on the brain via neuronal damage can occur through the production of free oxygen radicals. Theoretically, the neurons exit G0 to enter the G1 phase of the cell cycle; unable to complete the cell cycle, they become more susceptible to damage by oxidative stress (the "double-hit" theory).[22] However, central nervous system effects are better understood for individual components of MS, especially diabetes and hypertension.[8,23]

Hyperglycemia could be the most important component of MS involved in the development of AD.[17] In the current study, abnormalities of metabolism of glucose were the only isolated component of MS statistically associated with AD. Both chronic hyperglycemia and diabetes have been associated with alterations in mental processes (e.g., the ability to learn, evoke, mental flexibility, etc.) as well as with the acceleration of cognitive impairment.[24] In diabetic patients, a possible direct effect of insulin resistance on the brain and hyperinsulinemia could increase the levels and deposition of β-amyloid, as well as promote the phosphorylation of tau protein.[23] Therefore, these metabolic abnormalities may be involved in the formation of senile plaques, neurofibrillary tangles, and neuronal loss, all key pathological elements of AD.[25]

Despite the fact that hypertension is one of the cardiovascular risk factors associated with vascular dementia,[4,26,27] its relationship to the development of AD has not been clarified.[28] Skoog, *et al.*, reported that both patients with vascular cognitive impairment and AD had a history of hypertension at least 15 years before the diagnosis of dementia. Indeed, postmortem studies showed that these patients frequently had more senile plaques and neurofibrillary tangles compared to cognitively unimpaired controls.[26] The European Systolic Hypertension Study reported that antihypertensive treatment could reduce the risk of developing AD as well as vascular dementia.[29] However, it has also been reported that low blood pressure is associated with cognitive decline and dementia.[30] The relationship between blood pressure and AD remains to be clarified, but it likely depends on ischemia, changes in vascular permeability, and the production of free oxygen radicals in the brain.[31]

In contrast, little is known about the relevance of other components of MS on AD.[32] A higher BMI has been associated with the risk of developing dementia.[33] Whitmer et al. report that midlife obesity increased by 3.1-fold the risk of AD, even after adjusting for stroke, cardiovascular disease, diabetes, and others comorbidities.[27] Chiang et al. reported a higher risk of dementia in patients with a BMI ≥ 25.5.[34] Dyslipidemia has not been shown to play a key role in the development of AD.[35] However, hypertriglyceridemia and low plasma HDL levels could partly explain the changes in brain vasculature seen in patients with AD.[5,36] The ε4 allele of apolipoprotein E is the only cardiovascular risk factor related to AD. While this association has been shown among Asian and Caucasian populations, it has not been demonstrated in Mexican Mestizos.[10] Interactions between this allele and cardiovascular risk factors (e.g., diabetes, smoking, or hypercholesterolemia) seem to increase endothelial damage, deposition of β-amyloid, and production of inflammatory cytokines (interleukin-6, tumor necrosis factor-α), all of which eventually promote oxidative stress.[31] However, since these findings are not widespread, they suggest that other unknown genetic factors besides the ε4 allele could be involved in the onset of AD. West et al. recently described the possible role of the PPARγ gene Pro12Ala polymorphism in the risk for cognitive impairment through a longitudinal study on dementia and Cognitive Impairment without Dementia (CIND) in a cohort of older Latinos.[37] Among those with diabetes at baseline, there was an increased rate of dementia/CIND for Ala carriers compared to non-carriers, but not among non-diabetic participants. The PPARγ 2 Ala12 allele has also been associated with the risk of being overweight or obese in Mestizos and two Amerindian populations in Mexico.[38] On the other hand, an altered expression of PPARγ coactivator 1α (PGC-1α) has been involved in a decrease of non-amyloidogenic degradation of amyloid precursor protein which promotes formation and deposition of β-amyloid. Hyperglycemia also decreases the activity of PGC-1α, which has been associated with insulin resistance and diabetes. This abnormality could be the common pathway between MS and AD.[39] However, these polymorphisms deserve to be explored in future research. Thus, the higher prevalence of cardiovascular risk factors in our study population (such as those included in MS) could be related to the strong association found with AD. In addition, since hyperglycemia was the only component of MS associated with AD, this suggests a synergistic effect of diabetes

with other MS components because the strength of association was lower with abnormalities of metabolism of glucose alone.[40]

The main limitation of this study is its case-control design, making the direction of the observed effects unclear. Alternatively, since the WHO criteria are more sensitive than the ATP III criteria for diagnosing MS, a selection bias could result from only including those with the most serious forms of the metabolic syndrome.[41] However, the association demonstrated between MS and AD was strong, which suggests that using the ATP III criteria would result in detecting an even stronger association. In addition, all cases were recruited in the same dementia clinic, which could also introduce selection bias. Another limitation is the lack of imaging studies to rule out any vascular damage in patients meeting the clinical criteria for AD. Thus, we cannot exclude the possibility that some vascular component explains the association between MS and dementia, considering that the prevalence of mixed dementia is probably higher than supposed in our population.

Despite these limits, the current study shows that MS, an entity that encompasses a range of diverse chronic diseases, could be a better indicator of risk for adverse health outcomes (including AD) compared to the individual components of MS alone. In addition, our study underscores the harmful role of the metabolic syndrome in the health status of the elderly. These results have potential implications for the development of evidence-based interventions to promote health in older adults. However, longitudinal studies are needed to establish a causal relationship between MS and AD, and thus improve strategies for better monitoring and disease control in patients with the metabolic syndrome.

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