Title: Mental slowness and executive dysfunctions in patients with Metabolic Syndrome.

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KEYWORDS

Ageing. Cerebrovascular disease. Cognition. Metabolic Syndrome X. Neuropsychological assessment. Risk factors.

ABSTRACT

Metabolic Syndrome is a cluster of vascular risk factors which has been related to dementia and cognitive decline. The aim of this study was to describe the neuropsychological profile of Metabolic Syndrome patients. An extensive neuropsychological protocol was administered to 55 patients and 35 controls assessing memory, executive, visuoperceptual and visuoconstructive functions, language and speed of processing. There were differences between groups in speed of processing and some executive functions after controlling for the influences of education and gender. The results suggest that Metabolic Syndrome may be a prodromal state of vascular cognitive impairment.

INTRODUCTION

At the beginning of the twentieth century, Kylin described a syndrome which included hypertension, hyperglycemia and hyperuricemia (1). Over the last twenty years the syndrome has been studied by various disciplines and has received different names: the "deadly quartet" (2), hypertriglyceridemic waist (3), X syndrome, or insulin resistance (4). At present the most widely-used name is Metabolic Syndrome (MetSd), which has been defined by the National Cholesterol Education Program (NCEP) (5) as the presence of at least three of the following vascular risk factors: hypertension, hyperglycemia, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, and obesity as measured by waist circumference (Supplementary data 1).

To date, several epidemiological studies have highlighted the effects of vascular risk factors on cognition (6), and there is some evidence of the neuropsychological effects of obesity (7), impaired fasting glucose (8), dyslipemia (9) and hypertension (10), as individual vascular risk factors of the syndrome.

Yaffe et al. (2004) reported that MetSd patients obtained lower Mini Mental State Examination (MMSE) scores than healthy people. MetSd patients also showed a decline in memory and MMSE scores in a three-year follow-up (11). A prospective cohort study of cardiovascular disease performed in 1965 and in 1991 (12) reported an association between the presence of vascular risk factors at baseline with evolution to dementia after a 25-year period in MetSd patients. More recently, studies have linked MetSd to a higher risk of Alzheimer's disease (13), fronto-subcortical symptoms, and poorer neuropsychological performance associated with ageing (14,15). However, some authors have reported better cognitive performance in very old people with MetSd (16,17),

To our knowledge, most studies of MetSd are cross-sectional (29, 32) and use regression analysis to evaluate the association between the syndrome and cognitive decline. Only a few of them include an extensive neuropsychological assessment of MetSd patients.

The aim of the present study was to investigate the neuropsychological impairment of MetSd using a case-control design in which the control group did not manifest any of the risk factors included in the syndrome. We hypothesized that MetSd patients would show a specific cognitive profile, due to the combined effects of vascular risk factors on the brain. Specifically, this profile would probably reflect the impact of the syndrome on white matter (WM) integrity. Therefore, MetSd patients may show differences in processing speed and in correct performance of executive functions.

MATERIALS AND METHODS

Research participants

A medical team reviewed the medical records of 600 patients from two public medical centers of Barcelona province (*Centres d'atenció primària*) in Cerdanyola del Vallés and Sant Just Desvern, Barcelona (Spain). All the participants were volunteers, right handed, aged between 50 and 80 years old, and literate. The exclusion criteria were: uncorrected visual or auditory deficits, drug abuse or alcoholism (more than 28 standard drink units per week for men and more than 17 standard drink units per week for women (18)), a history of developmental pathology, and current neurological, hematological, hormonal, nutritional pathology and/or neoplasm. All selected participants also completed a screening interview in order to check the medical information from their records, to measure

their general cognitive capacity according to MMSE score (19) and to estimate their intelligence coefficient using the Vocabulary subtest of the Wechsler Adult Intelligence Scale—3rd edition (WAIS-III) (19). In the same session participants also underwent a modified interview based on the Structured Clinical Interview for DSM-IV Axis I disorders (20) to exclude major psychiatric diseases. Subjects with an MMSE score below 26 and estimated intelligence coefficients below 85 were excluded. Praxis skills were preserved in the whole sample and were assessed by bilateral imitation of hand positions (19). Hand dominance was assessed by Edinburgh test (19). Years of education and occupational level (low, medium or high) were also recorded.

Ninety volunteers were finally selected, 55 of whom fulfilled the criteria for MetSd as described by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) (5). Measures of glucose, HDL-cholesterol and triglycerides for all participants were obtained by a blood test; blood test analyses were performed in the reference laboratory of each medical center. Blood pressure measures and waist circumference of participants were recorded during the screening sessions. The final sample comprised a patient group of 36 women and 19 men with a mean age of 63.80 years (SD 7.3) and mean of 8.55 years of education (SD 3.6), and 35 healthy controls without any of the vascular risk factors included in the MetSd criteria. The controls were 17 women and 18 men, with a mean age of 61.66 (SD 7.7) and a mean of 10.20 years of education (SD 4.56). All enrolled subjects signed an informed consent form prior to taking part in the study, and the research was conducted in accordance with the Helsinki Declaration.

Neuropsychological assessment

All participants underwent a comprehensive neuropsychological evaluation. The tests were administered by a trained neuropsychologist in a fixed order during two 90-min sessions.

Verbal memory was assessed by Rey's Auditory Verbal Learning Test (RAVLT) (19). The RAVLT variables computed were total learning (sum of correct responses from trial I to trial V), delayed memory recall after 20 min (VI) and retroactive interference, which was defined as the influence of new learning (list b) on the previously achieved learning (list a) (19). Visual memory was assessed by the Faces I subtest of the Wechsler Memory Scale III (WMS-III) (19).

Immediate memory span was evaluated with the forward digit scores of the Digit subtest of the WAIS-III, while measures of working memory were based on backward digit scores of the Digit subtest and the Arithmetic subtest of the WAIS III (19).

Visuoperceptual and visuoconstructive functions were evaluated by the number of correct items on the Benton Facial Recognition Test—Short Form (19) and the score on the Block Design subtest of the WAIS-III (19) respectively.

The short-form version of the Wisconsin Card Sorting Test (19) and part B of the Trail Making Test (19) were administered to evaluate high level executive functions. On the WCST, perseverative errors and the total number of categories obtained were recorded.

Verbal fluency was measured by the number of words produced within two restricted categories: semantic (animals) and phonemic (beginning with the letter "p"), within a 1-min limit. The Stroop test (19) was administered to obtain a measure of interference response.

The processing speed variables used were total correct responses in 90 s on the orally-administered Symbol Digit Modalities Test (SDMT) (19) number of seconds taken to solve the Trail Making Test Part A, time taken to complete the Grooved Pegboard Test (19) with the dominant and non-dominant hands, and reaction time in CPT-II (Continuous Performance Test II) (19).

Finally, the total number of correct responses on the short form of the Boston Naming Test (Spanish version) was used to assess language (19).

Statistical analysis

Demographic and neuropsychological differences between groups were compared using the Statistical Package for the Social Sciences (SPSS WIN; v.14.0). The Student's t test or its non-parametric equivalent, the Mann-Whitney U test, were used for quantitative variables when required, while the χ^2 test was used to analyze qualitative variables. Effects of education and gender were controlled by an analysis of covariance (ANCOVA) of significant variables; some of them were converted to guarantee the ANCOVA assumptions. The magnitude of the observed effect was calculated by the r effect size. The discriminative power of the neuropsychological test between MetSd patients and controls was determined by a discriminant analysis (21) in which we included the significant tests obtained in the group comparison analysis, using a stepwise method.

RESULTS

There were no differences between the groups in age (t=1.3 p=0.186), education (U=737, p=0.059), occupational level (χ^2= 3.2 p=0.198), scores on the Vocabulary subtest (t=-1.4, p=0.152) or gender (χ^2=2.5, p=0.113). Detailed description of the

sample can be found in supplementary data 2. More than half of the sample (56.3%) fulfilled three of the MetSd diagnostic criteria, 27.3% met four criteria, and 16.4% fulfilled five. The most prevalent vascular risk factor among patients was obesity (92.7%), followed by hypertension (76.4%), low levels of HDL cholesterol (75%), fasting glucose (69.1%) and hypertriglyceridemia (48.1%) (Supplementary data 3)

The group comparison analyses showed significant differences in some cognitive functions (Table 1). Specifically, we found a reduction in processing speed and poor results in some executive functions. Several neuropsychological differences between patients and controls remained significant after controlling for the effect of education and gender through ANCOVA. The differences were significant for GPT dominant ($F=11.9$, $p= 0.001$) and non-dominant hand ($F=12.9$, $p=0.001$), retroactive interference of RAVLT ($F= 4.4$, $p= 0.040$), semantic fluency ($F=4.4$, 0.039) and Arithmetic subtest of WAIS-III ($F= 4.5$, $p=0.039$).

We entered the variables that achieved significance on group comparison into a discriminant analysis. Reaction time on the CPT-II and the Block Design subtest were the variables with the best power to differentiate between patients and controls. These tests correctly classified 71.4% of the patients and 53.8% of the controls (Supplementary data 4).

DISCUSSION

The results of this study show that MetSd involves a decrease in cognitive performance. Specifically, the neuropsychological profile of MetSd patients is characterized by dysfunction in two cognitive domains: slowness in mental processing and executive dysfunctions.

Processing speed is assessed by GPT dominant and non-dominant hand. We measured the time taken to insert all the pegs necessary to fill a table with four or five holes, using first the dominant hand and then the non-dominant hand.

Mild executive dysfunction is evidenced by several measures: retroactive interference, semantic fluency and arithmetic subtest on the WAIS-III. Retroactive interference is calculated by subtracting the trial V score from the trial VI score on the RAVLT. This score shows the interference effect of new material in the recall of previous learning. The semantic fluency test measures the number of words (names of animals) elicited in 1 minute; a poor semantic fluency is related to difficulties in retrieval strategies. Finally, the arithmetic subtest on the WAIS-III requires the ability to solve verbal arithmetic problems presented in a story format. This test assesses the ability to organize the elements of the problems as well as working memory and attention resources. (19)

The differences between patients and controls remained after controlling for the possible effect of education and gender. In contrast, several cognitive functions remained unaffected by the syndrome. We found non-significant differences in: visuoperceptual and visuospatial abilities, assessed by the Benton Facial Recognition Test—Short Form, verbal learning and long term recall measured by RAVLT, and high-level executive functions tested by WCST, TMT B and Stroop test.

Our results corroborate previous findings from studies that investigated isolated vascular risk factors (6-10). Processing speed deficits and executive dysfunctions have been reported in patients with vascular risk factors and in subjects without cognitive impairment which progress to vascular cognitive impairment (22). Dik et al. (2007) (15) showed a relationship between MetSd and processing speed, immediate recall, fluid intelligence and the MMSE score in a cross-sectional study.

However, in this study the general cognitive level was not controlled: we provide evidence for the specificity of speed of mental processing and executive dysfunctions in MetSd.

Our results agree with those of van der Berg et al., (2008) (23), who compared three groups, a control group, a group of MetSd patients, and a group of patients with type 2 diabetes (DM-II). Those authors found poorer performance in processing speed in both patient groups in comparison to controls. The processing speed was measured by a composite score of Trail Making Test Part A, the Stroop Color-Word Test (parts I and II), and the Digit Symbol subtest of the WAIS-III.

They also found poorer cognitive performance in the DM-II group. This group showed additional differences in executive functioning assessed by a composite score of Trail Making Test Part B, the Stroop Color-Word Test (part III), the Brixton Spatial Anticipation Test, and semantic and phonetic verbal fluencies. Both patient groups had very similar vascular risk factor profiles, apart from their glucose metabolism, indicating that the risk factors clustered in the metabolic syndrome may play a role in the decreases in cognitive functioning in DMII patients, and that these decreases may even develop in prediabetic stages. However, in this study the control group included subjects with vascular risk factors. In our healthy group, we controlled this aspect by including only subjects without any of the risk factors for MetSd. This may have been the reason for our results, we found both deficits, mental slowness and mild executive dysfunction, in our metabolic syndrome group.

One possible explanation for the cognitive impairment in our sample is subcortical brain damage produced by silent vascular pathology. MetSd is associated both with atherosclerosis (24) and with increased cellular oxidative stress (25). The

molecular and structural alterations in MetSd are the consequence of the presence of vascular risk factors. In fact this syndromic effect has been described previously in relation to the risk of suffering stroke and coronary diseases (26), and has been associated with intracranial atherosclerosis (27), which may be the cause of small-vessel disease.

Although there is no direct proof of vascular involvement in the neuropsychological impairment reported in the present sample, a diffusion tensor imaging (DTI) study performed in a subsample of 38 of our 90 subjects indicated microstructural WM alterations in patients with MetSd mainly involving the frontal lobe. Patients with MetSd showed an anterior-posterior pattern of deterioration in WM with reduced fractional anisotropy (FA) and increased apparent diffusion coefficient (ADC) values compared to controls. WM changes were not related to any isolated vascular risk factor (28). Although the specific mechanism of this damage is not clear, the use of this non-invasive method provides information on subtle WM changes. Small-vessel disease could be responsible for the microstructural alteration, due to the chronic state of vascular dysregulation in the brain. Therefore, the consequences of MetSd in vascular dysregulation may be taken as representing a specific neuropsychological profile. Indeed, DTI results of previous studies are in agreement with our neuropsychological findings: WM degeneration associated to aging, specifically in the frontal lobe, is related to slower processing and working memory deficits (29). Therefore, the anterior-predominance in the deterioration agrees with the neuropsychological deficit observed in our sample of patients. Similarly, the preservation of other cognitive domains assessed indicated the integrity of posterior parts of the brain and their connections.

Our results suggest that MetSd is a prodromal state for mild vascular cognitive impairment, in the sense that it implies a specific cognitive profile with attentional and executive function deficits (30) as well as psychomotor slowness and immediate memory deficits.

Nordlund et al. (2007)(31) found significant differences between vascular MCI and non-vascular MCI subjects in executive functions, speed, attention and language. in a sample that included subjects with stroke and transitory ischemic attack, Sachdev et al. (2004)(32) reported similar results: they found that vascular MCI patients differed from controls in executive functions, information processing speed, visual memory, abstraction, and visuoconstruction. In this connection, our results showing a specific neuropsychological profile with processing speed deficit and executive dysfunctions indicate a prodromal state of vascular cognitive impairment. Longitudinal studies are required to elucidate whether MetSd may be a prior stage of vascular cognitive impairment. Follow-up studies of these patients are therefore of great interest.

Previous studies of MetSd (16,23) compared patients with the syndrome with normal controls, but they did not exclude all the vascular risk factors associated with MetSd in the control subjects. The effects of independent risk factors of the syndrome have been described, and so the inclusion of control group with single or coupled vascular risk factors may influence the results obtained. In our study, in which rigorous exclusion criteria were applied, the controls had none of the vascular risk factors included in the diagnosis of MetSd. We also performed a comprehensive neuropsychological assessment, using a case-control design to compare the effect of the syndrome in different cognitive domains. As our subjects showed normal MMSE scores and the effects of education and gender were

controlled, our findings may indicate a subtle initiation of vascular impairment, which can be followed up over time. Indeed, the discriminant analysis results showed that the CPT-II reaction time and the Blocks subtest of WAIS-III are the variables that best discriminate between patients and controls. We propose that these measures should be taken in account in clinical protocols, because they can provide information about the evolution of the neuropsychological profile in MetSd patients and the differences between this profile and that of normal ageing.

While our findings are suggestive, the study is limited in several ways. The most important limitation is the sample size, due to the high comorbidity of MetSd and ageing with some of the exclusion criteria such as vascular pathology. Similarly, due to the sample size we were unable to study the effect of gender in depth. It would be particularly interesting to study the interaction effect of gender and age, and the associated risk of MetSd.

Future studies with groups of intermediate subjects with one or two risk factors and larger sample sizes may establish whether MetSd really causes a syndromic effect in the central nervous system that is greater than the sum of its parts.

In conclusion, MetSd patients show a specific neuropsychological profile. The detection of its specific manifestations appears to be the next step in preventing cognitive decline. We therefore propose that MetSd be included as a variable in research studies on cognitive impairment associated with ageing, in order to study its role in the differences between normal and successful ageing.

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Table 1. Neuropsychological results of Metabolic Syndrome and Control Groups. Raw scores (Mean± SD, range and number of subjects).

	Metabolic Syndrome	**Control**			
	M (SD)Range (n)	M (SD) Range (n)	t/U	p	ESr
RAVLT Total	46.07 (8.99)28-66(55)	48.23 (9.64)33-69(35)	-1.08†	NS	-
RAVLT Del	9.51 (2.40)5-15(55)	10.34 (2.00)6-15 (35)	-1.71†	NS	-
RAVLT RI	3.37 (1.89)0-8(54)	2.35 (1.77)0-7(34)	2.52†	0.014	0.27
Faces I	35.42 (4.95)23-48(55)	37.74 (5.00)26-46(35)	-2.16†	0.033	0.24
Forward D.	6.96 (1.81)4-13(55)	8.09 (1.88)4-12(34)	-2.81†	0.006	0.29
Semantic F	18.55 (4.80)10-31(55)	21.43 (4.95)12-31(35)	-2.75†	0.007	0.28
Phonetic F	12.67 (4.80)4-22(55)	14.09 (4.54)7-25 (35)	-1.39†	NS	-
WCST Persev	16.38 (14.16)2-63(55)	11.14 (9.48)1-34 (35)	1.92†	NS	-
WCST Cat	1.85 (1.08)0-3(55)	2.23 (0.97)0-3(35)	-1.67†	NS	-
TMT B	131.70(72.25)50-385(43)	112.87(57.51)39-55(31)	1.20†	NS	-
Stroop test	2.54 (8.52)(*-18)*-22 (53)	4.78 (8.45)(*-12)*-26 (35)	-1.21†	NS	-
Arithmetic	9.44 (3.44)5-22(39)	11.88 (4.13)5-18(26)	325††	0.014	0.32
SDMT oral	33.67 (16.19)9-76(55)	38.29 (14.51)15-74(35)	-2.81†	0.006	0.15
GPT DH	89.87 (27.72)59-221(55)	74.03 (15.39)62-233(34)	3.05†	0.003	0.33
GPT NDH	101.02 (32.40)62-233(54)	82.29 (20.26)55-170(34)	528††	0.001	0.36
CPT-II RT	453.23 (63.30)305-557(42)	414.57 (49.79)322-487 (26)	334††	0.007	0.33
TMT A	52.73 (22.64)24-126(52)	46.45 (22.98)22-146(33)	1.24†	NS	-
Facial Benton	47.18 (4.05)39-55(55)	48.00 (3.75)40-54(34)	-0.95†	NS	-
Block	27.22 (11.74)10-54(55)	35.09 (11.45)12-59(35)	3.13†	0.002	0.32
BNT	12.60 (1.38)8-15(55)	12.83 (1.12)10-15(35)	-0.82†	NS	-

Note: RAVLT = Rey Auditory Verbal Learning Test, Del= Delayed, RI = retroactive interference; Faces I: Faces I subtest of Wechsler Memory scale III; Forward D= Forward Digits subtest Wechsler Adult Intelligence Scale III; F= Fluency; WCST = Wisconsin Card Sorting Test; Perserv= perseverative responses, Cat= number of Categories; TMT B = Trail Making Test Part B; Backward D = Backward Digits subtest of Wechsler Adult Intelligence Scale III; Arithmetic= Arithmetic subtest of Wechsler Adult Intelligence Scale III; SDMT = Symbol Digit Modalities Test; GPT = Grooved Pegboard Test, DH = Dominant Hand, NDH = Non Dominant Hand; CPT-II RT = Continuous Performance Test Reaction time; TMT A = Trail Making Test Part A; Block= Block subtest of Wechsler Adult Intelligence Scale III;
BNT= Boston Naming Test. † = t d' Students test; †† = U Mann Whitney test; ES r = Effect size r absolute value. NS= Non significant values.

Supplementary data 1. Metabolic Syndrome Criteria. (Grundy et al., 2005)
Metabolic Syndrome diagnosis requires 3 of 5 of the following criteria.

Measure	**Categorical Cutpoints**
Elevated waist circumference	≥ 102 cm in men ≥ 88 cm in women
Elevated triglycerides	≥ 150 mg/dL or On drug treatment for elevated triglycerides
Reduced HDL-Cholesterol	< 40 mg/dL in men < 50 mg/dL in women Or On drug treatment for reduced HDL-C..
Elevated blood pressure	≥ 130 mm Hg systolic blood pressure or ≥ 85 mm Hg diastolic blood pressure or On antihypertensive drug treatment a patient with history of hypertension.
Elevated fasting glucose	≥ 100 mg/dL or On drug treatment for elevated glucose.

Supplementary data 2. Demographic characteristics of Metabolic Syndrome group and control group.

	Metabolic Syndrome		**Control**	
	M (SD)	Range	M (SD)	Range
Age (years)	63.80 (7.28)	50-80	61.66 (7.69)	51-78
Education (years)	8.55 (3.63)	1-16	10.20 (4.56)	1-16
Vocabulary	37.71 (11.0)	12-58	40.97 (9.53)	24-60
MMSE	28.94 (1.12)	26-30	29.31 (0.86)	27-30
Praxis	8 (0)	8	8 (0)	8

M: mean SD: Standard Deviation

	Metabolic Syndrome	**Control**
Gender (M/F)	19/36	18/17
Occupation Level		
Low	37	17
Medium	10	9
High	8	9

M: male, F: female

Supplementary data 3. Laboratory data of Metabolic Syndrome group and control group.

	Metabolic Syndrome		**Control**	
	M (SD)	Range	M (SD)	Range
Glucose (mg/dL)	112.03 (30.77)	76-238	86.97 (7.62)	66-99
HDL-Cholesterol (mg/dL)	53.26 (15.10)	25-98	67.78 (14.79)	40-111
Triglycerides (mg/dL)	150.30 (87.41)	51-453	79.67 (25.79)	44-141
SBP (mmHg)	133.37 (15.90)	106-204	121.71 (8.40)	109-133
DBP (mmHg)	78.31 (9.60)	58-104	75.26 (6.59)	58-83
WC (cm)	104.91 (10.42)	88-133	85.45 (8.78)	68.5-101

M: mean SD: Standard Deviation. SBP: systolic blood pressure. DBP: diastolic blood pressure. WC: Waist Circumference.

Supplementary data 4. Discriminat analysis.

Wilkins λ	**Chi²**	**p**	**Variables**	**Coefficients (Standardized)**
0.787	13.861	0.001	CPT-II RT	0.741
			Block WAIS-III	-0.647

CPT-II RT = Continuous Performance Test II Reaction Time; WAIS-III = Wechsler Adult Intelligence Scale III.