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The clock drawing test as a cognitive screening tool for assessment of hypertension-mediated brain damage

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KEYWORDS
Hypertension;
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Mini-mental statement examination

Abstract
Introduction: Hypertension (HTN) is the most frequent cause of subcortical vascular brain injury (VBI) and its cognitive consequences. The aims were to show the usefulness of the Clock Drawing Test (CDT) to detect cognitive impairment in hypertensive patients and to compare it with the Mini-Mental Test (MMSE).
Methods: A subset of hypertensive patients of the Heart-Brain Study in Argentina was included. Demographic characteristics, vascular risk factors, blood pressure (BP) and schooling level were recorded. The MMSE and CDT tests were used for neurocognitive assessment and Hospital Anxiety Depression scale (HAD) for mood disorder evaluation.
Results: 1414 hypertensive patients (age 59.7 ± 13.8 years, female (62.3%). The prevalence of cognitive impairment was 20.7% (using MMSE) and 36.1% (using CDT). Among hypertensive patients with normal MMSE (>24) 29.3% had cognitive impairment (abnormal CDT). The CDT was associated with level of education but not with age or mood status.
Conclusions: The CDT is a useful screening tool to detect hypertension-mediated brain damage earlier (especially in midlife) and is more sensitive than MMSE.

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PALABRAS CLAVE
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Test de dibujo del reloj;
Test mini-mental

Test de dibujo del reloj como herramienta de cribado cognitivo para evaluar el daño cerebral mediado por hipertensión

Resumen
Introducción: La hipertensión es la causa más frecuente de lesión cerebral vascular subcortical y de sus consecuencias cognitivas. El objetivo de este estudio fue mostrar la utilidad del Test del dibujo del reloj (TDR) para detectar el deterioro cognitivo en pacientes hipertensos y compararlo con el test *Mini-mental statement examination* (MMSE).
Métodos: Se incluyó a un subconjunto de pacientes hipertensos del Estudio Corazón-Cerebro de Argentina. Se registraron las características demográficas, los factores de riesgo vasculares, la presión arterial y el nivel educativo. Se utilizaron TDR y MMSE para la evaluación neurocognitiva, y la escala *Hospital Anxiety Depression* (HAD) para evaluar los trastornos emocionales.
Resultados: Se evaluaron 1.414 pacientes hipertensos (edad 59,7 ± 13,8 años; mujeres, 62,3%). La prevalencia de deterioro cognitivo fue del 20,7% (utilizando MMSE) y del 36,1% (utilizando TDR). Entre los pacientes hipertensos con MMSE normal (> 24) el 29,3% tenían deterioro cognitivo (TDR anormal). Se asoció el TDR al nivel de formación, pero no a la edad ni al estado emocional.
Conclusiones: El TDR constituye una herramienta de cribado útil para detectar tempranamente el daño cerebral mediado por hipertensión (especialmente en la mediana edad), con mayor sensibilidad que el MMSE.

Introduction

Nowadays a growing body of evidence supports the strong link between hypertension (HTN), vascular brain injury (VBI) and its clinical expressions: stroke, cognitive impairment and dementia.[1,2] Given that, the HTN is consider the main modifiable vascular risk factor for cognitive impairment and dementia,[3] the burden and progression of the VBI and cognitive status depend on HTN treatment and control.[4–6] One-third of the patients with HTN have impairment of the executive functions,[7,8] which are the most typically affected cognitive functions in the vascular brain damage, and this condition doubles the risk to convert it into dementia.[9] The guidelines for management of HTN recommend the assessment of hypertension-mediated organ damage to help stratify the risk, but the brain, as a target organ, is not usually included in the screening.[10,11] The use of the brain imaging cannot be thought as screening tool, but the assessment to cognitive status may be adequate subrogate. In this sense, the Mini-Mental Statement Examination (MMSE),[12] considered as the ''gold standard'' test, was used for more than 25 years, but it is known to be an non-specific measure of global cognitive function, influenced by the age, schooling level, and mood disorders and does not explore the executive functions. On the other hand, the Clock Drawing Test (CDT)[13,14] has been employ in clinical setting to detect cognitive impairment (particularly in patients with vascular risk factors), predicting dementia,[15,16] Alzheimer's disease,[17] mortality risk and it is useful to evaluate longitudinal changes in the cognitive status.[18] Although the effect of the education level on the CDT is controversial, it is not influence by age, mood disorders and it is strongly associated with the executive functions.[19] From an epidemiological point of view, the CDT could be a simple and easy cognitive test to be apply in the clinical routine practice on hypertensive patients.[20] Thus, our aims were to demonstrate the usefulness of the CDT as a screening tool to evaluate the brain function, as subrogate of the hypertension-mediated brain damage, and to compare it with the traditional MMSE.

Methods

Study population

The characteristic of the study population has been published previously.[8] Briefly, the participants were a subset of the Heart-Brain Study in Argentina, a multicentre and cross-sectional study that included hypertensive patients, both genders and ≥21 years of age and older. The patients were enrolled from 18 centres in 5 on the 7 regions of Argentina. The sample did not include pregnant women, subjects having history of stroke or neurologic deficit or medical condition precluding a bad prognosis and life expentancy <1 year (e.g. severe chronic obstructive pulmonary disease, advanced cancer, etc.) or subjects with neuro-psychiatric disorders diagnosed (e.g. dementia according to DSM-IV/V, schizophrenia, bipolar disorders, major depression, Parkinson disease, etc.) as well as those on cholinesterase inhibitors, glutamatergic or antipsychotic inhibitors (the use of benzodiazepine was not exclusion criteria but were suspended 48 h before the testing). Finally, a total of 1414 hypertensives patients were included in the final analysis.

Clinical assessment

We evaluated demographic factors such as age, sex, schooling level and vascular risk factors. The schooling level of the participants was classified in 3 categories: level 0: no schooling, level 1: ≤7 years of education, level 2: between 8 and

12 years of education and level 3: ≥12 years. The vascular risk factors included reported diagnosis of diabetes mellitus, hyperlipidemia and current smoking.

The blood pressure (BP) was measured according to standard protocol by validated BP monitors (Omron HEM-780-E). HTN was defined according to Argentine Hypertension Consensus Guidelines (Argentine Society of Cardiology-SAC, Argentine Federation of Cardiology-FAC and Argentine Society of Arterial Hypertension-SAHA),[11] according to the European Society of Hypertension (ESH) guidelines[10] (systolic BP ≥140 mmHg and/or their diastolic BP ≥90 mmHg or if they had been prescribed antihypertensive medication). All patients received antihypertensive treatment, the numbers of drugs and adequate doses by to reach therapeutic objective. The patients were divided into 3 groups according to treatment and control condition: (1) treated/controlled PA ≤140–90 mm Hg, (2) treated/non-controlled >140–90 mm Hg and (3) untreated.

Neuropsychological assessment

The CDT[13] was employed following the modified format developed by the Neurocognitive Diseases Service of the CEMIC Institute (Argentina), based on other scoring systems.[17,19] The application of the test followed two steps: (1) a predrawn circle of 10 cm in diameter on paper was presented to the subject (the predrawn circle increases the sensitivity of the test and prevents the small size or distortion of the circle from interfering with the location of the numbers) and (2) two orders: first, *''Imagine that this circle represents the face of a clock, please draw all the numbers in order and correct position on it''* and after this was done the patients were asked *''to draw the hands pointing twenty to four''*. We used a scoring system from 0 to 7 points, assigning 3 points for draw the number and 4 points to draw the hands. It was considered a cut-off ≤5 points. The maximun scoring (7 points) was defined by: normal drawing, all numbers in correct position and two hands with different length, one pointing to four and one pointing to eight. The addition or loss of points in the scoring system is shown in the Appendix. The test score was blindly evaluated by 2 previously trained physicians.

The MMSE[12] was applied following the recommendations of the Neuropsychological Working Group of the Argentine Society of Neurology according to international norms. The scoring scale from 0 to 30 points was used and the cut-off ≤24 points, according to education level and average age of the all sample.

The Hospital Anxiety and Depression scale (HAD)[21] was used for the mood status assessment. The scale has 7 questions for each mood disorder (anxiety or depression), the scoring system for each question is based on Likert's scale (frequency of the symptoms) from 0 to 3 points and cut-off ≥11 points were used.

Ethical considerations

All participants signed an informed consent form before participating in the trial and were not subjected to any procedure other than the customary protocols indicated for good clinical practice, and regulatory including ethical approvals. The information is anonymous in accordance with the Argentine Law for Personal Data Protection (Nro. 25.326). The protocol was made pursuant to the guidelines of Good Clinical Practice, local regulations, and the Declaration of Helsinki and its amendment.

Statistical analysis

A descriptive analysis was carried out based on the frequency distribution of the categorical variables and the summary measures of the measurable variables. The comparisons between the categories were made by the adjusted Chi-square test and the associations of the measurable variables from ANOVA or Student's test as appropriate. Spearman's Rho coefficient was used for the correlation of ordinal categories. In all cases, we worked with a 95% confidence level.

Results

The characteristics of the study sample are summarized in Table 1. A total of 1414 were assessed (average age: 59.7 ± 13.8 years, range 18 to 95 years). The female's population of the sample was higher (62.3%) than male but there not were statistic differences in the average of age. The females presented lowest schooling level than male, especially in level 1 (51.2% vs 38.8%; $p < 0.0001$) and level 3 (19.3% vs 27.3%; $p < 0.0001$). The vascular risk factors (hyperlipidemia, diabetes and smoking) were more prevalent in female.

The systolic and diastolic BP values of the sample were 143.6 ± 21.2 mm Hg and 83.6 ± 12.3 mm Hg respectively. The distribution groups of the hypertensive patients according to treated or controlled condition was as follows: (1) treated/controlled 546 (38.6%); (2) treated/non-controlled 544 (38.4%); and (3) untreated 325 (22.9%). The prevalence of the hypertensive female with treated and controlled BP was higher (40.7% vs 35%; $p < 0.0001$) and the untreated condition was lower (22.5% vs 26.2%; $p < 0.0001$) than male.

The average scores of the test performed were: HAD-Anxiety 6.1 ± 4.0, HAD-Depression 4.2 ± 3.0, MMSE 26.7 ± 3.5 and CDT 5.5 ± 1.7. The prevalence of cognitive impairment evaluated by the MMSE (≤24) was 20.7% ($n = 293$) and by the CDT (≤5) 36.1% ($n = 511$). Among hypertensive patients with normal MMSE (>24) 29.3% had abnormal CDT. The CDT was significantly more effective to detect cognitive impairment in all age group (decades) except in hypertensive patients over 80 years and older (Fig. 1). The most common errors in the execution of CDT orders were those related to drawing the numbers; missing numbers (37.2%), their order (32.6%) and their position (21.6%) (Fig. 2). The prevalence of mood disorders, according to HAD results, and executive dysfunction according to CDT was more frequent in female than male (anxiety 18.5% vs 4.3%; $p < 0.0001$ and depression 11.5% vs 3.5%; $p < 0.0001$ and executive dysfunction 37.8% vs 31.1%; $p < 0.01$).

We did not find association between the abnormal MMSE or CDT and the treatment groups (p 0.56). The CDT did not associate with the HAD (anxiety = p 0.14 or depression = p 0.53). There was an association between MMSE and HAD results, depression was more frequent among hypertensive

Table 1 Baseline characteristics ($n = 1414$).

	Total sample	Female	Male	*p* value
Variables[a]				
Sample[a]	1414	882 (62)	533 (38)	
Age (years)[b]	59.7 ± 13.8	59.6 ± 13.8	60 ± 13.8	ns
Schooling level[a]				
Level 0	28 (1.9)	22 (2.4)	6 (1.1)	ns
Level 1	658 (46.6)	452 (51.2)	207 (38.8)	<0.0001
Level	439 (31)	259 (29.3)	180 (33.7)	ns
Level 3	317 (22.4)	171 (19.3)	146 (27.3)	<0.0001
Vascular risk factors[a]				
Hyperlipidemia	428 (30.2)	334 (37.8)	94 (17.6)	<0.0001
Diabetes mellitus	379 (26.8)	275 (31.1)	104 (19.5)	<0.0001
Current smoking	191 (13.5)	146 (16.5)	45 (8.4)	<0.0001
Cognitive and behaviour assessment[a]				
CDT ≤ 5 pts,	511 (36.1)	333 (37.8)	165 (31.1)	0.01
MMSE (≤24)	293 (20.7)	184 (20.9)	107 (20.2)	ns
HAD-Anxiety ≥ 11 pts	187 (13.2)	164 (18.5)	23 (4.3)	<0.0001
HAD-Depresion ≥ 11 pts	121 (8.5)	102 (11.5)	19 (3.5)	<0.0001
BP (mm Hg)				
SBP[b]	143.6 ± 21.2	143.3 ± 21.2	144.2 ± 21.2	ns
DBP[b]	86.3 ± 12.3	82.9 ± 12.3	84.6 ± 12.3	0.01
Treated/controlled[a]	546 (38.6)	359 (40.7)	197 (35)	0.03
Treated/non-controlled[a]	544 (38.4)	338 (38.2)	206 (38.6)	ns
Untreated[a]	325 (22.9)	185 (22.5)	140 (26.2)	0.02

[a] Values are absolute pathological findings, frequencies and percentages between brackets.
[b] Values are average and its SD.
Abbreviations: Level 0: non schooling; Level 1: ≤7 years of schooling; Level 2: 8–12 years of schooling; level 3: ≥12 years of schooling; MMSE: Mini-mental Statement Examination; CDT: Clock-drawing test; HAD-A/D: Hospital Anxiety and Depression scale; BP: Blood pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Table 2 Relationship between Clock Drawing Test (CDT) and Minimal Mental Statement Examination (MMSE) results and behaviour status (Hospital Anxiety-depression scale).

	Clock Drawing Test				Mini-Metal Test			
	Abnormal	Normal	IC (95%)	*p* value	Abnormal	Normal	IC (95%)	*p* value
Anxiety	74 (14.8)	109 (12.0)	0.027 (−0.010–0.065)	0.14	47 (16.0)	139 (12.4)	0.036(−0.010–0.082)	0.102
Depression	44 (8.8)	71 (7.8)	0.009 (−0.021–0.040)	0.53	43 (14.6)	77 (6.8)	0.078(0.035–0.121)	<0.0001

The values are absolute pathological findings, frequencies and percentages between brackets.

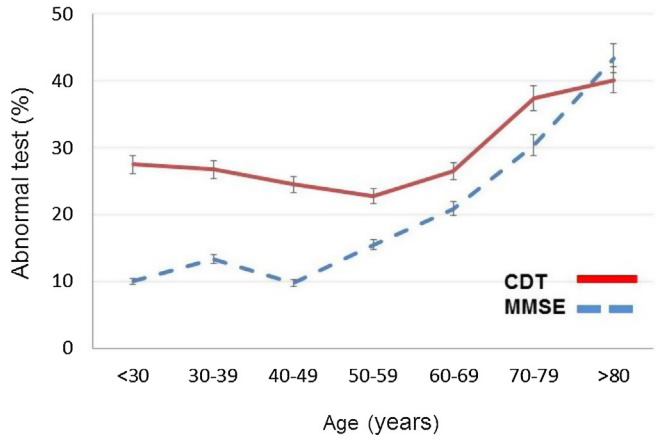
patients with abnormal MMSE (14.6% vs. 6.8%, OR 95% 0.035–0.121; $p < 0.0001$) (Table 2).

There was an inverse association between the schooling level and the abnormal CDT (level 0: 71.4%, level 1: 45%, level 2: 29.6% and level 3: 20.8%, *p* 0.000) (Table 3).

When we compared the CDT with the different proof of the MMSE (orientation, attention, memory – registration and recall–, language – compression and naming-, and visuoconstruction skill) to identify associations, we found out a positive correlation with the attention (reverse spell the word ''world'') (Rho 0.40 ± 0.03, $p < 0.0001$) and visuo-construction proof (pentagons) (Rho 0.45 ± 0.04, $p < 0.0001$).

Discussion

We think that this is a significant study that evaluates the usefulness of the CDT as a cognitive screening tool of hypertension-mediated brain damage. The most important finding was that the 29.3% of the hypertensive patients with normal MMSE (>24) had abnormal CDT. Thus, the CDT becomes a simple, fast and easily administered test to evaluate cognitive status in hypertensive patients. The CDT reflects the functioning of the frontal lobe (executive functions) and temporoparietal regions (memory).[22] The executive functions are the most vulnerable cognitive domain to the affects of the HTN and these function



Age (decades-years)	Total sample	MMSE	CDT	IC (95%)	p value
Average sample	1414	293 (20.7)	511 (36.1)	0.151 (0.124-0.176)	<0.0001
<30	40 (2.8)	4 (10)	11 (27.5)	0.175 (0.008-0.224)	0.03
30-39	82 (5.7)	11 (13.4)	26 (31.7)	0.183 (0.078-0.226)	0.001
40-49	163 (11.5)	16 (9.8)	49 (30)	0.202 (0.139-0.232)	<0.0001
50-59	354 (25)	56 (15.2)	93 (26.2)	0.110 (0.057-0.156)	<0.0001
60-69	420 (29.7)	89 (20.9)	151 (35.5)	0.152 (0.097-0.202)	<0.0001
70-79	253 (17.8)	77 (30.4)	120 (47.7)	0.170 (0.093-0.236)	<0.0001
≥80	105 (7.4)	40 (43.4)	49 (53.2)	-0.048 (-0.113 -0.094)	ns

Figure 1 Abnormal CDT and MMSE in hypertensive patients according to life's decades.

Table 3 Relationship between schoolar level and abnormal test (MMSE and CDT).

Schooling level	Total	MMSE	CDT	IC (95%)	*p* value
Level 0	28 (1.9)	20 (71.4)	20 (71.4)	0.000 (−0.237, 0.237)	ns
Level 1	631 (46.4)	187 (29.6)	284 (45)	−0.154 (−0.206, −0.101)	<0.0001
Level 2	439 (31)	66 (15)	130 (29.6)	−0.146 (−0.200, −0.092)	<0.0001
Level 3	317 (22.4)	20 (6.3)	66 (20.8)	−0.145 (−0.197, −0.093)	<0.0001

The values are absolute pathological findings, frequencies and percentages between brackets.
MMSE: Mini-mental Statement Examination; CDT: Clock Drawing Test.

depend on the integrity of the neuronal circuits between the pre-frontal cortex and subcortical nucleus.[23] The small vessel disease (white matter hyper intensities), consequence of the HTN, causes subcortical demyelination and disconnects these circuits. All executive functions, defined as the set of cognitive skills that control complex tasks such as: planning, working memory, attention, abstract thinking, visuospatiality and decision making among others, can be evaluated by the CDT. Without a doubt, a control group would have improved the scientific quality of the research. However, based on our previously published studies with control groups,[7,24,26] we found out that the executive dysfunction is more prevalent in hypertensive patients than in normotensive,[7] progresses independently of the blood pressure control[25] and the HTN increases the risk of executive dysfunctions by 5 times.[26] The CDT is quick to administer, is well acceptable among physician and patients, it is easy to score, and independent of the culture, language, age and mood disorders. The sensitivity (between 77% and 94%) and specificity (between 65% and 96%) are high, varying according to scoring system used.[19] In this sample of the hypertensive patients the most frequent mistakes in the CDT were those related to the drawing of the numbers, their order and position (Fig. 2), tasks specifically linked

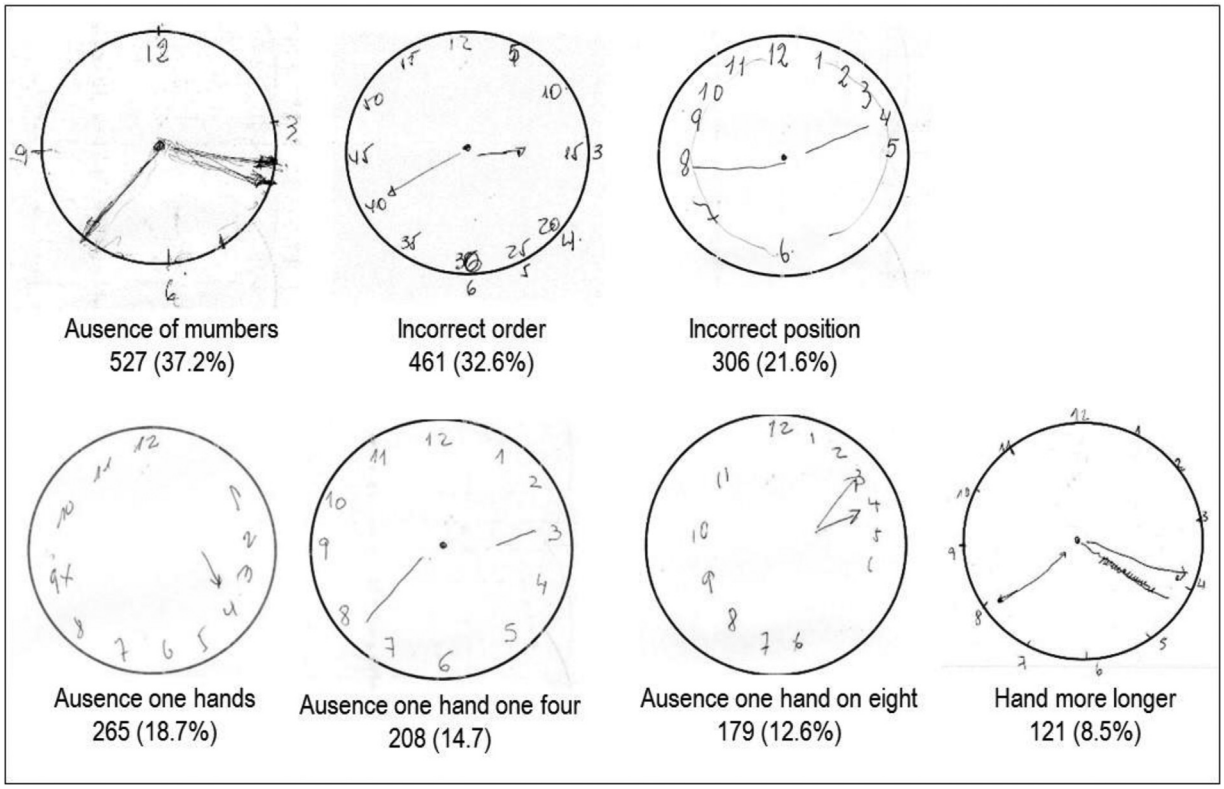


Figure 2 More prevalente mistaken in the CDT execution.

to the executive function, while, the failure in the drawing of the hands (semantic impairment) was less prevalent and observed in cognitive impairment advanced cases.

Approximately, one-third of the patients with diagnosis of HTN have silent VBI as target brain damage regardless cardio-renal impairment,[27] and beyond the stroke risk, its burden and progression increase the risk of cognitive impairment and dementia.[28] Thus, it is imperative to detect the cognitive impairment, as clinical expression of the hypertension-mediated brain damage, because the stratifying risk could change.

Several authors have compared the CDT with the MMSE, concluded that the CDT was more sensitive to detect cognitive impairment than MMSE[19] but, the CDT added to MMSE increase the sensibility and specifity.[19,29–31] We compared both tests, the CDT demonstrated to be more effective to detect cognitive impairment in middle-age than MMSE, while in hypertensive patients over 80 years and older both tests are equally effective. A plausible explanation could be due to the impairment of other cognitive domains, so that the MMSE loses score. So from an epidemiologic point of view the CDT is better than MMSE to detect early cognitive impairment in hypertensive patients but in older people the MMSE could complement the CDT test and get to know other cognitive impairment.

When we compared each proof of the MMSE with the CDT, we found an association just in the attention proof (reverse spell the word ''world'') and visuoconstruction proof (drawing overlapped pentagons), two tasks relatively involved with the executive functions. Although both tests are not diagnostic, the CDT evaluated better the cognitive domains (executive functions) impairment linked to vascular damage. Another advantage of the CDT over MMSE was not being influenced by mood disorders, even in the female sex in which the prevalence of anxiety and depression was higher than in men (Table 2).

The effects of education on the MMSE are known but than remain controversial on the CDT, while some researchers question the validity of CDT in illiterate people or with low schooling level others do not find association.[32] In this hypertensive sample we find a significantly inverse association between schooling level and CDT results, the authors consider that more research is necessary to define their association (Table 3).

From the gender analysis resulted that the executive dysfunction between hypertensive patients was more frequent in female than male. We could suggest an explanation based on the lowest schoolar level and the higher association with others vascular risk factors, such as hyperlipidemia, diabetes mellitus or smoking in female. Since the education, is considered the most important modifiable non-vascular risk factor for cognitive impairment and dementia, and the vascular risk factors are contributing to progression of the VBI.

Finally, given that this is a cross-sectional study, we did not find association between cognitive status and treated condition of the BP.

Thus, it is essential to evaluate the brain as a hypertension-mediated organ damage and given the practical and economic impossibility of systematically assessing the brain damage by performing brain imaging (Magnetic Resonance Imagen) the CDT becomes a simple, fast and

Appendix. Clock Drawing Test scoring system

Variable	Add one point	Substract one point
Number of numbers	12 numbers present. *(Twelve roman numbers is acceptable)*	There are less than or more than 12 numbers or numbers missing from the clock face or preservative numbers or replacement of numbers by dots or line.
Position numbers	Numbers placement in correct position. (*Numbers around outside or on the line but in order and correct position are acceptable)*	There are spacing between numbers shows a gap or grouped on one side or numbers aligned vertical or horizontal or placement on incorrect quadrant or numbers outside of the clock.
Sequence of numbers	Correlative numbers (1–12)	The sequence of numbers are incorrect or distorted or reversal order.
Two hands	Drawn 2 hands	Drawn only one hand or none hand.
Hand on four	One hand pointing number 4 or not exactly placement on it.	Hand is placement on others numbers or two hands together or hand not drawn from the centre of the clock or not clearly represented or hand missing.
Hand on eight	One hand pointing number 8 or not exactly placement on it.	The same to number 4
Hands lenght	Two hands (hour and minute) drawn with different length	The hands have the same length or hand of hours more long than hand of minutes

easily administered test to evaluate cognitive status in hypertensive patients and to monitor their evolution. This is an important topic because the dys-executive function increases twofold the risk of conversion to dementia, but on other hand, the early detection opens an opportunity window to modify the cognitive trajectory.

We are aware that this research has some limitations. First, although we have assumed, based on our own epidemiological research that the prevalence of abnormal CDT in hypertensive patients is higher than in the non-hypertensive population,[7,8] the absence of a control group could be a limitation of the study. However, given the exploratory characteristics of the investigation and the size of the sample, we consider that the research has been adequate to demonstrate that the CDT is a suitable first step cognitive screening instrument to detect incipient cognitive impairment (executive dysfunction) in patients with hypertension. Second, although it is a cross-sectional study without predictive capacity, it would be interesting to correlate the results with other cognitive tests and even with the findings in neuroimaging.

Conclusion

In conclusion, to known the HTN's impact on the brain helps to improve the stratification of the cardio and cerebrovascular risk in hypertensive patients and to recognize a group of patients, potentially treatable, with early cognitive deficit. The cognitive status could be an important subrogate of the VBI and the CDT a good cognitive screening tool in hypertensive patients that can be used by clinicians during routine medical practice.

Authors' contribution

All authors drafted and critically revised the manuscript.

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Conflict of interests

The authors declare no conflict of interests with respect to the research, authorship, and/or publication of this article.

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