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Three explanatory hypotheses of the correlation between hypertension and cognitive impairment. Current data analysis and future prospects.

Tres hipótesis explicativas de la correlación entre hipertensión y deterioro cognitivo. Análisis de la producción actual y perspectivas futuras.

Três hipoteses explicativas da correlação entre hipertensão e deterioro cognitivo. Análise da produção atual e perspectivas futuras.

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VOLUMEN 11. NÚMERO 3. SEP-DIC 2017. DOI: 10.7714/CNPS/11.3.204

ORIGINALES / ORIGINAL PAPERS

VOLUMEN 11. NÚMERO 3. SEP-DIC 2017. DOI: 10.7714/CNPS/11.3.204

ABSTRACT

Prevalence of hypertension related disorders is increasing on the total population. This phenomenon seems to be connected to population ageing and has led to an increment of chronic drug treatments. The cost of chronic treatment in this age group will increase, given the demographic changes that are anticipated. Objective: To revise empirical articles concerning to correlation between hypertension and cognitive impairment published in digital databases, responding to the purpose of collect current knowledge and identify possible pathways for future research. Results: The correlation between these two terms is summarized in three theoretical explanations, watching: 1) cognitive impairment as a comorbid disorder with hypertensive diseases, 2) hypertension as a brain damage causal that lead to cognitive impairment, and 3) cognitive impairment as an undesirable effect of antihypertensive medication. Conclusions: Results pretend to provide an overview about the impact of hypertension on cognitive performance at different levels, and to formulate objectives for new investigations that could clarify and improve these theoretical elucidations.

Keywords: hypertension; cognitive impairment; antihypertensive drugs; demographic ageing; theoretical study.

RESUMEN

La prevalencia de patologías relacionadas con hipertensión se está incrementando en el total de la población. Este fenómeno parece estar relacionado con el envejecimiento poblacional, provocando también un incremento en los tratamientos con medicación crónica. El costo de los tratamientos crónicos aumentó en este rango etario provocando una anticipación de los cambios demográficos previstos. Objetivo: Revisar artículos empíricos concernientes a la correlación entre hipertensión y deterioro cognitivo publicados en base de datos digitales, con el propósito de reunir los conocimientos actuales e identificar posibles caminos para futuras investigaciones. Resultados: La correlación entre esos dos términos es resumida en tres explicaciones teóricas, observando: 1) deterioro cognitivo como desorden comórbido de trastornos hipertensivos, 2) deterioro cognitivo como consecuencia del daño cerebral provocado por hipertensión, y 3) deterioro cognitivo como efecto indeseable de la medicación antihipertensiva. Conclusiones: Los resultados pretenden brindar una visión general del impacto de la hipertensión en el desempeño cognitivo en sus diferentes niveles; al mismo tiempo, formular objetivos para nuevas investigaciones tendientes a clarificar y mejorar estas elucidaciones teóricas.

Palabras clave: hipertensión; deterioro cognitivo; drogas antihipertensivas; envejecimiento cognitivo; estudio teórico.

RESUMO

A prevalência de patologias relacionadas com a hipertensão está incrementando no total da população. Este fenômeno parece estar relacionado com o envelhecimento populacional, provocando também um incremento nos tratamentos com medicação crônica. O custo dos tratamentos crônicos aumentou neste rango etário provocando uma antecipação dos câmbios demográficos previstos. Objetivo: Revisar artigos empíricos concernentes à correlação entre hipertensão e deterioro cognitivo publicados em base de dados digitais, com o propósito de reunir os conhecimentos atuais e identificar possíveis caminhos para futuras investigações. Resultados: A correlação entre esses dois termos é resumida em três explicações teóricas, observando: 1) deterioro cognitivo como desordem comórbido de transtornos hipertensivos, 2) deterioro cognitivo como consequência do dano cerebral provocado por hipertensão, e 3) deterioro cognitivo como efeito indesejável da medicação anti-hipertensiva. Conclusões: Os resultados pretendem brindar uma visão geral do impacto da hipertensão no desempenho cognitivo em seus diferentes níveis; ao mesmo tempo, formular objetivos para novas investigações tendentes a clarificar e melhorar estas elucidações teóricas.

Palavras-chave: hipertensão; deterioro cognitivo; drogas anti-hipertensivas; envelhecimento cognitivo; estudo teórico; desempenho

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The raise of life expectancy has increased the incidence and prevalence of age-related diseases. The demographic changes of occidental world, characterized by an explosive growth up of population over 65 years, made expected that the problem size will become epidemic during the first half of this century (Gómez Viera, Rodríguez, Gómez, Fernández & González Zaldívar, 2003). The considered disorders include neurodegenerative ones. Among them, dementias have the higher impact on public health due to their high social and economic costs (Butman et al, 2003). The patients, their families and their caregivers must face a significant loss of life quality and a consequent economic burden (Lima Argimon, Quarti Irrigaray & Milnitsky Stein, 2014).

Neurodegenerative disorders do not appear suddenly, but are preceded by early stages of gradual deterioration that usually can go unnoticed for the person and their family. This process, known as mild cognitive impairment (MCI), it's characterized by a progressive loss of cognitive functions at a higher lever than the attributable to normal aging (Petersen et. al, 1999). Their early detection is useful for family and medical guidance of the future patient, as well as for the planning of compensatory strategies applicable to daily life (Albert, 2011; Artero, Petersen, Touchon y Ritchie, 2006). It should be noted that the conservation of practical –implicit- intelligence usually attenuates the impacts of cognitive decline in the everyday life of people who are passing through normal aging (Miranda, Pruvost, Palau, Rimoldi, Viale y Cáceres, 2015).

Hypertension (HT) is a chronic heart disturbance linked to numerous comorbid diseases, with a higher prevalence in low and mid-income countries. This appears as an obstacle to life quality improvement, worsened by the relative low budget destined to its control and prevention (World Bank, 2014). The impact of HT can be verified in several body systems and activities. As consequence, this pathology may be even linked to cognitive and behavioral changes (Ovale Jaramillo, Álvarez Diez & Ibañez Pinilla, 2012).

Longitudinal studies on hypertensive patients proved that various cognitive functions impaired more as longer as the hypertensive disorder was conserved (Birkenhäger, Forette, Seux, Wang & Staessen, 2001). This correlation between hypertensive disease and low neuropsychological performance has been verified in samples of middle-aged subjects (Singh-Manoux & Marmot, 2005), like in older adults (Saxby, Harrington, McKeith, Wesnes & Ford, 2003).

Although there are differences in the methods used for the analysis and different hypotheses regarding the causes, there is actually enough evidence to support the relation between hypertensive disorders and cognitive impairment.

Thus, it has been shown that hypertension is positively correlated with visual memory decrease (Elias et. al, 1997), increasing global mental deterioration of subjects in their last decades. It has been also verified that hypertensive patients get lower yields in complex cognitive functions, such as spatial orientation and calculus; deficits that could also be related with any other of the behavioral expressions of dementia (Arias de Castillo, 2014; Chávez-Romero, Núñez-López, Díaz-Vélez y Poma-Ortíz, 2014; Espinoza, Quijada, Chuki y Berbesi, 2017). Accordingly, patients with hypertension concomitant diseases have shown a depletion of their attention capacity (Lama & Jeninson, 2013).

Longitudinal studies have analyzed samples with hypertensive subjects in contrast to normotensive subjects. These investigations managed to isolate the hypertensive factor and to relate it with the differences found in its neuropsychological results (Matoso, Santos, Moreira, Lourenço & Correira, 2013).

Method

A search for articles referred to cognitive performance impact of hypertension was performed utilizing the keywords: hypertenson and cognitive impairment in five

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scientific databases: Ebsco, Redalyc, Dialnet, Scielo, and Directory Of Open Acces Journals. Based on the information gathered, a categorization was made to justify the correlation between hypertension and cognitive impairment starting with the theoretical explanations with major empirical support. In the present article, the most relevant evidences are analyzed in relation to each one of the hypotheses and their concordances and divergences are discussed. Applied inclusion criteria were as follows: abstract in English and published in the period 2000-2015. Papers before 2000 were cited only to reference general concepts. Being a theoretical work with exploration targets, the performed screening should not be considered as exhaustive.

Results

Having found enough evidence about the link between hypertensive diseases and the decrease of various cognitive functions, it is necessary to detail the factors that currently intend to justify this relation.

The three postulates that currently have higher empirical support and represent the themes addressed by a majority of studies are listed below: 1) cognitive impairment as a comorbid disorder with hypertensive diseases; 2) hypertension as a brain damage causal that lead to cognitive impairment, and 3) cognitive impairment as an undesirable effect of antihypertensive medication. It must be noticed that, although each postulates is presented separately, literature shows that the association of cognitive performance and hypertension disorders could probably be sustained by a convergence of the three statements. The proposed order in this article responds uniquely to expository reasons.

Hypertension and cognitive decline as related by comorbidities

Hypertension is a present condition in different disorders, so it is reasonable to assume that cognitive impairment would be concomitant to broader pathologies. Some of these diseases are the following:

Diabetes type II

Studies concerning diabetes mellitus type II have yielded significant evidence tending to prove the concomitance hypothesis. Being a high morbidity disorder, it facilitates accomplishment of detailed longitudinal studies, allowing to assess its impact on cognitive performance. The presence of hyperglycemia seems to be an important variable, since it has been found a lower cognitive impairment in patients without hyperglycemia (Morris, Vidoni, Honea, Burns & Alzheimer's Disease Neuroimaging Initiative, 2014). Current data appears to be conclusive in the consideration of cognitive impairment as one consequence of diabetes mellitus type II (Yaffe et. al, 2013).

Dyslipidemias

Dyslipidemia involves a symptomatic scenario that signs presence of metabolic disorders as a common factor. It has been verified the impact that metabolic disorders have on some expressions counted as mood states. Recent studies have positively correlated the presence of dyslipidemia related disorders with negative adjustments in cognitive abilities (Bulhões et. al, 2013).

Obesity

Similar consequences have been observed in obesity. Although it can be considered a precisely-defined disorder, it appears related with others disorders in different systems. Thus, the links between obesity and cognitive impairment has shown contradictory results (Benito-León, Mitchell, Hernández-Gallego & Bermejo-Pareja, 2013). Although it is possible to indicate that cognitive decline may be tied to several obesity-related phenomena and possibly not with the specific obesity phenomenon, it does not result illogical to considerer a more broad conco-

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mitance between obesity and cognitive impairment (Sellbom & Gustand, 2011).

Heart diseases

Hypertension can be one of direct consequences of heart disease. Thereby, samples of hypertensive subjects usually integrates a considerable number of cardiopathic individuals. The vast variability of disturbances, causes, installation time and morbidity rate, caused different appreciations about the impact that might have on cognitive performance. However, this relation has extensive evidence to be considered (Eggermont, De Boer, Muller, Jaschke, Camp & Scherder, 2012).

Cerebrovascular disorders

The association between disorders of the cerebral vasculature and cognitive impairment -which will be expanded in section Hypertension and cognitive impairment of this article- has been extensively studied due high prevalence of dementias secondary to cerebrovascular accidents, with a relatively quick impact of these conditions on the patient behavior (Marchant et. al, 2013).

Other pathologies

Deterioration of cognitive ability seems to be related as well with other diseases in several systems. Correlations of these deficits with functional shifts on central nervous system and reproductive system, such as benign prostatic hypertrophy in hypotensive patients have been confirmed (Park, Rha & Ko, 2013); also, respiratory diseases such as asthma seems to have an impact on these symptoms (Caldera-Alvarado, Khan, Delfina, Pieper & Brown, 2013). These linkages have various but inconclusive empirical evidences. However, we have included them in this review with the purpose of demonstrate the wide range of disorders that involves concomitant hypertension and cognitive decline.

Hypertension and cognitive impairment as related to brain damage

Hypertension promotes changes in the arterial system and cerebral vessels. These changes constitute an adaptive response to excessive pulsatile blood pressures which provokes an anatomical modification leading to atherosclerosis, arteriolesclerosis, arterial wall thickening, narrowing arterial diameter, and smooth muscle hypertrophy. The lack of blood flow in brain key areas leads to neural performance decrease, and to corresponding efficiency decline on various cognitive functions whose might cause executive dysfunction. There is also enough evidence to indicate that blood pressure disorders can be considered as prognostic predictors of cognitive dysfunctions for elderly patients (Paulson, Strandgaard & Edvinsson, 1989).

One of the possible derivations of hypertension is the thickening of vessel walls, which tends to cause cerebral microangiopathy. Those disorders have been positively correlated with low efficiency in global cognitive performance assessments, and with memory especially when the damage is located in the frontoparietal lobe (Quinque et. al, 2012).

Insufficient blood supply is also often caused by hypertension-related accidents, such as brain microinfarcts and multiple strokes. These episodes might lead to vascular dementia, the second most prevalent dementia type in older adults (Zhang et. al, 2012), with typical memory dysfunction symptoms, and decrease of at least two higher cognitive functions (Davies, Ben-Shlomo & Martin, 2011).

Adaptive degenerative changes observed as result of HT on circulatory system provokes, as overall impact, cortical atrophy. Cognitive impact of this disease tends to worsen as anatomo-physiological effects are accentuated. Naturally, the dementia location focus and etiology are usually related to specific types of cognitive effects. Longitudinal studies describes the dementia progress as a gradual ability loss to daily task perform, plus a gra-

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dual impoverishment in neurocognitive performance tests (Chan et. al, 2015).

Although magnetic resonance studies can determine the focus and areas affected by cerebral microcirculation disorders, it's still difficult to predict the cognitive effects of neural injuries, since technologies needed to determine small vascular damages are not completely developed with required efficiency.

Hypertension and cognitive impairment associated by medication side effects

Antihypertensive drugs can be categorized based on its action mechanisms used to modify the blood pressure, as follows: beta blockers, angiotensin enzyme converting inhibitors, angiotensin receptor blockers, and calcium antagonists. Although numerous drugs apply more than one active principle, it remains useful to analyze the influence of each one of these groups in cognitive performance.

Beta blockers works reducing myocardial rhythm and potency, resulting in: a decrease of blood volume and flow rate; inhibition of rennin production; stimulation of kinins production; and the generation of a central antisympathetic effect. Cognitive impacts of those drugs might vary in relation to each specific chemical compounds ones, but in general are positively correlated with a decrease in memory performance (Fogari et. al, 2003).

Instead, angiotensin converting enzyme inhibitors produces a renin decrease by declining its precursor, the angiotensin. It produces relaxation of blood vessels by increasing its luminal space. It seems that its administration finds positive linkages with cortical shifts, which integrate similar features to various memory disorders markers (Savaskan et. al, 2001).

Likewise, the called angiotensin receptor blockers, inhibits the angiotensin cellular receptors, reducing its performance on renin production. Some scientific literature denominates those drugs as angiotensin blockers type II. It was found that several drugs of this type could be responsible for neuropathologies (Hajjar, I., Brown, L., Mack, W. J., & Chui, H., 2012).

Also, calcium antagonists inhibit calcium entrance into cells, reducing the narrowing tendency of small arteries. This allows to reduce myocardial contractility and peripheral vascular resistance. It seems that its supplying could acts as source of shifts in memory functions (Johnson, Ait-Daoud & Wells, 2000).

Diuretic drugs produce sodium elimination through nephro-urologyc system, which reduces the circulatory flow volume. Data concerning its cognitive impact is striking, since some studies found a positive relation between the administration of these drugs and an increase in learning tasks performance. Nor does it appears to cause negative effects on memory performance (Yasar et. al, 2012). Despite these evidences, it is necessary to say that diuretics drugs are not antihypertensive drugs themselves, but are supplied in early stages of this disorder due to its contribution to some symptomatic attenuation.

While chronic medication can be necessary for a number hypertensive disorders wich could otherwise result in serious drawbacks, it is important to consider its potential impact on brain functioning. Drug treatment is usually sustained for several decades, which would maximize the possibility of a cognitive decline.

Conclusions

The expose of the three theoretical explanations given in this article seems to show that correlation between hypertension and cognitive impairment could be a multi-causal phenomenon, and that each scenario should be considered without excluding the others.

It is expected that technological advances on neurologic diagnoses techniques will allow to elucidate with greater accuracy the causal relations behind the scenarios that currently can only be expressed on correlative means. We wish to emphasize the consideration given to the advantages and disadvantages of chronic antihyper-

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tensive medication, due the proven negative impact which most of this drugs cause on cognition. In this same theme, there is a critical disproportion among the available scientific data related to functions such as memory and attention, to detriment of the data over higher processes such as executive functions. Finally, we appeal to a techniques homogenization for diagnosis and monitoring of disorders related to cognitive impairment.

Discussion

Given the gathered information, it seems reasonable to hold the existence of a significant association between hypertension and cognitive impairment. However, it is necessary to evaluate new interpretations of existing data, and to encourage further researches to clarify the link.

We located vast evidence about changes in memory functions, but we could not find the same amount of scientific production in reference to higher cognitive abilities, such as executive functions. Would be reasonable to ask if the environment-related adaptive sensitivity of executive functions results in a protective trait or, conversely, in a vulnerability trait regarding the effects of hypertension.

In this meaning, we emphasize the relevance of interdisciplinary dialogue and integral training of professionals. In scenarios where the factor convergence can be considered as an overlap, the organic approach of one disorder should not deprive the consideration of its neuropsychological derivations. Being HT as common as broad in consequences, is convenient to consider the full impact spectrum of its treatment on the patient daily life.

We believe that diagnostic techniques advances will allow a more detailed observation of the small-scale effects of hypertension over specific brain structures. Meanwhile, we insist on the need of accurately warn about benefits and harms of chronic use of antihypertensive medication. Likewise, it corresponds to privilege the consensus generation of criteria and methodology. Otherwise, heterogeneity of data, classifications and tests, may limit the concrete application of any progress accomplished in the researches. Hypertensive disorders and cognitive impairment are diseases typically associated to the age span of which we expect a major growth in coming decades. Therefore, addressing these issues has a pronounced preventive and epidemiological importance for health containment. Under current demographic data, strategies aimed to reduce health care cost, and to improve protection and integration of these age groups will represent targets and urgencies with growing importance.

Considering that pharmacological strategies have been found ineffective over mild cognitive impairment, we reinforce the early detection importance, as well as preventive or palliative approaches which include: periodic cognitive assessment, clinical and psychological follow-up, stimulation activities that reinforce the conserved neuroplastic capacity, and guidance for family and caregivers. By this way, it is possible to expect concrete improvements of life quality for patients and their families.

Received: 02/05/2017
Accepted: 29/08/2017

VOLUMEN 11. NÚMERO 3. SEP-DIC 2017. DOI: 10.7714/CNPS/11.3.204

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