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The Top Five Articles In Dementia 2018-2020

Carolyn M Tan
MD
Resident, Department of Medicine, University of Toronto

Carla O Rosario
MD, PhD
Sub-Specialty Resident, Department of Medicine, Division of Geriatrics, University of Toronto

Dov Gandell
MDCM, FRCPC
Assistant Professor, Department of Medicine, Division of Geriatrics, University of Toronto

Corresponding Author:
Carolyn M Tan
Carolyn.tan@sunnybrook.ca

Abstract

Dementia is one of the greatest global health challenges of the early 21st century. We present for review five leading articles, published in the last three years that expand the understanding of the dementia syndrome. The topics include intensive blood pressure targets and the risk of incident dementia, modifiable risk factors that may prevent up to 40% of new dementia cases, a description of a novel biological basis for dementia syndrome, and a new definition of Alzheimer's disease based on biomarkers.

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Key points

1. Intensive blood pressure treatment may reduce the risk of developing mild cognitive impairment and also leads to small decreases in white matter lesions, a risk factor for cognitive decline.
2. Twelve modifiable risk factors can prevent or delay up to 40% of dementia cases, which encourages clinicians to take specific actions for prevention.
3. A novel disease mechanism, LATE-NC, could be present in a substantial number of Alzheimer's dementia cases and advances our understanding of the molecular changes in dementia.
4. Viewing Alzheimer's disease as a biologic construct based on the presence of biomarkers rather than in combination with clinical criteria pushes a research framework forward.

Introduction

The prevalence of dementia continues to increase as the world's population ages. Our understanding of the etiology of dementia is advancing, with new pathologic mechanisms and potential risk factors being described. Novel diagnostic approaches and investigative frameworks incorporating greater depth of biomarker understanding offers hope.

We present the top five articles on dementia reported in the last three years. In the summer of 2019, the third author (DG) surveyed geriatricians (N = 53) at the University of Toronto by e-mail requesting articles they considered important to the field of geriatrics, published in the last year without further specific criteria.[1] A list of 17 articles was produced then shortened by selecting articles that focused on dementia. The articles presented below were chosen by consensus between the three authors for being the most likely to influence practice or deepen the understanding of practice.

REVIEW OF THE TOP 5 ARTICLES IN DEMENTIA

Intensive blood pressure treatment does not reduce the risk of probable dementia[2]

The SPRINT MIND Investigators for the SPRINT Research Group. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. JAMA. 2019;321(6):553-61. https://jamanetwork.com/journals/jama/fullarticle/2723256

Background

Hypertension is a potentially modifiable risk factor for mild cognitive impairment (MCI) and dementia. Evidence to support treating hypertension to prevent MCI or dementia is lacking.

Methods

The 2015 Systolic Pressure Intervention Trial (SPRINT) enrolled 9,361 community-dwelling adults aged 50 years or older with a systolic blood pressure (SBP) between 130 and 180 mmHg and increased cardiovascular risk but without diagnosed diabetes, stroke, or dementia.[3] The mean age of the cohort was 67.9 years (SD 9.4 years), with 28.2% of participants aged 75 or older. SPRINT MIND was a pre-planned substudy that examined whether targeting an SBP < 120 mmHg versus < 140 mmHg would reduce the primary outcome of all-cause probable dementia. Alongside the main trial, cognitive assessments were performed at baseline, every two years, and at study completion. Secondary outcomes included MCI and a composite outcome of MCI or probable dementia. Probable dementia was adjudicated according to the DSM-IV criteria and MCI was defined as a deficit in performance in one or more cognitive domains in the absence of significant functional impairment.

Findings

At baseline, the cohort had a mean SBP of 139.7 mmHg and median Montreal Cognitive Assessment score of 23. During a median intervention period of 3.34 years, the mean between-group difference in SBP was 13.3 mmHg. Over a median follow-up period of 5.11 years, there was a nonsignificant reduction in probable dementia (7.2 vs. 8.6 cases per 1000 person-years, HR 0.83, 95% CI 0.67 – 1.04) but a significant reduction in the secondary outcome of MCI (14.6 vs. 18.3 cases per 1000 person-years, HR 0.81, 95% CI 0.69 – 0.95) and the composite outcome of MCI or probable dementia (20.2 vs. 24.1 cases per 1000 person-years, HR 0.85, 95% CI 0.74 – 0.97). Rates of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not injurious falls, were higher in the intensive treatment group.[3] A subgroup analysis of serious adverse events in participants over the age of 75 revealed similar findings; however, none reached statistical significance.[4]

Cautions

Failure to detect an effect on probable dementia may have been due to the main SPRINT trial being terminated early with short follow-up interval, once a cardiovascular and mortality benefit was demonstrated. There were fewer than expected cases of probable dementia and details of specific cognitive domain analyses were not reported. Lastly, the baseline rate of MCI was not determined, which could have generated an interesting subgroup analysis of higher risk individuals in the trial.

Implications

In practice, based on this study, physicians cannot base decisions to pursue an intensive SBP on the intent to reduce the risk of probable dementia. Interestingly, the intensive SBP target did not make cognition worse. Albeit a secondary outcome, which remains hypothesis generating, this is the first RCT to demonstrate an intervention that reduced incident MCI, a well-known risk factor for dementia.

MRI substudy of SPRINT MIND finds smaller increase in cerebral white matter lesions with intensive blood pressure treatment[5]

The SPRINT MIND Investigators for the SPRINT Research Group. Association of Intensive vs Standard Blood Pressure Control With Cerebral White Matter Lesions. JAMA. 2019;322(6):524-34. https://jamanetwork.com/journals/jama/fullarticle/2747671

Background

White matter lesions (WMLs) on magnetic resonance imaging (MRI) are a manifestation of small vessel ischemic disease and an independent risk factor for cognitive decline and dementia. Hypertension is the strongest modifiable risk factor for progression of WMLs, but intensive blood pressure treatment has not been shown to reduce WML progression in patients without diabetes.[6]

Methods

MRI scans were obtained at baseline and 48 months in a subgroup of 670 participants (mean age 67.3) from the SPRINT MIND study to evaluate the association between targeting an SBP < 120 mmHg versus < 140 mmHg and progression of small vessel ischemic disease. The primary outcome was change in total WML volume and the secondary outcome was change in total brain volume (TBV).

Findings

Mean SBP achieved over a median of 3.40 years in the intensive treatment group was 14.2 mmHg lower than in the standard group. In the intensive treatment group, WML progression was 0.54cm^3 (95% CI, 0.20 – 0.87) lower but TBV loss was 3.7cm^3 (95% CI, 1.1 – 6.3) higher than in the standard treatment group. Mean WML volume increased by 0.92 cm^3 (95% CI, 0.69 – 1.14) in the intensive treatment group and 1.45 cm^3 (95% CI, 1.21 – 1.70) in the standard treatment group. Mean TBV decreased by 30.6 cm^3 (95% CI, 28.8 – 32.3) in the intensive treatment group and 26.9 cm^3 (95% CI, 24.8 – 28.8) in the standard treatment group.

Cautions

Only 67% of trial participants completed the follow-up MRI. Different MRI scanners with differing magnet strengths may have impacted the standardization of volume measurements across the study. Clinical implications of these anatomical differences were determined in only a small number of participants, with 23 adjudicated as MCI and six adjudicated as probable dementia. These participants had significantly larger increases in WML volume and significantly larger decreases in TBV compared to participants without cognitive impairment. A defined threshold for WML volume change associated with development of MCI or dementia, either an absolute threshold or change over time, was not determined. It remains unclear whether the between-group difference in TBV is secondary to loss of brain tissue in the setting of hypoperfusion or another factor, such as hydration status, which could be impacted by antihypertensives, particularly diuretics.

Implications

Targeting an SBP < 120 mmHg in hypertensive community-dwelling adults may represent an opportunity to decrease WMLs, a risk factor for cognitive decline and dementia, but the results of this SPRINT substudy remain hypothesis generating given that this study was not powered to detect differences in clinical outcomes. Routine measurement of cerebral WML volume or TBV to monitor effectiveness of antihypertensive therapy is not recommended.

A comprehensive review of dementia identifies 12 modifiable risk factors and estimates 40% of cases are potentially preventable[7]

Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413-46. https://www.thelancet.com/article/S0140-6736(20)30367-6/fulltext

Background

The 2017 Lancet Commission on Dementia Prevention, Intervention, and Care reconvened to identify new evidence for advances in dementia prevention, intervention, and care.

Methods

Systematic reviews and meta-analyses were conducted for three newly identified risk factors for dementia. Data from the 2017 commission were used for the nine previously identified risk factors. As in 2017, the authors calculated the population attributable fraction (PAF), which is the fraction of all cases in a population that is attributable to a specific risk factor. The calculation was made based on risk factor prevalence and the strength of its association (based on meta-analysis) with an adjustment for risk factors that clustered together.

Findings

Three new potentially modifiable risk factors (with their PAF) were identified – traumatic brain injury (3%), air pollution (2%), and alcohol consumption > 21 units per week (1%). The nine risk factors identified in 2017 were hearing loss (8%), less education (7%), smoking (5%), depression (4%), social isolation (4%), hypertension (2%), physical inactivity (2%), obesity (1%), and diabetes (1%). Together, these 12 modifiable risk factors account for around 40% of worldwide dementias. Specific actions to address these risk factors, intervention, and care were also reviewed.

Cautions

A causative link is required for an intervention to lead to a reduction in dementia incidence. Given the lack of evidence from RCTs, this link was assumed between dementia and the identified risk factors, based on fulfillment of causality criteria by observational data. The risk factors are known to overlap, and it cannot be established from non-multivariate analysis what cumulative effect having multiple risk factors confers. That is, the presence of multiple risk factors may confer risk that is less than, equal to, or greater than the sum of their parts.

Implications

This article identifies three new risk factors for dementia for a total of 12 risk factors, all of them actionable at some level of health or governmental systems. Targeted interventions across the life course may help prevent or delay the development of dementia. The yield of such interventions may be largest in low- and middle-income countries due to the presence of a higher frequency of identified risk factors in those areas of the world.

A substantial number of Alzheimer's dementia cases may be secondary to a novel disease mechanism[8]

Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain. 2019;142(6):1503-27. https://academic.oup.com/brain/article/142/6/1503/5481202

Background

Autopsy studies have revealed that the aged human brain often has multiple comorbid pathologies. Transactive response DNA binding protein of 43kDa (TDP-43) proteinopathy in limbic brain structures has been associated with substantial cognitive impairment that mimics Alzheimer's disease clinical syndrome (ADCS). The frequency of this proteinopathy in adults over age 80 has raised interest in further describing this clinical entity. This paper proposes new terminology: limbic predominant age-related TDP-43 encephalopathy (LATE), to describe an increasingly recognized disease in older adults with dementia syndrome.

Methods

A working group reviewed the medical literature pertaining to LATE, including cognitive manifestations, neuroimaging, potential disease burden, and genetics. The goal was to develop guidelines for the autopsy diagnosis and staging of LATE neuropathological change (LATE-NC).

Findings

The prevalence of LATE-NC is estimated to be over 20% in adults over age 80. Genetic risk factors for LATE have some overlap with Alzheimer's disease and frontotemporal dementia. For routine autopsy evaluation of LATE-NC, the authors propose a staging system based on anatomical distribution of the proteinopathy. Stage 1 involves the amygdala, stage 2 the hippocampus, and stage 3 the middle frontal gyrus. LATE-NC and Alzheimer's disease neuropathological changes (ADNC) are often comorbid and those with both tend to have a faster decline and more severe cognitive impairment. The presence of more gradual clinical decline compared to patients with pure ADNC or preserved verbal fluency despite profound deficiency in word list delayed recall should raise suspicion for LATE-NC. The authors estimate that the disease burden of LATE is approximately half that of ADNC and predict that LATE will represent an increasing burden in the future given our growing population of older adults.

Cautions

Given the comorbid pathologies of amyloid plaques and tauopathy, it is difficult to make a statement on the sole influence of LATE-NC in the pathophysiology of dementia. These diagnostic criteria should be considered preliminary and were developed mainly to catalyze research and raise awareness of this entity.

Implications

LATE-NC augments our understanding of the complexity of the pathophysiology of dementia syndromes. Clinicians now have a new theory to consider and to communicate to patients and their families when assessing and differentiating dementia syndromes at the bedside.

A research framework defines Alzheimer's disease based on biomarkers rather than clinical criteria[9]

Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia. 2018;14(4):535-62. https://alz-journals.onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2018.02.018

Background

In 2011, the National Institute on Aging and Alzheimer's Association (NIA-AA) created diagnostic criteria for the MCI and dementia stages of Alzheimer's disease (AD) based on clinical symptoms. A stage called "preclinical AD" was also defined to identify those with abnormal AD biomarkers but without overt symptoms. Advances in the understanding of AD as a continuum and the role of biomarkers prompted an update in 2018.

Methods

The NIA-AA working group updated the 2011 guidelines with the objective of creating a scheme for defining and staging AD across its entire spectrum. The recommendations were intended as a research framework rather than for general clinical practice.

Findings

The research framework presented shifts the definition of AD from a syndromal to a biologic construct, such that AD refers to an aggregate of neuropathologic changes defined in living persons by biomarkers. The authors propose that in the absence of biomarkers, the term "Alzheimer's clinical syndrome" should be used rather than the term "probable AD," which was recommended in the 2011 guidelines. The biomarkers of β-amyloid plaques (A), fibrillar tau (T), and neurodegeneration or neuronal injury (N), now form the AT(N) classification scheme. Each biomarker can be measured by CSF analysis or by neuroimaging. Based on a biomarker category being positive or negative, eight possible permutations become possible (table 1). Amyloid biomarkers likely represent the earliest evidence of AD neuropathologic change while both amyloid and tau deposits are required to fulfill neuropathologic criteria for AD. Therefore, the authors use the term "Alzheimer's pathologic change" for A+T-(N) individuals and reserve "Alzheimer's disease" for A+T+(N) individuals. Clinical phenotypes no longer contribute to the definition of AD in this scheme.

Cautions

This research framework does not eliminate the need for research without biomarkers, which will continue to provide valuable information about risk factors for clinically defined syndromes. Current biomarkers are not widely available in clinical settings and are either expensive or invasive making this framework difficult to apply in a clinical setting.

Implications

Viewing AD as a biologic construct may facilitate more accurate characterization and understanding of the sequence of events that lead to cognitive impairment. It allows us to consider how we would intervene in the pre-clinical phase of the disease, in patients without symptoms but with positive biomarkers. As a research framework, the AT(N) system creates a common language for hypothesis generation and testing. The ongoing work to develop new biomarkers (e.g., TDP-43, α-synuclein, and vascular biomarkers) and less expensive and invasive forms of existing biomarkers, may further increase the utility of this classification system.

Table 1. Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

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