

Revisiting the Concept of Multi-Infarct Dementia: The Continuum of Vascular Cognitive Impairment



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This is to acknowledge that Belinda Vicioso, MD has disclosed that she does not have any financial relationships or other relationships with commercial concerns related directly or indirectly to this program. Dr. Vicioso will not be discussing off-label use of FDA-approved drugs.

Purpose:

Dementia is the leading cause of dependence and disability among the geriatric population worldwide. Average life expectancy increases, the prevalence of dementia and its associated costs are expected to rise exponentially.

As we think about the causes of dementia, most of us are familiar with the term “Multi-Infarct Dementia” and have been taught that vascular brain injury is a less common cause of cognitive impairment than AD. Over the past decade, however, our understanding of the continuum of vascular cognitive impairment that culminates in the dementia syndrome has changed.

Educational Objectives:

- 1) Understand the distinction between Major and Mild Neurocognitive Disorder
- 2) Understand that the impact of cerebrovascular risk factors on the brain begins in middle age and increases the risk of the dementia syndrome later in life
- 3) Understand that the failure of dementia treatment trials to date may be a reflection of pathological overlap
- 4) Realize that patients with vascular cognitive impairment may present with executive dysfunction and slowed, shortened gait rather than memory loss
- 5) Manage risk factors and propose treatment options based on emerging evidence and time- to benefit- considerations

Biosketch:

Dr. Vicioso is currently a Professor of Internal Medicine in the Division of Geriatric Medicine at the University of Texas Southwestern Medical Center, where she has been a faculty member since 1995. She graduated from Instituto Tecnologico de Santo Domingo, Dominican Republic, with Honors in 1979. Residency at St. Francis Medical Center in Trenton, NJ and a Fellowship in Geriatric Medicine at the University of Pennsylvania Medical School followed by a Fellowship at DHHS in Washington, DC. Her clinical interests involve memory loss, cognitive impairment and health care policy.

INTRODUCTION

Dementia is the leading cause of dependence and disability among the geriatric population worldwide. Average life expectancy increases, the prevalence of dementia and its associated costs are expected to rise exponentially.

As we think about the causes of dementia, most of us are familiar with the term “Multi-Infarct Dementia” and have been taught that vascular brain injury is a less common cause of cognitive impairment than AD. Over the past decade, however, our understanding of the continuum of vascular cognitive impairment that culminates in the dementia syndrome has changed.

DEFINITIONS

The nomenclature of cognitive impairment has changed. In 2013 the Neurocognitive Disorders Work Group of the APA’s Diagnostic and Statistical Manual of Mental Disorders Task force recommended to the DSM 5 a new framework for the classification of cognitive syndromes into “Major Neurocognitive Disorder” and “Mild Neurocognitive Disorder”.

DSM 5
<ul style="list-style-type: none">• Major neurocognitive disorder<ul style="list-style-type: none">– Impairment in cognitive realms with loss of independence– Specify whether “due to AD, LBD, vascular disease”– Mild neurocognitive disorder<ul style="list-style-type: none">– Patient with measurable cognitive deficits but able to engage in compensatory behaviors to help maintain independence and perform ADL’s

This new classification noticeably and controversially omits the word “dementia”. Writing for the work group, Mary Ganguli [1] explained that in discarding the well-known term, the intention was to subsume all entities known as dementia under a broader category allowing for the realization that NCDs can span several age groups and etiologies. Thus, in patients who have impairment in several cognitive realms such as complete attention, language, executive function, perceptual motor problems, social cognition and who have experienced a **loss of independence**, we now speak of “Major Neurocognitive Disorder “due to “Alzheimer’s Disease” or “Vascular Disease”. Patients who have measurable cognitive deficits but are otherwise **able to engage in compensatory behaviors** to help maintain their independence are said to have “Mild Neurocognitive Disorder “.

The distinction between “Major” or “Mild” is an inherently arbitrary one but the intent is to encompass a more diverse group of entities, including those affecting younger patients with traumatic brain disorder or HIV. For all patients, whether or not the etiology is known, reserving the term “dementia” for the major syndrome and the functional disability it entails helps protect patients at the mild level from inappropriate discrimination or legal consequences. [2]

EPIDEMIOLOGY

Major Neurocognitive Disorders , NCD's, causing the dementia syndrome affect as many as 10% of those over age 65 and 50% of individuals over the age of 85. More specifically, the prevalence of dementia has been said to double with every five year increase in age.[2]

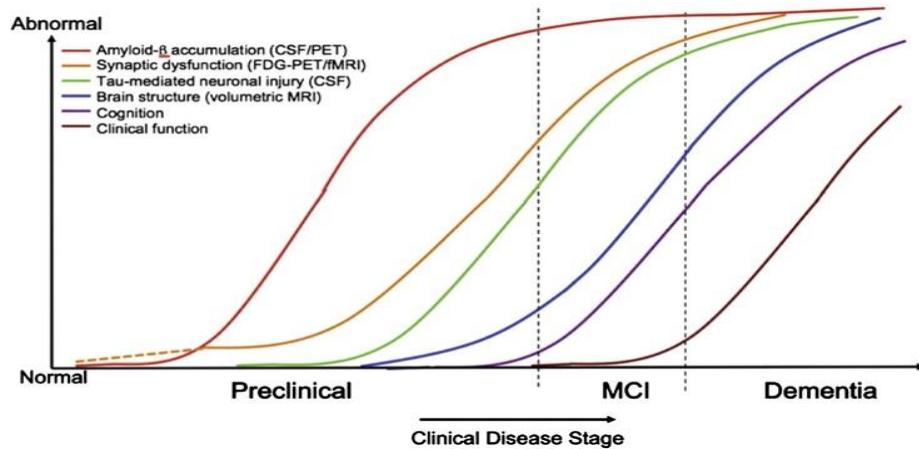
It is estimated that by the year 2025, there will be 10 million cases of dementia; by 2050, there may well be 20 million cases.

ETIOLOGY

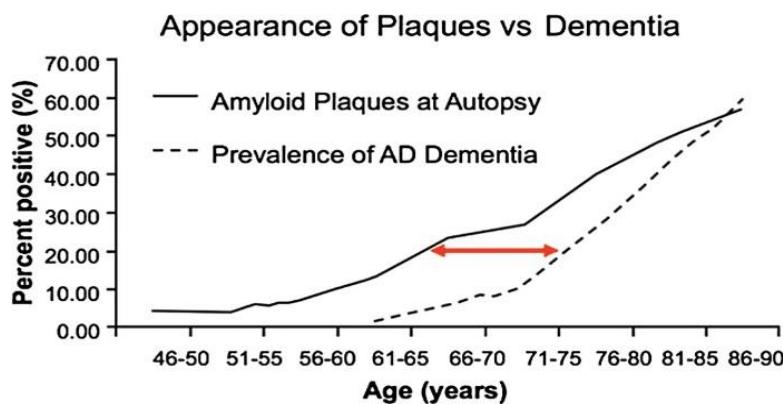
In the United States, Alzheimer's disease is the single most common cause of the dementia syndrome. Vascular brain injury, the frontotemporal degenerative disorders, and Lewy body disease make up the other major pieces of the dementia pie. Until quite recently, distinctions among these various causes of the dementia syndrome were made using clinical criteria that favored the diagnosis of Alzheimer's disease. Originally developed to distinguish between AD and vascular disease, they had been used universally, and perhaps artificially, for case definition in population studies and drug trials.

In the past ten years, the spate of negative - or clinically insignificant- results of dementia treatment trials, has led researchers to posit that these diagnostic criteria are too insensitive and that the diagnosis is being made too late and too “downstream”.

Seeking to better define clinical phenotypes and integrate biomarkers into the diagnostic process, the International Working Group(IWG-2) for New Research Criteria for the Diagnosis of Alzheimer's Disease and the US National Institute on Aging-Alzheimer's Association, MIA-AA, have re-described AD as a clinical biological syndrome that can be recognized *in vivo* before the onset of the dementia syndrome by a specific core clinical phenotype comprising an amnestic syndrome and supportive evidence from biomarkers reflecting the presence of AD pathology via functional imaging.

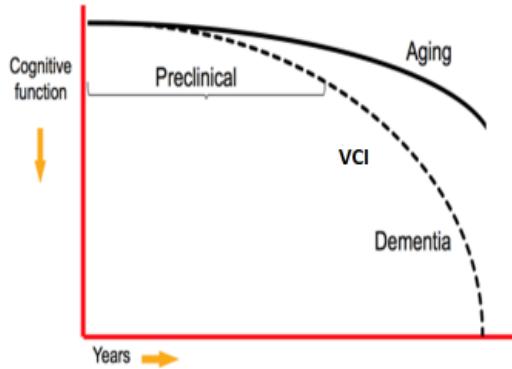


Largely envisioned as a framework for research, a key point in this new conceptualization of Alzheimer's disease is that it occurs along a **CONTINUUM** of severity. Thus, especially in the context of prevention trials of familial AD, we now speak of pre-dementia as a period of gradual accumulation of pathological changes before the onset of measurable cognitive changes.



A similar continuum concept has been proposed for the spectrum of brain disease that culminates in the syndrome of vascular dementia. Thus, in patients with a history of vascular risk factors, the NIND is now encouraging the use of terms like **Vascular Brain Injury** and **Vascular Cognitive impairment** to describe precursor states that include asymptomatic brain infarctions and white matter hyper intensities detected by MRI. As in the AD paradigm, the implication is that the impact of cerebrovascular risk factors on the brain begins in middle age and additively increases the risk of the dementia syndrome later in life.

VASCULAR BRAIN DISEASE



But this idea of diagnostic reductionism--AD versus VaD --may also be something we need to put to rest. Indeed, multiple studies show that cerebrovascular brain injury, neurofibrillary tangles and neuritic plaques, tauopathy, beta amyloid deposition and Parkinson's changes like Lewy bodies or alphasynucleinopathy often coexist especially in the older old.

In a large, community based prospective study of prevalent and incident dementia,[3] all brains of individuals dying from ages 70-103 in the United Kingdom went to necropsy.

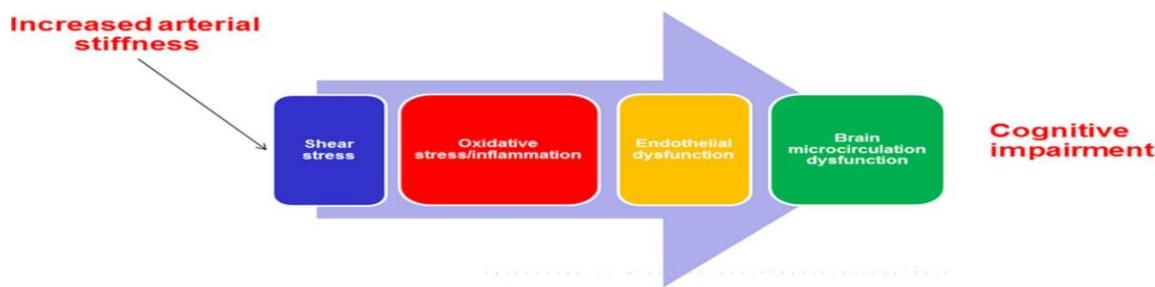
Neuropathological examination was carried out without knowledge of clinical or interview data. Median age at death was 85 years for men and 86 years for women. Dementia was present in 100 (48%) subjects of whom 64% had features consistent with AD. However, 33% of the 109 non-demented subjects had equivalent densities of neuritic plaques. Researchers report that degrees of neurofibrillary pathology: plaques and tangles were found in 61% of demented and 34% of non-demented individuals. Unexpectedly, vascular lesions were equally common in both groups, although the proportion with vascular pathology was higher in the demented group (46% compared to 33%). Cerebrovascular disease (78%) and Alzheimer's type pathology were equally common and often coincident.

Another landmark study further illustrates this correlation. In the Nuns Study, [4]David Snowdon collected cognitive data, including early autobiographical essays, from a total of 102 college educated women aged 76 through 100 who lived in convents in the United States. At autopsy, he quantified lacunar and larger brain infarcts along with senile plaques and tangles. He found that among the 61 participants who met the criteria for AD, those with brain infarcts had poorer cognitive function and a higher prevalence of the dementia syndrome than those without infarcts. Participants with lacunar infarcts in the basal ganglia, thalamus or deep white

matter had an especially high prevalence of the dementia syndrome compared to those without infarcts.[4]

PATHOPHYSIOLOGY

With its rich vascularization and low resistance to flow, the brain is particularly susceptible to cardiovascular dynamics. Recently, researchers have sought to explain the spectrum of common vascular pathology as one of arterial stiffness leading to shear vessel stress by arterial wave propagation during systole. In the low impedance environment of the brain, this arterial stiffness exposes its microvasculature to damaging flow. This in turn causes oxidative stress and inflammation which lead to endothelial dysfunction and ultimately results in dysfunction and remodeling of the microcirculation.



[5]

Thus, several pathological entities are thought to contribute to the spectrum of vascular brain injury and vascular cognitive impairment. Large artery infarctions and small artery infarctions that are often silent, lacunas and white matter hyper intensities often occur simultaneously and, even in younger cohorts like the Framingham Third-Generation Cohort Study, predict cognitive impairment.[6],[7]. Going beyond arterial stiffness, the most common arrhythmia in the elderly, atrial fibrillation is associated to silent brain infarcts but not white matter hyperintensities, WMH's, suggesting that embolic mechanisms causing infarction may be different from the mechanisms underlying WMH's.

Vascular brain injury can also be caused by watershed infarction in the setting of profound hypotension or shock or hypoxic ischemic encephalopathy. These events and the associated cognitive impairment and can be catastrophic and if extensive and disabling can fall under the rubric of Major Neurocognitive Disorder.

CLINICAL PRESENTATION

The mild and major neurocognitive disorders related to vascular brain injury result from a dysfunction of neurons subserving cognition that often goes unrecognized. In clinical practice, patients are usually referred to clinics and specialists according to their presenting complaint. Patients with CKD go to a nephrologist; those with CAD see a cardiologist. Patients with acute focal neurological signs are sent to the ED and seen by a stroke team. These care patterns distort the frequency and spectrum of vascular brain injury. Thus, signs of cognitive impairment often go unnoticed even in patients known to have significant involvement of other target organs such as the heart, kidney or eyes. Opportunities for better risk reduction and identification of covert functional decline affecting both patient safety and re-admission rates are lost. Silent but clinically significant vascular brain injury is also common in hospitalized patients with delirium, hypotension, organ failure or disproportionate loss of function.

Classically, the **Hachinski Ischemic Score[8]** has been used to differentiate between AD, vascular dementia and 'mixed' dementia. Autopsy studies show that the best cut-offs are \leq to 4 for AD, and \geq seven for vascular dementia. With a sensitivity of 89.0% and a specificity of 89.3%, the best HIS items distinguishing vascular dementia from AD are stepwise deterioration, fluctuating course, HTN, history of stroke and focal neurological symptoms. Only stepwise deterioration and emotional incontinence distinguish vascular dementia from mixed and only a fluctuating course and history of stroke distinguish AD from mixed.

Hachinski ischemic score

Feature	Value
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
Hypertension	1
History of stroke	2
Associated atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

A high score (≥ 7) suggests vascular dementia, while a low score (≤ 4) suggests Alzheimer disease.

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On the other side of the continuum, mild vascular cognitive impairment can present variably depending on the location and number of injuries. The most often described phenotype is one of **executive dysfunction** with impaired judgement or impaired ability to make decisions plan or organize complex activities of daily living. This is different from AD - predominant mild

cognitive impairment, where memory loss leads the way. In addition, individuals with vascular cognitive impairment can have difficulty with motor function especially slow gait and poor balance. Gait evaluation of a patient with otherwise silent basal ganglia involvement may reveal a slower, almost Parkinsonian gait with decreased arm swing and shorter steps.

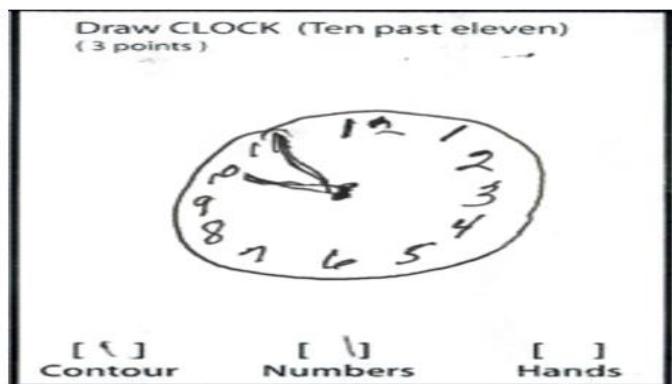
These findings have lead researchers to propose a “**motoric cognitive risk syndrome**” as a pre dementia finding. In a study appearing in Neurology in 2014[9], authors reported on a prevalence analysis of individual data from 26,802 adults, mean age 71.6 without dementia or mobility-related disability from 22 cohorts in 17 countries. They identified slowed gait in 4,812 patients and found that its presence predicted onset of the dementia syndrome six to eight years later. Recently, researchers have proposed that in large population studies, the presence of MRC in individuals with MMSE > 28 could be used as a preclinical predictor of incident dementia in the way that more expensive PET imaging is being used in limited research settings now.

DIAGNOSIS

Cognitive testing

At an individual level, cognitive testing allows for a closer probe of intellectual function. In general, multi-realm tests like the MMSE and the Montreal Cognitive Assessment are insensitive to clinically significant cognitive changes seen patients with vascular disease. [10]

A **clock drawing test, CDT** is easy to do and sensitive to the executive dysfunction seen in the non-AD cognitive disorders. One study comparing AD patients with VaD showed that the VaD group had lower scores and was especially challenged by hand placement[11]. The clock drawing is also a useful screen of ability to perform important complex activities of daily living such as medication adherence. [12]



The clock drawing test is part of the **Mini-Cog**, a useful cognitive screen that we teach all our students and residents.[13] Patients with vascular cognitive impairment will often have preserved delayed recall memory but difficulty completing the clock. In patients who are unable to draw a clock because of vision or motor deficits or lack of education, the “Fototest” may be a comparable option. On this test, they can recall the six objects shown but may have trouble making categorical lists. [14]



[14]

Brain imaging

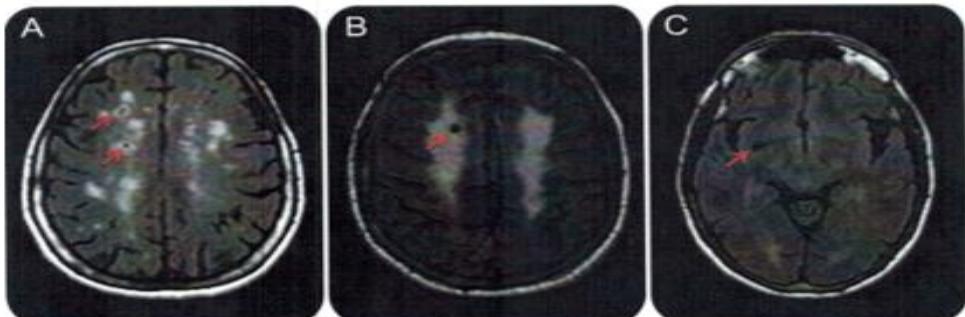
Brain imaging in dementing illnesses has undergone revolutionary changes in the ten years with the increasing availability of a dizzying array of new and very expensive techniques. Despite the proliferation of these sophisticated modalities, presently, neuroimaging alone cannot tell us whether a patient has a disorder of cognition or not. Uniquely, the diagnosis of cognitive impairment is a clinical one based on history and the findings of physical and cognitive testing. Imaging modalities like CT or MRI can rule out structural lesions such as brain tumors, abscesses, strokes or hematomas but the diagnosis of the dementia phenotype can only be made based on clinical findings.

Once the clinical diagnosis of cognitive impairment has been made, the role of imaging in the identification of its primary etiology --taking into consideration the likelihood of overlap --is very much a function of the clinical picture and diagnostic intent.

MRI is a very sensitive descriptor of vascular brain injury. Even with the advent of more precise imaging variations, researchers are struggling to clarify the clinical significance of the changes noted commonly in the subcortical white matter and periventricular matter.

A large number of cognitively healthy individuals develop these WMH's as they age. Over decades, these changes have been associated with increased risk of the dementia syndrome [15]but the exact time course, preventability and reversibility of these events remain unclear.

Figure Imaging markers of cerebrovascular damage



(A) Small subcortical lesions (arrows) with cavities and surrounding gliosis are probably chronic infarcts. (B) Subcortical lesions within areas of confluent hyperintensity are cystic in appearance and are also likely infarcts (arrow). (C) Intraputaminal lacunes occur lateral to the anterior commissure and are not infarcts (arrow), but their etiology is unclear and vascular disease may be a contributor.

As part of the Oregon Brain Health Study, Lisa Silbert and colleagues have been following a cohort of cognitively healthy elders since 1989. She has found that the progression of total and periventricular white matter intensity volumes are better predictors of persistent cognitive impairment than baseline WMH burden. [16]

At the Dallas Heart Study, imaging markers of subclinical atherosclerosis are associated with WMH scores. Young individuals with higher marker burden had lower Montreal Cognitive Assessment test scores than those that did not. [17]

In all patients, included the middle aged, white matter hyper intensity changes leading to cognitive impairment appear to be accelerated by risk factors for small vessel CVD such as hypertension, smoking, DM, atrial fibrillation and hyperlipidemia and metabolic syndrome.[18]

TREATMENT

Risk factor modification

The pace and stealth of the continuum of vascular brain disease and associated cognitive impairment may lend itself to treatment opportunities.

In recognition of the contribution of vascular brain injury to cognitive impairment syndromes, the American Heart Association and the American Stroke Association have called for an organized approach to identification of risk factors and determination of whether their modification can ameliorate their impact on the prevalence and incidence of the dementia syndrome.

The Hypertension in the Very Elderly Trial, HYVET, and enrolled patients aged 80 or older with hypertension and normal MMSE's. It was stopped at prematurely at the second interim analysis after treatment to blood pressures lower than 140 mmHg resulted in a reduction in stroke and mortality. The rates of incident dementia –as defined by a drop of more than three points in one year or a MMSE of <24 were not statistically different but mean follow-up was only of 2.2 years. More recently, authors of the SPRINT[19] study which was also stopped prematurely, reported that lowering BP to a SBP of less than 120 mmHg compared with a systolic BP of less than 140 mmHg resulted in significantly lower rates of fatal and non-fatal major cardiovascular events among elders, 30% of whom were frail, over the age of 75. Over the study's abbreviated course, there was no difference in the scores of the study's global measure of cognition, the Montreal Cognitive Assessment. Interestingly, however, both treatment groups had a median score of 22.0 on the MoCA with 25 being suggested cut-off for the test. This may be a reflection of silent vascular brain burden in the hypertensive study subjects. Further information from this study of community dwelling elders, many of whom were Parkland patients, is yet to come. A sub study, SPRINT MIND, added serial MRI's to cognitive testing and is examining outcomes such as all cause dementia and cognitive and daily function.

In a Cochrane review update published this year, investigators found no good evidence that statins given in late life to individuals at risk of vascular brain disease prevent cognitive decline or ameliorate the features of the dementia syndrome. Mean follow-up of both RCT's included was 3.2 in one and 5 in another. [20]

Cholinesterase inhibitors and memantine

There is no evidence that cholinesterase inhibitors or memantine help to prevent the progression of vascular dementia. Both agents have very small beneficial, clinically measurable effect (2.97 to 3.2 points on a scale of 100) on cognitive function and functional decline measured at 6 months in patients with moderate to severe AD. This small effect was not clinically detectable for memantine in patients clinically diagnosed with vascular dementia.

Structured care goals

Treatment of the vascular cognitive spectrum should be individualized and directed to specific goals of care. In the widely heterogeneous geriatric population ranging from the very active to

The very frail, lag time to benefit – which has been discussed in this forum by Dr. Makam -- and life expectancy should be taken into account when decisions to treat or forgo treatment are being considered. Web sites like E prognosis [21] or, for the nursing home residents, the Porock index, [22] can help busy primary care providers and subspecialists formulate benefits versus harms discussions that go beyond age considerations alone.

It is also important to remember that many of our most cited RCT's have not been designed to ascertain outcomes that are clinically important to older patients, including cognition. Thus, the extrapolation of treatment decisions from healthier populations to frail older persons, especially those with known generalized vascular disease is fraught with the potential for underestimation or over estimation of benefits and harms.

Prevention

In addition to the effect of vascular brain changes, gray matter decline results from neural shrinkage and neuronal loss. These changes are detectable with MRI as volumetric declines in subcortical regions and throughout the cortical mantle. Although volumetric decline is a common aspect of aging, the rate and degree of decline is highly variable across regions of the brain and between individuals. Furthermore, differences in lifetime exposures such as years of education or physical activity have been associated with gray matter decline more than with advancing age.

Brain aging thus, can be conceptualized as comprising 2 mechanisms, the inevitable and universal effects of advancing age and the effects resulting from a lifetime of exposures such as disease, a healthy lifestyle and enriched environments. The culmination of a lifetime of genetic, developmental and lifetime exposures produces large variation in the physiological age of our brains [19]

Recently, there have been reports that population rates of dementia and cognitive impairment are declining.

Selected Recent Studies of the Dementia Epidemic				
Study	Outcome	Data Source	Key Findings	Factors
Schrijvers et al. (Rotterdam) ³	Incidence of dementia	Population-based cohort ≥55yr of age in 1991, extended in 2000	Incidence rate ratios (6.56 per 1000 person-yr in 1990 vs. 4.92 per 1000 person-yr in 2000)	Higher educational level, reduction in vascular risk, decline in stroke incidence
Qiu et al. (Stockholm) ⁴	Prevalence of DSM-III-R dementia*	Cross-sectional survey of people ≥75yr of age, 1987-1989 and 2001-2004	Age-and sex-standardized dementia prevalence (17.5% in 1987-1989 vs. 17.9% in 2001-2004); lower hazard ratio for death in later cohort suggests decreased dementia incidence	Favorable changes in risk factors, especially vascular risk; healthier lifestyles
Matthews et al. (England) ^{5†}	Prevalence of dementia in 3 regions	Survey interviews of people ≥65yr of age, 1989-1994 (in CFAS I) and 2008-2011 (in CFAS II)	Dementia prevalence (8.3% in CFAS I vs. 6.5% in CFAS II)	Higher educational level, better prevention of vascular disease
Satizabal et al. (United States) ⁶	Incidence of dementia	Framingham Heart Study	Dementia incidence over four epochs declined 44% relative to first epoch.	Higher educational level; more BP and more lipid lowering agents

As we think about prevention of cognitive impairment, three studies are worth noting.

In the United Kingdom, the Cognitive Function and Ageing Study (CFAS) I and II were carried out between 1989 and 1994 and 2008 and 2011, respectively. Each contained a sample of more than 7500 community dwelling individuals over the age of 65. Authors reported dementia prevalence rates of 8.3 in CFAS 1as compared with 6.5% in CFAS II. Researchers concluded that later cohorts have a lower risk of dementia than those born earlier perhaps because of higher education levels and better prevention of vascular disease. [23]

Here in the United States, earlier this year, using data from the Framingham Heart Study, Saitzabal and colleagues also reported on “robust evidence” of this decline in dementia rates. They noted a 20% decrease in incidence each decade over the course of three decades. Adjustment for the Framingham Stroke Risk Profile score and its components did not entirely explain the decline.[24] Still, the temptation is to attribute this change in population rates to better education and life experiences, healthier life styles and risk factor modification. [24]

Finally, also this year, Yaakov Stern and colleagues reported on the intriguing relationship between education and physical activity. Cortical and subcortical gray matter brain volumes were calculated from 331 healthy adults in Montreal (age range 19-79). They found that the difference between chronological brain age and actual brain age was predicted by education and self-reported measures of physical activity. Brain age decreased, for instance by .95 years for every year of education and by .58 year for every flight of stairs climbed daily. Changes in brain volume were largely dictated by changes noted in the temporal and subcortical regions. Researchers did not comment on the presence of concomitant vascular brain lesions. [25]

CONCLUSIONS

- 1) The nomenclature of cognitive impairment has changed
- 2) The failure of treatment trials to date may be a reflection of pathology overlap and the challenge of diagnostic parsimony
- 3) Vascular brain injury is the second most common pathological finding in patients with the dementia syndrome and an important contributor to most dementia phenotypes.
- 4) There is a spectrum of vascular brain injury that predates the diagnosis of the dementia syndrome
- 5) Unlike Alzheimer's Disease, it may not present with memory loss and is a common cause of executive dysfunction and gait disturbances
- 6) The diagnosis of cognitive impairment related to vascular brain injury is a clinical one that can be made using tools like the CDT
- 7) When available, serial MRI's displaying an increasing burden of WMH's and silent infarcts can help clinch the diagnosis
- 8) In those patients with little or no time to benefit, address functional problems including medication adherence to avoid excess morbidity and disability
- 9) There is mounting evidence of a decline in the incidence of the dementia syndrome
- 10) The reason for this is unclear but certainly makes for exciting research opportunities

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