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Featured Article

Mechanical stress related to brain atrophy in Alzheimer's disease

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Abstract

Background: The effects related to endogenous mechanical energy in Alzheimer's disease (AD) pathology have been widely overlooked. With the support of available data from literature and mathematical arguments, we hypothesize that brain atrophy in AD could be co-driven by the cumulative impact of the pressure within brain tissues.

Methods: Brain volumetric and physical data in AD and normal aging (NA) were extracted from the literature. Average brain shrinkage and axial deformations were evaluated mathematically. Mechanical stress equivalents related to brain shrinkage were calculated using a conservation law derived from fluid and solid mechanics.

Results: Pressure equivalents of 5.92 and 3.43 mm Hg were estimated in AD and in NA, respectively.

Conclusions: The calculated increments of brain mechanical stress in AD, which could be impacted by marked dampening of arterial pulse waves, may point to the need to expand the focus on the mechanical processes underpinning pathologic aging of the brain.

Keywords: Brain atrophy; Total brain volume; Alzheimer's disease; Mechanical stress; Fluid mechanics; Brain stiffness

1. Introduction

During evolution and through the external environment, all human body organs are constantly influenced by mechanical forces. In the brain, cellular process and tissue structures are continuously affected by mechanical stress, e.g., through gravity [1]. Fluid-solid mechanical interactions constantly occur between brain parenchyma and cerebral blood and cerebrospinal fluid (CSF) [2]. These intracranial pressures interacting with brain compartments are confined within the progressively rigid structure of the skull. A variety of brain diseases alter intracranial pressure dynamics that may, in turn, result in physical alterations in the brain. However, the extent to which mechanical dynamics influence brain structure still remains unclear.

Morphologic brain shrinkage is largely investigated using structural magnetic resonance imaging (MRI), which differentiates Alzheimer's disease (AD) from normal aging (NA) subjects on measures of global and regional brain volume, tissue morphology, and rate of atrophy [3]. By the time of diagnosis of the late-stage syndromal AD dementia, statistically significant atrophy is usually found throughout wide neocortical and subcortical regions with a relative sparing of primary sensory and motor cortices [4]. Chronically

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progressive neuronal and synaptic loss are the main pathologic substrates of brain atrophy [5].

Interestingly, beyond volume and neuronal depletion, brain atrophy has been correlated to alterations in brain mechanical properties, both in AD and NA. Magnetic resonance elastography (MRE) estimates the stiffness of tissues by imaging their responses to sound (shear) waves propagated through the body. MRE is useful for characterizing and mapping brain viscoelastic properties and it has shown the reduction of brain stiffness in NA [6] and specially in AD [7]. As a result, it might indicate a role of the chronic impact of classical mechanics in brain shrinkage due to neurodegeneration and other pathophysiological molecular and cellular mechanisms.

In the past, the effects related to endogenous mechanical energy [1] in AD pathology have been widely overlooked in postulated hypotheses such as mono-linear, mono-system amyloidocentric molecular pathway models (the amyloid cascade theory [8] conceiving AD as a protein misfolding disorder) derived from reductionist transgenic animal mutation models that do not integrate principles of mechanics. The aim of this article was, therefore, to revisit an old hypothesis: the fact that mechanical principles play a key role in the pathogenesis of AD and dementia.

Applying principles of fluid and solid mechanics, the equivalents of mechanical stress associated with brain shrinkage in AD were estimated. Our hypothesis is that the biological cascade of neurodegeneration could be impacted and/or driven by cerebrovascular hemodynamic stress. This is an alternative or complementary hypothesis which is not aimed against other hypotheses but is rather integrative. Selecting AD as a primary model of a nonlinear dynamic, chronically progressive degenerative disease [9–11], equivalents of pressure related to brain atrophy were calculated using data from published studies that provide measures of volume and mechanical properties of the brain in AD, NA, and adulthood conditions. These results were compared with compatible measures of cerebrovascular hemodynamic stress. Assuming that these equivalents of pressure could be exerted by intracranial environment, we compared them with the measures of physiological intracranial dynamics attained from the literature.

2. Methods

2.1. Literature review and data retrieval

2.1.1. Brain volumetry

An overview of the methods used in this work is summarized in Fig. 1. As a first step, a review of the literature was performed to extract data of the total brain volume (BV) in AD, NA, and normal adulthood situations. We carried a MEDLINE/PubMed research of publications providing brain volumetric MRI data using the following keywords: "total brain volume," "brain volume," "Alzheimer," "aging," and "age." The actual number of studies including >50 participants and providing measures of total BV and total intracranial volumes (ICV) in AD, NA, and adulthood conditions were selected. Then, volumetric data attended from the literature search were compared with those from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort [12]. The ADNI population provides one of the largest groups of probable AD subjects with standardized

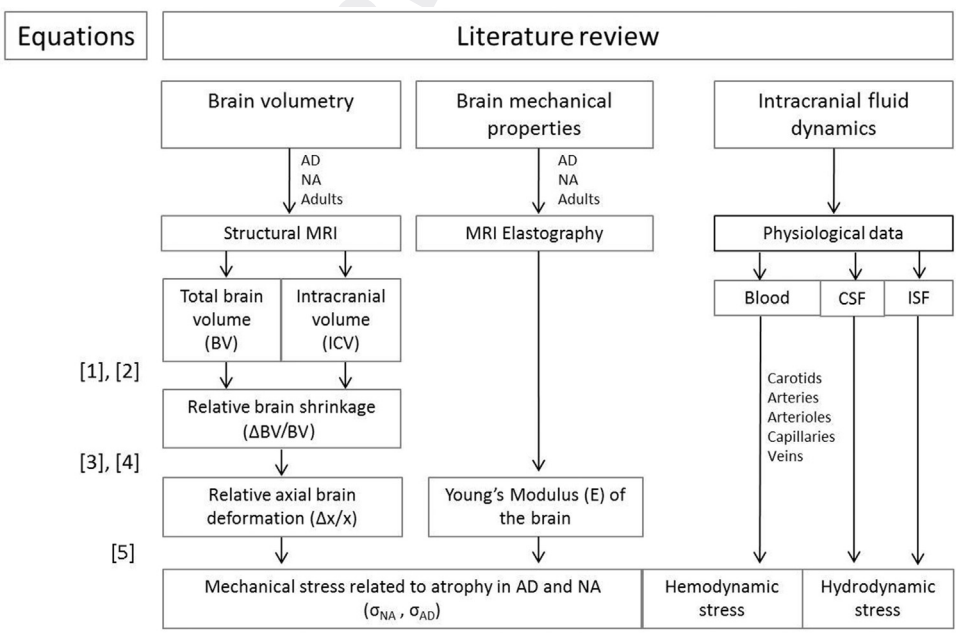

Fig. 1. Resume of the methods. Abbreviations: AD, Alzheimer's disease; NA, normal aging; MRI, magnetic resonance imaging; σ, mechanical stress; CSF, cerebrospinal fluid.