Alzheimer's & Dementia 11 (2015) 1358-1366

Featured Article

Combined Alzheimer's disease and cerebrovascular staging explains advanced dementia cognition

María Ascensión Zea-Sevilla[a,*], Miguel Angel Fernández-Blázquez[a], Miguel Calero[a,b], Pedro Bermejo-Velasco[c], Alberto Rábano[a]

[a]*Alzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health, Alzheimer Center Reina Sofia Foundation, Madrid, Spain*
[b]*Unidad Funcional de Investigación en Enfermedades Crónicas and CIBERNED, Instituto de Salud Carlos III, Madrid, Spain*
[c]*Hospital Universitario Puerta de Hierro, Neurology Unit, Madrid, Spain*

Abstract

Introduction: The absence of a consensus system for full neuropathological evaluation limits clinicopathological studies and comparability between laboratories. Combined staging for Alzheimer's type and cerebral vascular pathology may allow a better classification of cases for clinical and cognitive correlation.

Methods: Cognitive and postmortem neuropathological data were obtained from 70 brains donated to the Tissue Bank of the Centro de Investigación de Enfermedades Neurológicas (CIEN) Foundation according to recently developed staging schemes for Alzheimer's type and vascular pathology. Subjects belonged to a cohort of institutionalized patients with moderate or severe dementia and a mean follow-up period of 7 years.

Results: Cases were classified into three groups: Alzheimer's predominant (64.1%), vascular predominant (6.3%) and mixed pathology (29.6%). Significant differences were observed in Severe Mini-Mental State Examination and verbal fluency between the vascular predominant and the other groups of patients.

Discussion: The combination of scales measuring cerebral vascular and Alzheimer's type pathology allowed a classification of patients that reveals differences between groups in premortem cognitive features.

Keywords: Vascular changes; NIA; Neuropathological changes; Dementia; Staging system

1. Introduction

Alzheimer's disease (AD) is the main cause of dementia in our environment. Either as a single pathology or in combination with cerebrovascular disease, AD represents more than 75% of the etiology of dementia, with an estimated prevalence around 15% in the population older than 65 years [1,2]. Furthermore, the progressive aging of the population heralds an increased prevalence worldwide. Global estimates indicate that 113 million people will have developed dementia by 2050 [3].

The frequent occurrence of microvascular and small macrovascular lesions combined with AD-related pathology is a well-established phenomenon in the aging human brain [4]. In autopsy series, vascular pathology (VP) is present in 30–50% of elderly cases that also exhibit neurofibrillary tangles (NFT), amyloid-β (Aβ) deposits, and synaptic loss [5–11]. It is widely accepted that Alzheimer's type and cerebrovascular pathology may contribute simultaneously to cognitive decline in patients with so-called mixed dementia [12,13]. A possible synergistic pathogenesis of Alzheimer and vascular disease neuropathology could be a

*Corresponding author. Tel.: 0034 913852200; Fax: 0034 913852118.
E-mail address: mazea@fundaciocien.es

http://dx.doi.org/10.1016/j.jalz.2015.01.004
1552-5260/

new paradigm to advance research in prevention and therapy [14–16].

As occurs with other lesions that may present in combination with Alzheimer's pathology (e.g. Lewy bodies, argyrophilic grains), the presence of VP either results in the increase of the severity of cognitive decline in AD or is associated with lower burdens of Alzheimer's pathology in postmortem brains with dementia [17,18].

However, the status of mixed dementia, in terms of prevalence, morphological substrate, and clinical correlation, is highly dependent on the neuropathological criteria applied [19]. A new diagnostic scheme has been recently recommended for the neuropathological classification of Alzheimer's pathology [20,21]. To the previously considered features of neuritic plaque frequency [22] and Braak stage [23], a staging system for total Aβ burden [24] has been added. The combination of all three lesion types ("ABC system") yields a certain level of probability of clinical AD for each individual case. By contrast, the neuropathological assessment of cerebrovascular pathology has not met a comparable degree of consensus until present [12,25], due to the great heterogeneity of lesions and poor clinicopathological correlation [26].

A new evaluation system for cerebrovascular pathology has been also recently proposed that can be applied as a staging system [27]. In contrast to previous protocols, it focuses on brain regions most directly related to cognitive functions (frontal and temporal lobes, basal ganglia, and hippocampus) and evaluates conjointly vascular lesions with different etiology (e.g., hyaline sclerosis and amyloid angiopathy) though with a presumed similar impact on brain tissue integrity and function.

Validation of different cognitive profiles specifically associated with Alzheimer's and cerebrovascular pathologies would be clinically relevant. At present, while a loss of episodic memory is well-established as the main symptom of AD, cerebrovascular pathology is more likely to produce deficits in executive processes as a consequence of both lacunar infarcts and white matter lesions in subcortical frontal regions [28,29]. Furthermore, loss of verbal fluency in dementia, as revealed by a semantic fluency test like animal naming, is considered to reflect the actual deterioration of the semantic network rather than a deficit in the retrieval process and it exhibits ongoing deterioration with the progression of disease [30]. Nevertheless, although current evidence highlights that association between memory and semantic loss and AD is very strong, the relationship between VP and executive functions impairment is less consistent. This suggests that cerebrovascular disease has got the same degree of impact on executive functions as AD changes have on memory [31]. Similarly, previous studies show that comorbid vascular burden barely modifies the cognitive profile of AD, suggesting that once Alzheimer's pathology is largely spread throughout the cerebral cortex vascular disease has no significant additional effect on cognitive status [32].

The aim of this study is to apply new criteria for the postmortem evaluation of Alzheimer's and cerebrovascular pathology to a cohort of moderate to advanced dementia patients with a detailed clinical follow-up. Likewise, the cognitive and motor profiles associated with these staging systems are assessed.

2. Methods

2.1. Sample

Postmortem neuropathological data were obtained retrospectively from all brains (n = 70) donated to the CIEN Foundation Tissue Bank (CFTB) between June 2007 and June 2014. All brain donors were institutionalized at the Alzheimer Center Reina Sofía Foundation, Madrid, Spain, a center specifically dedicated to Alzheimer's patients with a diagnosis of moderate to severe dementia [33].

2.2. Clinical assessment

After obtaining informed consent, institutionalized patients entered a clinical follow-up program with six monthly evaluations. The assessment protocol included sociodemographic, personal history, neurological, cognitive and laboratory (biochemical and genetics) data. Two simple cognitive tests were used to avoid a floor effect on scoring: the Severe Mini-Mental State Examination (SMMSE) [34] and a task for verbal fluency (VF; animal naming in 1 minute). Neurological evaluation included a scale of motor assessment with a specific item for on-freezing (Motor Scales for Outcomes in Parkinson's disease [SCOPA], OnF) [35]. All tests were individually administered by neurologists and neuropsychologists with wide experience in dementia.

2.3. Neuropathological assessment

In all cases postmortem examination was limited to the cranial cavity, according to the brain bank protocol [36]. After fixation, a full neuropathological study was performed in the left half brain by obtaining 25 tissue blocks from cortical and subcortical brain regions. Neuropathological classification of cases was based on the examination of hematoxylin-eosin stained paraffin sections of all blocks, and immunostaining with a panel of antibodies (Aβ, tau AT100, alpha-synuclein, ubiquitin, and transactive response DNA binding protein 43kDa [TDP-43]) or solochromocyanine stain (myelin stain) in selected regions. Consensus criteria were used for disease diagnosis and staging.

Alzheimer's type changes were assessed following National Institute on Aging and Alzheimer's Association (NIA-AA) guidelines [21]. Accordingly, total amyloid stage ("A" in the "ABC system") was determined and classified along a 0–3 scale on the basis of immunohistochemistry for Aβ in the occipital isocortex, hippocampus, basal