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Featured Article

Cerebral amyloid angiopathy in Down syndrome and sporadic and autosomal-dominant Alzheimer's disease

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Abstract

Introduction: We aimed to investigate if cerebral amyloid angiopathy (CAA) is more frequent in genetically determined than in sporadic early-onset forms of Alzheimer's disease (AD) (early-onset AD [EOAD]).

Methods: Neuroimaging features of CAA, apolipoprotein (*APOE*), and cerebrospinal fluid amyloid-β (Aβ) 40 levels were studied in subjects with Down syndrome (DS, $n = 117$), autosomal-dominant AD (ADAD, $n = 29$), sporadic EOAD ($n = 42$), and healthy controls ($n = 68$).

Results: CAA was present in 31%, 38%, and 12% of cognitively impaired DS, symptomatic ADAD, and sporadic EOAD subjects and in 13% and 4% of cognitively unimpaired DS individuals and healthy controls, respectively. *APOE* ε4 genotype was borderline significantly associated with CAA in sporadic EOAD ($P = .06$) but not with DS or ADAD. There were no differences in Aβ040 levels between groups or between subjects with and without CAA.

Discussion: CAA is more frequently found in genetically determined AD than in sporadic EOAD. Cerebrospinal fluid Aβ40 levels are not a useful biomarker for CAA in AD.

Keywords: Cerebral amyloid angiopathy; Sporadic early-onset Alzheimer's disease; Autosomal-dominant Alzheimer's disease; Down syndrome; Neuroimaging; Cerebrospinal fluid biomarkers

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1. Introduction

Most cases of Alzheimer's disease (AD) are sporadic and caused by complex interactions between genetic and environmental factors. In approximately 5% of cases, AD can present clinically before the age of 65 years (early-onset AD [EOAD]) [1]. These patients frequently present with nonamnestic phenotypes and faster clinical decline than older sporadic AD cases [1]. In 0.1% to 0.5% of cases, AD is transmitted with an autosomal-dominant pattern of inheritance (autosomal-dominant AD [ADAD]) due to the presence of mutations in presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), or amyloid precursor protein (*APP*) genes [2]. Down syndrome (DS) is also recognized as a form of genetically determined AD, mainly caused by the *APP* gene triplication [2]. Despite the different genetic background, the AD neuropathologic findings in sporadic EOAD, ADAD, and DS are very similar [3,4].

Cerebral amyloid angiopathy (CAA) is a major cause of lobar intracerebral hemorrhage (ICH) in the elderly and is present in up to 90% of AD brains at autopsy [3]. Previous neuropathologic studies have suggested a more severe CAA in ADAD than in sporadic AD [4]. CAA in some *APP* mutations or duplication carriers drives the clinical presentation [4] and is also consistently observed in subjects with DS [5]. The modified Boston criteria for CAA (mBCAA)–related hemorrhage have been validated to attribute in vivo an ICH to CAA based on several neuroimaging features and are frequently used in clinical practice [6]. There are no previous studies systematically assessing the CAA neuroimaging features in DS and ADAD.

Amyloid β (Aβ)40 is the major form of Aβ deposited in the vessel walls in individuals with CAA. Low levels of Aβ40 and Aβ42 have been found in the cerebrospinal fluid (CSF) of subjects with sporadic CAA [7]. However, scarce and contradictory data are available about the CAA CSF biomarker profile in sporadic AD patients [8–10], and no previous studies have assessed this profile in DS or ADAD. Moreover, the apolipoprotein (*APOE*) ε4 genotype is a risk factor for both sporadic AD and sporadic CAA [11], as it increases Aβ deposition in both the parenchyma and blood vessels [12]. However, the effect of the *APOE* genotype in AD dementia within DS and ADAD is controversial, and there are no studies assessing the influence of the *APOE* genotype on CAA in ADAD or DS [13].

The differences in the CAA neuroimaging features and CSF biomarkers profile in the different forms of AD are, thus, not established. Our primary objective was to determine the CAA presence by assessing the fulfillment of the mBCAA and the CSF Aβ40 levels in three different AD populations (DS, ADAD, and EOAD). We hypothesized that patients with genetically determined AD would have more CAA neuroimaging and biochemical features than EOAD.

2. Materials and methods

2.1. Study design and participants

A total of 256 subjects were recruited from five centers: Hospital de Sant Pau, Hospital Clínic de Barcelona, and Barcelona Down Medical Center in Barcelona, Spain; and the Sanders-Brown Center on Aging in Kentucky, and the Down Syndrome Biomarker Initiative project in San Diego, USA. Four study groups were evaluated: EOAD, ADAD, DS, and healthy controls (HCs).

EOAD ($N = 42$): patients were recruited at the Memory Unit of Hospital de Sant Pau from the Sant Pau Initiative on Neurodegeneration (Barcelona SPIN cohort) [14]. We used the International Working Group-2 for AD with in vivo evidence of AD based on CSF biomarkers [2]. This group included 19 individuals with prodromal EOAD (p-EOAD) and 23 subjects with probable dementia in EOAD (d-EOAD).

ADAD ($N = 29$): participants were recruited from the Genetic Counseling Program for familial dementias (PICOGEN) at the Hospital Clínic de Barcelona [15]. Fifteen symptomatic carriers (CDR ≥ 0.5) carrying nine different *PSEN1* mutations (M139T, S169P, L173F, G209E, L235R, K239N, L282R, L286P, and I439S) and one symptomatic carrier of the *APP* I716T mutation were included. The symptomatic carriers were further classified as prodromal AD in ADAD (pAD-ADAD, $n = 5$) and dementia in ADAD (dADAD, $n = 11$). Twelve presymptomatic mutation carriers (CDR = 0) carrying seven different *PSEN1* mutations (M139T, S169P, L173F, R220G, K239N, L282R, and I439S) and one presymptomatic carrier of *APP* mutation (I716T) were labeled as asymptomatic ADAD. We used the International Working Group-2 diagnostic criteria for AD [2].

DS ($N = 117$): adults with DS were recruited from three centers—the Down Alzheimer Barcelona Neuroimaging Initiative in the Barcelona Down Medical Center [16]; the Sanders-Brown Center on Aging; and the Down Syndrome Biomarker Initiative pilot project [17]. Adapted neuropsychological batteries (detailed in the Appendix section) covering all cognitive domains classified DS participants into "without cognitive decline" (asymptomatic DS, $n = 91$), prodromal AD in DS (pAD-DS, $n = 13$), and AD dementia in DS (dAD-DS, $n = 13$). Participants with pAD-DS and dAD-DS were also labeled as symptomatic DS participants.

HCs ($N = 68$): participants were recruited at Hospital de Sant Pau ($n = 60$) and Hospital Clínic de Barcelona ($n = 8$) enrolled among patients' caregivers. They did not have cognitive complaints, scored zero on CDR, had normal neuropsychological evaluation, and normal core AD CSF biomarkers [18,19].

2.2. Procedures

Medical records were reviewed for potential confounders; and effect modifiers, age, sex, and presence of