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Original article

Bloodstream Amyloid-beta (1-40) Peptide, Cognition, and Outcomes in Heart Failure

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ABSTRACT

Introduction and objectives: In the brain, amyloid-beta generation participates in the pathophysiology of cognitive disorders; in the bloodstream, the role of amyloid-beta is uncertain but may be linked to sterile inflammation and senescence. We explored the relationship between blood levels of amyloid-beta 1-40 peptide (Aβ40), cognition, and mortality (all-cause, cardiovascular, and heart failure [HF]-related) in ambulatory patients with HF.

Methods: Bloodstream Aβ40 was measured in 939 consecutive patients with HF. Cognition was evaluated with the Pfeiffer questionnaire (adjusted for educational level) at baseline and during follow-up. Multivariate Cox regression analyses and measurements of performance (discrimination, calibration, and reclassification) were used, with competing risk for specific causes of death.

Results: Over 5.1 ± 2.9 years, 471 patients died (all-cause): 250 from cardiovascular causes and 131 HF-related. The median Aβ40 concentration was 519.1 pg/mL [Q1-Q3: 361.8-749.9 pg/mL]. The Aβ40 concentration correlated with age, body mass index, renal dysfunction, and New York Heart Association functional class (all $P < .001$). There were no differences in Aβ40 in patients with and without cognitive impairment at baseline ($P = .97$) or during follow-up ($P = .20$). In multivariable analysis, including relevant clinical predictors and N-terminal pro-B-type natriuretic peptide, Aβ40 remained significantly associated with all-cause death (HR, 1.22; 95%CI, 1.10-1.35; $P < .001$) and cardiovascular death (HR, 1.18; 95%CI, 1.03-1.36; $P = .02$), but not with HF-related death (HR, 1.13; 95%CI, 0.93-1.37; $P = .22$). Circulating Aβ40 improved calibration and patient reclassification.

Conclusions: Blood levels of Aβ40 are not associated with cognitive decline in HF. Circulating Aβ40 was predictive of mortality and may indicate systemic aging.

Amiloide beta (1-40) en sangre, cognición y pronóstico en insuficiencia cardiaca

Palabras clave:
Amiloide-beta
Insuficiencia cardiaca
Cognición
Pronóstico
Biomarcadores

RESUMEN

Introducción y objetivos: A nivel cerebral, el amiloide-beta participa en la fisiopatología de trastornos cognitivos; en la circulación, el papel del amiloide-beta es incierto pero podría estar relacionado con procesos de inflamación estéril y senescencia. Se ha analizado la relación entre concentraciones circulantes de amiloide-beta 1-40 (Aβ40), cognición y mortalidad (global, cardiovascular y por insuficiencia cardiaca [IC]) en pacientes ambulatorios con IC.

Métodos: El Aβ40 circulante se midió en 939 pacientes consecutivos con IC. El estado cognitivo se evaluó con el cuestionario de Pfeiffer (ajustado al nivel educacional) en condiciones basales y durante el seguimiento. Se utilizaron análisis de regresión múltiple de Cox y medidas de función (discriminación, calibración y reclasificación), ajustando por riesgos competitivos para causas de muerte específicas.

Resultados: Durante 5.1 ± 2.9 años, 471 pacientes murieron: 250 de causa cardiovascular y 131 por IC. La mediana de Aβ40 circulante fue de 519,1 pg/ml [Q1-Q3: 361,8-749,9 pg/ml]. La concentración de Aβ40 correlacionó con la edad, índice de masa corporal, insuficiencia renal y clase funcional de la *New York Heart Association* (todas p < 0,001). No hubo diferencias en Aβ40 en pacientes con y sin trastorno cognitivo a nivel

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basal (p = 0,97) o durante el seguimiento (p = 0,20). En el análisis multivariado, que incluye predictores clínicos relevantes y la fracción aminoterminal del propéptido natriurético cerebral, Aβ40 permaneció asociado a mortalidad global (HR = 1,22; IC95%, 1,10-1,35; p < 0,001) y cardiovascular (HR = 1,18; IC95%, 1,03-1,36; p = 0,02), pero no con mortalidad por IC (HR = 1,13; IC95%, 0,93-1,37; p = 0,22). El Aβ40 circulante mejoró la calibración y reclasificación de los pacientes.

Conclusiones: Las concentraciones circulantes de Aβ40 no se asocian a trastorno cognitivo en la IC. Aβ40 fue predictor de mortalidad y podría indicar envejecimiento sistémico.

Abbreviations

Aβ40: amyloid-beta 1-40 peptide
CV: cardiovascular
eGFR: estimated glomerular filtration rate
HF: heart failure
NEP: neprilysin

INTRODUCTION

Heart failure (HF) is a growing epidemic with an important social and economic burden.[1] Over the past 3 decades, treatment advances in HF have been made, mainly due to a better understanding of neurohormonal activation and its blockade. Presently, beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and mineralocorticoid receptor antagonists are the cornerstone for HF treatment.[2] Sacubitril/valsartan, the latest treatment in the HF armamentarium, has proved to have superiority over enalapril for treating HF patients with reduced ejection fraction.[3] Sacubitril/valsartan belongs to a new class of dual action drugs that provide simultaneous inhibition of neprilysin (NEP) and blockade of the angiotensin receptor blocker.

Several lines of evidence suggest that diseases caused by age-related chronic "sterile" inflammation, such as heart disease and Alzheimer disease, may have common molecular pathways and share epidemiological, genetic, and environmental risk factors.[4,5] The identification and monitoring of cellular senescence associated with such processes has not been conclusively achieved, but candidate circulating biomarkers may exist toward this goal. For example, generation of toxic amyloid-beta is one of the key events in the pathophysiology of Alzheimer disease.[6–8] The amyloid-beta 1-40 peptide (Aβ40) is generated in the brain from amyloid precursor protein by β- and γ-secretase activities. Amyloid-beta 1-40 peptide is recognized as a proinflammatory peptide that acts through several mechanisms.[9] In normal metabolism, Aβ40 is removed from the brain by multiple processes, including degradation by NEP.[10]

While circulating concentrations of Aβ40 have been linked with subclinical atherosclerosis and progression of arterial stiffness, independent of other conventional risk factors, along with prognosis,[11] it is unclear whether bloodstream concentrations of this proinflammatory biomarker are associated with outcomes and/or cognitive decline in HF.

Accordingly, this study sought to evaluate the prognostic meaning of Aβ40 in a cohort of patients with chronic ambulatory HF untreated by NEP inhibition. In addition, we examined associations between bloodstream Aβ40 concentration, cognition assessed by the Pfeiffer questionnaire,[12] and the following biomarkers: soluble NEP,[13] soluble suppression of tumorigenicity-2 (ST2), and high-sensitivity C-reactive protein, a well-established inflammatory biomarker.

METHODS

Study Population

Ambulatory patients treated at a multidisciplinary HF clinic between May 2006 and May 2013 were consecutively included in the study. The referral inclusion criteria and blood sample collection have been described elsewhere.[13] In brief, patients were referred to the HF clinic by cardiology or internal medicine departments and, to a lesser extent, from the emergency or other hospital departments. The principal referral criterion was HF according to the European Society of Cardiology guidelines irrespective of etiology and at least 1 hospitalization for HF. Amyloid-beta 1-40 peptide and all other biomarkers were analyzed from the same blood sample, which was stored −80 °C, without previous freeze-thaw cycles. All samples were obtained between 9:00 AM and 12:00 PM. All participants provided written informed consent and the study was approved by the local ethics committee. All study procedures were conducted in accordance with the ethical standards outlined in the Helsinki Declaration of 1975, revised in 1983.

Cognitive Assessment

Cognition was evaluated using the Pfeiffer questionnaire, a short mental status survey, in 802 patients at baseline (within 6 months of blood sampling) and in 405 patients during follow-up (median 3.4 years [2.1-6.1]). The test was considered diagnostic of cognitive impairment if the score was > 3. The patients' educational levels were considered for scoring (± 1 scoring points relative to educational level), as previously reported.[14]

Follow-up and Outcomes

All patients were followed up at regular intervals, with additional visits, as required, in cases of decompensation.[13] Patients who did not attend regular visits were contacted by telephone. The primary outcomes were all-cause death, cardiovascular (CV) death, and HF-related death. A death was considered of CV origin if it was caused by HF (decompensated HF or treatment-resistant HF, in the absence of another cause); sudden death (unexpected death, witnessed or not, of a previously stable patient with no evidence of worsening HF or any other cause of death); acute myocardial infarction (death directly related with acute myocardial infarction, whether due to mechanic, hemodynamic, or arrhythmic complications); stroke (associated with recent acute neurologic deficit); procedural (postdiagnostic or posttherapeutic death); or other CV causes (eg, rupture of an aneurysm, peripheral ischemia, or aortic dissection). Fatal events

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