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RESEARCH ARTICLE

Comparison of β2-microglobulin serum level between Alzheimer's patients, cognitive healthy and mild cognitive impaired individuals

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ABSTRACT

Background: Several studies performed in the last years on the brain, showed that beta2-microglobulin (β2m) and MHC can act independently of their canonical immune function to regulate normal brain development, synaptic plasticity and behaviour. Increased systemic levels of soluble β2m have been implicated in cognitive impairments like that associated with chronic haemodialysis, or aortic valve replacement. Increased soluble β2m has also been detected in the cerebral spinal fluid (CSF) of patients with HIV-associated dementia and Alzheimer's disease (AD).

Objective: To compare plasma β2m levels in healthy subjects and subjects with dementia or cognitive impairment.

Methods: We measured the concentration of β2m in a cohort of 245 individuals and compared sex matched, cognitive healthy individuals.

Results: We found higher levels of β2m in AD patients compared to non-AD MCI and healthy controls (2063 ng/mL ±852 versus 1613 ± 503 and 1832 ± 382 ng/mL, $p < 0.001$ and < 0.033, respectively), while there was no difference between mild cognitive impairment (MCI) and healthy controls ($p > 0.05$).

Conclusions: Our data confirm that β2m could play a role in AD. However, a replication study in an independent cohort would be necessary to confirm our preliminary results.

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KEYWORDS
β2-microglobulin; Alzheimer disease; mild cognitive impairment; serum biomarkers

Introduction

Imaging, cerebrospinal fluid (CSF) and blood-based biomarkers have the potential to improve the accuracy by which specific causes of dementia can be diagnosed *in vivo*, provide insights into the underlying pathophysiology, and may be used as inclusion criteria and outcome measures for clinical trials. While a number of imaging and CSF biomarkers are currently used for each of these purposes, this is an evolving field, with numerous potential biomarkers in varying stages of research and development. β2-microglobulin (β2m) is a low molecular weight (11.8 KDa) non-glycosylated polypeptide. The gene is located on chromosome 15q21.1 and the encoded, functional protein forms the invariant or light β-chain of HLA class I molecules on the surface of all nucleated cells, in non-covalent association with the 43 KDa heavy α-chain of MHC class I antigens (Cunningham and Berggard 1974, Mátrai *et al.* 2009). The small size of the molecule allows β2m to pass through the glomerular membrane, but normally less of 1% of protein is excreted in the urine; the remainder is reabsorbed and catabolized in the proximal tubules of the kidney. Nonetheless, it was firstly identified in the urine of patients with renal tubular disease. Since it is processed by glomerular filtration and subsequent tubular reabsorption, increases in serum concentrations are a sensitive marker of impaired renal function. Increased plasma concentrations have also been found in solid tumours, haematological malignancies, autoimmune diseases and infections including AIDS. In particular, β2m is regarded as a robust marker of disease activity and prognosis in lymphoproliferative conditions like myeloma, chronic lymphocytic leukaemia, other lymphomas and infections. Interestingly, some variants of human β2m were associated to increased β2m-amyloid deposition and to dialysis-related amyloidosis (Corazza *et al.* 2004, Corlin *et al.* 2005, Murray 2008, Foster *et al.* 2013, Kim *et al.* 2017). Increased systemic levels of soluble β2m have been implicated in cognitive impairments associated with chronic haemodialysis (Murray 2008, Kim *et al.* 2017). Despite its important role in prognosis assessment and disease monitoring, relatively few studies are available on its expression in healthy individuals. These reports show remarkable variations in the methods used, age and number of reference individuals and statistical analyses of the data. Further complexity is introduced by the dependence of β2m expression, with respect to race and ethnicity (Cunningham and Berggard 1974, Mátrai *et al.* 2009). Recently a study investigated the

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association between β2m and incident frailty, concluding with the observation that higher β2m levels were independently associated with greater frailty at baseline in older adults but only slightly associated with greater risk of incident frailty over four years of follow-up (Kim *et al.* 2017). Furthermore, high β2m levels were recently reported to be associated with cardiovascular disease and mortality in the general population (Astor *et al.* 2012, Juraschek *et al.* 2012, Kim *et al.* 2017, Załęska-Kocięcka *et al.* 2017). In a study performed on seventy-one patients undergoing aortic valve replacement, patients with β2m increase over the median change (>0.42 mg/L) experienced a significant in-hospital drop in MMSE ($p = 0.005$). Patients with β2m increase over the median change also failed to improve a delayed-word-recall domain of the test ($p = 0.826$) while patients with a lower increase improved results in the domain ($p = 0.004$). After six months, MMSE improvement was associated with a significant decrease in β2m ($p = 0.042$) and these authors suggested, the first time in humans, a possible relation between changes in cognition and β2m serum levels (Juraschek *et al.* 2012, Załęska-Kocięcka *et al.* 2017). Increased systemic levels of soluble β2m have been implicated in cognitive impairments associated with chronic haemodialysis (Murray, 2008). Moreover, increased soluble β2m has also been detected in the cerebral spinal fluid (CSF) of patients with HIV-associated dementia and Alzheimer's disease (AD) (McArthur *et al.* 1992, Brew *et al.* 1996). As reported by Villeda *et al.*, in the brain, β2m and MHC I molecules can act independent of their canonical immune function to regulate normal brain development, synaptic plasticity and behaviour (Smith *et al.*, 2015). Significant changes in the concentration of β2m in mouse plasma have been documented during normal aging, and in the experimental aging model of heterochronic parabiosis. Notably, human genome-wide association studies (GWASs) have linked the MHC locus on chromosome 6p21 with age-related degenerative diseases, further suggesting an active role for these molecules in age-dependent impairments (Huh *et al.* 2000, Boulanger and Shatz 2004, Goddard *et al.* 2007, Shatz 2009, Glynn *et al.* 2011, Lee *et al.* 2014, Smith *et al.* 2015). From the above-mentioned studies, β2m is associated with aging, frailty, some types of cognitive impairment and, limited to CSF, with AD. The experimental studies have confirmed the association with cognitive impairment. Our aim in this study is to provide data about a possible association between cognitive status and β2m plasma levels.

Clinical significance

- Plasma β2m concentration may improve the accuracy in the identification of individuals with AD.

Materials and method

Populations and plasma samples

In this retrospective study, we measured the concentration of β2m in a cohort of 245 individuals and compared sex matched, cognitive healthy individuals. Plasma samples were randomly selected form biobanks collected by different research units and programs: healthy controls (HC) samples derived from the longitudinal InveCe.Ab study (Guaita *et al.* 2013), while the mild cognitive impairment (MCI) and Alzheimer disease (AD) samples were collected from patients population of Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico Milano.

Informed consent was obtained from human subjects according to the institutional review board guidelines at the respective centres, and the study was approved by the Institutional local Ethics Committee.

AD and MCI patients

All AD and MCI patients underwent a standard battery of examinations, including medical history, physical and neurological examination, screening laboratory evaluation with full blood count, measurement of aspartate and alanine aminotransferase (AST, ALT),VDRL and virology (HIV, hepatitis B and C tests). We genotyped for ApoEε4 polymorphisms, for the converging role of ApoEε4 and β2m for the amyloid beta deposition, a key point for cognitive functions and for AD (Stoppini and Bellotti 2015, Di Battista *et al.* 2016). Patients with monoclonal gammapathies (MGUS) or active malignant disease and low life expectancy were excluded from the study. A complete neurocognitive and memory evaluation: clinical dementia rating (CDR), mini mental state examination (MMSE), the frontal assessment battery (FAB), the Wisconsin card sorting test (WCST), and the Tower of London test assessed cognitive dysfunctions; imaging was also performed. The presence of significant vascular brain damage was excluded (Hachinski Ischemic Score <4). Lumbar puncture was performed after one-night fasting.

Diagnosis of clinical MCI was done according to Petersen *et al.* (2001). These subjects then underwent lumbar puncture and were classified as non-AD MCI, i.e. subjects with CSF amyloid, tau and phospho-tau (P-tau) in the normality range, or prodromal AD (MCI with positive biomarkers, i.e. Amyloid beta <600 pg/ml, total Tau >450 pg/m and P-tau >61 pg/ml) according to current research criteria (Dubois *et al.* 2007, 2014), AD patients diagnosis fulfilled all criteria (McKhann *et al.* 1984, 2011), including CSF biomarkers. Nonetheless, we acknowledge that according to the new DSM5 criteria (American Psychiatric Association 2013) we cannot exclude that some of them may develop other dementia than AD.

Controls

The control group consisted of non-demented volunteers matched for ethnic background, cognitively preserved, without memory and psycho-behavioural dysfunctions (mean MMSE ≥28.59). They underwent a neuropsychological cognitive battery, medical examination, standard screening laboratory tests, genetic typing for ApoEε4 presence/absence. They remained intact and cognitively stable over a minimum follow-up of three years. The first hundred with better scores in the neuropsychological evaluation at the second follow-up were included in the study.

CSF processing and biomarker determination

Cerebral spinal fluid samples were obtained in polypropylene tubes by lumbar puncture at the L4/L5 or L3/L4 interspace, centrifuged at 4 °C at 2000 *g*. The serum and CSF samples were removed and dispensed in aliquots of 400 µL into cryotubes. Specimens were stored at −80 °C until use. Aβ42, tau and P-tau CSF levels were determined with human specific ELISA kits (Innogenetics, Ghent, Belgium), as previously reported (Andreasen and Blennow 2005).

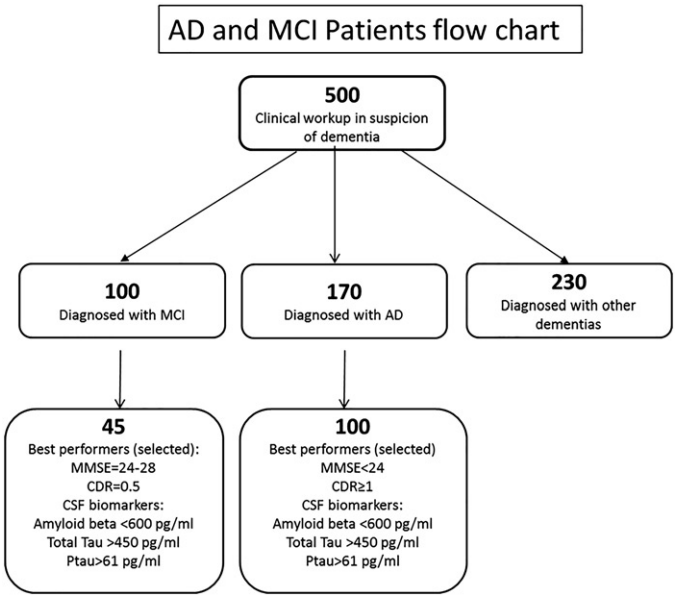
β2 Microglobulin analysis

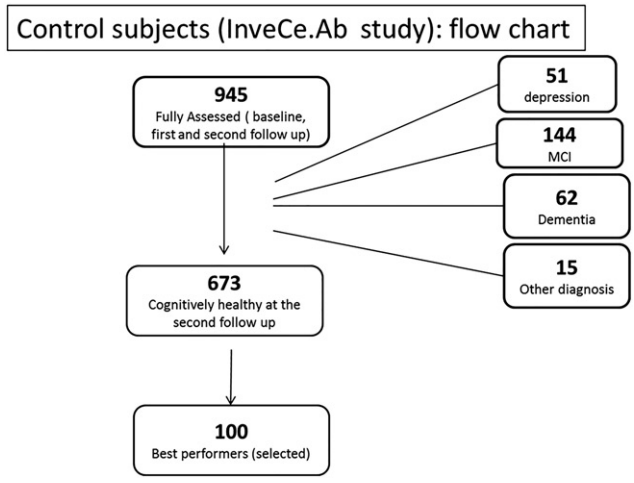
β2m was measured from frozen plasma samples (EDTA, −20 °C) (Lee *et al.* 2014) collected at the baseline study visit, with the use of a solid-phase, two site chemiluminescent immunometric assay on Immulite 2000 Automatic analyzer (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany).

Statistical analysis

We used one-way ANOVA for the continuous variables. In case of a significant *p*-value (<0.05), we performed a *post hoc* comparison (Bonferroni). For categorical variable we used the Chi square or Fisher Exact test when appropriate. The independent role of socio-demographic characteristics on outcomes was also verified, by multinomial regression analysis. Due to the different mean age of the three groups, age was introduced in the regression as main covariate: alone (first model), associated with gender (second model), associated with gender and ApoEε4 (third model), for undoing the effect of age on the possible association with the three diagnostic groups of the outcome (β2m level). In all cases a *p*-value less than 0.05 was considered significant. Data were processed using SPSS 11+ release.

Patients and controls flow charts





Results

Serum levels of β2m were measured in 100 HC, 45 MCI and 100 AD. Demographic and clinical characteristics of the three groups are reported in Table 1.

Mild cognitive impairment patients were significantly younger than HC and AD, while there was no difference between the last two. Gender distribution was similar among the groups. APOEε4 was present at higher percentage in the MCI and AD groups, but with a borderline significance ($p = 0.078$).

No interaction between gender and APOEε4 was detected. There was no effect of age on gender or APOEε4 distribution, but a significant linear correlation between age and β2m serum levels ("r" = 0.247; $p < 0.001$). The difference in β2m mean levels among HC, MCI and AD, are reported in Figure 1 and in Table 2, with post-hoc analysis. AD patients showed values higher than MCI and HC ($p < 0.001$ and $p = 0.033$, respectively), while there was no significant difference between HC and MCI.

Due to the importance of age in the serum levels of β2m, we performed a multinomial regression with AD as reference with respect to HC and MCI and β2m plasma levels as dependent variable, then applying three models with age, age + gender, age + gender + APOEε4. In all models β2m levels are significantly higher in AD patients compared to MCI subjects (firstst model: $p < 0.001$; OR: 0.886; 95%CI: 0.833–0.943; second model: $p = 0.005$; OR: 0.999; 95%CI: 0.998–1.000; third model: $p = 0.019$; OR: 0.999; 95%CI: 0.998–1.000). Compared to HC, AD patients show higher levels of β2m levels, significantly for first two models and borderline for the third (first model: $p = 0.039$; OR: 0.999; 95%CI: 0.999–1.000; second model: $p = 0.04$; OR: 0.999; 95%CI: 0.999–1.000; third model: $p = 0.055$; OR: 1.000; 95%CI: 0.999–1.000).

Table 1. Demographic characteristics and presence of ApoEε4 in the three groups.

	HC (N: 100)	MCI (N: 45)	AD (N: 100)
Years of age	72.02 (SD: 1.271)	67.34 (SD: 8.402)	73.17 (SD: 7.411)
Female (%)	52	53.3	61
ApoEε4 (%)	19	34.2	31

The mean age are lower for MCI ($p < 0.001$); the gender and ApoE4 percentages are not different in the three groups (HC: Healthy Controls; MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease).

Discussion

Alzheimer's disease can only be definitively diagnosed at autopsy since its manifestations of senile plaques and neurofibrillary tangles throughout the brain cannot yet be fully captured with current imaging technologies. The identification and validation of biomarkers for diagnosing AD and other forms of dementia are increasingly important. To date, ELISA measurement of β-amyloid peptide (1–42), total tau and phospho-tau-181 in cerebrospinal fluid (CSF) is the most advanced and accepted method to diagnose probable AD with high specificity and sensitivity.

Besides identifying markers that distinguish AD from controls, there has been a recent drive to identify better biomarkers that can predict the rates of cognitive decline and neocortical amyloid burden in those who exhibit preclinical, prodromal, or clinical AD. In addition to studying CSF biomarkers, researchers have sought less invasive sources, such as blood (O'Bryanta *et al.* 2017).

Although saliva or urine can be easily collected, blood analysis is the gold standard (Blennow 2017); yet, it is still unknown how the concentration of analytes in the blood directly correlates with pathological changes in the brain, especially in AD. The search for blood biomarkers that correlate with AD should therefore begin with accepted CSF markers, such as Aβ and tau-related biomarkers, and further include factors involved in inflammation, protein aging and cell death, and cerebrovascular dysfunctions. It seems very plausible that, at some point in the next years, the combination of different blood-derived AD biomarkers leads to the definition of a patient-specific signature. The pilot European trial on AD neuroimaging Initiatives (E-ADNI) measured both CSF and plasma derived Aβ and found that higher diagnostic accuracy was obtained with frozen than fresh samples. Obtaining blood samples is relatively painless and inexpensive, giving potential blood-based biomarkers further advantage over the CSF-based markers. Furthermore some of the blood biomarkers appear to be just as diagnostically accurate as the CSF-based and genetic biomarkers though further validation is warranted. Useful biomarkers could predict the progression of MCI to AD so that early preventative treatment can be delivered to AD-presymptomatic patients.

Acknowledging that peripheral biomarkers (blood or otherwise) of brain disorders are more difficult to identify and lockdown, there are many potential advantages for blood-based AD biomarkers, including, but not limited to, primary care screening, diagnostics, predictive risk (i.e. risk for incident AD, risk for progression from MCI to AD), disease monitoring, stratification into clinical trials, and pharmacodynamics or treatment response monitoring (positive or adverse). Indeed, an important potential of AD blood biomarkers could be to increase the likelihood of subjects being positive on more expensive (e.g. positron emission tomography [PET] imaging) or invasive (lumbar puncture for CSF sampling) biomarkers used later to determine trial eligibility (McKhann *et al.* 1984, 2011, Andreasen and Blennow 2005).

In this work, we provide a preliminary evidence of different plasma concentrations of β2m in patients with AD respect to MCI and healthy controls. Though old age is a main factor for serum levels of β2m, we found that the difference remained significant after controlling for age. Nevertheless, the effect is weak, with OR 0.99 that cannot allow to draw other than

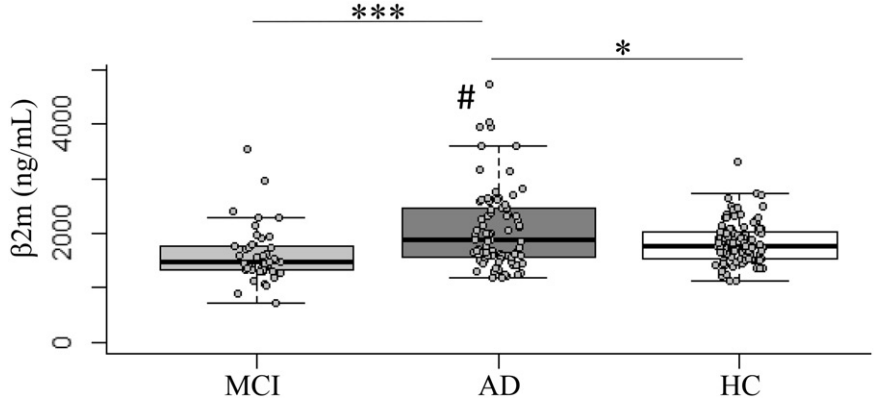


Figure 1. Box and whiskers plot of β2 m serum levels in MCI, AD, and HC. Mean concentration of β2m in MCI 1613 ng/mL±509 SD, AD 2063 ng/mL±852 SD, and HC 1832 ng/mL±384 SD. *$p = 0.033$; ***$p < 0.001$, ANOVA *post hoc* analyses (Bonferroni). #An outlier value of 6955 ng/mL in the AD population has been omitted from the graph.

Table 2. β2m mean difference between the three groups.

Dependent variable: β2m (ng/mL)					
				95% Confidence interval	
	β2m (ng/mL) Mean difference	Std. Error	Sig.	Lower bound	Upper bound
HC–MCI	219.88	114.13457	0.166	−55.2674	495.0296
HC–AD	−230.41*	89.91962	0.033	−447.1826	−13.6374
MCI–AD	−450.29***	114.13457	<0.001	−725.4396	−175.1426

In ANOVA *post hoc* analyses (Bonferroni) AD subjects show higher mean levels of β2 m than MCI and HC (***$p < 0.001$ and *$p = 0.033$, respectively). MCI do not show difference from HC ($p = 0.166$).

preliminary considerations. The slightly reduction of statistically significant AD-HC difference after introducing APOEε4 in regression model is explained by the limited number of the sample and by the higher β2m level, though non-significant, in the APOEε4 + subjects.

Actually our study has some important limitations. First of all the number of participants is very small in the MCI group, that was and second, age that is significantly different for MCI compared to AD and healthy controls. Nevertheless, strengths include the diagnosis made with the use of biomarkers and the follow up of controls, that remained cognitively intact over a minimum follow up of three years. Aging remains the most dominant risk factor for dementia-related neurodegenerative diseases, such as AD. The experimental evidences of the Villeda paper showed that β2m could affect hippocampal functions in mice, in fact this protein, as a circulating factor negatively regulates cognitive and regenerative function in the adult hippocampus in an age-dependent manner. β2m is elevated in the blood of aging humans and mice, and is increased within the hippocampus of aged mice and in the model of young heterochronic parabionts. These author with their data indicate that systemic β2m accumulating in aging blood promotes age-related cognitive dysfunction and impaired neurogenesis, in part via MHC I, suggesting β2m may be targeted in old age (Smith *et al.* 2015).

Herein, we showed that plasma β2m levels are specifically increased in AD, independent of the phase (prodromal or fully symptomatic AD). Notably, clinical diagnosis of patients included in the study was supported by the analysis of CSF biomarkers, which allowed us to classify patients, basing on the demonstration of an amyloid and tau underlying pathology, in MCI due to AD (prodromal AD) from MCI due to other causes. The use of such biomarkers allows to discriminate between MCI due to AD, i.e. prodromal AD, from MCI due to other causes (non-AD MCI) with a very high accuracy (Blennow 2017, O'Bryanta *et al.* 2017), and represents the best surrogate biomarker to be used in the absence of the demonstration of the pathology at autopsy. In order to explain the discrepancy between MCI and AD, we speculate that, in according with the new criteria of classification (McKhann *et al.* 1984, 2011, Andreasen and Blennow 2005, Dubois *et al.* 2007, 2014, American Psychiatric Association 2013), a clinically defined MCI with the demonstration of CSF biomarkers (low Aβ and high tau) is to consider as 'prodromal' AD, while if the biomarker do not fit with AD, MCI is not to correlate or attribute to AD pathology.

Recent experimental evidences have suggested the pathogenetic contribution of glia to progression of disease; in particular when it has lost the neuronal homeostatic functions and acquired the pro-inflammatory phenotype. Activated microglial cells express MHC class I and β2m on their surface, and in response to the pathogenic noxae can amplify the inflammatory cascade responsible of exacerbation of neurodegenerative process (Boche and Nicoll 2008, McQuillan *et al.* 2010).

Conclusions

We measured plasma levels of β2m in 100 HC, 100 AD and 45 MCI. The study revealed a statistically significant difference of β2m concentration in patients with advanced AD respect to MCI and a borderline difference with HC. This suggests that plasma β2m may be a useful biomarker to distinguish subjects with AD from MCI and possibly HC. However, a replication study in a larger and independent cohort would be necessary to confirm our preliminary results.

Disclosure statement

No potential conflict of interest was reported by the authors.

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