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Plasma and cerebrospinal fluid amyloid-β levels in late-life depression: A systematic review and meta-analysis

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ABSTRACT

This study aimed to evaluate differences in plasma and cerebrospinal fluid (CSF) levels of Aβ peptides in older adults with late-life depression compared to non-depressed older controls. We conducted a systematic review and meta-analysis of the literature using PubMed, Web of science and Scopus databases with no search limits for publication dates or languages. Two independent reviewers extracted data and assessed quality. Six hundred references were retrieved, and we included 12 studies in the meta-analysis after eligibility screening. Older adults with late-life depression (LLD) had a higher plasma $A\beta_{40}$:$A_{\beta 42}$ ratio compared to non-depressed participants (SMD = 1.10, $CI_{95\%}$ [0.28; 1.96], p = 0.01), and marginally significant reduction of CSF $A\beta_{42}$ levels (SMD = −1.12, $CI_{95\%}$ [−2.47; 0.22], p = 0.1). The present results evidence that older adults with depression have significant differences in Aβ metabolism, in the same direction observed in individuals with AD. These differences in the Aβ metabolism may help identify a subgroup of subjects with LLD at higher risk of developing AD.

1. Introduction

Late-life depression (LLD) is a common disorder in the elderly and is associated with cognitive impairment and a higher risk of dementia, especially Alzheimer's disease (AD) and vascular dementia (Byers and Yaffe, 2011; da Silva et al., 2013; Diniz et al., 2013). The mechanisms linking depression and the risk of dementia are unknown, but may involve abnormalities in multiple biological cascades, including the metabolism of amyloid-β (Aβ) peptide in the brain (Butters et al., 2008a). Neuroimaging studies using *in vivo* brain amyloid ligands show higher Aβ load in older adults with LLD, in particular, those with late-onset depression, compared with healthy controls (Butters et al., 2008b; Tateno et al., 2014). Nonetheless, other studies reported no significant differences in Aβ burden between LLD and healthy controls (Madsen et al., 2012) what is in line with recent neuropathological studies (Royall and Palmer, 2013; Wilson et al., 2014).

The metabolism of the amyloid precursor protein (APP) yields two common Aβ peptides, the $A\beta_{40}$ and $A\beta_{42}$, that can be readily measured in the cerebrospinal (CSF) and plasma (Blennow et al., 2010). Reduced CSF $A\beta_{42}$ levels is associated with an increased risk of progression of mild cognitive impairment (MCI) to AD (Diniz et al., 2008). Previous clinico and epidemiological studies have reported that increased $A\beta_{42}$ levels and lower plasma $A\beta_{42}$:$A\beta_{40}$ ratio can be an indicator of a higher risk of progression from MCI to AD; though other studies have also found no association between plasma Aβ biomarkers and increased risk of progression (Hansson et al., 2012; Fei et al., 2011; Koyama et al., 2012; Gabelle et al., 2013). Previous studies investigated the levels of Aβ peptides in the CSF and plasma of LLD patients. Pomara et al. (2006) showed that the CSF $A\beta_{42}$ levels are reduced in older adults with depression compared to healthy controls. In contrast, other studies did not find significant differences or even found increased CSF $A\beta_{42}$ levels in older depressed individuals (Gudmundsson et al., 2007; Kramberger et al., 2012; Reis et al., 2012). Other studies evaluated the plasma levels of Aβ peptides. Most studies found a significant reduction of plasma $A\beta_{42}$ and increased $A\beta_{40}$:$A\beta_{42}$ ratio in LLD; although non-significant results have also been reported (Sun et al., 2008; Baba et al., 2012; Benitez et al., 2009; Kita et al., 2009).

The current knowledge about the dynamics of Aβ peptides in

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the CSF and plasma of LLD patients are limited by the small sample size of individual studies that are generally underpowered to detect small, but significant, group differences. Due to the importance of understanding the role of abnormalities of Aβ metabolism in LLD, and the lack of power of individual studies, we aim to carry out a meta-analysis on the levels of CSF and plasma Aβ peptides in LLD.

2. Methods

2.1. Search strategy

This study followed the guidelines for conducting and reporting systematic reviews and meta-analysis methods proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) working group (Moher et al., 2009). We conducted a comprehensive literature search for potentially relevant studies in the electronic databases PubMed, Scopus and Web of Science. There were no search limits for publication language. We used the following string term for the literature search: "(depression OR depressive disorder OR major depressive disorder) AND (amyloid)". Additionally, we carried out a manual search for relevant articles in the references of the original articles included in the meta-analysis, as well as in review articles about this subject. We conducted the literature search in January 2015, and all papers published until December 31, 2014 were included.

2.2. Study selection, data extraction and quality assessment

We selected studies for data extraction and analysis based on the following criteria: (a) identification of depression "caseness"; (b) age over 50 years at baseline assessment for participants with major depression and controls; (c) assessment of human plasma and/or CSF of Aβ peptide levels ($A\beta_{40}$, $A\beta_{42}$, and/or $A\beta_{40}$:$A\beta_{42}$ ratio) in participants with depression as compared with participants without depression (regarded as controls in the original studies). Two investigators (K.K.F.N and K.S.P) independently reviewed the title and abstract of each article retrieved from the literature search to identify potentially relevant studies. The selected articles were revised to verify whether they fulfilled the inclusion criteria for data extraction. If there was any disagreement in study selection, a third investigator (B.S.D.) made the final decision on the inclusion of the selected article. If different publications reported data from the same population, we included data from the publication with the larger sample size.

Data was extracted by two independent investigators (K.K.F.N and K.S.P) using a standardized data extraction form. The following data were extracted for each study: year of publication, country, study design, depression assessment method, demographic variables, sample size and mean and standard deviation, or median and interquartile range, for each analyte. When the study provided only the median and interquartile range, we transformed these values into mean and standard deviation (Hozo et al., 2005). We used the Newcastle–Ottawa Scale (NOS) to assess the scientific method quality of each study selected for inclusion in the meta-analysis (Wells et al., 2013). This scale assesses methodological aspects of non-randomized observational studies such as selection criteria for inclusion of cases and controls, comparability of population ascertainment of exposure to risk, quality of case ascertainment and outcome assessment.

2.3. Statistical analysis

We carried out the meta-analysis using the standardized mean difference (SMD) method with a Hedges' correction for bias in small samples to evaluate differences between LLD and control subjects for plasma $A\beta_{40}$, $A\beta_{42}$ levels, and $A\beta_{40}$:$A\beta_{42}$ ratio; and for CSF $A\beta_{40}$, $A\beta_{42}$ levels (Hedges and Olkin, 1985). We assessed heterogeneity in the analysis with the Q-test and I^2 index. If the p-value was equal to or below 0.05 in the Q-test and/or the I^2 index was higher than 50%, the pooled analysis was considered significantly heterogeneous. Random- or fixed-effect model was used based on the statistical evidence of heterogeneity. We performed sensitivity analyses by excluding one study at a time and recalculating the summary effect (i.e. 'leave-one-out' technique) to evaluate whether any individual study biased the result of the meta-analysis. Publication bias was ascertained by visual inspection of a funnel plot. All analyses were carried with the statistical software RevMan 5.1 for Windows 7 (The Nordic Cochrane Centre, Copenhagen, Denmark, http://ims.cochrane.org/revman/download).

3. Results

3.1. Study selection and description of studies

Two hundred forty-eight studies were retrieved from PubMed, 591 from the Web of Science and 143 from Scopus databases. After removing duplicate studies, we included 600 studies for revision. Twelve studies met all inclusion criteria and were included in the meta-analysis. The flowchart shows all steps for the study assessment and selection (Fig. 1). The main characteristics of studies included are summarized in Tables 1 and 2.

3.2. Plasma Aβ peptides ($A\beta_{40}$, $A\beta_{42}$, and $A\beta_{40}$:$A\beta_{42}$ ratio)

The LLD group had a higher Aβ40:Aβ42 ratio compared to non-depressed participants (SMD = 1.10, $CI_{95\%}$ [0.28, 1.96], z = 2.52, p = 0.01; Q = 92.50, p < 0.00001; I2 = 97%). We found no significant differences in plasma $A\beta_{42}$ (SMD = −0.44, $CI_{95\%}$ [−1.00, 0.11], z = 1.57, p = 0.1; Q = 42.8, p < 0.001; I2 = 91%) or plasma $A\beta_{40}$ levels (SMD = −0.10, $CI_{95\%}$ [−0.45, 0.25], z = 0.54, p = 0.59; Q = 20.82, p = 0.00003; I2 = 81%) between groups (Fig. 2).

Sensitivity analysis showed no significant effect of individual studies on results for plasma Aβ40:Aβ42 ratio or $A\beta_{40}$ levels. On the other hand, sensitivity analysis showed that after the exclusion of Blasko et al. (2010) study, plasma $A\beta_{42}$ levels were significantly reduced in the LLD group (SMD = −0.68 $CI_{95\%}$ [−1.07, −0.29], z = 3.42, p < 0.001). This result suggests that the data from Blasko et al. (2010) is biasing the meta-analysis results for plasma $A\beta_{42}$ levels.

3.3. CSF peptide ($A\beta_{40}$ and $A\beta_{42}$)

As there were only two studies that evaluated CSF $A\beta_{40}$ levels, we did not carry out a meta-analysis for this peptide. There was no significant difference in the CSF $A\beta_{42}$ levels between groups (SMD = −1.12, $CI_{95\%}$ [−2.47; 0.22], z = 1.64 p = 0.10; Q = 130.83, p < 0.00001; I2 = 96%, Fig. 3). Nonetheless, sensitivity analysis revealed that after excluding one study (Gudmundsson et al., 2007) depressed participants had a marginally significant lower level of CSF $A\beta_{42}$ compared to non-depressed participants (SMD = −1.51, $CI_{95\%}$ [−3.00; −0.01], z = 1.97, p = 0.05, Q = 107.32, p = 0.00001; I^2 = 96%). The visual inspection of funnel plots showed no evidence of publication bias for the CSF $A\beta_{40}$ and $A\beta_{42}$.

3.4. Additional analysis

Age is one of the most important risk factor for AD, and there is evidence of a positive correlation between age and increased deposition of Aβ peptide in the brain of non-demented older adults. We carried out additional analysis to assess whether there were