Brain, Behavior, and Immunity 62 (2017) 203–211

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Markers of neuroinflammation associated with Alzheimer's disease pathology in older adults

Julius Popp [a,*], Aikaterini Oikonomidi [a], Domilė Tautvydaitė [a], Loïc Dayon [b], Michael Bacher [c], Eugenia Migliavacca [b], Hugues Henry [d], Richard Kirkland [e], India Severin [b], Jérôme Wojcik [f], Gene L. Bowman [b]

[a] CHUV, Old Age Psychiatry, Department of Psychiatry, Lausanne, Switzerland
[b] Nestlé Institute of Health Sciences, EPFL Campus, Lausanne, Switzerland
[c] Philipps University of Marburg, Institute of Immunology, Marburg, Germany
[d] CHUV, Department of Laboratories, Lausanne, Switzerland
[e] Prometheus Laboratories, San Diego, USA
[f] Quartz Bio, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 14 October 2016
Received in revised form 15 January 2017
Accepted 30 January 2017
Available online 1 February 2017

Keywords:
Alzheimer's disease
Mild cognitive impairment
Neuroinflammation
Biomarkers
Amyloid
Tau

ABSTRACT

Background: *In vitro* and animal studies have linked neuroinflammation to Alzheimer's disease (AD) pathology. Studies on markers of inflammation in subjects with mild cognitive impairment or AD dementia provided inconsistent results. We hypothesized that distinct blood and cerebrospinal fluid (CSF) inflammatory markers are associated with biomarkers of amyloid and tau pathology in older adults without cognitive impairment or with beginning cognitive decline.

Objective: To identify blood-based and CSF neuroinflammation marker signatures associated with AD pathology (i.e. an AD CSF biomarker profile) and to investigate associations of inflammation markers with CSF biomarkers of amyloid, tau pathology, and neuronal injury.

Design/methods: Cross-sectional analysis was performed on data from 120 older community-dwelling adults with normal cognition (n = 48) or with cognitive impairment (n = 72). CSF Aβ1–42, tau and p-tau181, and a panel of 37 neuroinflammatory markers in both CSF and serum were quantified. Least absolute shrinkage and selection operator (LASSO) regression was applied to determine a reference model that best predicts an AD CSF biomarker profile defined *a priori* as p-tau181/Aβ1–42 ratio >0.0779. It was then compared to a second model that included the inflammatory markers from either serum or CSF. In addition, the correlations between inflammatory markers and CSF Aβ1–42, tau and p-tau181 levels were assessed.

Results: Forty-two subjects met criteria for having an AD CSF biomarker profile. The best predictive models included 8 serum or 3 CSF neuroinflammatory markers related to cytokine mediated inflammation, vascular injury, and angiogenesis. Both models improved the accuracy to predict an AD biomarker profile when compared to the reference model. In analyses separately performed in the subgroup of participants with cognitive impairment, adding the serum or the CSF neuroinflammation markers also improved the accuracy of the diagnosis of AD pathology.

Results: None of the inflammatory markers correlated with the CSF Aβ1–42 levels. Six CSF markers (IL-15, MCP-1, VEGFR-1, sICAM1, sVCAM-1, and VEGF-D) correlated with the CSF tau and p-tau181 levels, and these associations remained significant after controlling for age, sex, cognitive impairment, and APOEε4 status.

Conclusions: The identified serum and CSF neuroinflammation biomarker signatures improve the accuracy of classification for AD pathology in older adults. Our results suggest that inflammation, vascular injury, and angiogenesis as reflected by CSF markers are closely related to cerebral tau pathology.

1. Introduction

Neuroinflammation has long been known as an accompanying pathology of Alzheimer's disease (AD). It is now well-established that localized low-level inflammation occurs early in the AD brain.

* Corresponding author at: Old Age Psychiatry, Department of Psychiatry, University Hospital of Lausanne, Chemin de Mont-Paisible 16, CH-1011 Lausanne, Switzerland.
E-mail address: Julius.Popp@chuv.ch (J. Popp).

http://dx.doi.org/10.1016/j.bbi.2017.01.020
0889-1591/

In vitro and animal studies demonstrated the activation of different inflammatory pathways in association with amyloid pathology and tau-related neurodegeneration during the course of the disease. (Calsolaro and Edison, 2016; Heppner et al., 2015) In humans, genetic studies identified associations between polymorphisms in genes related to the immune system and the risk of AD (Calsolaro and Edison, 2016; Heneka et al., 2015), while histopathological studies suggested that glial activation is an important mediator of neurotoxicity and altered cognition in the presence of amyloid and tau pathology (Perez-Nievas et al., 2013). The inflammatory process driven by activated and proliferating glial cells, but also astrocytes, other myeloid cells, epithelium and other reactive elements leads to increased production and release of proinflammatory cytokines, chemokines and other mediators of inflammation. These factors may exacerbate amyloid production and toxicity, and contribute to tau hyperphosphorylation and neuronal injury. Vascular injury and endothelial dysfunction in relation to inflammation are also common in AD. They lead to the accumulation of several vasculotoxic and neurotoxic molecules within brain parenchyma, thus likely contributing to a noxious milieu finally promoting neuronal dysfunction and death (Grammas, 2011; Zlokovic, 2011). Several studies in subjects with mid cognitive impairment (MCI) and AD dementia revealed increased inflammatory activity in both the CNS and the circulating blood. However, reports on cytokines and other markers of inflammation in MCI or AD were controversial or inconsistent so far (Brosseron et al., 2014; Delaby et al., 2015; Hesse et al., 2016).

The development of AD pathology starts many years before the onset of the first clinical signs. Older subjects with normal cognition may already have cerebral AD pathology and may be seen as being at the preclinical stage of the disease (Sperling et al., 2011). On the other hand, subjects with cognitive deficits may have cognitive impairment not primarily or only in part related to AD pathology. New research criteria consider AD as a biological continuum across the clinical spectrum from asymptomatic stage to advanced dementia, and emphasize the utility of biomarkers of AD pathology for an accurate diagnosis, in particular at the preclinical and prodromal disease stages (Albert et al., 2011; Dubois et al., 2014; Sperling et al., 2011).

In this study, we aimed at identifying blood and cerebrospinal fluid (CSF) inflammation marker profiles related to the presence of cerebral AD pathology in older adults without cognitive impairment and with beginning cognitive decline. Furthermore, we hypothesized that blood and CSF inflammatory markers of cytokine mediated inflammation, vascular injury, and angiogenesis are associated with CSF biomarkers of amyloid and tau pathology.

2. Material and methods

2.1. Subjects

One hundred and twenty community dwelling participants were included in this study, of whom 48 were cognitively healthy volunteers and 72 had mild cognitive impairment (MCI, N = 63) or mild dementia of AD type (N = 9). The participants with cognitive impairment were recruited among patients attending the Memory Clinic of the Old-Age Psychiatry service and the Leenaards Memory Centre of the Lausanne University Hospital. They had no major psychiatric or neurological disorders, nor substance abuse or severe or unstable physical illness that may contribute to cognitive impairment, and met the diagnostic criteria for MCI (Winblad et al., 2004) or mild dementia. The control subjects were recruited through journal announcements or word of mouth and had no history, symptoms, or signs of relevant psychiatric or neurologic disease and no cognitive impairment. All participants had a comprehensive medical, psychiatric, neuropsychological and psychosocial evaluation, as well as brain MRI or CT scans, and venous and lumbar punctures. The MRI and CT scans were used in order to exclude cerebral pathologies possibly interfering with the cognitive performance.

The diagnosis of MCI or mild dementia of AD type was based on neuropsychological and clinical evaluation and was made by a consensus conference of neuropsychologists, psychiatrists, and/or neurologists prior to inclusion into the study. MCI was diagnosed according to consensus recommendations (Winblad et al., 2004). The participants in this group had memory impairment (<−1.5 standard deviation (SD) below the mean, adjusted for gender, age and education in the verbal memory task of Buschke Double Memory Test (Buschke et al., 1997a)) and/or impairment in another cognitive domain, and a Clinical Dementia Rating (CDR) (Morris, 1993) score of 0.5. The diagnosis of mild AD dementia was based on the clinical diagnostic criteria for probable dementia due to AD according to recommendations from the National Institute on Aging and Alzheimer's Association (McKhann et al., 2011) and DSM-IV criteria for dementia of the Alzheimer type (American-Psychiatric-Association, 1994). Participants in this group had a CDR score of 1. The subjects with MCI and mild dementia were considered as one group with CDR >0). The participants without cognitive impairment had no history or evidence of cognitive deficits, and their CDR score was 0.

Neuropsychological tests were used to assess cognitive performance in the domains of memory – Buschke Double Memory Test (Buschke et al., 1997b), language – a verbal fluency task (categorical and literal fluency in 2 min) executive functions: a speed of processing and cognitive flexibility task – the Trail Making Test A and B (Reitan, 1958), an inhibition task – the Stroop test (Bayard et al., 2009), and visuo-constructive functions (CERAD copy image test). The Mini Mental State Examination (Folstein et al., 1975) was used to assess participants' global cognitive performance. Depression and anxiety were assessed using the Hospital Anxiety and Depression scale (HAD) (Zigmond and Snaith, 1983). The psychosocial and functional assessment included the ADL (Katz, 1997) and instrumental ADL (Lawton and Brody, 1970), the NPIQ (Cummings et al., 1994) and the IQCODE (Jorm and Jacomb, 1989) questionnaires and were completed by the family members of the participants. All tests and scales are validated and widely used in the field.

The study was approved by the local ethics committee and written informed consent to participate in the study was obtained from all participants.

2.2. Cerebrospinal fluid AD biomarkers and APOE genotyping

Venous and lumbar punctures were performed between 8:30 and 9:30 am after overnight fasting at the recruiting memory centre. CSF was collected by lumbar puncture, using a standardized technique with a 22G "atraumatical" spinal needle while the patient was sitting or lying (Popp et al., 2007). Ten to twelve ml of CSF and 40 ml of blood were obtained using polypropylene tubes. Routine cell count and protein quantification were performed. Remaining CSF and serum (blood was centrifugated 12 min at 3000 rpm, 6 °C) was frozen in aliquots no later than 1 h after collection and stored at −80 °C without thawing until assay. CSF Aβ1–42, total-tau (tau), and tau phosphorylated at threonine 181 (ptau181) concentrations were measured using commercially available ELISA kits (Fujirebio, Gent, Belgium). The APOE genotype was determined and considered in all main analytical steps to evaluate possible interactions and effects on the addressed relationships (Jansen et al., 2015; Popp et al., 2010). DNA was extracted from whole blood using the QIAsymphony DSP DNA Kit (Qiagen, Hombrechtikon, Switzerland). The SNV rs429358 and rs7412 were genotyped using the Taqman assays C___3084793_20 and