Biochimica et Biophysica Acta xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Attenuation of functional hyperemia to visual stimulation in mild Alzheimer's disease and its sensitivity to cholinesterase inhibition☆

Rafal Janik [a,b,*], Lynsie A.M. Thomason [a], Simone Chaudhary [a,b], Adrienne Dorr [a], Amy Scouten [a,b], Graeme Schwindt [a], Mario Masellis [a,d], Greg J. Stanisz [a,b,g], Sandra E. Black [a,c,d,e,f], Bojana Stefanovic [a,b,f]

[a] Sunnybrook Research Institute, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada
[b] Department of Medical Biophysics, University of Toronto, 610 University Avenue, Toronto, ON M5G 2M9, Canada
[c] Institute of Medical Sciences, University of Toronto, 1 King's College Circle, Toronto, ON M5S 1A8, Canada
[d] Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada
[e] Department of Medicine (Neurology), Sunnybrook Health Sciences Centre University of Toronto, Canada
[f] Canadian Partnership for Stroke Recovery Sunnybrook Site, Canada
[g] Department of Nerurosurgery and Pediatrics Neurosurgery, Medical University of Lublin, Aleje Raclawickie 1, 20-059 Lublin, Poland

ARTICLE INFO

Article history:
Received 1 July 2015
Received in revised form 21 October 2015
Accepted 25 October 2015
Available online xxxx

Keywords:
Early stage Alzheimer's disease
Vascular impairment
Functional hyperemia
Cholinesterase inhibitors
Arterial spin labeling MRI

ABSTRACT

Despite the growing recognition of the significance of cerebrovascular impairment in the etiology and progression of Alzheimer's disease (AD), the early stage brain vascular dysfunction and its sensitivity to pharmacological interventions is still not fully characterized. Due to the early and aggressive treatment of probable AD with cholinesterase inhibitors (ChEI), which in and of themselves have direct effects on brain vasculature, the vast majority of hemodynamic measurements in early AD subjects reported hitherto have consequently been made only after the start of treatment, complicating the disentanglement of disease- *vs.* treatment-related effects on the cerebral vasculature. To address this gap, we used pseudo continuous arterial spin labeling MRI to measure resting perfusion and visual stimulation elicited changes in cerebral blood flow (CBF) and blood oxygenation dependent (BOLD) fMRI signal in a cohort of mild AD patients immediately prior to, 6 months post, and 12 months post commencement of open label cholinesterase inhibitor treatment. Although patients exhibited no gray matter atrophy prior to treatment and their resting perfusion was not distinguishable from that in age, education and gender-matched controls, the patients' visual stimulation-elicited changes in BOLD fMRI and blood flow were decreased by 10 ± 4% (BOLD) and 23 ± 2% (CBF), relative to those in controls. Induction of cholinesterase inhibition treatment was associated with a further, 7 ± 2% reduction in patients' CBF response to visual stimulation, but it stabilized, at this new lower level, over the follow-up period. Likewise, MMSE scores remained stable during the treatment; furthermore, higher MMSE scores were associated with higher perfusion responses to visual stimulation. This study represents the initial step in disentangling the effects of AD pathology from those of the first line treatment with cholinesterase inhibitors on cerebral hemodynamics and supports the use of arterial spin labeling MRI for quantitative evaluation of the brain vascular function in mild Alzheimer's disease. The findings provide evidence of a pronounced deficit in the visual cortex hyperemia despite the relative sparing of visual function in early stage AD, its reduction with ChEI treatment induction, and its stabilization in the first year of cholinesterase inhibition treatment. This article is part of a Special Issue entitled: Vascular Contributions to Cognitive Impairment and Dementia edited by M. Paul Murphy, Roderick A. Corriveau and Donna M. Wilcock.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

There is mounting evidence of the importance of the hemodynamic changes and neurovascular uncoupling in the development and progression of Alzheimer's disease [1]. On postmortem histology, the AD brain exhibits decreased vascular density, increased vessel curvature [2], degeneration of smooth muscle cells, vascular endothelium alterations [3,4], capillary fragmentation, abnormal blood–brain barrier permeability [5] and amyloid deposition on leptomeningeal and cortical penetrating arteries (cerebral amyloid angiopathy or CAA). Clinically, the degree of CAA correlates to cognitive impairment [6], white matter

☆ Sources of support. This work was supported by the Canadian Institutes of Health Research (CIHR MOP13129 held by SEB and BS; MOP 106485 held by SEB, GS and BS; PhD scholarship to RJ). Drs. Masellis and Black are grateful for salary support from the Brain Sciences Research program, Sunnybrook Research Institute and the Department of Medicine, Sunnybrook Health Sciences Center. Dr. Black also receives salary support from the Brill Chair in Neurology.

* Corresponding author at: Sunnybrook Research Institute, 2075 Bayview Avenue S605, Toronto, ON M4N 3M5, Canada.
E-mail address: rjanik@sri.utoronto.ca (R. Janik).

http://dx.doi.org/10.1016/j.bbadis.2015.10.023
0925-4439/© 2015 Elsevier B.V. All rights reserved.

hyperintensities [7] and cortical infarcts [8]. Like neuronal loss [9] and amyloid and tau deposition [10,11], the cerebrovascular changes are thought to precede clinical symptoms of the disease [38]. Furthermore, due to the relative ease of noninvasive vascular (*vs.* neuronal) state assessment, cerebrovascular impairment presents a potential noninvasive biomarker for identification of cognitively intact individuals who are in 'prodromal' phase of AD, a period that may offer the greatest hope for effective treatments to save residual neuronal function [12–14].

Regional hypometabolism and hypoperfusion, most notably of the right inferior parietal cortex, are frequently observed in AD patients; these findings typically persist even after correction for gray matter atrophy and can sometimes be extended to mild cognitive impairment [15,69,71]. However, much less data are available on changes in the functional stimulation elicited blood flow response in either group, even though functional perfusion response may be a more sensitive marker of the underlying pathology than the resting hemodynamic measures, as reported in a study of individuals with MCI [16]. The blood oxygenation level dependent (BOLD) responses suggest highly dynamic – and heterogeneous – changes in the functional responses to memory tasks: from frequent, though inconsistent [17] hyperactivation in healthy subjects at genetic risk for AD [18] to hypoactivation in AD subjects [19,20], and with variable findings in MCI [21]. Increased BOLD responses in neocortical areas have also been observed, and viewed as potentially compensatory to the disruption in medial temporal regions [22,23]. Due to the established dependence of BOLD response on resting cerebral blood flow, and its sensitivity to the interplay between hemodynamic and metabolic changes accompanying neuronal activation, the interpretation of BOLD data in these patients is markedly complex. In addition to the evolving changes in neuronal and vascular function and hence a disease-stage dependence of these measures, the vast majority of AD patients studied are medicated, typically with a form of a cholinesterase inhibitor (ChEI). While the effects of acute ChEI administration on cortical activation in AD patients have been well characterized, the data on the long-term treatment with ChEIs in this population are limited and, for the most part, focused on resting perfusion and metabolism [24–28]. Since acetylcholine is a potent vasodilator, the ChEI treatment itself poses a further confound in the interpretation of the observed hemodynamically weighted signals. To date, no longitudinal pharmacological functional study of AD patients has controlled for scan-rescan effects, resting perfusion differences, and behavioral performance/effort, all the while quantifying the stimulation elicited functional hyperemia.

The current study, part of a larger longitudinal investigation, aimed to fill some of the current gaps in our understanding of brain hemodynamic changes in early stage AD by quantifying perfusion, *via* pseudo continuous arterial spin labeling (PCASL), in a cohort of early stage AD patients that have not yet commenced treatment, thus isolating the disease-related vascular changes in these subjects, compared to age, gender, and education matched healthy volunteers. To identify the vascular changes *in the absence of neuronal impairment*, we investigated the hemodynamic responses in the primary visual cortex, a region widely appreciated as being spared until the very late stages of typical AD-related neurodegeneration [29,30] and apparently sensitive to treatment with ChEIs [31–35]. Simple visual stimulation conferred additional advantages of eliciting robust activations while minimizing the confounding effects arising from the differences in task demands and performance, thus allowing us to isolate the effects on cerebrovascular function and to correlate the neuroimaging metrics with overall cognitive status.

2. Experimental methods

2.1. Participants

Thirty-five ChEI naïve patients with mild AD were recruited from the Sunnybrook Cognitive Neurology Clinic and Multidisciplinary Memory Clinic at the Sunnybrook Health Sciences Centre. Patients met revised criteria for probable AD [36] and were referred to this study when an experienced senior neurologist (SEB or MM) considered them to be of mild severity yet judged it appropriate for them to commence ChEI treatment. Patients were not excluded on the basis of other risk factors or pathology, except where these suggested a mixed disease picture, precluding a diagnosis of probable Alzheimer's disease. Immediately after the initial scan, patients began treatment with a cholinesterase inhibitor following standard dose titration guidelines. Of note, since this was an observational study of routine treatment for AD, no changes were made to the existing medication regimen of the participants. Twenty-nine healthy matched elderly volunteers were recruited from the community and screened to exclude any current or prior neurological or psychiatric history. All subjects underwent neuropsychological testing at the time of the initial imaging session. Table 1 lists the demographic and clinical details. All subjects consented to multiple MRI sessions and neuropsychological testing in line with the Research Ethics Board at the Sunnybrook Health Science Centre. Moreover, supplemental consent was obtained from patients' caregivers at intake.

2.2. Imaging data acquisition

Subjects were imaged immediately prior to the start of ChEI therapy, 6 months thereafter (14 controls and 26 patients) and 12 months following the initial scan (3 controls and 11 patients). The attrition resulted from withdrawal of consent (likely influenced in controls by the long, 1.5-hour imaging time), treatment cessation in patients due to tolerance issues, and technical problems with the scanner (backward incompatible software upgrades). Patients and controls underwent identical imaging protocols at each time point. To familiarize them with the scanning environment, head coil and mirror system, task, and response paddles, all participants completed a mock-scanning session prior to the first imaging session. At this time, they performed two full practice runs in the mock scanner environment and were instructed to minimize head motion throughout the scanning sessions. To minimize the delay in beginning therapy, the patients were started on their prescribed ChEI immediately following the initial scan, which occurred within two weeks of study enrollment. Each scanning session was preceded by a practice task session and task and head motion-related instructions were reiterated on entering the MRI scanner.

At each time point, the scanning protocol included a 3D fast spoiled gradient-echo sequence for anatomical reference (TR/TE = 8.1 ms/3.1 ms, with nominal spatial resolution of $0.86 \times 0.86 \times 0.86$ mm^3), followed by a 3D time-of-flight MRA scan to facilitate the prescription of the labeling plane in all PCASL acquisitions. For resting flow quantification, 6 different post-labeling delays (PLDs of 100, 500, 900, 1300, 1700, and 2100 ms) were sampled, with 12 repetitions of control and labeled volume pairs each, using a PCASL sequence, with a TE/TR of 17 ms/3.5-5 s, for a total PCASL scan time of under 10 min. Seventeen

Table 1
Participant characteristics and cognitive scores. Values are displayed as mean (standard deviation, minimum-maximum). Cognitive scores during the initial testing at study enrollment and at each of the two follow-up instances are listed. At baseline, MMSE scores were significantly lower in patients relative to controls (by 3.4 ± 0.4, $p < 1e\text{-}3$). MMSE score in patients was higher before treatment with respect to its level during treatment (by 1.1 ± 0.5, $p = 0.03$), whereas no time-dependence in MMSE scores was observed in controls.

	Healthy controls	AD patients
Demographics		
Age (years)	73.4(8.0)	76.0(8.6)
Education (years)	15.7(3.2)	14.8(3.1)
Time since disease onset (years)	Not applicable	4.1(2.9)
Time to follow-up 1 (weeks)	33.2(9.0)	31.7(10.6)
Time to follow-up 2 (weeks)	53.0(21.7)	64.6(10.6)
Cognitive scores		
MMSE @ baseline	28.5(1.1, 25–30)	25.1(2.0, 22–28)
MMSE @ follow-up 1	29.3(0.9, 28–30)	24.3(2.1, 21–29)
MMSE @ follow-up 2	28.0(1.4, 27–29)	23.2(3.4, 14–27)

Please cite this article as: R. Janik, et al., Attenuation of functional hyperemia to visual stimulation in mild Alzheimer's disease and its sensitivity to cholinesterase inhibi..., Biochim. Biophys. Acta (2015), http://dx.doi.org/10.1016/j.bbadis.2015.10.023

Download English Version:

https://daneshyari.com/en/article/8259375

Download Persian Version:

https://daneshyari.com/article/8259375

Daneshyari.com