Clinical Neurophysiology 124 (2013) 851–856

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

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

Tissue oxygen saturation and pulsatility index as markers for amnestic mild cognitive impairment: NIRS and TCD study

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ARTICLE INFO

Article history:
Accepted 19 November 2012
Available online 21 December 2012

Keywords:
Near-infrared spectroscopy
Transcranial Doppler
Mild cognitive impairment
Cerebral oxygen deficiency
Brain hypoperfusion

HIGHLIGHTS

- New application of near-infrared spectroscopy to study amnestic mild cognitive impairment.
- The TOI reduction on the temporal-parietal cortex of both side and increase of pulsatility index in both MCA are associated with a clinical diagnosis of amnestic mild cognitive impairment.
- The reduction of cerebral tissue oxygen saturation, especially when combined with the increase of pulsatility index, may be considered a new marker for amnestic mild cognitive impairment.

ABSTRACT

Objective: To evaluate the utility of near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) parameters as potential markers for amnestic mild cognitive impairment (aMCI).
Methods: By means of NIRS and TCD, noninvasive and inexpensive technologies, we studied 21 patients with aMCI (10 M and 11 F, 70.2 ± 7.3 years) and 10 age matched healthy controls.
Results: By means of NIRS, we found a significant mean decrease of tissue oxygen saturation of cortex microcirculation (TOI), – 27%, $p < 0.0005$, on the temporal–parietal cortex of both side compared to the controls. By means of TCD, we found a significant mean increase of pulsatility index (PI), $p < 0.0007$, of middle cerebral artery (MCA) of both side compared to the controls. Cerebrovascular risk factors were present in 81% of the aMCI patients.
Conclusions: Our study reveals that the TOI reduction on the temporal-parietal cortex of both side and the increase of PI in both MCA are associated with a clinical diagnosis of aMCI patients.
Significance: The reduction of TOI may be considered a new marker for aMCI, especially when combined with the increase of PI in MCA.

1. Introduction

Mild cognitive impairment (MCI), or isolated memory impairment, is a brain-function syndrome involving the onset and evolution of cognitive impairments beyond those expected based on the age and education of the individual, but which are not significant enough to interfere with their daily activities (Petersen et al., 1999). Although MCI can present with a variety of symptoms, when memory loss is the predominant symptom it is termed "amnestic MCI" (aMCI) (Petersen et al., 1999). There is evidence suggesting that aMCI patients may be in a transitional stage of evolving Alzheimer's disease (AD) (de la Torre, 2004); patients in this hypothesized stage demonstrate diffuse amyloid in the neocortex and frequent neurofibrillary tangles in the medial temporal lobe (Petersen et al., 2006). There is emerging evidence that magnetic resonance imaging can observe deterioration, including progressive loss of gray matter in the brain, from aMCI to full-blown Alzheimer disease (Whitwell et al., 2008). A technique known as PiB PET imaging is used to clearly show the sites and shapes of β-amyloid deposits in living aMCI subjects using a C_{11} tracer that binds selectively to such deposits (Jack et al., 2008).

aMCI has a prevalence between 17% and 34% in the population aged over 65 years. Up to 40% of the subjects with aMCI convert to AD after 3 years (de la Torre, 2004). A large body of evidence indicates that sporadic AD (90–95% of AD) is a vascular disorder with neurodegenerative consequences and cerebral hypoperfusion is one of the earliest pathological signs in the development of cognitive failure (de la Torre, 2004). De la Torre proposes that advanced aging with a comorbid condition, such as a vascular risk factor that further decreases cerebral perfusion, promotes a critically attained threshold of cerebral hypoperfusion (CATCH), during the first stage

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1388-2457/$36.00
http://dx.doi.org/10.1016/j.clinph.2012.11.013

of sporadic AD, corresponding to aMCI. CATCH induces suboptimal delivery of energy substrates to neuronal tissue. Because glucose is the main fuel of brain cells, its deficient delivery, together with a deficient delivery of oxygen, compromise neuronal stability because the substrates for aerobic glycolysis fail to meet brain tissue demand. The outcome of CATCH is a metabolic cascade that involves, among other things, mitochondrial dysfunction, oxidative stress, decreased ATP production and increased calcium entry, abnormal protein synthesis, cell ionic pump deficiency, signal transduction defects and neurotransmission failure. With time, these events contribute to the characteristic progressive cognitive decline of patients with AD, as well as regional anatomic pathology consisting of synaptic loss, tissue atrophy and neurodegeneration (de la Torre, 2008).

In patients with aMCI, HMPAO SPECT imaging studies show a statistically significant reduction of cerebral blood flow (CBF) in temporal and parietal cortex of both hemispheres compared with controls (Johnson and Albert, 2000; Kogure et al., 2000). In the same cortical areas, FDG PET studies show hypometabolism in aMCI patients compared with controls (Chetelat et al., 2003).There is a PET study, using oxygen-15 labeled compounds, that has measured quantitatively CBF, cerebral metabolic rate of oxygen and oxygen extraction fraction (OEF) during the resting state in 13 patients with probable AD. In the probable AD group, the typical parieto–temporal pattern of hypoperfusion and hypometabolism was observed and, additionally, there was a significant increase in OEF in and around the parieto–temporal cortices (Nagata et al., 2000). Deposition of amyloid-β protein (Aβ) in the brain is the hallmark of AD pathology (Mattson, 2004). Aβ, the major component of neuritic plaques, is derived from β-amyloid precursor protein (APP) after sequential cleavage by β- and γ-secretase. β-Site APP cleavage enzyme 1 (BACE1) is the major β-secretase in vivo. In a recent study, the author demonstrates that chronic hypoxia up-regulated β-secretase cleavage of APP and Aβ production by increasing BACE1 gene transcription and expression. The chronic hypoxia treatment markedly increased Aβ deposition and neuritic plaque formation and potentiated the memory deficit in Swedish mutant APP transgenic mice (Sun et al., 2006). Taken together, these results clearly demonstrate that hypoxia can facilitate sporadic AD pathogenesis, and they provide a molecular mechanism linking vascular factors to sporadic AD (Sun et al., 2006). Finally, the author suggests that interventions to improve cerebral perfusion may benefit sporadic AD patients. Previous studies (Yang et al., 2003; Li et al., 2004) show that BACE1 expression is elevated in the brains of sporadic AD patients, and the degree of elevation is correlated with Aβ production.

Near-infrared spectroscopy (NIRS) is a safe, repeatable, inexpensive technology of monitoring microcirculation at the bedside without the use of radioisotopes or other contrast agents. The diagnostic potential of this optical methods has been widely known since Wiernsperger et al. (1981), first demonstrated that transmittance measurements of near-infrared radiation (690–900 nm) (IR) could be used to monitor the degree of oxygenation of cerebral tissue. By using IR, NIRS measures oxygenated (HbO_2) and deoxygenated (Hbr) haemoglobin concentration (called DC signal or component) and the relative tissue oxygen saturation of cortex microcirculation (TOI) that reflects cerebral function and metabolism (Culver et al., 2003). The microcirculation consists of the smallest blood vessels (<100 μm diameter) where the oxygen release to the tissues takes place, and consists of arterioles, capillaries, and venules (Culver et al., 2003). Within the 650–1000 nm window it is possible, with sensitive instrumentation, to detect IR which has traversed cerebral tissue. Near-infrared photons can achieve a sufficient penetration depth, about 2 cm, (Ohmae et al., 2005) for non-invasive probing of cerebral cortex hemodynamics in humans.

Transcranial Doppler (TCD) ultrasound is a noninvasive and inexpensive technology that has been used to appraise cerebral hemodynamics in aMCI and AD (Roher et al., 2011). Many researchers are trying to identify functional markers by brain neuroimaging, TDC, NIRS or biomarkers that may increase the diagnostic specificity allowing to identify the dementia in a pre-clinical stage and to anticipate the start of treatment to delay the onset of the disease (Schuff and Zhu, 2007).

The objective of our article is to evaluate the utility of NIRS and TCD parameters as potential markers for aMCI.

2. Methods

2.1. Procedure

According to the rules of the local hospital in which the tests were held, healthy subjects and patients were asked to sign an informed consent and the study was approved by the local ethics committee. By means of a NIRS system, we studied 21 patients with aMCI, (10 M and 11 F, mean age: 70.2 ± 7.3 years), according to Petersen criteria (Petersen et al.,1999) and 10 age matched healthy controls (4 M and 6 F, mean age 69.5 ± 6.8 years). The patients and controls were also studied by means of Mini-Mental State Examination (MMSE) and Rey Memory Test (RMT) – 15 words immediate and delayed recall (WIR and WDR) –; in our study, the inclusion criteria of aMCI are: MMSE range 24–28; WIR <25.14 and WDR <3.44 (cutoff values of aMCI diagnosis); Activities of Daily Living (ADL): normal; Instrumental Activities of Daily Living (IADL) subnormal; Clinical Dementia Rating Scale (CDR): 0.5. The patients underwent clinical examinations and were also studied by means of cranial CT scan, extracranial Doppler, TCD and blood tests to exclude secondary forms. The inclusion criteria of controls are: MMSE and RMT in normal range: MMSE 29–30, WIR >25, 14 and WDR >3.44; the healthy human volunteers were recruited from our hospital. They were non-smokers. Before being included in this study, all the healthy subjects underwent clinical examinations intended to exclude cerebral, cardiac, and circulatory diseases. By means of NIRS in both group, we measured TOI (Figs. 1 and 2) on frontal and parietal–temporal cortex of both side with our probe on position F2–F8 and F1–F7, and P4–T4 and P3–T3 of the international 10–20 EEG system, respectively (Fig. 3).

The patients and controls were allowed to rest in a dimmed and quiet room, laying comfortably in a sitting position with eyes closed and breathing room air. The probe of our NIRS was secured to the subjects' head by an elastic custom tape. To avoid bias from environmental light a black cloth covered the probe. The subject were instructed to minimize his or her movements during the measurements for minimizing motion artifacts.

The patients and controls were also studied by means of TCD (model-64 EME-Pioneer) using a 2-MHz probe. In both MCA, mean cerebral blood flow velocity (MBFV), systolic blood flow velocity (SBFV) and diastolic blood flow velocity (DBFV), in cm/s were measured by the transtemporal approach at a depth of 50–55 mm. The position of the probe was adjusted until a maximal signal was obtained.

Pulsatility index (PI) was calculated using the following formula;

$$PI = (SBFV - DBFV)/MBFV \quad (1)$$

In both group, hemoglobin concentration in blood and systemic arterial pressure were initially measured. Finally, in both groups, peripheral arterial saturation (SpO_2) was recorded with the use of a pulse oximeter (Nellcor N-550) at finger.