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Predicting the conversion of mild cognitive impairment to Alzheimer's disease based on the volumetric measurements of the selected brain structures in magnetic resonance imaging

Marta Nesteruk [a,*], Tomasz Nesteruk [b], Maria Styczyńska [c], Anna Barczak [c], Monika Mandecka [c], Jerzy Walecki [d], Maria Barcikowska-Kotowicz [a,c]

[a] Department of Neurology, Central Clinical Hospital of the Ministry of Interior, Warsaw, Poland
[b] Department of Radiology, Central Clinical Hospital of the Ministry of Interior, Warsaw, Poland
[c] Department of Neurodegenerative Disorders, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
[d] Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

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ABSTRACT

Introduction: Mild cognitive impairment (MCI) is defined as abnormal cognitive state, but does not meet the criteria for the diagnosis of dementia. According to the new guidelines Alzheimer's disease (AD) involves not only dementia's phase but also predementia phase which is asymptomatic and pathological process in the brain is already present. For this reason it is very important to determine the suitability of markers which should be positive before onset of the first symptoms. One of these biomarkers is a structural magnetic resonance imaging with hippocampal volumetric assessment.

The aim of this study was to investigate the usefulness of structural brain magnetic resonance imaging with volumetric assessment of the hippocampus and entorhinal cortex, posterior cingulate gyrus, parahippocampal gyrus, temporal gyri: superior, medial and inferior, to predict the conversion of MCI to AD.

Material and methods: Magnetic resonance imaging of brain was performed at the baseline visit in 101 patients diagnosed with MCI. Clinic follow-ups were scheduled after 6.12 and 24 months.

Results: Amongst 101 patients with MCI, 17 (16.8%) converted into AD within two years of observation. All measured volumes were lower in converters than non-converters. Discriminant analysis was conducted and sensitivity for MCI conversion to AD was 64.7%, specificity 96.4%. 91% of patients were correctly classified (converter or non-converter).

Conclusions: Volumetric measurements may help clinicians to predict MCI conversion to AD but due to low sensitivity it cannot be use separately. The study group requires further observation.

* *Corresponding author at*: Neurology Clinic, Central Hospital of the Ministry of Interior in Warsaw, 137 Woloska Str., 02-507 Warsaw, Poland. Tel.: +48 22 508 18 60; fax: +48 22 508 18 80.
E-mail address: msuchcicka@gmail.com (M. Nesteruk).

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1. Introduction

Mild cognitive impairment (MCI) is defined as abnormal cognitive state, but does not meet the criteria for the diagnosis of dementia. In the past MCI was treated as a transitional state between the physiological aging and dementia. Currently it is a separate diagnosis, although it is considered that MCI is a stage of pathophysiological process of AD [1]. Patients with MCI do not have problems with function in daily life, sometimes they only need minimal aid [2]. Patient diagnosed with MCI can present stable, non-progressive symptoms until the end of his life, but there can also be observed progression of the disease (usually gradual), leading to the development of dementia. It is estimated that the percentage of the conversion to Alzheimer's disease (AD) is about 10–15% per year [3]. Criteria for diagnosis of MCI from 2011 [1] in addition to core clinical criteria distinguish research criteria. The research criteria include an assessment of the biological markers of neurons' injury, namely:

- markers of β-amyloid (Aβ) deposition by assessing the levels of Aβ42 in cerebrospinal fluid or PET amyloid imaging
- markers of neuronal injury by evaluating the levels of total and phosphorylated tau protein or a reduction in hippocampal volume, or atrophy of the medial temporal lobe in the magnetic resonance imaging, or hypometabolism in FDG-PET, or hypoperfusion in SPECT.

These criteria are important because pathophysiological process of AD can last even twenty years before onset of clinical symptoms and MCI is considered as a stage of this pathophysiological processes following the preclinical phase of Alzheimer's disease. In MCI phase biomarkers should be already positive (both markers of Aβ deposition and markers of neuronal injury). A sensitive biomarker will play key role when causative treatment of AD will be found because then it will be possible to treat this disease even before the onset of clinical symptoms.

The aim of this study was to investigate the usefulness of structural brain magnetic resonance imaging with volumetric assessment of the hippocampus and entorhinal cortex, posterior cingulate gyrus, parahippocampal gyrus, temporal gyri: superior, medial and inferior, to predict the conversion of MCI to AD.

The first abnormalities in patients who are at risk of AD are positive markers of deposition of β-amyloid (decreased Aβ concentration in the cerebrospinal fluid and/or positive PET amyloid imaging). In this study the marker of neuronal injury was used – structural MRI with volumetric assessment of selected brain structures (inter alia hippocampus, entorhinal cortex) because of good availability of magnetic resonance in Poland (the best of neuroimaging biomarkers) and its non-invasive nature. Furthermore, according to Jack, in the MRI pathological changes are observed as one of the last biomarkers [4] and our patients were not in the preclinical phase – they were diagnosed with MCI. Reduction of the measured volumes was expected in patients who were at risk of conversion to AD.

2. Material and methods

In the study initially participated 163 patients diagnosed with MCI who were evaluated in Alzheimer's Department of MSW Hospital in Warsaw. 101 patients remained for further data analysis (due to lack of follow-up visits or errors in MRI which precluded further analysis of the data). The patients were aged 50–80 years, mean age 62.7. Neurological assessment, MMSE (Mini-Mental State Examination), CDT (clock drawing test) and GDS (Global Deterioration Scale) were performed. The average score of MMSE was 27.4/30 (range 25–30 points). The average score of CDT was 8.5/10 points (range 6–10 points) and the mean score of GDS 2.7 points (range 2–3 points). Laboratory tests included morphology, TSH, blood glucose, urea, creatinine, transaminases, VDRL (veneral disease research laboratory), levels of vitamin B12 and folic acid and there was no significant abnormalities. Each patient was assessed using standard neuropsychological tests (according to the standards described by Gabryelewicz [5]). On CDR scale (Clinical Dementia Rating), all patients received 0.5 or 0/0.5. For each patient, follow-up visits were scheduled after 6 months (±14 days), 12 months (±30 days) and 24 months (±50 days). Then patients were again evaluated neurologically (included MMSE, CDT, GDS assessment). Neuropsychological examination was performed to assess potential disease progression. In patients diagnosed with conversion to AD acetylcholinesterase inhibitor treatment was initiated. All patients remain under the care of the Memory Disorders Outpatient Clinic of MSW Hospital in Warsaw.

Brain MRI was performed for each of the patients on a 1.5 T Toshiba apparatus in the Department of Radiology of MSW Hospital. Scans were obtained in T2-weighted, FLAIR, DWI images and also thin 3D T1 Alzheimer sequence. Using FreeSurfer software volumes of selected structures were calculated, that is: hippocampus, entorhinal cortex, posterior cingulate gyrus, parahippocampal gyrus, temporal gyri: superior, medial, inferior and total intracranial volume. Subsequently, the results have been checked by the same radiologist to detect and eliminate possible errors which may arise in the process of segmentation. Each volume (hippocampus, entorhinal cortex, posterior cingulate gyrus, parahippocampal gyrus, temporal gyri: superior, medial, inferior) was divided by the total intracranial volume to normalize results and to make possible comparison between patients and eliminate differences in the brain size (according to Whitwell [6]). All volumes were multiplied by 1000 in order to facilitate comparison between them.

3. Results

17 of the 101 patients diagnosed with MCI converted into AD within two years of observation, namely 16.8% (distribution of diagnosed patients for each visit, Table 1). The study population was divided into two subgroups:

- Subgroup 1 – non-converters, who did not converted into AD (84 patients).
- Subgroup 2 – converters, who converted into AD (17 patients).