The use of the Hungarian Test Your Memory (TYM-HUN), MMSE and ADAS-Cog tests for patients with Mild Cognitive Impairment (MCI) in a Hungarian population: a cross-sectional study

Szabolcs Garbóczy
Debreceni Egyetem
Éva Magócs
Debreceni Egyetem
Gergő Szőllősi
Debreceni Egyetem
Szilvia Harsányi
Debreceni Egyetem
Égerházi Anikó
Debreceni Egyetem
László Kolozsvári (dr.laszlo.kolozsvari@gmail.com)
Debreceni Egyetem https://orcid.org/0000-0001-9426-0898

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Abstract

BACKGROUND Alzheimer's Disease (AD) is a growing disease process with aging. If we could recognize the disease at an early stage and increase the number of years spent in a better condition through preventive and treatment measures, we could reduce the pressure both directly on families and indirectly on society. There is a need for testing methods that are easy to perform even in general practitioner’s office, inexpensive and non-invasive, which could help early recognition of mental decline. We have selected Test Your Memory (TYM), which has proven to be reliable for detecting AD and mild cognitive impairment (MCI) in several countries. Our study was designed to test the usability of the TYM-HUN comparing with the ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive Subscale) in MCI recognition in the Hungarian population.

METHODS TYM test was translated and validated into Hungarian (TYM-HUN). The TYM-HUN test was used in conjunction with and compared with the Mini-Mental State Examination (MMSE) and the ADAS-Cog. For our study, 50 subjects were selected, 25 MCI patients and 25 healthy controls. Spearman’s rank correlation was used to analyze the correlation between the scores of MMSE and ADAS-Cog with TYM-HUN.

RESULTS MCI can be distinguished from AD and normal aging using ADAS-Cog and MMSE is a useful tool to detect dementia. We established a 'cut-off' point of TYM-HUN (44/45points) where optimal sensitivity and specificity values were obtained to screen MCI. The total TYM-HUN scores significantly correlated with the MMSE scores ($\rho=0.626$; $p<0.001$) and ADAS-Cog scores ($\rho=-0.723$; $p<0.001$).

CONCLUSIONS Our results showed that the Hungarian version of TYM (TYM-HUN) is an easy, fast, self-administered questionnaire with the right low threshold regarding MCI and can be used for the early diagnosis of cognitive impairment.

Background

The dreaded global burden of dementia, its extensive research and the possible available tools of prevention have led to the need to be able to differentiate early between normal and pathological aging. Therefore, the concept of mild cognitive impairment (MCI) has been introduced in recent decades. The history of mild cognitive impairment has gone through many stages throughout until it has reached its nowadays accepted, but ever-changing state. As early as 1962, the concept of Benign and Malignant Senescent Forgetfulness was used [1]. In 1986, the National Institute of Mental Health (NIMH) proposed Age-Associated Memory Impairment to distinguish more easily between the two [2]. From 1982, the predecessor of MCI, the mild cognitive decline, was used to correspond to grade 3 on the Global Deterioration Scale, and from 1988 onwards as MCI [3]. In 1994, the concept of Age-Associated Cognitive Decline was introduced, with dementia being the exclusion criterion [4]. The concept of Cognitive Impairment No Dementia was introduced in 1997 and included a larger patient population because the

underlying cause was irrelevant and could include mental decline in psychiatric or somatic and neurological diseases [5]. And beyond that, the conceptualists came up with more ideas.

Diagnostic criteria

In 2003, an international committee (Key Symposium) was held to discuss and consolidate the knowledge gained so far, establishing criteria, organizing the knowledge available, and formulating guidelines for disease assessment regarding the involvement of neuroimaging, biomarkers and genetics [6-8]. According to this committee, the MCI criteria are shown in **Table 1**.

Once diagnosed as MCI, the path of the subtypes can be divided in two ways: if memory is impaired, it is the amnestic type, or, if not, the non-amnestic type. Within each, we distinguish single or multiple domain involvement [7].

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) established specific criteria for MCI due to Alzheimer's and later to Parkinson's disease [9]. The diagnostic categorization of the Mayo Clinic's Alzheimer's Disease Research Center places the disease (MCI) between normal aging and dementia. Their diagnostic criteria are as follows: 1, memory complaint, preferably confirmed by an informant; 2, objective memory impairment for age and education; 3, preserved general cognitive function; 4, intact activities of daily living; and 5, not demented [10]. Earlier diagnostic manuals [e.g. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)] have been used to encode this heterogeneous group of diseases with different coding. According to the current Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), it can be categorized as Mild Neurocognitive Disorder [11]. See **Table 2.** for the diagnostic criteria.

Epidemiology

The results of epidemiological studies have led to significant differences due to the immaturity of the concepts and the different formulations of criteria. To overcome these difficulties, a 2015 cohort study combined the criteria and found that the prevalence of MCI among those over 60 was 5.9% [12]. A Mayo Clinic study published in 2012 found that the incidence of MCI in the 70-89 population was 63.6/1000 person-years [13] A smaller follow-up study found that the conversion rate for community-selected participants was 5% person-years [14]. We found no data about the incidence or prevalence of the Hungarian MCI or AD population, the number of the patients available is based on the estimated number of patients of the international literature.

Assessment

The most commonly used procedures in Hungary for the identification of the disease are the Mini-Mental State Exam or the Early Mental Test developed by the University of Szeged [15]. There is no international consensus on which is the best test and with which cut-off points. In recent years, the Montreal Cognitive Assessment and the Short Test of Mental Status have been used for this purpose, the Hungarian version of which is not yet available [16]. In the field of biomarkers, amyloid deposits or neuronal degeneration

are being investigated, which we have not been able to do in routine clinical practice, as well as genetic testing, for which there is no accepted gold standard yet.

We have selected a short, self-completed test method developed by the English author Jeremy Brown, which is validated in different countries worldwide, also in Hungary (TYM-HUN) [17, 18]. This is the Test Your Memory (TYM), which examines a fairly wide range of cognitive functions in a short period of time and provides reliable information to the clinician when properly evaluated [19]. Our study aimed to compare the diagnostic utility of the TYM-HUN with the MMSE and the ADAS-Cog tests for MCI in a Hungarian population. We determined a 'cut-off' point of TYM-HUN where optimal sensitivity and specificity values were obtained to screen MCI.

Methods

Inclusion and exclusion criteria

50 persons (25 MCI patients) and 25 healthy controls (HC) were recruited into the observational cross-sectional study at the Psychiatric Clinic and Hospital of the University of Debrecen between January 2018 and August 2019. Adults (patients/healthy controls) from the age of 18 and over were included. The diagnosis of mild cognitive impairment was made according to published criteria [6-8]. Patients were seen and diagnosed by a consultant psychiatrist and underwent neurological assessment, MMSE, ADAS-Cog, structural imaging [eg. CT (computed tomography), MRI (magnetic resonance imaging)], and blood tests. Depressive patients with cognitive problems related to mood disorders were excluded with the Beck depression scale.

Healthy controls were recruited from relatives accompanying patients to the clinic and the hospital, as well as from relatives of patients attending psychiatric outpatients' departments at these two institutions. The people with a history of neurological disease, memory problems, or brain injury were excluded. All participants gave written informed consent and they filled out all our questionnaires completely.

TYM test was translated to Hungarian Language and validated for AD (TYM-HUN) [18]. The MMSE, ADAS-Cog and TYM-HUN tests, and to exclude the depression, the Beck Depression Inventory was filled out by the patients and controls, as well.

The age distribution for normality of the sample was tested with the Shapiro-Wilk test and the age difference between the MCI patients and controls was tested with Mann-Whitney-Wilcoxon rank sum test. We used Fisher's exact test to investigate the gender distribution and the Kruskal-Wallis test for testing the educational differences.

Spearman's rank correlation and a multivariate logistic regression model was used to investigate the correlations between the different tests.

The receiver operating characteristic (ROC) curve and the sensitivity, specificity, positive (PPV) and negative predictive values (NPV) we also established.

We performed the statistical analyses with STATA 11.1 software (Statacorp LP. College Station, TX, USA).

Results

We evaluated the TYM-HUN results of 50 adults aged 55–84 years. 25 MCI patients (mean age 74.84 ± 6.22 years) and 25 healthy control (HC) participants (mean age 71.32 ± 7.69 years) were investigated. The female to male ratios were 6:19 and 8:17 in the MCI and HC groups, respectively. The MCI patients reached an average score of 39.52 ± 5.73/25 on the TYM-HUN, 26.32 ± 2.98/25 points on the MMSE and 16.80 ± 6.11/25 on the ADAS-Cog tests. The average results of the healthy control group members were 47.40 ± 1.68/25 with the TYM-HUN, 29.04 ± 1.06/25 with the MMSE and 5.80 ± 3.64/25 with the ADAS-Cog tests. The age distribution of the sample was significantly ($p < 0.001$) different from the normal distribution, therefore no significant ($p = 0.057$) difference was observed between the MCI and HC group's mean age. There was no significant difference between the gender distribution of the two groups ($p = 0.754$). These calculations suggest that our sample was comparable with respect to age and gender. In case of patients with MCI, no significant difference was found between the subjects' mean TYM-HUN score when comparing them according to their gender (male = 43.33, female = 38.32, $p = 0.060$). There were no significant differences between when the educational level was analyzed (primary = 38.00; secondary = 38.60; tertiary = 41.55; $p = 0.467$).

Spearman's rank correlation was used to analyze the correlation between the scores of MMSE and ADAS-Cog with TYM-HUN. The total TYM-HUN scores significantly correlated with the MMSE scores ($\rho = 0.626$; $p < 0.001$) and ADAS-Cog scores ($\rho=-0.723$; $p < 0.001$).

A multivariate logistic regression model which was adjusted for age, gender and level of education was used to determine how the TYM-HUN score affects the outcome of being a patient suffers from MCI according to the diagnosis established by ADAS-Cog. A 1 point increase in the TYM-HUN score resulted in a 79% reduction of the probability of developing mild cognitive function disease. (OR = 0.21, $p = 0.005$).

The receiver operating characteristic (ROC) curve created based on the TYM-HUN scores using the presence/absence of mild cognitive function as the criterion variable is presented in Fig. 1.

According to the scores of the TYM-HUN reached by our patients, the sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were established. In the light of our data, it seems that the ideal cut-off score should be at 44/45 between HC and MCI patients (Table 3.).

Discussion

The increasing number of the patient with dementia and MCI, the financial and social burdens of these diseases made it necessary, to investigate the possibilities of the earliest detection of the pathological cognitive impairment.

According to our findings, the Hungarian version of the TYM test (TYM-HUN) seems to be a useful tool for the early detection of the MCI. The Hungarian version of the MMSE is a good diagnostic test for AD but is not sensitive to the recognition of MCI. MCI can be distinguished from AD and normal aging using ADAS-Cog, which takes a long time to perform [20]. The TYM-HUN test also can be used outside the hospital settings, for example in the primary care or family medicine practices, as it is self-administered, takes a short time to fill out (eg. while waiting to be seen in the waiting room with a minimal supervision by a nurse or an administrator) and it might be easier for the patient or health care staff to invite more people to participate in the examination. The TYM test also has a version, where it can be performed via telephone, that can make the patients easier to reach [17].

While MCI subjects had an average score of 45 in the original publication, our study found it to be 39.52 [19]. Studies in Spanish and Japanese have found, like ours, that the cut-off value of 44 for the MCI to choose. Based on this, the test has 85.7% and 76% sensitivity, 69% and 74% specificity respectively, while our results show that these values are 80 and 92% [21, 22]. Polish and French investigators did not find the test useful in differentiating between MCI and healthy controls [23, 24].

Japanese researchers in a larger sample, like us, found no difference in test scores with regard to gender and education level [22]. According to French data, there is no correlation between gender and years spent in education ($p = 0.34$) and performance on TYM, but this can be observed regarding age ($p = 0.004$) [24]. According to the Chilean study, the performance was influenced by the highest level of education (β coefficient = 0.31, $p < 0.001$), but age ($p = 0.849$) had no relation to performance on the TYM test [21]. The Polish study (which divided the subjects into two groups and drew the cut-off at 75) found that age ($p < 0.003$) and the number of years of education ($p < 0.001$) influence the score on TYM [23].

Conclusions

One of the main strengths of our study, that the TYM-HUN test is the first short self-administered test in Hungarian language, that detect the mild cognitive impairment. The ADAS-Cog is also sensitive enough, but the administration of the ADAS-Cog is time-consuming, difficult to use in the everyday outpatient and primary care settings.

The limitation of the study is the relatively low number of cases, but most of the other studies (especially from small countries, like Hungary) the clinicians could not find a lot of patients with suspected MCI and who fit the inclusion criteria are willing to take part in the study. The refusal of the patients had been one of the greatest challenges, maybe because they don't have a sense of illness or don't want to know about the MCI or early stage of AD or fearing of the stigmatisation.

Although a specially developed version of the test is available for the detection of MCI (TYM-MCI), according to our study, TYM-HUN alone can detect patients with MCI in a Hungarian sample [25].

Summarizing, the TYM-HUN test is a reliable and easy-to-administer tool for assessing people with suspected mild cognitive impairment in Hungarian language. The adapted versions into different

languages of the TYM test can be useful tools to recognize the early stages of dementia in hospital, outpatient and primary care settings and make an international comparison between the countries' population regarding the different forms of cognitive impairment, as well.

Abbreviations

AA – Alzheimer's Association

AD – Alzheimer's disease

ADAS-Cog – Alzheimer's Disease Assessment Scale-Cognitive Subscale

CT – computed tomography

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

DSM-IV-TR - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision

HC – healthy control

MCI – mild cognitive impairment

MMSE – Mini-Mental State Examination

MRI – magnetic resonance imaging

NIA – National Institute on Aging

NPV – negative predictive values

PPV – negative predictive positive

ROC – receiver operating characteristic

TYM – Test Your Memory

TYM-HUN – Hungarian version of the Test Your Memory

Declarations

Ethics approval and consent to participate

The ethical permission was approved by the Hajdu-Bihar County's Government Office of Public Health's Services according to the recommendations of the Regional and Institutional Research Ethics Committee of the Medical and Health Science Centre of the University of Debrecen (Number of permission: DE OEC

RKEB/IKEB 3852-2013), and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Informed written consent was obtained from all patients for being included in the study and all persons gave their written informed consent prior to their inclusion in the study.

Consent for publication

The manuscript does not contain data from any individual person, this section is “Not applicable”.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

SG and ÉM collected the patients’ data and took part in the text writing and manuscript editing. GJS made the statistical analyses and wrote parts of the text. AÉ, HSZ and KLR wrote, critically reviewed and finalized the text and the manuscript. All authors read and approved the final manuscript. All authors have agreed to authorship and order of authorship for this manuscript and that all authors have the appropriate permissions and rights to the reported data.

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Tables

Table 1. MCI Criteria recommendations, Key Symposium [6]

General criteria for MCI
1, Not normal, not demented (Does not meet criteria (DSM IV, ICD 10) for dementia syndrome)
2, Cognitive decline - Self and/or informant report and impairment on objective cognitive tasks - Evidence of decline over time on objective cognitive tasks
and/or 3, Preserved basic activities of daily living / minimal impairment in complex instrumental functions

Table 2. DSM5 criteria for Mild Neurocognitive Disorder [11]

A, Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B, The cognitive deficits do not interfere with the capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medication are preserved, but greater effort, compensatory strategies, or accommodation may be required).
C, The cognitive deficits do not occur exclusively in the context of a delirium.
D, The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia). Specify whether due to: Alzheimer disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance/medication use, HIV infection, prion disease, Parkinson disease, Huntington disease, another medical condition, multiple etiologies, or unspecified.

Table 3. The scores of the TYM-HUN, HC and MCI (diagnosed with ADAS-Cog) patients and the sensitivity, specificity, positive (PPV) and negative predictive values (NPV)

TYM-HUN	HC	MCI	Sensitivity	Specificity	PPV	NPV
25	0	1	4%	100%	100%	51%
26	0	0	4%	100%	100%	51%
27	0	0	4%	100%	100%	51%
28	0	0	4%	100%	100%	51%
29	0	1	8%	100%	100%	52%
30	0	0	8%	100%	100%	52%
31	0	1	12%	100%	100%	53%
32	0	0	12%	100%	100%	53%
33	0	0	12%	100%	100%	53%
34	0	2	20%	100%	100%	56%
35	0	0	20%	100%	100%	56%
36	0	1	24%	100%	100%	57%
37	0	1	28%	100%	100%	58%
38	0	2	36%	100%	100%	61%
39	0	2	44%	100%	100%	64%
40	0	2	52%	100%	100%	68%
41	0	3	64%	100%	100%	74%
42	0	1	68%	100%	100%	76%
43	1	2	76%	96%	95%	80%
44	0	1	80%	96%	95%	83%
45	1	0	80%	92%	91%	82%
46	5	2	88%	72%	76%	86%
47	7	3	100%	44%	64%	100%
48	4	0	100%	28%	58%	100%
49	4	0	100%	12%	53%	100%
50	3	0	100%	11%	50%	100%

Figures

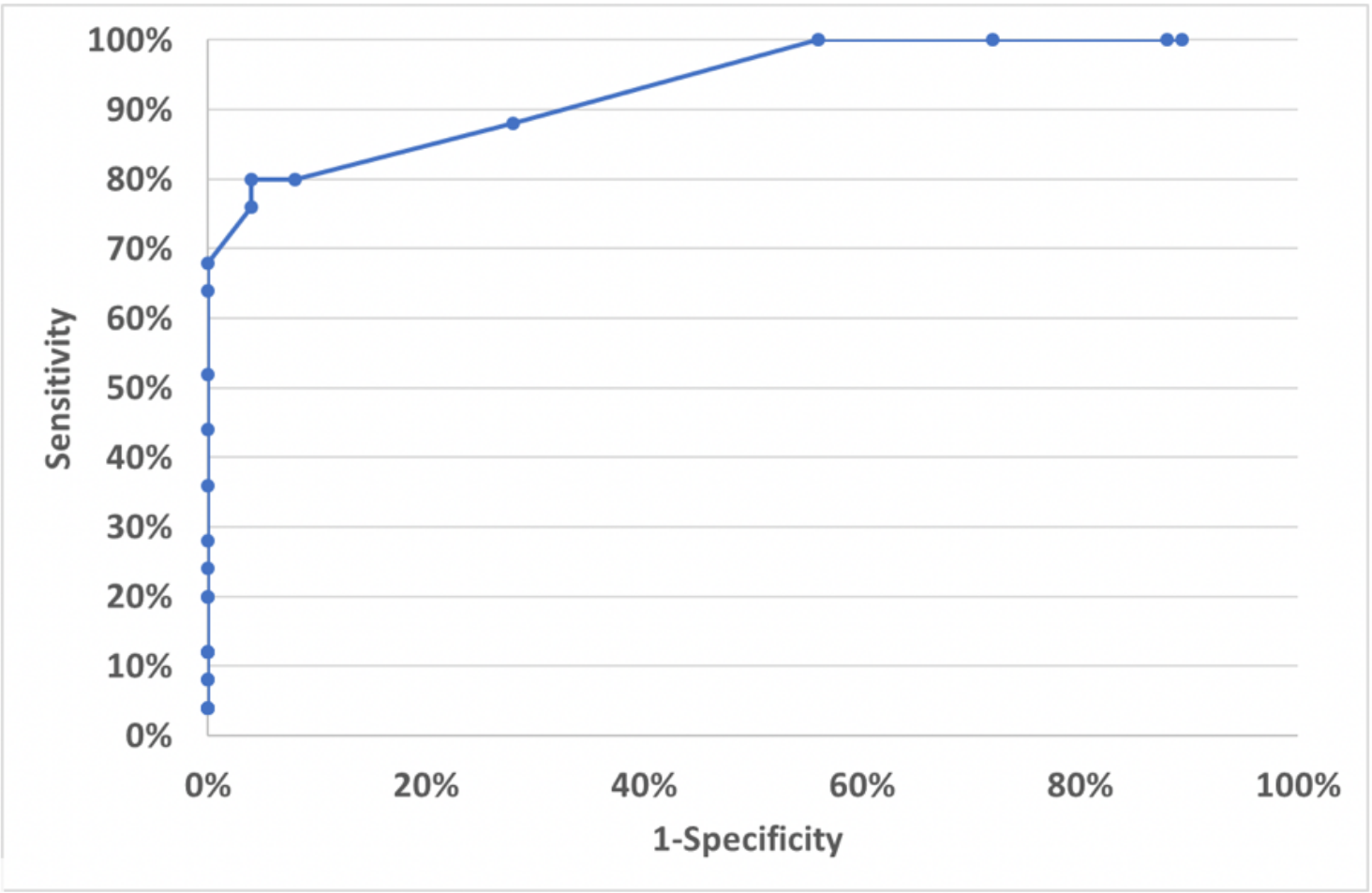

Figure 1

The ROC curve shows the Sensitivity and 1/ Specificity of the TYM-HUN test with MCI patients

Supplementary Files

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- STROBEchecklistcrosssectional.doc