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Polysomnography, brain volumetry, and mismatch negativity as early biomarkers of amnestic mild cognitive impairment progression

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Abstract

Background: Mild cognitive impairment (MCI) is a heterogenous disorder in which a proportion of patients follow stationary or regressive courses while others undergo clinical progression to dementia.

Methods: This study was conducted on 60 amnestic mild cognitive impairment (amMCI) and 20 healthy control subjects submitted to baseline Montreal Cognitive Assessment (MoCA) scale, one-night polysomnography (PSG), hippocampal/entorhinal cortex (HPC/ERC) MRI volumetry, and auditory mismatch negativity (MMN). Fifty-six amMCI subjects continued the study and underwent follow-up MoCA scale 1 year after their baseline evaluation, 17 showed amMCI progression (≥ 3 points decrease in MoCA scale), and 39 had stationary or regressive courses.

Results: Progressive amMCI patients showed reduced sleep efficiency and shortened rapid eye movement (REM) sleep in PSG, decreased HPC/ERC–MRI volumetry and reduced amplitudes with delayed latencies of the MMN evoked potentials.

Conclusions: PSG shortened REM sleep, MRI–HPC/ERC volumes reduction, and low amplitude delayed auditory MMN are valuable non-invasive screening predictors of amMCI progression.

Keywords: Amnestic MCI, MoCA, Polysomnogram, REM sleep, Hippocampal/entorhinal cortex MRI volumetry, Auditory mismatch negativity

Background

Mild cognitive impairment (MCI) is a transitional phase between normal aging and dementia in which the individual retains his usual daily activities but with subnormal performance in standardized neurocognitive tests (Beratisa et al. 2017). MCI is classified to amnestic (amMCI) with episodic memory impairment or non-amnestic characterized by other cognitive domains deficits (attention, visuospatial, social cognition, language and executive functions), and each type may be single or multiple domain MCI (Díaz-Mardomingo et al. 2017a).

Amnestic MCI is a heterogenous disorder in which some patients pass stationary or regressive courses while others undergo progression to dementia notably Alzheimer's disease (AD) (Pandy et al. 2016). Early differentiation between stationary amMCI subjects and those with progressive course becomes a crucial step for proper selection of those candidate for disease-modifying therapy before irreversible neuronal damage takes place. The introduction of non-invasive, sensitive, inexpensive early pre-symptomatic amMCI progression biomarkers is necessary for large population screening and reduces the budgets especially in middle- and low-income countries (Handels et al. 2017).

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Rapid eye movement (REM) sleep disturbances are a common finding in amMCI patients prone to AD conversion possibly due to dysfunctions in the lateral dorsal tegmental, lateral hypothalamic, and pedunculopontine nuclei (Liguori et al. 2016a). Reductions of the hippocampus (HPC) and entorhinal cortex (ERC) volumes as well as their dysfunctions are common indicators of amMCI subjects liable for AD progression (Wolk et al. 2017). At the same time, auditory event-related potential parameters including the mismatch negativity (MMN) can be also used as biomarkers that distinguish amMCI individuals at high risk of progression (Tsolaki et al. 2017).

The aim of the work was to evaluate the values of polysomnography (PSG), MRI–HPC and ERC volumetry, and auditory MMN as early amMCI progression predictors.

Methods

This work was a prospective study conducted on 60 amMCI patients attending the outpatient clinics of The Neuropsychiatry Department, Tanta University Hospitals in the period from 4 April 2016 to 15 December 2017.

The included patients' ages were 55–65 years (to avoid age-related changes in the studied parameters). Amnestic MCI was diagnosed according to the DSM-V criteria of mild neurocognitive disorder in which the person's concerned persistent memory decline ≥ 6 months with Montreal Cognitive Assessment (MoCA) scale of 23–25 points which is a valid scale used in MCI assessment (Nasreddine and Patel 2016; Abdel Rahman and El Gaafary 2009).

The included 60 amMCI patients underwent baseline full neurological examination, MoCA, PSG, MRI–HPC and ERC volumetry, and auditory MMN at the beginning of the study. Fifty-six of the included patients continued the study, which they continued follow-up for 1 year; at the end of which, the MoCA scale was repeated and divided the included subjects to 17 progressive amMCI patients (group I) and 39 amMCI subjects passed a stationary or regressive course (group II) (37 stationary and 2 regressive). The study also included 20 age- and body mass index (BMI)-matched healthy control subjects (HCS) (group III). Amnestic MCI was considered progressive if the follow-up MoCA score is lowered ≥ 3 points (≥ 1.5 standard deviation of normal), stationary if the score changed 1–2 points, and regressive if the score increases ≥ 3 points (Horton et al. 2015).

Exclusion criteria included illiterate subjects (to unify the MoCA scale and keep homogeneity of the studied sample), people with MRI contraindications, patients with history of cerebrovascular disorders, major depressive disorder, chronic metabolic or endocrinal disorders, chronic sleep disorders, drug abusers, and chronic use of medications affecting cognition. Patients with hearing problems or middle ear dysfunctions were also excluded after doing a full audiological history, otological examination, and basic audiological evaluation including pure tone audiometry for the frequency range 250–8000 Hz and speech audiometry (using GSI-61 audiometer) and immittancemetry (using Zodiac Madsen).

The protocol of this study was approved by The Research Ethics Committee and Quality Assurance Unit, Faculty of Medicine, Tanta University. Participations were voluntary, informed consents were obtained from all participants prior to their commencements in the study, and detailed information concerning the aims of the study and the possible risks were clarified.

Polysomnography was done by Somon Medics Gmbh machine (Type: SOMNO screenTMplus, SN: 4259, kw45: 2014, Am SonnenstuhL63, D-97236 Rander Sacker, Germany), modified V2 lead ECG, electrooculography (LOC-A1/A2 and ROC-A1/A2), EEG channel montages (O1/A2, C3/A2, C4/A1, and O2/A1), and surface tibial and submental EMG. Thermal airflow sensors were used for nasal and oral signals, and microphone was applied for tracheal sounds assessment. Chest and abdominal efforts were measured by dual thoracoabdominal RIP (respiratory inductance plethysmography) belts. PSG was scored according to The American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, (version 2.4), 2017 (Berry et al. 2017)

Three-dimensional HPC/ERC–MRI volumetric assessment were performed according to Bonilha and colleague (2012) and by the practice of The Harvard University Slicer version software (http://www.slicer.org/) Functool, GE Healthcare, Milwaukee, WI, USA. The images were attained by a 1.5-Tesla, General Electric Scanner (GE Medical Systems, Milwaukee, USA) with quadrature eight-channel head coil.

Auditory MMN was done using Smart Evoke Potential, Home Intelligence Service (HIS), USA and used the oddball paradigm with tone stimuli at 1000 and 2000 Hz as standard and deviant stimuli, respectively, 150 ms durations, 1/s repetition rate, 15% deviant probability and at 70 dB nHL (decibel above normal adult hearing level). MMN was defined as the most prominent negativity following N100 and was calculated according to manual specification of SmartEP, HIS.

Statistical analysis was conducted using SPSS version 19, 2011, created by IBM, Chicago, IL, USA. For numerical values, the range and mean ± SD were calculated. The differences between subcategories were tested using the z-score, ANOVA, and post-ANOVA tests. p value < 0.05 was considered statistically significant.

Results

The study included 60 amMCI subjects aged 61.8 ± 3.1 years, 37 (61.7%) females and 23 (38.3%) males; their approximate duration of subjective memory decline was 1.98 ± 0.5 years, their MoCA score was 23.98 ± 0.96 and BMI was 25.23 ± 1.68 kg/m^2.

Fifty-six amMCI attained regular follow-up for 1 year; 17 (30.4%) of them passed a progressive course (11 scored 23, 5 scored 24, and 1 scored 25 in their initial baseline MoCA scale). The age of progressive amMCI group was 63.43 ± 2.07 years which was significantly higher than that of stationary amMCI and HCS groups (60.58 ± 2.68 and 59.8 ± 3.94 years with p values = 0.024 and 0.009 respectively). The latter two groups had non-significant age difference (p value = 0.429). At the same time, the progressive amMCI group had significantly higher female proportion (female/male ratio 12/5) compared to stationary amMCI and HCS groups (14/25 and 7/13 respectively with p value = 0.037). The duration of subjective memory decline in progressive amMCI group was 1.5 ± 0.5 years which was significantly shorter than that of stationary amMCI groups (2.32 ± 0.41 years) with p value = 0.027.

Regarding PSG, the present study showed significant decrease in sleep efficiency (SE) and REM % of total sleep time (TST), delayed REM latency, and increase in each of wake after sleep onset (WASO) and N3% of TST in progressive amMCI patients' group compared to stationary amMCI and HCS groups with p value = 0.003 for SE and < 0.0001 for the remaining four parameters (Table 1 and Fig. 1). On the other hand, stationary amMCI group was non-significantly different from HCS group regarding the same parameters with p values = 0.508, 0.838, 0.951, 0.773, and 0.051 respectively. At the same time, REM sleep without atonia (RSWA) index showed significant increase in each of progressive and stationary amMCI groups than HCS group with p values = 0.022 and 0.024 respectively without significant difference between both (p value = 0.476).

Sleep architecture studying showed that 13 (33.3%) subjects with stationary amMCI had mild to moderate obstructive sleep apnea (OSA) which was significantly higher than both progressive amMCI and HCS groups (11.7 and 10% respectively) with p value = 0.036. The stationary amMCI group also showed significant increase in each of the apnea-hypopnea, sleep stage transition, and arousal and snore indices compared to progressive amMCI and HCS groups with p value < 0.0001 for each parameter (Table 1).

One of the PSG observations is the higher number of progressive amMCI patients (58.87%) who needed PSG repetition because of insufficient sleep in the first trial (first night PSG insomnia) compared to stationary amMCI and HCS (20.5 and 15% respectively). Other studied PSG parameters showed non-significant differences between the three studied groups regarding TST, sleep latencies, and periodic limb movements (PLMs) index with p values = 0.264, 0.54, and 0.334 respectively (Table 1).

Neuroimaging studies showed significant decrease of the right and left HPC volumes in progressive amMCI group compared to stationary amMCI group and HCS group with p value < 0.0001 for each side without significant side to side difference. Stationary amMCI and HCS groups had non-significant differences with p values = 0.548 and 0.562 for right and left sides respectively (Table 1).

Regarding ERC volumes, the three studied groups had non-observable laterality difference, but there were significant decreases in progressive amMCI group than stationary amMCI and HCS groups with p value < 0.0001 for the right and left sides respectively (Table 1). The stationary amMCI showed non-significant differences relative to HCS groups with p-values = 0.548 and 0.562 for right and left sides respectively (Figs. 2 and 3).

Auditory MMN showed significantly delayed right and left latencies in progressive amMCI group than stationary amMCI and HCS groups with p value < 0.0001 for each side. At the same time, there were non-significant difference between stationary amMCI and HCS groups with p values = 0.483 and 0.565 for right and left sides respectively (Table 1).

At the same time, the MMN showed significantly reduced right and left amplitudes of the evoked potential in progressive amMCI group than stationary amMCI and HCS groups with p value < 0.0001 for each side. The stationary amMCI group showed non-significant difference with the HCS group and p values were 0.369 and 0.555 for right and left sides respectively (Table 1).

The progressive amMCI group showed positive correlations between each of SE and REM % of TST with each of HPC/ER cortices volumes and the amplitudes of MMN evoked potentials and negative correlations with the MMN latencies (Table 2).

The study showed that 15 (88.2%) progressive and 5 (12.8%) stationary amMCI subjects had at least one affected studied parameter below the range of HCS. For progressive amMCI group, 13 (76.5%) had shortened REM % of TST, 12 (70.6%) had reduced HPC/ERC volumetry, and 13 (76.5%) had abnormal MMN response.

Discussion

Mild cognitive impairment is defined over a long period of time as an intermediate phase between normal cognition and dementia, but meticulous follow-up showed that a high proportion of patients exhibits stationary or regressive courses. Early differentiation between progressive and stationary amMCI is an important step to avoid the over-estimation of the terrible pre-dementia states

Table 1 Comparison between progressive amnestic MCI (group I), stationary amnestic MCI (group II), and healthy control (group III) regarding polysomnographic, hippocampus/entorhinal cortex MRI volumetry, and mismatch negativity

	Group I	Group II	Group III	ANOVA	
	Mean ± SD	Mean ± SD	Mean ± SD	*f* value	*p* value
Polysomnographic parameters					
Total sleep time (min)	408 ± 31.9	404.8 ± 43.2	426.4 ± 41.1	1.37	0.264
Sleep latency (min)	14.63 ± 3.21	11.4 ± 2.9	12.17 ± 3.11	0.082	0.54
WASO (min)	59.43 ± 9.3	32.71 ± 7.03	32.02 ± 7.14	44.18	0.0001*
Sleep efficiency (%)	76.3 ± 3.55	82.56 ± 5.03	82.45 ± 3.98	6.70	0.003*
REM latency (min)	121.8 ± 12.1	80.56 ± 9.94	81.2 ± 7.66	51.83	0.0001*
REM % TST	9.82 ± 3.57	21.5 ± 3.51	22.21 ± 3.41	79.40	0.0001*
RSWA index	14.9 ± 4.8	13.41 ± 5.14	5.93 ± 2.10	9.74	0.0001*
N1% TST	10.46 ± 2.02	7.27 ± 1.47	7.07 ± 1.56	14.28	0.0001*
N2% TST	38.08 ± 2.75	40.64 ± 4.14	41.87 ± 3.57	2.61	0.084
N3% TST	35.85 ± 3.34	23.14 ± 4.99	20.24 ± 3.99	33.42	0.0001*
AHI (/h)	7.05 ± 4.5	12.08 ± 5.8	7.25 ± 2.34	10.68	0.0001*
Arousal index (/h)	11.18 ± 4.27	20.21 ± 7.95	8.22 ± 1.96	18.61	0.0001*
SSTI (/h)	13.87 ± 4.48	19.06 ± 4.68	11.28 ± 2.64	9.61	0.0001*
PLMs index (/h)	14.25 ± 6.79	13.66 ± 4.24	15.85 ± 3.63	1.12	0.334
Snore index (/h)	17.08 ± 5.77	26.86 ± 8.25	14.62 ± 3.13	18.03	0.0001*
MRI volumetry					
Right hippocampus (cm^3)	1.28 ± 0.13	2.02 ± 0.28	2.05 ± 0.28	21.41	0.0001*
Left hippocampus (cm^3)	1.27 ± 0.12	2.03 ± 0.29	2.07 ± 0.31	21.33	0.0001*
Right entorhinal cortex (cm^3)	1.26 ± 0.13	1.85 ± 0.12	1.85 ± 0.12	64.31	0.0001*
Left entorhinal cortex (cm^3)	1.27 ± 0.11	1.86 ± 0.11	1.85 ± 0.12	72.11	0.0001*
Auditory mismatch negativity					
Right MMN latency (ms)	252.2 ± 20.2	190.4 ± 18.7	194.5 ± 15.8	37.46	0.0001*
Left MMN latency (ms)	251.2 ± 21.2	191.7 ± 19.4	195.3 ± 15.2	32.82	0.0001*
Right MMN amplitude (μV)	2.02 ± 0.66	3.89 ± 0.88	3.65 ± 0.88	15.13	0.0001*
Left MMN amplitude (μV)	2.03 ± 0.65	3.89 ± 0.88	3.73 ± 1.04	13.58	0.0001*

*Significant; *AHI* apnea hypopnea index, *MMN* mismatch negativity, *N1, N2, N3* non-rapid eye movement stages 1, 2, 3, *PLMs* periodic limb movements, *REM* rapid eye movement, *RSWA* REM sleep without atonia, *SSTI* sleep stage transition index, *TST* total sleep time, *WASO* wake after sleep onset

and the abuse of AD therapies (Díaz-Mardomingo et al. 2017b).

The study showed that only 30.4% of amMCI subjects underwent clinical progression within 1 year of follow-up which was higher in those with lower initial MoCA score (23 points) while the remaining passed stationary or regressive courses. This incidence was lower than the work of Abner and colleagues (2017) who estimated 40% MCI progression rate possibly due to their longer follow-up study (about 8 years). Amnestic MCI progression was higher among older aged female subjects, and this is passing with the work of Au and colleagues (2017) who declared the importance of old age and female sex as risks of amMCI conversion to dementia. The absence of sex difference among stationary amMCI persons denoted that females pass a shorter transitory MCI stage to develop

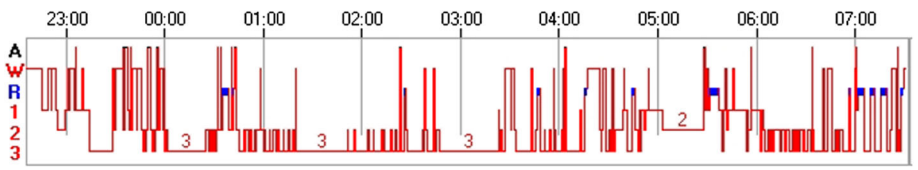

Fig. 1 Hypnogram of a 63-year female progressive amnestic mild cognitive impairment patient showing decreased sleep efficiency, delayed rapid eye movement sleep latency, reduced REM % of total sleep time, and increased N3 non-rapid eye movement % of TST

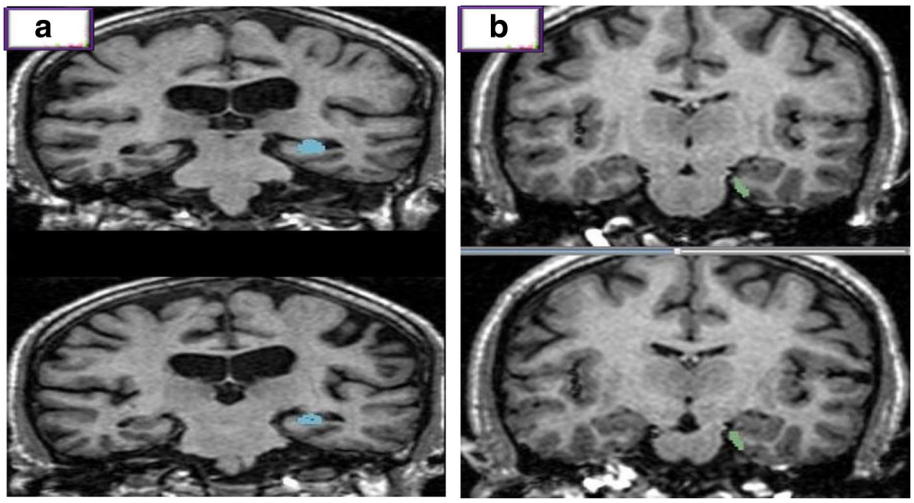

Fig. 2 Coronal T1-weighted 3D spoiled gradient magnetic resonance images at the level of the midbrain for a 64-year progressive amnestic mild cognitive impairment patient showing **a** reduced right hippocampal volume (1.37 cm^3) and **b** decreased right entorhinal cortex (1.35 cm^3)

dementia. Vest and Pike (2013) also agreed with these results and stated that AD disproportionately has higher female incidence due to the rapid tapering of gonadal sex hormones after menopause in comparison to the slow male andropause with loss of their potent neurotrophic anti-AD action.

Medical researches stated a bidirectional relationship between MCI and sleep disturbances. This study declared that stationary amMCI persons had a higher incidence of OSA suggesting that their cognitive decline is possibly the effect of excessive daytime sleepiness due to repeated arousals and decreased sleep quality. These results are in harmony with the work of Mu and colleagues (2017) who stated that OSA must be excluded in amMCI subjects as its consecutive sleep fragmentation and recurrent hypoxia impair several cognitive domains including episodic and working memories.

The study also stated that amMCI patients with progressive course exhibited deformed sleep microstructures in the form of reduced sleep efficiency, delayed REM latency, and decreased REM % of TST pointing to the importance of REM sleep studying as an early biomarker of amMCI progression. On the other hand, the RSWA index was mildly elevated in both progressive and stationary amMCI without observable difference. However, the mechanism of elevation in each group is different; in progressive cases, the elevation is due to REM behavior disorder (RBD) secondary to distorted REM sleep, but in stationary cases, the elevated tone is due to repeated arousals caused by the OSA which sometimes occur during REM sleep. Liguori and colleagues (2016b) and Brayet and colleagues (2017) agree with the previous results and declared that objective cognitive decline is usually associated with REM sleep reduction which can be used as a sensitive biomarker

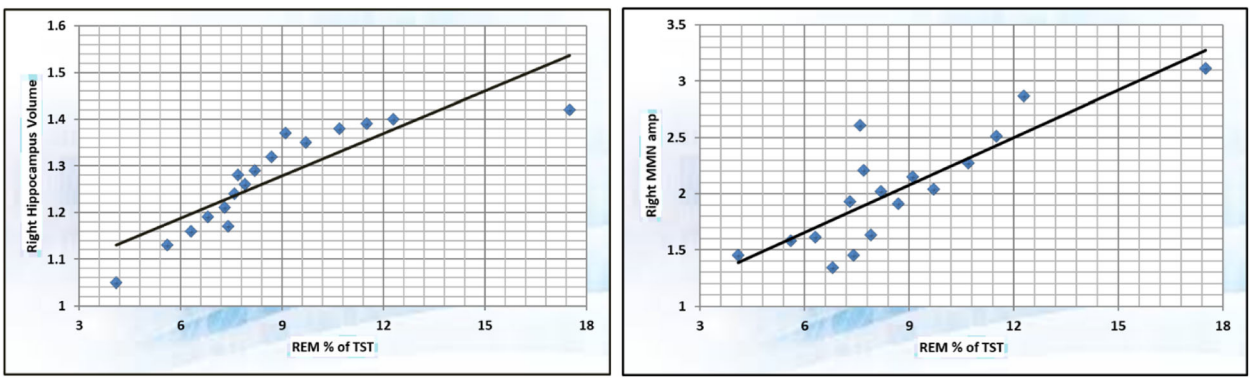

Fig. 3 Positive correlation between rapid eye movement sleep percent of total sleep time with each of right hippocampal volumes (left) and amplitudes of auditory mismatch negativity (right) in progressive amnestic mild cognitive impairment patients

Table 2 Correlations between each of sleep efficiency and rapid eye movement latency percent total sleep time with the hippocampal/entorhinal cortex volumetry and auditory mismatch negativity in progressive amnestic mild cognitive impairment patients

	Sleep efficiency		REM % of TST	
	r	*p*	*r*	*p*
Right hippocampus (cm^3)	0.884	< 0.0001*	0.861	< 0.0001*
Left hippocampus (cm^3)	0.886	< 0.0001*	0.850	< 0.0001*
Right entorhinal cortex (cm^3)	0.903	< 0.0001*	0.869	< 0.0001*
Left entorhinal cortex (cm^3)	0.912	< 0.0001*	0.864	< 0.0001*
Right MMN latency (ms)	− 0.828	< 0.0001*	− 0.894	< 0.0001*
Left MMN latency (ms)	− 0.827	< 0.0001*	− 0.869	< 0.0001*
Right MMN amplitude (μV)	0.866	< 0.0001*	0.838	< 0.0001*
Left MMN amplitude (μV)	0.872	< 0.0001*	0.844	< 0.0001*

*Significant; *MMN* mismatch negativity, *REM* rapid eye movement, *TST* total sleep time

MCI progression. They attributed these REM sleep changes to impaired cholinergic and glutamatergic neuron activities as well as dysregulated Orexin-A (hypocretin-1) secretion that regulate the sleep-wake cycle.

Typical AD pathological changes have distinct temporo-spatial progressions starting several years before its clinical onset in the medial temporal lobe then spread to other brain areas (Wolk et al. 2017). The present study showed significant decrease in HPC/ERC volumes in amMCI patients prone to progression which is in accordance with the study of Elshafey and colleagues (2014) who specified that semi-automated MR volumetric measurements of HPC and ERC atrophies can be used to differentiate healthy elderly from MCI subjects and can predict clinical decline of the MCI patients.

Mismatch negativity is a tool that governs the auditory discrimination abilities, attentional swift, and working memory (Tsolaki et al. 2017). The present study showed delayed, low amplitude MMN evoked responses among progressive amMCI patients without proportional abnormalities among stationary subjects. These results are in harmony with the work of Lindín and colleagues (2013) and Ji and colleagues (2015) who concluded that MMN amplitude and latency are sensitive and specific biomarkers for amMCI progression.

The study showed high correlations of the PSG changes (SE and REM% of TST) with each of HPC/ERC–MRI volumetry and MMN changes with a very little number of subjects had at least one affected included parameter pointing to that the combination of more than one parameter increase the sensitivity and specificity of amMCI progression prediction. These results are agreed by Sanchez-Espinosa and colleagues (2014) who found significant correlation between shortening of REM sleep and cortical thinning in amMCI patients prone to AD progression.

Conclusions

Polysomnographic decrease in SE with shortened REM sleep time, reduced MRI–HPC/ERC volumes, and delayed auditory MMN with low amplitude are valuable early biomarkers for amMCI progression to dementia. The combination of more than one parameter increases the sensitivity and specificity of their predictive values.

Limitations

Longer duration of follow-up may be needed with inclusion of a larger number of subjects for better detections of the cutoff values of the included parameters beyond which amMCI progression could be expected. The narrow MCI spectrum of the MoCA scale made the benefit from neuropsychological tests as additional early biomarkers were little but more detailed neurocognitive assessment may be needed in following phases of the research.

Abbreviations

AD: Alzheimer's disease; amMCI: Amnestic mild cognitive impairment; BMI: Body mass index; ERC: Entorhinal cortex; HCS: Healthy control subjects; HIC: Home Intelligence Service; HPC: Hippocampus; MCI: Mild cognitive impairment; MMN: Mismatch negativity; MoCA: Montreal Cognitive Assessment; N3: NREM stage 3; OSA: Obstructive sleep apnea; PSG: Polysomnography; RBD: REM behavior disorder; REM: Rapid eye movement; RSWA: REM sleep without atonia; SE: Sleep efficiency; TST: Total sleep time; WASO: Waking after sleep onset

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Consent of publication

All participants had signed an informed consent to participate and for the data to be published.

Availability of data and materials

The authors state that the raw data and materials could be publicly available.

Authors' contributions

WSB participated in the study's idea, design, and patients' selection and performed the statistical analysis, PSG interpretation, data analysis, references collection, manuscript writing, and revision and final approval YAH participated in study's idea and design, patients' assessment and inclusion, data analysis, and manuscript writing and revision, OAR participated in patients' selection and assessment, PSG analysis, data registry, references collection, statistical analysis, and manuscript revision. MYB participated in patients' clinical examination, follow-up of the patients and their registration, MSLT interpretation, imaging interpretation, statistics, and manuscript writing. MAS participated in study's design, patients' collection, evaluation and inclusion, statistical analysis, and revision and final approval. RAA participated in study's design, patients' collection, evaluation and inclusion, statistical analysis, and revision and final approval. RAE participated in study's design, patients' assessment, imaging interpretation including MRI brain volumetric studies performance, data analysis, and manuscript writing and revision. MAK participated in study's design, patients' audiological assessment and inclusion, mismatch negativity performance, data analysis, and manuscript writing and revision. All authors read and approved the final manuscript.

Competing interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

- The manuscript was approved from The Research Ethics Committee and Quality Assurance Unit, Faculty of Medicine, Tanta University.
- The URL: http://tqac.tanta.edu.eg/new-tqac/ QualityAssuranceUnit@hotmail.com
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- Name of the PI: Wafik Said Kamel El-Bahnasy
- Name of the department: Neuropsychiatry
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- Date of approval: April 2016
- The protocol of this study was approved by The Research Ethics Committee and Quality Assurance Unit, Faculty of Medicine, Tanta University. Participations were voluntary, informed consents were obtained from all participants prior to their commencements in the study, and detailed information concerning the aims of the study and the possible risks were clarified.

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