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Palliative Medicine in Practice

ISSN: 2545-0425

e-ISSN: 2545-1359

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DOI: 10.5603/PMPI.a2023.0021

Article type: Research paper

Submitted: 2023-05-16

Accepted: 2023-06-16

Published online: 2023-07-12

Original article

DOI: 10.5603/PMPI.a2023.0021

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The effect of hippocampal sparing during prophylactic cranial irradiation on the preservation of neurocognitive functions in patients with small cell lung cancer: a preliminary study

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Abstract

Background: Prophylactic cerebral irradiation (PCI) is the standard of care for patients with limited small cell lung cancer (SCLC). Cerebral irradiation is associated with the deterioration of the quality of life in terms of cognitive function, in which the hippocampus plays a critical role. Protection of the hippocampus during PCI aims to reduce the adverse effects of ionizing radiation on neurocognitive function, which may be important for optimal quality of life. To date, subjective psychological tests have been used as a methodical assessment of cognitive function in patients after PCI.

Patients and methods: In 20 patients with SCLC, it was attempted to evaluate the effect of hippocampal sparing during PCI on the preservation of cognitive functions in these patients, using two diagnostic and screening tests: Mini-Mental State Examination (MMSE) Short Scale and Montreal Cognitive Assessment (MoCA) Scale. The assessment was made at three time points: before the start of radiation, immediately after completion of irradiation and 3 months after radiation therapy.

Results: The results indicate that after radiation therapy there is a deterioration in cognitive functions. Additionally, it was found that the results of both tests after radiation therapy differed significantly according to the gender and education of patients.

Conclusions. Following PCI, cognitive functions deteriorate in SCLC patients, even when radiation doses are reduced in the hippocampal area. This trend persists for at least 3 months after the end of brain irradiation.

Key words: prophylactic cranial irradiation, hippocampal sparing, small cell lung cancer, neurocognitive dysfunction

Introduction

Small cell lung cancer (SCLC) is classified as neuroendocrine cancer [1–3]. It accounts for 13% of all primary lung cancers, with smoking playing a key role in its etiopathogenesis [1, 3]. Small-cell lung cancer is characterised by a high growth fraction and a short cell doubling time, which manifests itself clinically as a significant propensity to spread. At the time of diagnosis, around 70% of patients are found to have a generalised form of the disease, which makes the prognosis for patients with SCLS generally unfavourable. If no treatment is given, the average time of survival does not exceed 6–8 weeks [1, 2].

Small cell lung cancer usually occurs as a mass located in the mid-chest area or perihilar areas. The patient may experience dyspnoea and cough, general symptoms, as well as specific clinical symptoms related to the location of the metastasis. Patients with SCLC develop brain metastases, which shortens the time of survival and harms the quality of life [1, 2, 4].

Chemotherapy is the primary treatment for patients with SCLC. In the limited form of the disease, the rate of response to treatment is 70–80%, while in extensive disease, it amounts to 60–70% [2, 5]. Currently, the standard treatment for patients with a limited form of SCLC is to combine cisplatin and etoposide chemotherapy with radiotherapy applied to the mediastinal region (CHT-RT) and prophylactic cranial irradiation (PCI) [5, 6].

Due to the frequent occurrence of neuropsychological disorders following radiotherapy, a neurological examination and mental state evaluation are recommended when qualifying a patient for cranial irradiation [7, 8]. There has been significant interest in the search for parameters predicting the occurrence of cognitive impairment in patients following PCI.

The tools used to assess cognitive function include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) [8, 9]. The MMSE scale is used to assess a patient's mental state. It has a sensitivity and specificity in detecting stupor at the level of 87% and 82%, respectively. It is the most popular and most frequently used diagnostic tool, which allows for a comprehensive evaluation of cognitive impairment in clinical, research, and community settings. It consists of 30 questions, which enable a quantitative assessment of numerous aspects of cognitive functioning, i.e. memorisation, reading, counting, and naming [10, 11]. Meanwhile, the MoCA is a screening tool that detects Mild Cognitive Impairment (MCI) with sensitivity and specificity of 90% and 87% respectively [10]. It assesses abstraction, short-term memory, visuospatial function, executive functions, language, verbal fluency, allopsychic orientation, and attention. The entire MoCA test takes around 10 minutes, and the maximum number of points that can be scored is 30 [10]. It is especially useful for patients who complain about memory problems and achieve a normal score on the MMSE scale [12]. The study aimed to assess whether and to what extent patients subject to hippocampal sparing during prophylactic cranial irradiation (PCI) experienced changes in cognitive functions.

Patients and methods

The study group consisted of 20 SCLC patients, including 11 men and 9 women, aged 60.9 ± 6.76 years, who had been subject to chemotherapy and for whom the presence of brain metastases was ruled out by imaging scans. Three of the patients in the study group (15%) were educated at the primary level, 7 patients (35%) had vocational education, 7 patients (35%) had secondary education, and 3 patients (15%) had university education. The patients received prophylactic irradiation to the brain area at the Department of Teleradiotherapy, Copernicus Memorial Hospital of Lodz in the period between 8 July 2019 and 10 February 2021. The patients were fitted with orfit masks to immobilise their heads during irradiation. A treatment plan was then developed based on a head CT scan with image fusion with a contrast-enhanced MRI scan performed following chemotherapy. During the treatment planning process, the treated volume was contoured; it included the brain and critical organs: the right and left optic nerves, the optic nerve junction, lenses and eyeballs on both sides, the brain stem, and the left and right hippocampi. Once the treatment plan was approved, the patients were irradiated to a total dose of 25 Gy fractionated into 2.5 Gy doses, receiving one fraction per day and five fractions per week.

Before the commencement of radiotherapy, the first part of the evaluation survey was conducted with a clinical psychologist. It involved the evaluation of cognitive functions according to MoCA 7.2 (the cut-off point adopted was < 26 points) and according to MMSE; a score of 20–25 points was assumed to indicate mild cognitive impairment [6]. A re-evaluation of patients' cognitive functions according to the MoCA and MMSE scales took place in the first week following the completion of PCI. It was repeated three months after the completion of irradiation. The study obtained the Bioethics Committee's approval RNN/05/19/KE.

The results were statistically processed using PQStat version 1.8.4 software. Where a normal distribution was present, the parametric ANOVA test for dependent groups and the r-Pearson parametric linear correlation test were applied. $P > 0.05$ was considered statistically significant.

Results

Points scored in the MoCA and MMSE tests in studies I, II, and III are shown in Table 1. Scores in the MoCA scale in study I were higher than the scores in study II and study III ($p = 0.014$; $p < 0.001$ respectively) (Figure 1). Scores in the MMSE scale in study I were higher than the scores in study II and study III ($p < 0.001$; $p < 0.001$ respectively) (Figure 2). Scores in study III were lower than the scores in study II both in the study employing the MoCA scale and in the study employing the MMSE scale ($p < 0.001$; $p < 0.001$ respectively) (Figure 2).

The doses delivered to the volume of the left hippocampus (LH) and right hippocampus (RH) were similar and amounted to 11–16.7 (13.16 ± 1.7) Gy and 11–16.7

(13.12 ± 1.62) Gy, respectively. No correlation was found between the average dose delivered to LH and the average scores in the MoCA scale in study II ($r = -0.108$; $p = 0.649$) and study III ($r = -0.03$; $p = 0.899$). There was no correlation between the average dose delivered to LH and average scores in the MMSE scale in study II ($r = -0.037$; $p = 0.874$) and study III ($r = 0.031$; $p = 0.895$). There was no correlation between the average dose delivered to RH and the average scores in the MoCA scale in study II ($r = -0.084$; $p = 0.722$) and study III ($r = -0.009$; $p = 0.969$). There was no correlation between the average dose delivered to RH and the average scores in the MMSE scale in study II ($r = -0.14$; $p = 0.553$) and study III ($r = -0.089$; $p = 0.707$).

No correlation was found between the age of the patients and the scores in MoCA and MMSE tests in studies I, II, and III. The scores in the MoCA test in Studies I and II and the scores in the MMSE test in study I were not dependent on the sex of patients. Scores in the MoCA test in study III were higher for women than for men ($p = 0.031$; Figure 3). Scores in the MMSE test in studies II and III were higher for women than for men ($p = 0.037$; $p = 0.019$; Figure 4). Scores in the MoCA test in study I did not depend on the patients' level of education. Scores in the MoCA test in studies II and III were dependent on the patients' level of education ($p = 0.017$; $p = 0.014$; Figure 5). Scores in the MMSE test in studies I, II, and III were dependent on the patients' level of education ($p = 0.015$; $p = 0.002$; $p = 0.003$; Figure 6). The exact correlations between age, sex, and level of education and scores in the MoCA and MMSE tests are shown in Table 2.

Discussion

Although they are only a preliminary to an ongoing study, the results presented above are original and interesting. Patients in the study group were treated according to the same protocol, at the same facility, and by the same team of radiation oncologists, which adds to the value of the results. The observation that radiotherapy leads to a reduction in both MoCA and MMSE scores and that the process continues for at least three months after the irradiation of the brain ceases is especially valuable.

The question of the impact of brain irradiation on cognitive functions has already been addressed. The observations made by various authors so far do not allow for definite conclusions to be drawn. The results of meta-analyses indicate slight deterioration in cognitive functions in SCLC patients following PCI, which mainly affects short-term memory, learning, and problems with minor sensorimotor functions [13–15]. However, Tarnawski et al. [16] believes that the selection of appropriate doses of radiation combined with modern radiotherapy techniques does not contribute to cognitive impairment, especially in geriatric patients. The results of the authors' studies show that even in patients who receive a reduced dose of radiation to the hippocampus, scores in MoCA and MMSE scales deteriorate during PCI and the trend continues for three months after the irradiation ceases. It is impossible to disagree with Pękała et al. that the impairment of cognitive function causes the quality of life of SCLS patients to deteriorate [17].

The study presented assessed the correlations between scores in MoCA and MMSE tests and the age, sex, and level of education of SCLC patients. Although Borland et al. [18] have also proved in their study that older age was correlated with a lower score in MoCA, no correlation between age and test scores was found in the present study. The sex of the patients was correlated with their scores in MoCA and MMSE tests but only after cranial irradiation. Scores in the MoCA and MMSE tests were also differentiated by patients' education. This is supported by the studies by Borland et al. [18] who showed that there was a significant correlation between the sex, level of education, and age of the patients and their total MoCA score. As in the results of the present study, the female sex and higher levels of education were correlated with a higher MoCA score. Meanwhile, Wu Y et al. [19] obtained positively correlated MMSE and MoCA scores, which were additionally dependent on the duration of patients' education. As in the present study, higher levels of education correlated with higher scores on both tests [18, 19]. Rambe et al. [20] demonstrated that MMSE scores were also correlated with the level of education, which agrees with the current observations. The prevailing view is that the MoCA test offers a better chance of identifying an impairment of cognitive function than the MMSE test [19, 21], which also agrees with the current results.

Recommendations for hippocampal tolerance doses during Whole Brain Radiotherapy (WBRT), in patients with brain metastases with a prognosis of survival of more than 6 months, were developed based on the results of the RTOG 0933 trial and amounted to: the total dose (TD) less than 7.8 Gy, maximum dose (D max) below 15.3 Gy, and the dose delivered to the entire hippocampus not larger than 10 Gy [22]. Phase III clinical trials conducted to date have demonstrated the benefits of the hippocampal sparing procedure, however, they were conducted for WBRT in brain metastases [23, 24].

In contrast to patients with confirmed metastatic disease, the prerequisite for PCI is a well-controlled primary disease. It is assumed that these patients will live longer, therefore, it is crucial to preserve their cognitive function and quality of life. Few studies on hippocampal sparing during PCI (PCI — HA) in SCLC have been conducted so far. Redmond et al. suggested that the dose delivered to the hippocampus during PCI be lower than 8 Gy, while the patients recruited for the study had low-stage SCLC and complete response after CHT-RT [25]. The patients were subject to the Hopkins Verbal Learning Test — Revised Delayed Recall at two points in time following the completion of PCI. No deterioration in cognitive test scores was demonstrated, which may provide clinical justification for this radiotherapy procedure. Recruitment for the NRG CC-003 study is underway, with preliminary phase IIR results allowing recruitment for phase III trials to be continued [26]. Patients eligible to take part in the study have a diagnosis of SCLC with at least partial response after CHT-RT, and with no brain metastases, which is confirmed by an MRI scan. According to the study protocol, the maximum dose delivered to the hippocampus should be lower than 13.5 Gy, however, doses below 15 Gy are acceptable, as they are similar to those administered in the present study. The results of the NRG CC-003 study may prove significant in terms of obtaining an unambiguous fractional dose and total dose that would make it possible to preserve the function of the limbic system. The study involving SCLC patients undergoing the PCI-HA procedure is also continuing at the current facility.

However, the present study has its limitations. The first one is the small number of patients in the study group. Moreover, the results obtained in the study group have not been compared with results obtained in patients subjected to PCI without hippocampal sparing. Studies aiming to find an objective, yet optimal method of assessing radiation damage in the hippocampal region continue. Therefore, the results presented here should be regarded as interesting clues, the actual significance of which should be evaluated in studies involving patient randomisation.

Conclusions

Following PCI, SCLC patients experience a deterioration in cognitive functions assessed with the MoCA and MMSE scales, even when the radiation dose in the hippocampal area is reduced. This trend continues for at least 3 months following the cessation of the irradiation of the brain.

Data availability statement

All authors declare availability of data.

Ethics statement

The study was approved by the Bioethics Commission of the Medical University of Lodz No. RNN/05/19/KE.

Author contributions

Karolina Loga — 30% — concept, study design, analysis and interpretation of data, article draft, acquisition of data; Bartosz Wójcik — 15% — figures, tables, references; Anna Stanisławek — 15% — planning of external beam radiation therapy, acquisition of data; Anna Papis-Ubych — 10% — acquisition of data; Jacek Fijuth — 10% — revised article critically; Leszek Gottwald — 20% — concept, study design, analysis and interpretation of data, article draft, revised article critically

Funding

None.

Declaration of conflict of interests

The author declares that there is no conflict of interest.

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Table 1. Scores in MoCA and MMSE scales in studies I, II, and III

Variable	Average	Standard deviation	Median value	Scope
MoCA I	25.70	2.66	26	20–29
MoCA II	25.20	2.97	26	19–29
MoCA III	24.20	3.04	25	18–28
MMSE I	26.75	2.65	27	21–30

Variable	Average	Standard deviation	Median value	Scope
MMSE II	25.65	2.46	26	21–30
MMSE III	24.60	2.50	25	20–29

MMSE — Mini-Mental State Examination; MoCA — Montreal Cognitive Assessment

Table 2. Correlation between age, sex, and level of education and MoCA and MMSE scores in subsequent studies

Study	Age		Sex		Education	
	R	p	R	p	R	p
MoCA I	−0.262	0.265	3.748	0.069	3.158	0.054
MoCA II	−0.293	0.210	3.947	0.062	4.596	0.017*
MoCA III	−0.409	0.073	5.453	0.031*	4.855	0.014*
MMSE I	−0.182	0.443	3.395	0.082	4.707	0.015*
MMSE II	−0.296	0.205	5.055	0.037*	7.678	0.002*
MMSE III	−0.348	0.132	6.657	0.019*	6.896	0.003*

MMSE — Mini-Mental State Examination; MoCA — Montreal Cognitive Assessment

* — statistically significant correlations

Figures

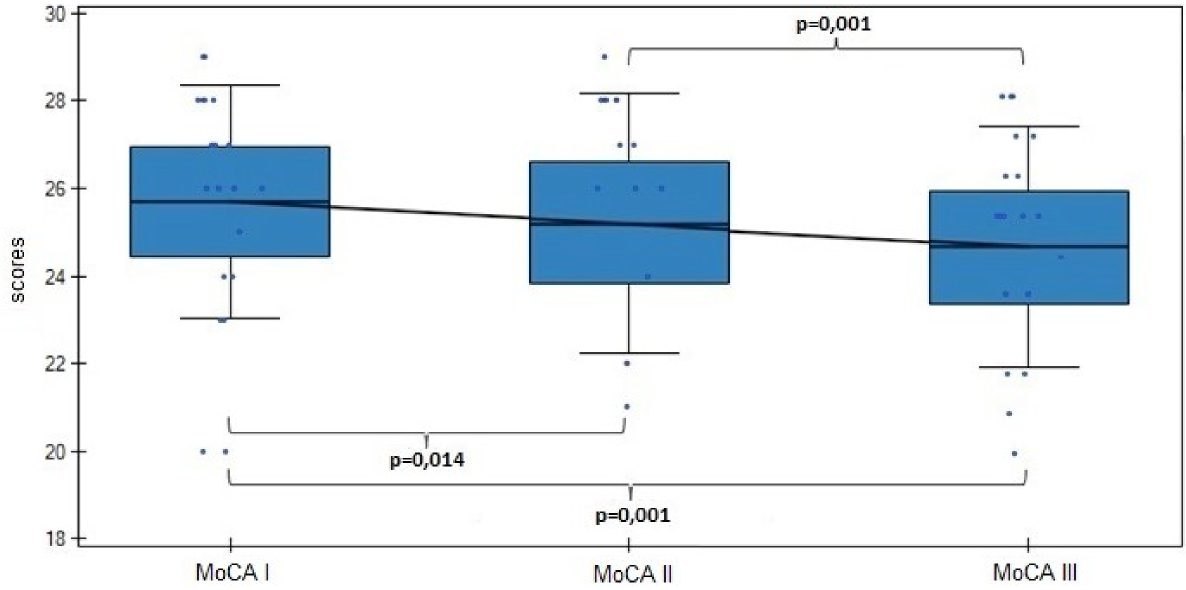

Figure 1. Differences in MoCA scores in studies I, II, and III

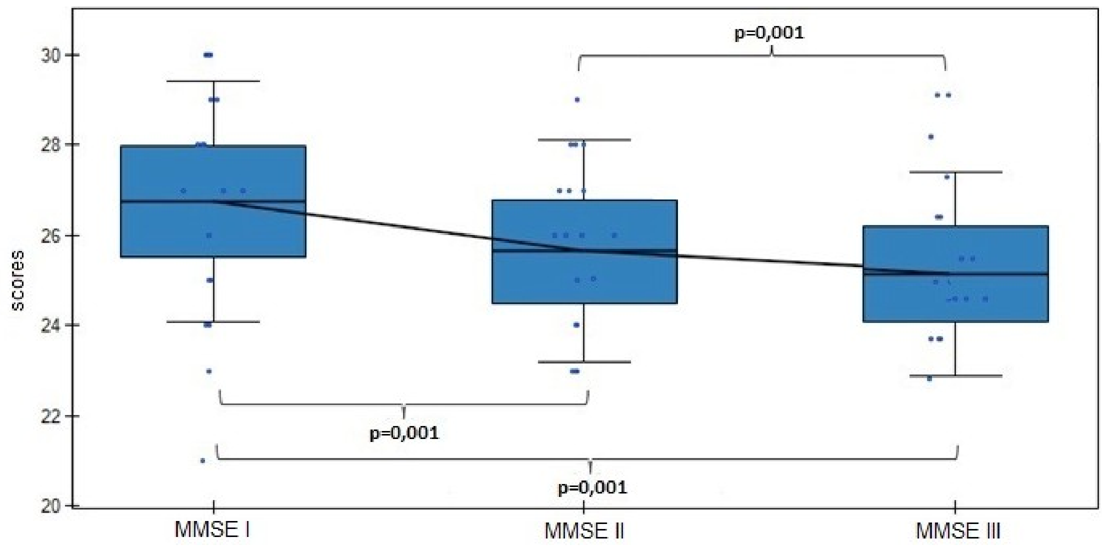

Figure 2. Differences in MMSE scores in studies I, II, and III

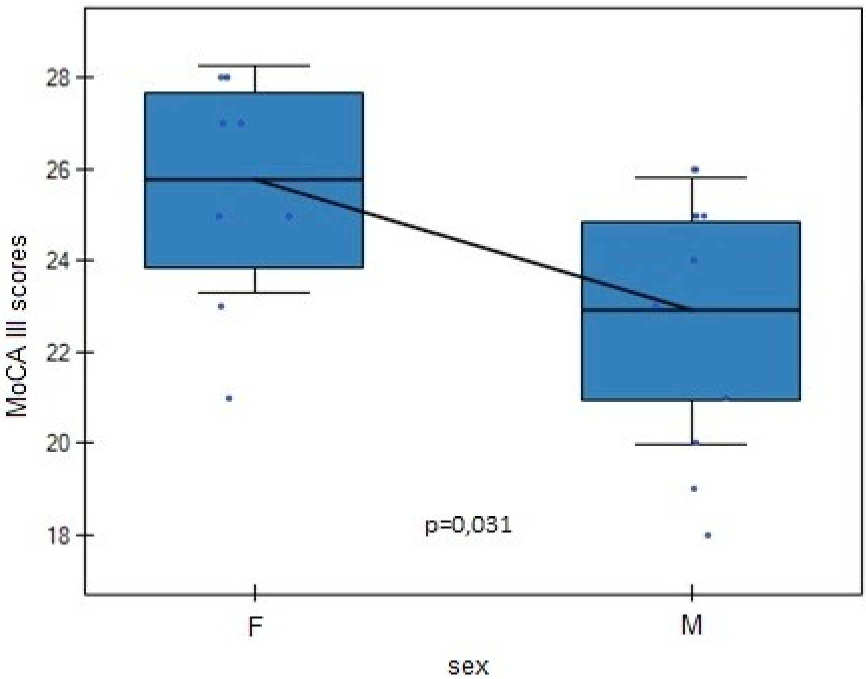

Figure 3. Differences in MoCA scores in study III depending on sex

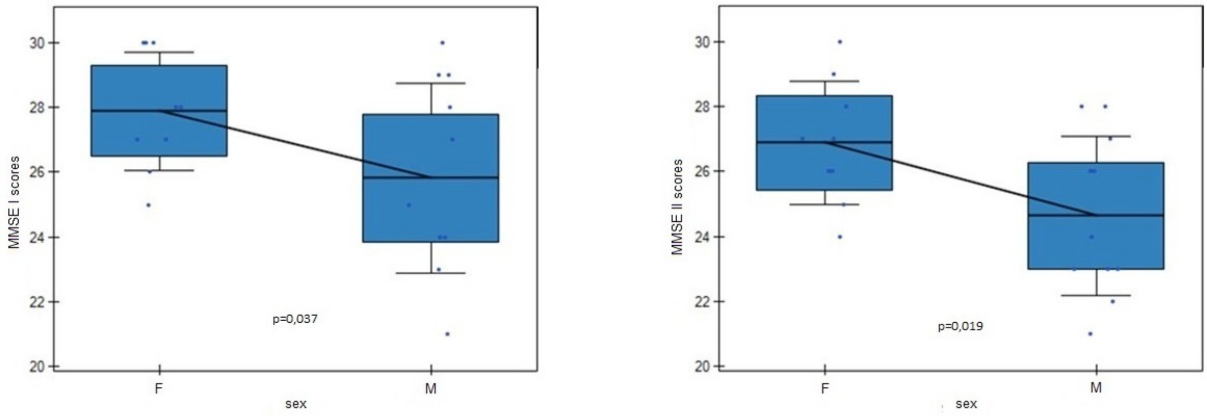

Figure 4. Differences in MMSE scores in studies I and II depending on sex

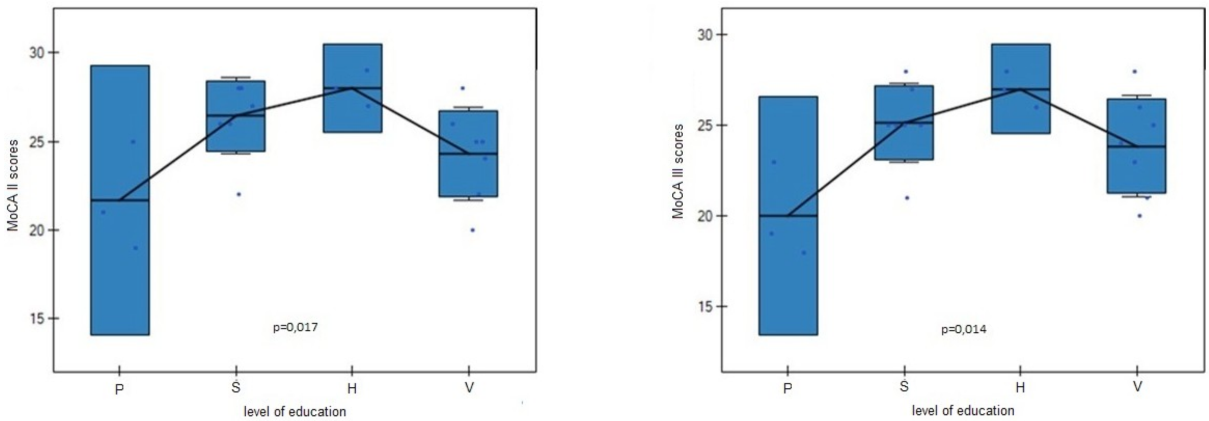

Figure 5. Differences in MoCA scores in studies II and III depending on the level of education: P — primary; S — secondary; H — higher; V — vocational

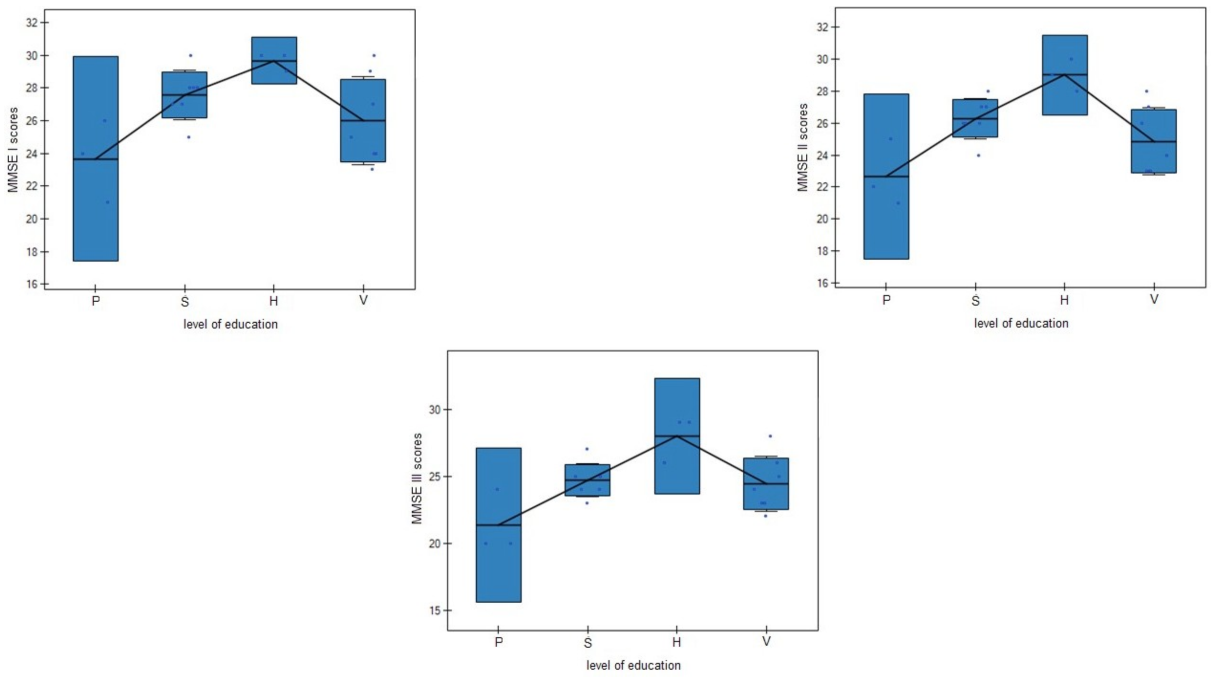

Figure 6. Differences in MMSE scores in studies I, II, and III depending on the level of education; footer under the figure: level of education: P — primary; S — secondary; H — higher; V — vocational