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The Effects of Early-Harvest Extra Virgin Olive Oil on Cognition and Mental Health of Primary (PPMS) or Secondary (SPMS) Progressive Multiple Sclerosis Patients

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Abstract

Aim of the study: Over the last years the cognitive and mental health impairment in Multiple Sclerosis (MS) are indicated as important clinical symptoms in the course of the disease. Every beneficial therapeutic management with this target could lessen the disability caused by the disease and improve the quality of life of MS patients. It is known that Extra Virgin Olive Oil (EVOO) can exert positive effects on cognition regarding neurodegenerative diseases. Phenolic compounds in EVOO have antioxidative and anti-inflammatory effects on the brain but all the mechanisms are not clear yet. The present pilot study examines the benefits of early harvest EVOO (EH EVOO) on cognition and mental health regarding MS.

Index terms— early harvest extra virgin olive oil, cognition, mental health, multiple sclerosis.

Multiple Sclerosis (MS) can be defined as an immune-mediated process in which an abnormal response of the body's defense system is directed against the central nervous system (CNS). In this way, the immune system can precipitate neuroinflammation that, in turn, leads to demyelination and, subsequently, to axonopathy and neurodegeneration. Because of these damages to the CNS, numerous neurological symptoms may be occurred with severity that differs among MS patients [1].

The diagnosis of MS is based on international diagnostic criteria, although there is a great probability of false diagnosis due to many neurodegenerative diseases mimicking MS symptoms. According to the Revised McDonald Criteria (2017) the use of brain Magnetic Resonance Imaging (MRI) and cerebrospinal fluid (CSF) analysis can expedite this process by confirming the damages. Besides these tests, the presence of oligoclonal bands in the CSF can confirm the diagnosis.

The International Advisory Committee on Clinical Trials of MS in 2013 has defined four types of MS: clinically isolated syndrome (CIS), relapsingremitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). Specifically, SPMS consists of an initial relapsingremitting course, which will be evolved to a progressive disability. Furthermore, SPMS can be defined as active, if there is evidence of new MRI activity, or no active, as well as worsening, if there is a confirmed increase of disability after a relapse or not worsening. PPMS does not include relapses and remissions, but the neurological functions get worse gradually after the first symptoms. The same classification is applied in this type too [2]. For every clinical attack approximately 10 "asymptomatic" lesions are noted on MRI [3].

In 5%-15% of cases there is a primary progressive onset (PPMS) typically with gradual increase of disability on one dominant neuronal system. A Some of the commonest symptoms are progressive spastic paraparesis, sensory ataxia, cerebral ataxia, cognitive and visual progressive decline [3]. Remyelination can be seen in all stages of the disease but most commonly in its progressive types. [2]

1 a) Cognitive and mental health impairment in MS

Over the last two decades, cognitive impairment has been recognized as an important factor that affects MS patients' quality of life [4]. It is proved that it affects up to 65% of patients, and yet cognitive testing remains uncommon, due to the lack of simple and reliable tests that have been validated for the MS population. For instance, the Mini Mental State Examination (MMSE) which is used to detect cognitive deficits due to dementia,

is deemed not to be appropriate for MS population [4,5]. Cognitive impairment can precipitate in all forms and stages of MS presenting with a variation of symptoms and a range of severity that differs among the patients [5].

At first, memory and especially free recall of verbal and visuospatial material seems to be affected [6]. Then, working memory and attention reportedly get impaired, because MS patients demonstrate reduced performance in complex attention tasks [7]. Executive functions, such as planning, problem-solving and selfmonitoring are, also, declined [8]. Nevertheless, one of the most common features of cognitive impairment in MS patients is reduced processing speed, manifested as longer reaction time to stimuli and reduced speed of memory scanning [9,10]. Some risk factors have been identified, such as age, the subtype of the disease, the disease's duration, the characteristics of the pathological lesions, progressive fatigue, the prescribed medication, as well as depression and anxiety disorders. Moreover, the fact that the patients may be aware of their cognitive decline can compound their negative attitude, which can lead the patients overestimating their cognitive deficits and being overwhelmed by them. For this reason, early detection is crucial to prevent further decline [5].

2 b) The benefits of EVOO

There is evidence that ?VOO has neuroprotective effects against aging and neurodegenerative diseases, such as prodromal stages of Alzheimer's disease. Phenolic compounds in olive oil have been found to exert positive effects on inflammatory markers, as well as cellular and neuropsychological functions [11]. Furthermore, Ruano et al (2005) presented that consumption of EVOO can lower markers of oxidative stress such as F2isoprostane [12].

The mechanisms behind ?V??'s neuroprotective effects are not yet crystallized. It is primarily known that it has antioxidative effects, because it contains antioxidant molecules and free radical scavengers, which neutralize the toxic moieties and scavenge many endogenous and exogenous free radicals and oxidants. Moreover, EVOO has antiinflammatory effects because its compounds inhibit many inflammatory mediators. Furthermore, EVOO is known regarding its anti-apoptotic properties. In other words, besides reducing toxins, oxidative stress and hypoxia, olive oil consumption, also, inhibits programmed cell death, called apoptosis, which is a very important parameter in neurodegenerative diseases [11]. Many parameters contribute to the effects of these compounds, such as their concentration and the extent of their absorption and metabolism [13].

3 c) Objectives

Taking into consideration that there are only a few published studies on the benefits of EVOO in cognition and mental health, the primary objective of this pilot study is to view the effects of EVOO in cognition and mental health of patients with progressive types of MS by using extensive neuropsychological assessment and evaluating participants' cognition and mental health for one year. Our hypothesis, therefore, was that the MS patients would show progressive improvement in their post-therapy assessments.

4 II.

5 Materials and Methods

6 a) Participants

The participants had the diagnosis of PPMS and SPMS and they were not receiving specific MS medication because previous treatments had failed. Twenty patients (12 women and 8 men aged 35-65 years old) took part in the present study as an intervention group and ten patients (7 women and 3 men) as a control group (Table 1). The patients were assigned randomly in each group and there were not statistically significant differences between them regarding gender, education and age.

7 b) Procedure

All study participants read the information sheet and signed an informed consent stating that the research group have the permission to use their demographic data, which would be anonymized, such as gender, age and education, as well as their performance in the neuropsychological tests, for research purposes. Before the administration of EH EVOO, the participants were evaluated using an extended neuropsychological assessment which includes measurements that cover a wide range of cognitive functions and are mentioned below. The neuropsychological assessment took place in a soundproof room in 1 st Department of Neurology of Aristotle University of Thessaloniki in Greece by a trained psychologist. Patients were instructed to take three tablespoons of EH EVOO per day. After six months and after one year they were called in for re-evaluation, using the same measurements but with alternative forms, wherever it was possible. The protocol of the present study is registered ClinicalTrials.gov with ID NCT04120675.

The EH EVOO, which was distributed to the participants, is Eliama D. V. Gold Health Claim High Phenolic Extra Virgin Olive Oil and contains high concentrations of polyphenol compounds (Oleocanthal, Oleacein, Oleuropein, Tyrosol & Hydroxytyrosol derivatives > 1200 mg /kg EVOO and very high concentration of Squalene 6800 mg and Tocoferol a). Eliama Daily Value Gold brings the certification of Health Claim. The health claim: The claim may be used only for olive oil which contains at least 5 mg of hydroxytyrosol and its derivatives (e.g. oleuropein complex and tyrosol) per 20g of EVOO. In order to bear the claim information shall be given to the

consumer that the beneficial effect is obtained with a daily intake of 20g of **??**VOO et Participants have to learn as many words as they can from a list with 16 words and this procedure is repeated five times. Form A was used for the assessment and form B for the retesting session. The total score equals to the total number of recalled words [16]. BVMT-R measures visual and spatial memory. In this test, participants must remember a page of six shapes which is presented for ten seconds and this procedure is repeated three times. Each shape is scored with zero, one or two points, depending on accuracy and location. The sum of the scores of the three trials is the total score of the test. [17].

3. The Perceived Deficits Questionnaire is a selfreporting questionnaire measuring subjective cognitive deficits and is designed specifically for MS patients. It covers the cognitive functions which are most often impaired in MS and it concludes four subscales: attention, retrospective memory, prospective memory and planning/organizing. The total score is computed by the sum of raw scores for all items and it can range from 0-80, with higher scores indicating greater perceived cognitive impairment [18].

8 The Mental Health Inventory (MHI) is a reliable

measure for patients' emotional condition. It consists of 18 items which are separated in four scales: anxiety, depression, behavioral control and positive affect. The total scores range from 0-100, with higher scores indicating better mental health [19].

9 The Beck Depression Inventory (BDI

) is used to measure depression. It is designed to examine both somatic and cognitive aspects of depression and the Greek version has been validated previously [20] and has been widely used to date. The BDI is a 21-item self-reporting scale scored on a 4-point scale (0-3). It has been shown to have good psychometric properties with test-retest correlations >0.90 in different studies. Moreover, it has shown satisfactory validity with agreement between BDI and psychiatrists' ratings of 56% and has also been shown sensitive to distinguish between depression and anxiety. Moreover, factor analysis generally reveals three inter-correlated factors indicating severity of depression. Scoring of the questionnaire is as follows: 0-9 no depression, 10-15 mild, 16-23 moderate, and 24-63severe depression [21]. The BDI has been validates for MS patients too and it is proved to be applicable for the evaluation of depression in this population [22,23]

10 d) Statistics

Statistical analysis was performed with the use of SPSS 25 Statistical package. A Wilcoxon Signed-Ranks Test was conducted in order to calculate the score differences in neuropsychological assessments before and after 1 year of therapy (intragroup comparisons). Moreover, an Independent Samples Ttest was conducted to compare the means of the two groups before and after EH-EVOO's consumption (intergroup comparisons).

11 III.

12 Results

At first, the differences between the two groups were calculated before the beginning of therapy, using Independent Samples T-test (Table 2). For this reason, the results of the first neuropsychological assessment of the two groups were compared in order to be insured that the two groups start from the same baseline. The results indicated that there were not statistically significant differences between the two groups and the Cohen's d test confirmed that the sample's size does not affect the results. An Independent Sample T-test was, also, conducted to compare the means of the two groups after one year of EVOO's consumption (Table 3) and there were some statistically significant results (Table 3). At first, in the FAB there was statistically significant difference between experimental group (M=17.55, Sd=0.759) and control group (M=15.30, Sd=3.164), t (30)=-3.058, p<.01. Secondly, there were differences in the two subtests of BICAMS, the BVMT and the SDMT. In the BVMT there was statistically significant difference between experimental group (M=26.35, Sd=4.056) and control group (M=20.50, Sd=5.442), t(30)=-3.321, p<.01. In the SDMT there was, also, statistically significant difference between experimental group (M=36.80, Sd=6.023) and control group (M=29.80, Sd=7.642), t(30)=-2.744, p<.05. As far as the intragroup comparisons (Table 4), the functions that are related to the frontal lobes were improved. Specifically, the FAB scores compared before and after therapy: Fourteen (14) out of twenty patients performed better after therapy. A Wilcoxon Signed-Ranked Test indicated that this difference was statistically significant, z=-3.329 p<.01. BICAMS scores, also, indicated improvement in specific cognitive functions. There were not statistically significant differences in GVLT score but there was statistically significant improvement in BVMT and SDMT scores. In the BVMT fifteen (15) out of twenty patients performed better after therapy and a Wilcoxon Signed-Ranked Test statistically significant improvement, z=-3.170, p<.01. In the SDMT, scores before and after therapy indicated statistically significant differences because seventeen (17) patients performed better after therapy than before, z=-3.467 p<.01.

As far as depression and negative emotions, great improvement was indicated by both the BDI and the MHI. Specifically, according to BDI, depressive symptoms were improved in 16 patients after therapy compared to their previous scores, z=-3.523 p< .01 Furthermore, MHI indicated statistically significant improvement in patients'

general mental health, because 17 patients had less mental health problems after therapy than before, z=-3.456p< .01. However, in control group there was no statistically significant changes (Table 5). These results of control group in combination with the statistically significant results of intervention group confirm EVOO's benefits in certain sectors of cognition. IV.

13 Discussion

The aim of the present study was to detect and quantify the benefits of EH ?VOO in protecting the cognition and mental health of MS patients. The hypothesis was that, because of the protective effects already attributed to EH EVOO consumption, the patients from the intervention group would demonstrate improved scores in their neuropsychological assessment after six months of EH-EVOO treatment. In general, the results showed that in the intervention group there was statistically significant improvement in the FAB, the BVMT and the SDMT. These results show that EH EVOO has positive effects in executive functions, visual memory and processing speed. At the same time, there were no statistically significant results regarding the control group. Although there are no studies about the benefits of EH EVOO in MS, there are studies supporting that EVOO (and the Mediterranean diet) can prevent cognitive decline and Alzheimer's disease in the elderly population [24,25]. So, EVOO may have an important role in neuroprotection and staving off neurodegeneration, even if there is still a need for more studies regarding MS and other neurodegenerative diseases, such as Parkinson's disease, ALS etc.

With the use of FAB, functions related to the frontal lobes were evaluated. The fact that the patients had statistically significant improvement in FAB means that the EH EVOO may be helpful in order to improve goal directed behaviors, mental flexibility and adaptation to the environment. Moreover, the statistically significant scores in SDMT may be indicative of improvement in the brain processing speed. These findings confirm that some cognitive functions, which are impaired due to the neurodegeneration of MS, can be improved with consumption of EH EVOO. However, the benefits are not limited to MS patients.

A three-city study has already claimed the beneficial effects of EVOO on cognition. This study was conducted in three French cities and used neuropsychological assessments repeated every two years to measure any cognitive decline and assess risk factors for dementia's symptoms. The results indicated that participants who were less luckily of demonstrating cognitive deficit for verbal fluency and visual memory, whereas, during the 4-year follow-up there was significant association between intensive use of olive oil and prevention of visual memory's decline [26].

In the present study, verbal fluency was evaluated with the second task of FAB and visual memory was evaluated by the BVMT. So, regarding cognitive decline, our extensive study expands the above findings, adding that EH EVOO is beneficial in these fields for MS patients too.

EVOO offers protection to neuronal functions in neurodegenerative diseases as well. Olive oil's phenolic compounds contain natural antioxidants, including vitamins E, which may reduce neuronal damage and death from oxidative reactions by inhibiting the generation of reactive oxygen species, apoptosis, protein oxidation, damages to cell membranes and ?amyloid toxicity. However, the mechanisms, which are used in order to achieve these benefits, are not clear yet and behest further study [11].

Another extensive study, the PREDIMED-NAVARRA randomized trial, which examined the benefits of Mediterranean diet, supplemented with EVOO, on people with high vascular risk, also advocate the present study's results. In this study, the neuropsychological assessment included Mini Mental State Examination (MMSE) and Clock Drawing Test (CDT), which evaluate cognitive deficits and cover a wide range of cognitive functions. The results of these assessments indicated that after 6,5 years of follow-up the participants had better global cognitive performance and supported the protective effects of Mediterranean diet with EVOO on cognitive function **??**27].

As far as patients' mental health, significant improvement was found in both BDI and MHI. Specifically, the majority of patients (16 out of 20) had lower scores in BDI, which means that the patients had fewer depressive symptoms after six months of using EH EVOO. In MHI, the majority of patients (17 out of 20) had higher scores after consumption of EVOO, which means that they had less mental health problems and this was confirmed by the findings of the BDI. Observational studies confirm these results because they have pointed to an inverse association between adherence to Mediterranean diet (MeDi) and risk for depression. Furthermore, two clinical trials have demonstrated significant improvement regarding depressive symptoms in patients who were following MeDi [17]. The PREDI-DEP trial was the first randomized clinical trial, designed to examine the role of the MeDi supplemented with EVOO in the prevention of recurrent depression. This study confirmed the positive effects of MeDi, in general, and EVOO in particular, in depression as it was found that they can reduce the recurrence of depression and increase the patients' quality of life [28]. Moreover, other studies have pointed that a low-fat diet supplemented with EVOO can reduce the physical and emotional disease burden in MS patients [29,30]. A possible mechanism behind the benefits of EVOO in mental health is that it can lower the markers of the above-mentioned oxidative stress, such as F2isoprostane **??**11, 12,].

A limitation of this pilot study is that apart from the three subtests of the BICAMS, and the BDI, the neuropsychological tests, which have been used, are not validated for the Greek MS population. However, this research is ongoing, and it will be continued for years to come. So, these specific neuropsychological tests will be validated for the Greek population soon. Another limitation is the limited number of participants (n=30) because this is a pilot study testing the effects of EH EVOO, the feasibility of the present research protocol.

There had been no previous evidence presented about the benefits of EH EVOO, and olive oil in general, in protecting the cognition and mental health of patients with MS. So, the innovation of the present pilot study is that these results can expand the research in this field and encourage the use of EVOO in holistic treatments of MS. For this reason, studies with increased sample size and even more bold approaches will be useful confirming the present study's results and identifying the specific mechanisms by which olive oil offers its benefits.

14 Declarations

Introduction
ccording to National Multiple Sclerosis Society

Figure 1:

1

	Gender		Education			Age
	Men	Women	M	Std	M	Std
Experimental group	12	8	15.25	9.031	47.85	11.726
Control group	7	3	12.80	4.237	41.50	14.470
p		0.592	0.436			0.367

Figure 2: Table 1 :

2

	Independent Samples T-test						
	Intervention group (n=20)		Control group (n=10)				
	M	Sd	M	Sd	t(30)	p	Cohen's d
FAB	16.00	1.806	15.00	2.494	-1.258	.219	.000459
GVLT	48.85	9.167	52.60	15.467	.837	.410	.4767
BVMT	22.85	5.373	22.00	5.249	-.411	.684	.4261
SDMT	31.70	7.540	30.00	11.785	-.481	.634	.0316
PDQ	5.15	3.746	4.90	2.601	-.189	.852	.0136
BDI	9.45	5.336	6.20	5.287	-1.577	.126	.0774
MHI	69.45	9.950	69.80	19.657	.065	.948	.0022
Significance levels: *p< .05 **p< .01							

Figure 3: Table 2 :

3

	Samples T-test						
	Intervention group		Control group				
	M	Sd	M	Sd	t(30)	p	Cohen's d
FAB	17.55	.759	15.30	3.164	-3.058	.005**	.0978
GVLT	52.90	7.567	51.10	14.888	-.443	.661	.0152
BVMT	26.35	4.056	20.50	5.442	-3.321	.002**	.1212
SDMT	36.80	6.023	29.80	7.642	-2.744	.010*	.1017
PDQ	4.25	3.007	6.30	2.497	1.856	.074	.0742
BDI	6.35	3.281	8.60	8.017	1.099	.281	.0367
MHI	77.35	4.987	67.70	20.618	-2.011	.054	.0643

Significance level: *p< .05
**p< .01

Figure 4: Table 3 :

4

	Ranks Test						Test Statistics		
	Negative ranks			Positive Ranks					
Before/ after	n	Mean rank	Sum of ranks	n	Mean rank	Sum of ranks	Ties	Z	p
FAB	0	.00	.00	14	7.50	105.00	6	-3.329	.0001**
GVLT	9	5.39	48.50	9	13.61	122.50	2	-1.615	.106
BVMT	3	4.33	13.00	15	10.53	158.00	2	-3.170	.002**
SDMT	1	6.00	6.00	17	9.71	165.00	2	-3.467	.0001**
PDQ	5	5.10	25.50	8	8.19	65.50	7	-1.419	.156
BDI	2	2.50	5.00	16	10.38	166.00	2	-3.523	.0001**
MHI	3	4.17	12.50	17	11.62	197.50	0	-3.456	.001**

Significance levels:
*p<.05
p<.01

Figure 5: Table 4 :

5

		Negative ranks			Positive ranks			Test Statistics	
Before/ after	n	Mean rank	Sum of ranks	n	Mean rank	Sum of ranks	Ties	Z	p
FAB	3	4.83	14.50	5	4.30	21.50	2	-.496	.620
GVLT	6	4.50	27.00	3	6.00	18.00	1	-.539	.590
BVMT	6	4.83	29.00	2	3.50	7.00	2	-1.611	.107
SDMT	3	6.33	19.00	5	3.40	17.00	2	-.140	.888
PDQ	7	5.71	40.00	2	2.50	5.00	1	-2.111	.035*
BDI	6	4.50	27.00	1	1.00	1.00	3	-2.111	.027*
MHI	5	4.90	24.50	4	5.13	20.50	1	-.237	.813
Significance levels: *p<.05 **p<.01									

Figure 6: Table 5 :

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.1 Conflicts of interest:

The authors declare that they have no conflict of interest.

.2 Ethics approval:

The study protocol has been approved by Bioethics Committee of Greek Association of Alzheimer's Disease and Related Disorders.

Consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki 1964 and was approved by the local ethics committee. All the participants gave informed consent prior to their inclusion in the study.

Consent for publication: All the authors have consented for the publication of the study.

Availability of data and material: Data available upon duly justified request.

.3 Conflicts of interest: none

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