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Short communication

1-H MRS Changes in Dorsolateral Prefrontal Cortex after Donepezil Treatment in Patients with Mild to Moderate Alzheimer's Disease

Neven Henigsberg[1,2], Petra Kalember[2,3], Pero Hrabač[4], Marko Radoš[4,5], Maja Bajs[5], Milan Radoš[4,5], Zrinka Kovačić[4], Mladen Lončar[5] and Tomo Madžar[4]

[1] University of Zagreb, »Vrapče« Psychiatric Hospital, Department of General and Forensic Psychiatry and Clinical Psychophysiology, Zagreb, Croatia
[2] University of Zagreb, Croatian Institute for Brain Research, Department of Neuropharmacology and Behavioural Pharmacology, Zagreb, Croatia
[3] »Neuron« Polyclinic, Zagreb, Croatia
[4] University of Zagreb, Croatian Institute for Brain Research, Zagreb, Croatia
[5] University of Zagreb, Zagreb University Hospital Center, Zagreb, Croatia

A B S T R A C T

Magnetic resonance spectroscopy (MRS) noninvasively provides information on the concentration of some cerebral metabolites in vivo. Among those measurable by proton magnetic resonance spectroscopy (1H-MRS), N-acetyl-aspartate (NAA) is decreased, and myo-inositol (mI) and choline (Cho) levels are increased in patients with Alzheimer's disease (AD). Donepezil, an acetylcholinesteraze inhibitor, has proven effect on cognitive symptoms in patients with AD. In previous studies, treatment response was associated with an increase of NAA and NAA/Cr in the parietal lobe and hippocampi. Correlation of longitudinal changes of 1H-MRS detectable metabolites in dorsolateral prefrontal cortex (DLPFC) with clinically observable changes is a poorly researched topic. The objective of this non-interventional study is to assess whether changes in 1H-MRS measurable metabolites correlate with clinical outcome after donepezil treatment. Twelve patients with mild to moderate AD were evaluated during 26 weeks of donepezil treatment. 1H-MRS parameters in DLPFC were assessed before and after 26 weeks of donepezil treatment. Cognition was assessed with Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog). A significant increase in NAA/Cr ratio and significantly lower decrease in mI/Cr ratio were found in AD patients with positive treatment response. The results of this study indicate possible modest donepezil effect on prevention of neuronal functional deterioration in DLPFC which correlates with clinical outcome and point the use of 1HMRS as technique of help in assessment of drug effect.

Key words: *1H-MRS, donepezil, Alzheimer's disease*

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive loss of memory and impaired social functioning. AD may additionally present with different comorbid psychiatric symptoms such as anxiety, depression and psychosis. The disease mostly affects the population over 65 years of age and is therefore the most common cause of age-related cognitive decline and dementia. However, it may appear in the younger individuals as well. Since the etiology of this disease is still mostly unknown there is much room for improvement in the area of diagnosing the disease before the clinical signs become apparent as well as the improvement in the treatment of the disease in its early stages.

One of the most commonly used medication for the treatment of AD is a cholinesterase inhibitor (ChEI), donepezil, which is used for the treatment of mild to moderate stages of the disease. The group of ChEI drugs, which also includes drugs as galantamine and rivastigmine (also used for treatment of AD), currently repre-

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sent the only alternative to treatment with N-methyl- D -aspartate antagonist memantine, used mainly to treat severe cases of dementia. Although there are some doubts with regard to donepezil's (and ChEI's in general) efficacy[1], most of the studies[2] found their effect stabilizing in terms of general disease progression. Additionally, donepezil is considered to be the drug with the best safety profile in the ChEI group[1]. In assessing both safety/tolerability as well as efficacy of any such treatment, an objective method should be employed. In everyday clinical practice as in the clinical studies, the improvement or worsening of the disease is usually monitored with two scales: Mini-Mental Status Exam (MMSE)[3] and the Alzheimer Disease Assessment Scale – cognitive subscale (ADAS-Cog)[4]. Mentioned scales are used widely and routinely so there is no need to discuss them further, except to say that, like any rating scale, these are susceptible to certain biases from both rater and the subject[5]. Therefore, it is interesting to compare outcome of two above mentioned scales to the more »objective» method. For this purpose, we employed 1-H magnetic resonance spectroscopy (1H MRS). It is an *in vivo*, non-invasive diagnostic procedure that enables the researcher to follow concentrations (i.e. concentration readings) of brain metabolites in selected brain regions. Method is used to detect and visualize carbon-bound, non-exchangeable protons in certain spectral regions. The most well-known metabolites detected include N-acetylaspartate (NAA) as an indirect expression of the integrity of neurons[6,7], choline (Cho) containing compounds as metabolites involved in phospholipid membrane synthesis and marker for glial activity, creatine (Cr) including phosphocreatine as a marker for energy metabolism, and lactate as an indicator for anaerobic glycolysis detected under pathological conditions[8–11].

In this study we have monitored the concentration of N- acetyl aspartate (NAA) since its decrease is usually considered to manifest neuronal loss, decreased neuronal viability or impaired neuronal function[12]. Study of Krishnan et al.[13] showed that NAA concentrations in subcortical gray, periventricular, cortical and white matter showed an increasing trend after donepezil treatment whereas concentration in the placebo group remained close to baseline values. However, only results from subcortical gray and periventricular matter managed to reach the significant change from the baseline. Bartha et al.[14] showed a significant decrease in NAA and NAA/Creatin (Cr) in hippocampus after a four-month donepezil treatment in AD patients.

In this study we have monitored the change in concentrations of NAA/Cr in dorsolateral prefrontal cortex in AD patients before and after 26 weeks of treatment with donepezil. NAA/Cr ratio was chosen since it is considered to be the most reliable marker of neuronal integrity available[15].

Subjects and Methods

All participants in the study were included as a part of the recruiting procedure for the clinical study determining long-term effects of Donepezil, a centrally acting reversible cholinesterase inhibitor. In an open-label study, subjects with moderate to severe Alzheimer's disease received 10 mg formulation of Donepezil. Before inclusion in the study, DSM IV diagnostic criteria were employed to appropriately differentiate subjects with AD. Subjects included were those with mild to moderate dementia according to their individual Mini Mental State (MMS) scores. Other criteria included presence of noticeable cognitive impairment measured for different cognitive domains. Instruments used to establish such impairment were: remembrance of the simple stories (immediate and after a certain period of time), lingual fluency, figure copying and memory scales. Also assessed were activities of daily living and clinical dementia rating scale (by using ADAS-Cog scale).

Following the above mentioned procedures, diagnostic MRI scans were done on a 3T MRI unit, to exclude potential cerebrovascular disease underlying the diagnosed clinical condition. Providing all of the above tests suggested diagnosis of AD and neuroradiological finding provided no proof of underlying cerebrovascular disease, subjects were diagnosed with AD. All subjects gave their voluntary informed consent, either themselves, or trough their caregiver, in case when their condition rendered them incapable of understanding the subject information sheet. Altogether 12 subjects (7 female and 5 male) were

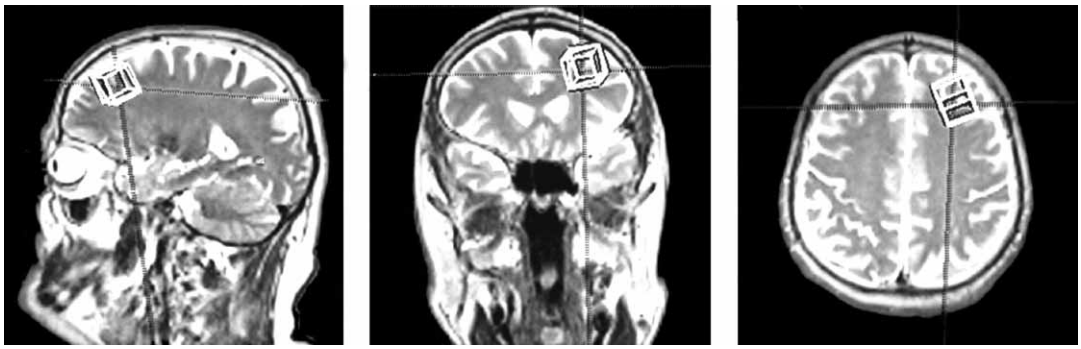

Fig. 1. Spectroscopic Volume of Interest (VOI) in the dorsolateral prefrontal cortex.

included in the study. Mean age of the subjects was 71.4 years (SD=7,04).

1-H MR spectroscopy was performed on a Siemens 3 T machine, using a radiofrequency transmit/receive head coil suited for cerebral MRI and magnetic resonance spectroscopy. The spectroscopic volume of interest (VOI) of 25x25x25 mm was positioned in the right dorsolateral prefrontal cortical region (Figure 1). The angulation of the VOI was achieved either directly by appropriate switching of the magnetic field gradients or by reclining the subject's head in an adequate position. Metabolite signal ratios of NAA and Cr were determined from the spectra with TE = 272 msec. Appropriate filtering was applied to improve the signal to-noise ratio and to convert the lines into a Gaussian shape.

Statistical analysis was done in Statistica software package (Statsoft, Tulsa, OK, USA), version 8. Due to small sample size, nonparametric methods had to be used to compare before NAA/Cr ratios before and after the 26-week treatment. To test the null hypothesis that there is no difference between the distributions of NAA/Cr ratios before and after Donepezil treatment was administered, i.e. to compare paired samples of ratios, Sign test was used.

Results

In all 12 subjects NAA and Cr levels were measured in the DLPFC area using the above mentioned technique before and after the 26 weeks (95% confidence intervals were 25,1 and 26,3 weeks) of Donepezil treatment. Measurement results were combined to calculate a NAA/Cr ratio and are displayed in Figure 2.

We found NAA/Cr ratios to be generally lower at the baseline visit compared to the visit after the treatment. This was true for 10 out of 12 subjects studied. Two subjects, Nos. 4 and 8, both females older than 70 years of age, showed a different pattern with higher NAA/Cr ratios at baseline. However, even in these subjects, a lower cognitive decline was observed than we expected, a fact also described by other authors[16].

Overall, mean NAA/Cr ratios before Donepezil treatment was administered were 1.39 (SD=0.207; 95% confidence intervals 1.26 and 1.52). After the treatment, mean ratio was 1.48 (SD=0.241; 95% CIs of 1.32 and 1.63). Mean difference between the first and the second measurement was thus 0.085 (SD=0.218; 95% CIs of –0.052 and 0.222). Differences between measurements were compared by the appropriate non-parametric test, as described before and were found to be statistically significant (p=0.043, Z=2.02). The conclusion can be made that there was statistically significant increase in NAA/Cr ratios after approximately 6 months of Donepezil treatment in subjects suffering from mild to moderate Alzheimer's disease.

Discussion

Practically all 1H-MRS studies published to date reveal lower NAA values in cortical areas of subjects with AD when compared to healthy people of the appropriate age[17]. On the other hand, myoinositol levels are found to be lower, while choline levels were reported to be both elevated[18] and not elevated[19] when such comparisons are performed. NAA therefore seemed like a logical choice for neuronal damage assessment in the present study. Additionally, it is, unlike myoinositol, found exclusively in the nervous system, where its levels depend on the intensity of oxidative phosphorylation processes in the neuronal mytochondria. It is quite possible that decrease in NAA seen by the 1H-MRS could be, at least in the beginning, consequence of mytochondrial dysfunction, rather than net grey matter neuronal loss. Or, in words of Krishnan et al.[20], NAA concentrations may reflect both neuronal function and content. Since our premise is that this function/content discrepancy may not happen at the same time, there could exist a specific time-point between the initial, possibly reversible, NAA decrease and later permanent decrease. This gap in return could (at least in theory) be the target of the pharmacological intervention by donepezil or any of the other available treatments. In this context, donepezil is known to increase relative NAA/Cr ratio compared to placebo in the beginning of the treatment, up to week 6[21] and possibly week 18[20]. We wanted to see what happens with NAA/Cr ratios after this stage, so we observed subjects for a pe-

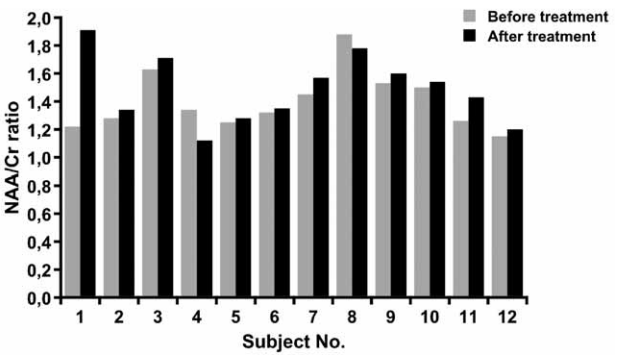

Fig. 2. NAA/Cr ratios for each of 12 subjects studied, before (grey) and after (black) the 26-weeks treatment with Donepezil.

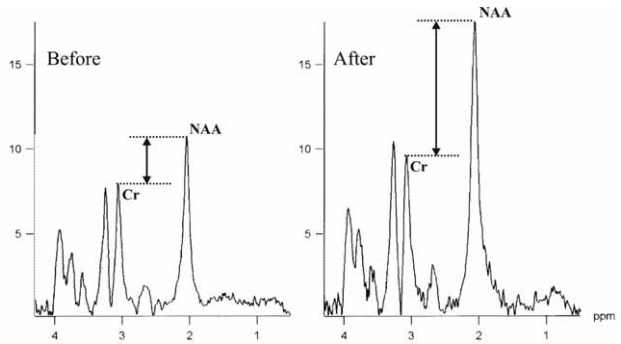

Fig. 3. Typical NAA/Cr ratios before and after donepezil treatment. Note relatively constant Cr levels as opposed to significant increase in levels of NAA.

riod of 26 weeks. Typical NAA/Cr ratio observed before treatment differed significantly from that after treatment (Figure 3).

With relatively constant Cr levels observed on both visits, NAA levels were elevated significantly after the treatment period, as mentioned in the Results section. These results, although derived from the relatively small number of subjects, suggest that positive effect of such treatment on NAA levels may be longer lasting that it was previously thought. While needing more confirmation, these results suggest that similar study, but with much longer follow-up period is needed to confirm our results and investigate the possibility of medium- to long-term effects on donepezil on NAA concentrations. In combination with previously mentioned finding that subjects initially described as non-responders could also benefit from donepezil treatment, a prolonged study of such type with a higher number of subjects would represent a welcome addition to current knowledge on this issue.

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P. Hrabač

University of Zagreb, Croatian Institute for Brain Research, School of Medicine, Šalata 12, 10000 Zagreb, Croatia
e-mail: phrabac@hiim.hr

1-H MRS PROMJENE U DORZOLATERALNOM PREFRONTALNOM KORTEKSU NAKON PRIMJENE DONEPEZILA U PACIJENATA S BLAGIM I UMJERENIM OBLICIMA ALZHEMIEROVE BOLESTI

SAŽETAK

Magnentno rezonantna spektroskopija (MRS) metoda je koja neinvazivno pruža informacije o in-vivo koncetraciji određenih metabolita u mozgu. Među metabolitima koji se mogu mjeriti protonskom magnentno rezonantnom spektroskopijom (1H-MRS) u bolesnika s Alzheimerovom bolešću (AD) snižene su razine N-acetil-aspartata (NAA), dok su razine mio-inozitola (mI) i kolina (Cho) povišene. Donepezil, inhibitor enzima acetilkolin esteraze, pokazao se učinkovitim u liječenju kognitivnih simptoma u bolesnika od AD. U prethodnim ispitivanjima, odgovor na liječenje bio je povezan s povišenim vrijednostima NAA i omjera NAA/Cr u parijetalnom režnju i hipokampusu. Ipak, povezanost promjene vrijednosti metabolita koji se mogu otkriti metodom 1H-MRS u području dorzolateralnog prefrontalnog korteksa (DLPFC) s klinički uočljivim promjenama slabo je istraženo područje. Cilj ovog neinterventnog ispitivanja je procijeniti da li promjene u metabolitima koji se mogu otkriti metodom 1H-MRS odgovara kliničkom rezultatu nakon liječenja donepezilom. Promatrano je 12 ispitanika s blagom do umjerenom AD tijekom 26 tjedana liječenja donepezilom. Parametri mjereni metodom 1H-MRS ispitani su prije i nakon 26-tjednog liječenja donepezilom. Korištena je i ljestvica »Alzheimer's Disease Assessment Scale cognitive subscale« (ADAS-Cog) za procjenu mentalnog stanja ispitanika. Znatno povećanje omjera NAA/Cr i znatno manje sniženje omjera mI/Cr pronađeni su u bolesnika s pozitivnim odgovorom na liječenje. Rezultati ovog ispitivanja upućuju na moguće blago pozitivne učinke donepezila na usporavanje funkcionalnog propadanja neurona u području DLPFC. Također, metoda 1H-MRS pokazala se korisnom u procjeni učinaka lijeka.