LETTER TO THE EDITOR

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Improvement of neuronal integrity with methylphenidate treatment for apathy in Alzheimer's disease

Introduction

Apathy, a profound loss of initiative, motivation, and persistence, is the most common behavioral problem in patients with dementia (Lyketsos *et al.*, 2002). The presence of apathy is associated with functional deficits, higher caregiver burden, and worsening neurodegenerative trajectory (Marin, 1991). Frontal lobe dysfunction, poor neuronal integrity, and hypodopaminergic state in the frontal lobe and reward circuitry are considered etiologic factors for apathy (Benoit *et al.*, 2002). Dopaminergic reuptake inhibitors such as methylphenidate (MPH) have been found to be effective in treating apathy in well-controlled randomized clinical trials (Padala *et al.*, 2017; Rosenberg *et al.*, 2013). It is unknown if MPH treatment of apathy in those with dementia changes frontal lobe metabolites which are a proxy for neuronal integrity. Use of MPH in children has shown increase in N-acetylaspartate (nAA), a marker of healthy, normally functioning neurons (Wiguna *et al.*, 2012). To date, no studies have been conducted on the effect of MPH on brain metabolites in patients with concomitant apathy and dementia. We hypothesized that nAA levels would increase in the right medial frontal (RMF) but not right parietal (RP) cortex as MPH is known to have preferential dopamine enhancement effects on the frontal cortex.

Methods

Mr. A, 74-year-old Caucasian male, was referred for management of Alzheimer's dementia (AD) with behavioral problems. The diagnosis of dementia was confirmed via a comprehensive evaluation in an interdisciplinary memory disorders clinic. Memory and behaviors were assessed with Mini Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), and the Apathy Evaluation Scale-Clinician version (AES-C) (Marin *et al.*, 1991). Patient scored 23 on MMSE, 56 on AES-C, which is considered clinically significant apathy, and the NPI was positive for clinically significant apathy and irritability. MPH was started at 5 mg BID and titrated to 10 mg BID at 2 weeks. MPH was continued for 12 weeks.

Magnetic resonance spectroscopy (MRS) was performed before and after treatment using a 3 Tesla GE scanner. Single voxel spectra $2 \times 2 \times 2$ cm point-resolved spectroscopy sequences (PRESS) at short echo time (35/2000 ms) were acquired and processed by fitting using the LC Model software package. Anatomic images were used to place the voxel at the same location pre- and post-intervention. Metabolite quantitation and database development were performed using water as an internal standard. nAA levels were measured pre-and post-treatment in the RMF and RP. Hunter's angle was calculated. It is a quick visual method for assessing the relative peak heights of major metabolites with the three largest spectral peaks (choline, creatine, and nAA) making a 45° angle (Lin *et al.*, 2005). In dementia, this is disrupted due to the relative high proportion of choline and is typically 15° (Lin *et al.*, 2005).

Results

No adverse events were reported. There was a clinically significant improvement in apathy at 12 weeks by both outcome measures (AES-C 33, 41% improvement and NPI apathy domain). nAA levels increased in the RMF region from 6.3 to 7.6 (20% improvement). nAA levels decreased in the RP region from 7.4 to 6.7 (9% decline). In our subject, the Hunter's angle was 15° at baseline and neared 45° after 12 weeks of MPH treatment (Figure 1).

Discussion

MRS is a safe and noninvasive tool that can be used to study aspects of brain chemistry and metabolism. nAA levels decline with neurodegeneration, with lowest levels noted in AD patients, followed by mild cognitive impairment (MCI) patients, compared to healthy controls (Gao and Barker, 2014). Lower nAA levels in the right frontal lobe and anterior cingulate are seen in those with apathy (Shinno *et al.*, 2014). In this subject, apathy improved significantly with MPH treatment. Improvement in nAA levels was seen in the RMF cortex but not in the RP cortex. Improvement in the neuronal integrity of the frontal cortex could potentially be the mechanism of action of MPH leading to improvement and apathy. This is consistent with ADHD literature (Wiguna *et al.*, 2012). This preliminary finding needs to be confirmed by larger studies.

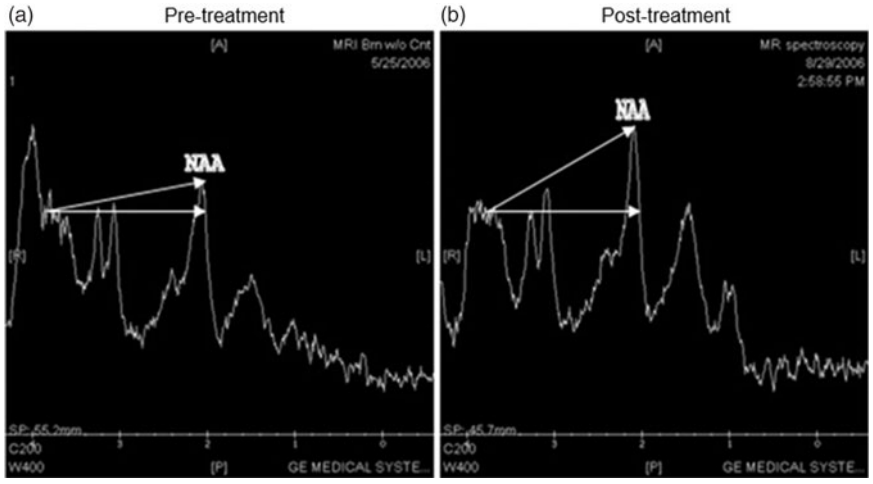

Figure 1. MRS changes after 12 weeks of MPH treatment.

Conflict of interest

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