



Ninjin'yoeito (Tsumura) Extract; a Kampo (traditional herbal medicine) Improved Apathy in a Mild Cognitive Impairment Patient

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ABSTRACT

Apathy, characterized by lack of motivation and loss of initiative, is a common symptom with all forms of dementia. The traditional Japanese medicine: Ninjin'yoeito (NYT) has been reported to improve anemia, fatigue, loss of appetite, and anorexia in patients with Alzheimer's disease. We reported here the case of a 71-year-old female with mild cognitive impairment (MCI) and apathy. NYT improved her apathy symptoms effectively, without any adverse effects, including cognitive decline. Our findings suggest that apathy symptoms in MCI patients can be improved without prescribing cholinesterase inhibitors.

Keywords: *apathy, mild cognitive impairment, traditional herbal medication, Ninjin'yoeito*

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Introduction

Apathy, a lack of motivation, is one of the most important symptoms in demented patients [1]. Apathy occurs due to the dysfunction of the frontal-subcortical circuit, and is associated with some adverse outcomes, including reduced daily living function, poor rehabilitation outcomes, and increased cognitive impairment [2]. Recently, the association between apathy and frailty has been discussed in patients with dementia [3]. Frailty is supposed to be due to the progressive decrease of mainly physiological reserves in elderly people. On the other hand, the issue has not been resolved yet, whether apathy symptoms might be responsible for hypomobility or be a consequence of worsening of

comorbidities [3].

The traditional Japanese medicine: Ninjin'yoeito (NYT) has been approved as a prescription medication in Japan to improve anemia, fatigue, loss of appetite, and anorexia. NYT is a multicomponent drug, including 12 herb and plant products: rehmannia root, angelica root, atractylodes rhizome, Poria sclerotium, ginseng, cinnamon bark, polygala root, peony root, citrus unshiu peel, astragalus root, glycyrrhiza and schisandra fruit [4-6].

In previous reports, Ohsawa et al. [4] reported that NYT improves apathy and loss of appetite in elderly patients, confirming Ozaki's earlier findings [5]. Furthermore, Kudoh et al. [6] revealed that Al-

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zheimer's (AD) patients receiving combined treatment of donepezil and NYT showed a significant improvement in both cognitive function and depressive symptoms compared to those who received donepezil only at the 2-year follow up. However, the effect of NYT for apathy alone in patients with mild cognitive impairment (MCI) has not yet been reported and remains unclear.

In this report, we describe the efficacy of NYT for the symptoms of apathy in a case of MCI. The patient provided her informed consent for this report, and her anonymity has been maintained.

Case Presentation

A 71-year-old female was referred to our outpatient department with amnesia and loss of motivation. She had been taking amlodipine (2.5 mg/day) for 20 years due to hypertension. Her neurological examination revealed no obvious abnormalities except slight rigidity of both upper limbs. Laboratory findings, including thyroid function, were normal. The patient's score on the Mini-Mental State Examination was 27/30. Her Geriatric Depression Scale (GDS)-short version result was 6/15, indicating that she was not in a depressive state. Both her logical memory and digit span were reduced by $>2SD$ on the Wechsler Memory Scale-Revised, her Clinical Dementia Rating (CDR) score was 0.5, and her Apathy Evaluation (AE) scale [1] was 24/42, i.e., above the cut-off point of 16. Brain magnetic resonance imaging (MRI) demonstrated mild global cerebral atrophy and white matter high-intensity lesions on T2-weighted images. Single photon emission computed tomography using ^{99m}Tc -ECD showed reduced regional cerebral blood flow matching an infarct lesion on both corona radiata and the basal ganglia. The patient's history, neuroimaging and cognitive results satisfied the revised Mayo Clinic criteria for MCI [6].

Although we first recommended treatment with a cholinesterase inhibitor, the patient refused it. We administered trazodone (25 mg/day) to improve her sleep. Two weeks later, her sleep had improved but her apathy had not. Additionally, she felt slight lethargy. We recommended adding NYT (Tsumura) extract (6 g/day). After 2 weeks of taking NYT, she gradually felt more energy without affective change, and she stopped taking the trazodone. Two weeks later, she was able to take a walk, which had been part of her previous daily routine. Her AE and GDS

scores fell to 10 and 4, respectively, which were below the cut-off points. One year after the patient started NYT treatment, her cognitive status and mood remained stable.

Discussion

To the best of our knowledge, this is the first report on the efficacy of NYT for apathy in a patient with MCI. Apathy is a common symptom in MCI patients. Robert *et al.* [2] investigated the prevalence of apathy in 251 outpatients fulfilling the criteria of amnesic MCI. They reported that apathy assessed with the Apathy Inventory occurred in 86 (39.8%) subjects. Furthermore, symptoms of apathy, but not of depression, were found to increase the risk of progression from MCI to AD [8]. To prevent declining cognitive function, efforts should be made to improve symptoms of apathy as soon as possible. Although, interventions for MCI have revealed that cholinesterase inhibitors are often effective for apathy [7], it can be sometimes difficult to convince MCI patients that they reject to take medications for adverse effects. Our patient's apathy improved without any adverse effects including cognitive decline, although we avoided prescribing any cholinesterase inhibitors.

The reasons why NYT can improve apathy remain to be clarified. Recent reports have revealed that myelin loss is an important factor in the pathology of MCI, as well as both degenerative and vascular dementia [9, 10]. The association between demyelination and apathy has also been reported in multiple sclerosis patients [11, 12]. Kudoh *et al.* [6] suggested that NYT has a myelin-protecting effect in patients with AD. Another possibility is that there is an association between inflammation and apathy symptoms [13]. NYT is reported to improve inflammation in particular [14], and thus might reduce apathy in MCI patients [15]. Confirmation of the effectiveness of NYT for the improvement of apathy in MCI a controlled study of a large number of MCI will be necessary to confirm these findings.

Disclosure Statement

There were no conflicts of interest.

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