Cerebellar Hemorrhage Provoked by Combined Use of Nattokinase and Aspirin in a Patient with Cerebral Microbleeds

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Abstract

Nattokinase is used as a health-promoting medicine for preventing thrombosis due to its fibrinolytic activity. Cerebral microbleed is remnant of blood extravasations from the damaged vessels related to cerebral microangiopathies. We report a patient, having used aspirin for secondary stroke prevention, who had an acute cerebellar hemorrhage after taking nattokinase 400 mg daily for 7 consecutive days. In addition to the hemorrhagic lesion, multiple microbleeds were demonstrated on brain MR images. We suggest that nattokinase may increase risk of intracerebral hemorrhage in patients who have bleeding-prone cerebral microangiopathy and are receiving other antithrombotic agent at the same time.

Key words: Nattokinase, Intracerebral hemorrhage, Cerebral microbleed

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Introduction

Nattokinase, an alkaline protease extracted from the traditional Japanese food “natto” (fermented soybean) is now widely used as a health-promoting over-the-counter medicine for reducing the risk of thrombosis due to its fibrinolytic activity. (1, 2) It is generally believed that nattokinase is a safe agent, however, there has been no large-scale study conducted to determine the suitable dosage for prevention of cardiovascular disease and avoiding bleeding side effects associated with its use. The thrombolytic activity of nattokinase has been found to be stronger than that of plasmin or elastase both in vitro and in vivo. (1, 2) Here we report a patient who had an acute cerebellar hemorrhage after taking nattokinase 400 mg daily for 7 consecutive days.

Case Report

A 52-year-old woman has had essential hypertension since her twenties and was diagnosed as having a minor ischemic stroke 1 year ago when brain CT revealed multiple lacunar infarctions and prominent leukoaraiosis. She was given antihypertensive agents and low-dose aspirin (100 mg/day) for secondary stroke prevention. Subsequently, vascular parkinsonism was diagnosed and antiparkinsonian agents were prescribed for gait disturbance, hypokinesia, and axial rigidity. One week before admission, she started taking nattokinase (400 mg/day) by herself hoping that it could further protect her from recurrent stroke. Because of an acute onset of vertigo and unsteady gait she was brought to our hospital. On admission she had high blood pressure (range, 145-230/60-110 mmHg). She had unsteady gait and easily tilted to her left side. A complete blood count (platelet 326×10^3/mm^3), activated partial thromboplastin time (29.9 seconds), prothrombin time (10.0 seconds), bleeding time (3.5 minutes), and biochemistry profile were normal. Brain CT revealed an acute hemorrhage in the left cerebellar hemisphere (Fig.1A). In addition, there were multiple signal-void areas characteristic of cerebral microbleeds on gradient-echo (GE) T2*-weighted MRI (Fig.1B-D). Considering that she had a positive family history in that her father and one of her paternal uncles also had a history of multiple cerebral hemorrhages and died from intracerebral hemorrhage (ICH), we included hereditary cerebral amyloid angiopathy in the differential diagnosis. However, a genetic study of mutation detection at exons 16 and 17 of the amyloid precursor protein gene and at exon 2 of the cystatin C gene showed negative
Figure 1. Brain CT shows a recent hemorrhage in the left cerebellum (A). Gradient-echo T2*-weighted MRI shows multiple foci of signal intensity loss (microbleeds) in the brainstem, cerebellum, thalamus, basal ganglia, and bilateral cerebral hemispheres (B-D) in addition to the recent cerebral hemorrhage in the right cerebellum (B).

Discussion

Cerebral microbleed has been defined as a 2-5 mm hypointense lesion on the GE T2*-weighted MRI due to deposition of hemosiderin (3). Histological studies have confirmed that this area is remnant of clinically silent hemorrhage from a bleeding-prone cerebral microangiopathy, e.g. lipohyalinosis and cerebral amyloid angiopathy (4). Clinically, cerebral microbleed is conferred an increased risk for primary ICH (4). At present, GE T2*-weighted sequence of MRI is the most sensitive modality for detecting the lesion which is often missed on fast spine echo T2 weighted study (5). It is probably worthwhile to include GE T2*-weighted series in the brain MRI study for stroke patients, as the additional information it provides may help in estimating the risk of future cerebral hemorrhage and adjusting antithrombotic regimen (3, 5).

In our patient, several factors may facilitate the development of the acute cerebellar hemorrhage. First, presence of multiple cerebral microbleeds suggested an underlying cerebral microangiopathy with increased risk of ICH. Second, the daily dose of nattokinase used was higher than recommended (300 mg/day) (2). At last, it is likely that inhibitory effects of nattokinase and aspirin on hemostasis could be additive if the two agents are used at the same time. However, data for interaction between nattokinase and aspirin is lacking, and more studies are needed to address the issue. Currently, the role of cerebral microbleed as a clinical guide for fibrinolytic or antithrombotic treatment has not been justified (6). We suggest that use of nattokinase should be cautious in patients who have bleeding-prone cerebral microangiopathy and are receiving other antithrombotic agent at the same time.
### References


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