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Case Report: Recovery from Schizophrenia Using Amyloban®3399, Compounds Extracted from *Hericium erinaceum*

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INTRODUCTION

Hericium erinaceum (HE) is a unique mushroom for its cognitive function improving actions. HE is known as Yamabushitake in Japanese and Lion's Mane in English.

Since the early 1990s, Kawagishi and his colleagues have been investigating the role of the compounds derived from HE in the treatment of dementia (Kawagishi et al., 1991; Kawagishi et al., 1992; Kawagishi et al., 2004; Kawagishi et al., 2008). Bioactive substances in HE have the potential to stimulate the production of NGF, repair neuronal damage and improve brain function if the substances in HE are able to cross the blood-brain barrier, then NGF may act to repair neuronal function. Nagai et al have found that HE exhibited important bioactive properties, including the induction of NGF synthesis, inhibition of the cytotoxicity of amyloid beta peptide, and protection against neuronal cell death caused by oxidative or endoplasmic reticulum stress (Nagai, Chiba, Nishino et al., 2006).

A double-blind placebo-controlled study confirmed the improvement on mild cognitive impairment with use of HE (Mori, Inatomi, Ouchi et al., 2009).

Amyloban®3399---contains Amycenon, a standardized extract of HE containing hericenones and amyloban – and is currently being tested for safety as a health food supplement (Mori, Inatomi, Ouchi et al., 2009). A clinical trial with 8 volunteers was conducted to demonstrate the cognition-enhancing properties of Amyloban®3399 (Lotter, 2012). Results of the study showed that Amyloban®3399 improved mood, memory and sense of wellbeing. Overall Amyloban®3399 was generally well tolerated.

Schizophrenia is the most devastating disease of the major psychoses. It has been repeatedly observed in clinical practice that although positive symptoms may be reduced within a few week treatment period, while it takes months or years to see improvements in cognitive symptoms. Atypical neuroleptic clozapine is associated with reduced liability for extrapyramidal symptoms and is effective in treatment-resistant schizophrenia. However, adverse effects limit the widespread use of clozapine.

Amyloban®3399 was originally thought to be a drug for dementia. However, based on my clinical observation, I asked a schizophrenia patient presented in this report to take Amyloban®3399. He had been treatment-resistant and suffered from severe side effects for more than 30 years. He agreed to take Amyloban®3399 and he has experienced dramatic life improvements and has been doing quite well for these three years.

CASE: MT 54-YEAR-OLD MALE

At 18 Years Old

The patient exhibited major psychiatric symptoms, including auditory hallucinations, delusions and sleep disorder. In February, his initial visit to a Psychiatric Department of a University Hospital began, where he was diagnosed with schizophrenia and treated as an outpatient. In February, at age 30, he was admitted to the Psychiatric Department of a University Hospital (first admission). His major symptoms were auditory hallucinations, delusions, sleep disorder and severe headache. From 31 to 40 years old: At the age of 33, he was admitted to Hospital C (second admission). He received treatment with risperidone and olanzapine. During these years, he had major side effects, such as akathisia and water intoxication. It was recommended that the dose of the antipsychotic drugs be limited, since he was prone to such side effects. His physician continued to have significant difficulty in using antipsychotic drugs for this patient.

From 41 to 52 years old

In October, at the age of 41, it was found that the patient had maintained a continual regimen of iced water and smoking for 1-2 months, along with accompanying anxiety symptoms. At age 45, he began to receive 10mg olanzapine, 3mg clonazepam, and a small dose of chlorpromazine. 10 or 20mg olanzapine was maintained, until the age 48, due to ease of compliance for the patient. During these years, water intake was large, with daily volume sometimes reaching high as 10 liters. At age 48, the administration of olanzapine was terminated and a course of aripiprazole was initiated. When aripiprazole was administered at 6mg, water intake was clearly decreased. After discharge from the hospital, he continued regular hospital visits and used day care service. However, at the age of 49, he was admitted to Hospital C (third admission) for negative thoughts, realistic distress and anxiety for the future. For some time after admission to the hospital, auditory hallucinations and delusions of guilt were observed, and his condition was not stable. Around mid-March, at the age of 50, he developed delusions of guilt and a strong desire to discharge himself from the hospital, and thus hospitalization for medical care and protection was provided to him in April 9. After that, drug administration was arranged, and his condition gradually became stable. A short stay at home began in June. Then, although loosening of association and decreased motivation were continuously observed, he participated in OT activity, etc. At 51 years of age, he again developed delusion of guilt and a strong desire to discharge himself from the hospital around mid-March, and thus hospitalization for medical care and protection was again implemented on April 9. Just as before, drug administration was arranged, and his condition gradually stabilized. Since the patient and his family expressed hope for discharge from the hospital, he was discharged on May 10, after experiencing a stay at a welfare home twice during the period from April to May at 52 years of age. Prescription at discharge from the hospital was aripiprazole 18mg and risperidone 2mg. In addition, lorazepam, ethyl lofrazepate, flunitrazepam and brotizolam were also used. He moved into "Y Heights" a care home located on the premises of the hospital, and visits the hospital as an outpatient and received day care services. On June 2, diaphoresis and a semi-stuporous state were confirmed during bed rest at his room in the care home. Since he was diagnosed with malignant syndrome, he was admitted to

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an isolation ward. On June 4, he developed acute drowsiness and grogginess during dinner. After receiving drip infusion for 6 days, his psychiatric condition became stable. On June 8, intramuscular injection of 25-mg risperidone (Consta) was commenced, and on September 30, he began to receive intramuscular injections of 37.5-mg risperidone (Consta) every second week, in addition to 200-mg quetiapine and 2-mg flunitrazepam at bedtime. He was discharged from the ward on November 19. Upon awakening at 11a.m, on December 2, he remained drowsy without feeling refreshed. During the day time, he continued to be less active with increased drowsiness. Psychological test results are as follows.

GHQ 17(4:3:7:3) STAI (80:80) PANSS 62

I had an insight that Amyloban®3399 might be useful for negative symptoms and cognitive dysfunction of schizophrenia, from my many years of treating mild cognitive disorders and depression.

After I told the patient that he had been refractory to each antipsychotic drugs and was extremely sensitive exhibiting adverse reactions for more than 30 years, I explained the possibility of the use of Amyloban®3399 to the patient. Amyloban®3399 has been used for patients with cognitive impairment, depression and sleep apnea and hypopnea patients. With the consent of the patient and his family, Amyloban®3399 was administered to the patient.

On December 7, 5 days after the use of Amyloban®3399, his facial expressions improved and he became stable. Day care facility personnel evaluations noted that he became more active than before. On December 16, 2 weeks after the use of Amyloban®3399, he was active and increasingly more conversant. His sleeping habits became more regular, going to bed at 10 p.m. and waking up at 7 a.m. Although he woke up once during a period from 3 to 5 a.m. he could sleep again without interruptions. During the daytime, his communications were increased with others and he enjoyed his life. He had increased motivation and no fatigue. His mother was surprised at his improved condition. His weight increased to 59kg (as opposed to 45 kg in his former state).

GHQ 1(0:0:1:0) STAI (35:29) PANSS 30

When compared with GHQ STAI and PANSS measured on December 2, his dramatic improvement during these 2 weeks was apparent (Table 1).

At 53 years of age, on January 6, he maintained improved expression and a stable condition at the start of the New Year. During the daytime, he regularly visited Plum Chikugo, a facility which encourages social rehabilitation of people with mental disorders, using a stable circadian rhythm. He continued to maintain a good sleeping routine and regularly received a steady dose of medication.

At 9 a.m. on January 13, he visited Plum Chikugo where he was observed to have made significant progress. Previously, he said that he had no communication with other people during hospitalization, and was nervous about other inpatients.

GHQ 0 STAI (20:32)

January 17: He was evaluated again and his expression remained improved. His condition was stable. He said that his depression had been improved by the administration of Amyloban®3399.

January 31: He continued to maintain an improved condition. However, on a day with no plan, he slept until late in the morning.

February 3: During the last 3 days, he had no motivation. However, he played table tennis in the morning, and enjoyed listening to music in the afternoon.

GHQ 10 (3:2:5:0)

February 10: He felt low when he thought about his future during 3 days of the previous week. However, his conditions became gradually improved, and he was able to wake up in the morning, exhibiting enhanced motivation and positive feelings.

GHQ 0 (0:0:0:0)

February 24: Prior to the use of Amyloban®3399, he had delusions, believing that he was blessed with more exceptional ability than others and should be a leader. He suffered from auditory hallucinations in which some people cursed him and criticized him.

However, a 70% improvement was achieved by injection of risperidpne (Consta), and 30% remained improved. After the use of Amyloban®3399, delusions and auditory hallucinations were completely gone in 2-3 weeks. Such mental changes were hidden and unnoticed by people around him.

June 2: Since the patient complained of a feeling of anxiety, palpitation, and discomfort in the late afternoon under administration of risperidone (Consta), the drug was changed to aripiprazole.

December: Mirtazapine was found to be effective in improving his sleep disorder.

The following drugs were then prescribed:

Prescription: Aripiprazole 24mg after breakfast, mirtazapine 45mg and zotepine 75mg before bedtime

The patient was requested to present his feelings freely in a report. In the report, a dramatic change in his mental condition was observed, such as “gained a burst of appreciation”, “increased motivation for learning”, “became interested in everything”, “ motivation for communication with others”, “positive thinking”, “lively nature”, “not negative, hopeless, and nihilistic for the future”, and “not regretful for the past.” As of August 2013, he participated in rehabilitation, maintained a stable condition, without problems in daily life and hence, was diagnosed fit to work. At 55 years old, he is still well and maintaining a stable condition. He stopped to taking aripiprazole after breakfast and still used mirtazapin and zotepin before bedtime. He is now writing of his own experiences with the disease.

Table 1.
Comparison of Before and After Use of Amyloban®3399

	Before use of Amyloban®3399	After use of Amyloban®3399
GHQ	17（4：3：7：3）	1（0：0：1：0）
STAI		
State	80	35
Trait	80	29
PANSS	62	30

DISCUSSION

Amyloban®3399---a product made of amycenone, a standardized extract of HE containing hericenones and amyloban---is currently being tested for safety as a health food supplement. It has been reported that Amyloban®3399 increases mental alertness, encourages positive behavior, and improves mood and attentiveness to one’s surroundings, thus, increasing learning and motivation, while promoting interactions with others. Carlsson and Lecrubier showed that one of the major problems of schizophrenia was the poor response of cognitive and negative symptoms to available treatments, even when the positive symptoms responded (Carlsson & Lecrubier, 2004).

Based on these observations, it is hypothesized that Amyloban®3399 may be beneficial for treating primary cognitive deficits and negative symptoms of schizophrenia.

We have already reported on 10 schizophrenia patients, randomly selected by psychiatrist, working at six different psychiatric hospitals (Inanaga, Matsuki, & Hoaki, 2014). All patients were refractory to currently available antipsychotic agents. After the use of Amyloban®3399, they improved without exception and also without adverse reactions. Average scores on PANSS (Positive and Negative Syndrome Scale) improved significantly for all items, including positive, negative, and general psychopathology.

Brain-Derived Neurotrophic Factors (BDNF) and Neurotrophin-3(NT-3) are members of the Nerve Growth Factor (NGF) family of peptides and are important molecular regulators of neuronal development and plasticity (Weickert, Hyde, Lipska et al., 2003).

Hashimoto (Weickert, Hyde, Lipska et al., 2003) pointed out that a number of preclinical and clinical findings suggest involvement of NMDA receptor in the development of negative symptoms and cognitive impairment, since this receptor mediates the release of neurotransmitters, such as dopamine, glutamate, acetylcholine and GABA (Hashimoto, 2014).

The mechanism of marked improvement of refractory schizophrenia patients using Amyloban®3399 will be explored in future investigations.

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