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腎不全モデル動物を用いたスギヒラタケとの関連が疑われる急性脳症の発症機序解明

平成16年度　総括研究報告書

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目次

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研究要旨　本研究は、腎不全患者に多発している急性脳症の原因を特定し、その機序を解明することを目的として開始された。申請者らは今年急性脳症が腎不全患者に集中的に発症することを重要視し、いち早く臨床症状についての情報収集を行い、その結果を本年11月5日に報告した（第34回日本腎臓学会東部学術大会、東京）。

本研究における調査から、本急性脳症発症には前提条件として腎不全状態が必要であり、スギヒラタケ摂取との関連について検討を進めなければならないことが分かった。そこで、本研究では、さらに本急性脳症の臨床像を明らかにするとともに、腎不全モデル動物を用いて、スギヒラタケ摂取による急性脳症の発症を再現し、その機序の解明を試みた。腎不全がどのようにこの脳症の発症過程に影響しているのか、スギヒラタケのどの成分が脳症発症の直接原因なのか、が明らかになれば、今後の対策に役立つばかりでなく、脳症の発症予防や治療にも大きな貢献を果たすものと考える。

A. 研究目的

平成16年10月ー11月にかけて、主に秋田、山形、新潟県などの本州日本海側の東北・北陸地方において、原因不明の脳症が多発していることが報告された。申請者らは、この脳症が腎不全患者に多発することを重視し、後述の方法で情報を収集した。その結果、本脳症の発症には、前提条件として腎不全状態の症例が大多数を占め、かつスギヒラタケと呼ばれる食用野生キノコ(一般名：*Pleurocybella porrigens*)の摂取との関連が疑わしいことが判明した。

そこで本研究では、腎不全患者に多発している急性脳症の原因を特定し、その機序を解明することを目的とし、臨床疫学的に本脳症の病像を明確にするとともに、腎不全動物モデルを用いて急性脳症の発症を再現することを試みた。

B. 研究方法

腎不全患者（透析治療中ならびに非透析の腎不全患者）に集中発症している急性脳症については、過去に全く報告がなく、申請者はまず、2004年10月22日に日本腎臓学会ホームページを介して情報提供を募った。その結果、57件の情報が寄せられ、これらの症例についてさらに詳細に臨床情報を聴取し、後述の臨床像が明らかとなった。

一方、この前段階的な調査でスギヒラタケ摂取との関連が疑われたため、発症地域の9カ所の透析関連施設において、524名の透析患者に対してスギヒラタケ摂取について聞き取り調査を行い、脳症発症とスギヒラタケ摂取との関連性を統計学的に推計した。

さらに、腎不全状態が本脳症発症の要因の一つであると考え、腎不全動物モデル（ラット）にスギヒラタケ、あるいはその抽出物を投与し、脳症が発症するか否かを検討した。

（倫理面への配慮）

動物実験は、すべて国際基準（National Institutes of Health Guide for the Care and use of Laboratory Animals）に基づいて行った。なお新潟大学内の動物実験に関する倫理審査申請を行い、承認された。

臨床材料の取り扱いに関しては、個人情報の保護に十分な配慮が必要であり、申請者らは臨床情報の研究利用については、十分な注意を払って行った。臨床情報は個人識別情報や個々のデータを公表することはなく、問題はないと判断した。

C. 研究結果

1. 臨床像 情報提供57件中、この一連の急性脳症と考えられるものは52例だった。そのうち死亡症例は15例（致死率29%）と高頻度であり、2004年11月5日時点で、なお呼吸管理されている患者もあり、極めて深刻な状態であることが判明した。

なお、興味深いことに、昨年以前の発症者2名の情報を得たが、いずれも東北・北陸地方に住む60代の女性で、安定した透析治療中の症例であった。

一名は2003年9月、スギヒラタケを食べた数日後にふらつきなどの症状が出現して入院し数日後に回復した。2004年にも9月にスギヒラタケを食べたところ、数日後に全身痙攣など以前よりも重篤な症状が出現し、現在も入院治療中であった。もう一例は1997年10月にスギヒラタケを食用し、10日後に意識障害が悪化して死亡した。今年集中発症した急性脳症とほぼ同様の経過であった。

本年発症の52件がスギヒラタケ関連の脳症と考えられたが、その平均年齢は68.5歳、摂取後平均約8日で神経症状が発症していた。家族内発症例はなかった。

一方、発症地域の9透析施設の協力で、計524名の患者のスギヒラタケ採取状況を調査した結果、今年スギヒラタケを食べた患者は278名で、そのうち発症者は12名（4.3%）であった。スギヒラタケ摂取歴の無い患者には、一例も発症者が無く、統計学的にスギヒラタケ摂取と脳症発症の関連は有意であった（$P = 0.0006$）。一方、食べた量と発症率は関係ないようであった。

典型例の経過は、スギヒラタケ摂取後数日で、運動失調もしくはミオクローヌス様の神経症状で発症し、軽症例では無治療で軽快するが、重症例ではその後急速に全身痙攣へと進行していた。多くは抗痙攣薬などが使われ神経症状は消失・軽快するが、重積発作から死亡する症例もあった*(Gejyo F et al. Kidney Int, 2005 in press)*。

いずれにしても、腎蔵疾患を有する患者はスギヒラタケの摂取を避けるべきと考え、警告を発した。

2. 動物モデルでの解析 マウスに対して、スギヒラタケ水抽出物を腹腔内投与すると、大多数が早期に死亡することは、他の研究者の報告（班会議、新聞報道など）と一致していた。しかし、経口投与では死亡せず、しかも腎不全との関連も現在の所、見出せない。死亡マウスの脳の病理学的評価を、現在行っている。

一方、腎不全ラットモデルを用いた実験では、ラット5/6腎摘術、すなわちラットの片腎を摘出し、さらに残腎の2/3を摘除するモデルを作成した。この処置により、数周間で血清尿素窒素、血清クレアチニンが上昇し、慢性腎不全状態を再現できた。この5/6腎摘出モデルに対して、発症地域から採取したスギヒラタケを経口的に投与した。希に死亡例を認めたが、腎不全自体による死亡も否定できず、明らかな神経症状を確認するまでには至っていない。現在、死亡例の脳病理所見の検討と、実験数を増やして再検討している。

D 考察

本研究により、この急性脳症の臨床像をある程度明らかにすることは出来たと考えている。この脳症を、キノコ中毒として位置づけた場合、全く消化器症状を呈さないこと、および接種後数日してから発症することは、特異的である。このような経過をとるキノコ中毒は、調べ得た範囲では、いままで全く報告はなく、新しい脳症として位置づけるのが妥当かもしれない。

本急性脳症に関する一連の報道がなされ、かつスギヒラタケの採取シーズンが終わった後は、新しい発症は皆無であり、この事実も間接的にスギヒラタケ犯人説を裏付けるものである。

また、腎不全症例に多発したという点では尿毒症性脳症との異同を明らかにする必要もある。この点については、発症者に対して頻回の透析治療が無効であったこと、病状の安定した維持透析患者や腎不全保存期の症例に発症したことなどから、本症と尿毒症性脳症とは、明らかに異なる病態であると考えられ

る。

スギヒラタケのどの成分が原因なのか？今年はスギヒラタケが豊作で採取時期が早かったが、なぜ今年集中的に多発したのか？なぜ一部の透析患者にのみ発症するのか？など、多くの疑問が残されており、今後の動物モデルでの解析が必要である。

E. 結論

平成16年10月ー11月にかけて、主に秋田、山形、新潟県などの本州日本海側の東北・北陸地方に多発した急性脳症は、腎機能障害を有する症例において多発し、スギヒラタケ摂取が原因であり、スギヒラタケを摂取した透析患者の約4%程度に発症した。52例中15例以上が死亡した。

腎不全に伴う尿毒症性脳症とは明らかに異なり、キノコ中毒としても全例が無い。新しい急性脳症として位置づけるべきである。

スギヒラタケのどの成分が直接の原因なのかは現在も不明であり、今後の解析が必要である。

G. 研究発表

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H. 知的財産権の出願・登録状況　なし

Rapid Communication

Title: A Novel Type of Encephalopathy Associated with Mushroom Sugihiratake Ingestion in Patients with Chronic Kidney Diseases

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Short title: A Novel Type of Encephalopathy Associated with Sugihiratake Ingestion

A Novel Type of Encephalopathy Associated with Sugihiratake Ingestion in Patients with Chronic Kidney Diseases

Abstract

Background: The etiology of encephalopathy in uremic patients is multiple. We recently encountered a novel type of encephalopathy which occurred exclusively in patients with chronic kidney diseases after ingestion of a mushroom called Sugihiratake. While the exact etiology of this encephalopathy remained mysterious, we aimed to describe its clinical features.

Methods: 32 patients with chronic kidney diseases who had presented with encephalopathy following ingestion of Sugihiratake were enrolled from seven prefectures in Japan. 24 of the 32 patients were undergoing regular hemodialysis. The patient's clinical data were from surveillance by The Japanese Society of Nephrology.

Results: There was a significant association between Sugihiratake ingestion and the occurrence of encephalopathy in 524 hemodialysis patients questioned for a recent ingestion of this mushroom ($P = 0.0006$). The latent asymptomatic period before the onset of symptoms varied from 1 to 31 (mean 9.1 ± 7.3) days. The patient's symptoms consisted of disturbed consciousness in 30 patients (93.8%), convulsions in 25 (78.1%), myoclonus in 15 (46.9%), dysarthria in 10 (31.3%), ataxia in 8 (25.0%), paresis or paralysis in 7 (21.9%), and skin parasthesia in 2 patients (6.3%). Nine (27.2%) patients died mostly due to respiratory failure. The other patients were either discharged or still in hospitals with various degrees of clinical improvement.

Conclusions: Patients with chronic kidney diseases are at risk of having serious encephalopathy following Sugihiratake ingestion, and must refrain from eating it. Physicians, in those parts of the world, where this mushroom harvesting is common, should be aware of this complication.

Introduction

Sugihiratake (Fig.1) is the Japanese name of the fungus *Pleurocybella porrigens*, which is a small mushroom that grows in abundance during the fall season, not only in the forest of northern Japan, but is also widely distributed across the northern hemisphere (1). It has an interesting flavor that many Japanese used to enjoy, usually consumed as a component of the highly popular miso (fermented bean paste) soup. Until now, there has been no report of significant adverse effect as a result of Sugihiratake ingestion. However, during the present fall in Japan, an outbreak of a serious encephalopathy exclusively occurred in patients with chronic kidney diseases after ingestion of this mushroom.

While the exact etiology of the encephalopathy remains mysterious and currently under investigation, we wish to report for the first time the neurotoxic effects of *Pleurocybella porrigens* mushroom intoxication in a series of Japanese patients with chronic kidney disease.

Patients and Methods

Data used for this study were from surveillance by The Japanese Society of Nephrology. From September through October 2004, a total of 45 patients with chronic kidney diseases presented to several hospitals in eight prefectures in Japan (Fig.2) because of acute neurological disturbances. Extensive workup to find out a possible cause was negative other than a history of ingesting Sugihiratake in 44 of the 45 patients during its harvesting season from the end of August through October. Among the 44 patients, 32 (19 females and 13 males) who had their clinical conditions reported to us by the physicians in charge were enrolled in the analysis. 24 patients previously had received regular hemodialysis, whereas 8 were not yet undergoing dialysis. The mean age of the patients was 69.2 ± 10.5 years. The underlying kidney diseases were chronic glomerulonephritis in 14 patients, diabetic nephropathy in 8, unknown etiology in 5, hypertension in 3 and polycystic kidney disease in 2 patients. All patients whether dialyzed or not, were in stable clinical condition before this event. We also inquired a total of 524 hemodialysis patients at nine hospitals in the affected area for any recent history of Sugihiratake ingestion, and the intoxication rate was calculated. Statistical analyses were conducted by Fisher exact probability test with StatView 5.0 software (Abacus Concepts, Inc., Berkeley CA).

Results

All cases of acute encephalopathy after Sugihiratake ingestion occurred in patients who had chronic kidney diseases, whereas none of the individuals with normal renal function who had eaten Sugihiratake were affected. Out of 524 hemodialysis patients, 278 (53%) admitted recent ingestion of Sugihiratake, but only 12 patients (4.3%) manifested symptoms of intoxication. By Fisher's exact probability test, there was a highly significant association between the mushroom ingestion by hemodialysis patients and the development of encephalopathy ($P = 0.0006$).

The clinical profile, time of symptom onset, and the outcome are listed in Table 1 for the patients on hemodialysis, and in Table 2 for **the patients with pre-end-stage renal disease**. Nine (28.1%) patients had died so far, 5 had been uneventfully discharged, and the other 18 patients have remained hospitalized with various degrees of clinical improvement. While many patients continued to eat the mushroom for several days before the symptoms appeared, the time from the start of ingestion to onset of symptoms varied from 1 to 31 (9.1 ± 7.3) days, with no difference between the patients who died or survived. The most common symptoms in all 32 patients included disturbed consciousness of various degrees in 30 patients (93.8%), convulsions in 25 (78.1%), myoclonus in 15 (46.9%), dysarthria in 10 (31.3%), ataxia in 8 (25.0%), paresis or paralysis in 7 (21.9%), and skin parasthesia in 2 patients (6.3%). **Typically, most patients presented initially with ataxia and/or myoclonus several days after Sugihiratake injestion, to be followed in a few days by generalized convulsions. The convulsive activities either stopped without neurological sequelae or progressed to status epilipticus and death. The terminal event was profound central apnea and bradycardia.** Noteworthily, all patients did

not experienced gastrointestinal symptoms, which are generally common features of mushroom poisoning. Fever was undetectable in almost all patients at the initial presentation; however, some patients had their temperature increased after admission secondary to a respiratory infection.

After being admitted, the patients were closely monitored either in a general ward or in an intensive care unit with the support of a neurologist. The differential diagnosis included metabolic encephalopathy, cerebrovascular accident, viral encephalitis, or possible drug intoxication. 19 Patients underwent computerized tomographic brain scans to role out stroke, but no organic lesion could be identified, though in 5 patients, who ultimately died, brain edema was evident. Lumber puncture was done in 10 patients, and the cerebrospinal fluid analysis showed a mild increase of protein content, but normal cell count and sugar. There were no significant changes in the blood biochemistry including blood sugar, liver function tests, serum aluminum levels, and blood gas analysis compared with the pre-intoxication levels in most patients.

Treatment depended on the severity of presenting symptoms. Fourteen patients on regular hemodialysis, and 2 other patients who are not yet on hemodialysis, were assigned to every-other-day dialysis. Ten patients with more severe mental confusion were managed in an intensive care unit with continuous venovenous hemodialysis (CVVHD) and mechanical ventilatory support. Nine patients died 4 to 15 (mean 8.2 ± 4.1) days after admission. The principle characteristics of these patients were severe mental confusion in all and convulsive activities in eight.

Discussion

Acute encephalopathy specifically related to patients with uremia may result from any of the following causes; uremic encephalopathy, dialysis dysequilibrium syndrome, cerebrovascular disease, electrolytes disorders and aluminum intoxication (2). Because of the impaired excretory function, uremic patients are also especially vulnerable to drugs and toxins from many different sources, including food. There have been reports of encephalopathy in uremic patients caused by star fruit (*Averrhoa carambola*) intoxication (3,4). However, acute encephalopathy related to mushroom poisoning in uremic patients have not been previously reported.

Two theories for the etiology of this encephalopathy have been speculated. The first theory suggested that an aberrant viral infection, to which uremic patients particularly susceptible, is to be the culprit. However, the absence of family history of similar symptoms, fever or other markers of acute inflammatory response, also the lack of cerebrospinal fluid pleocytosis stood against this theory. **Moreover, the examination for common viral infections was negative.** The second theory accused a toxin that is normally metabolized through the kidney. Reviewing the history for a possible intoxication disclosed that almost all of the patients had eaten Sugihiratake. Statistical analysis of hemodialysis patients in the affected area indicated a significant association between Sugihiratake ingestion and the intoxication episodes. Although these findings suggest a causal connection, several questions remained to be answered. If the mushroom is to blame, then, why intoxication occurred this year only, and why only a small percentage of hemodialysis patients who took the mushroom had turned to be symptomatic. What was the nature of this toxin, and how did it cause the encephalopathy?

Despite the fact that wild mushrooms are collected and consumed, becoming poisoned is still a probability. It is well-known that even some experts have difficulty in discriminating between the mushrooms. The extremely wet and hot regional weather this year may have boosted the growth of some poisonous species that are morphologically indistinguishable from the benign mushrooms. In fact, an exceptionally good harvest of Sugihiratake was reported this year in the affected areas, suggesting that somewhat change in property of the mushroom occurred in this season. In addition, this may support that the amount of ingested mushroom was higher in this season than previous years. The toxic characteristics of a mushroom may vary from region to another depending on the soil type (5), and the individual response to certain fungal toxins is also very variable (6). Taken together, these factors may explain why only limited number of hemodialysis patients was affected.

The connection of the encephalopathy to mushroom poisoning in our series was particularly difficult because of the extraordinary long latent period, and the lack of digestive and hepatic abnormalities, nonetheless, this possibility was worth considered after excluding the other common causes of encephalopathy in uremic patients. In orellanine-containing mushrooms, a latent period of 36 h to 17 days postingestion is usual before the onset of symptoms, although the clinical symptoms is incompatible (7). The presentation of mushroom poisoning generally depends on the species and the amount ingested. Encephalopathy was the hallmark of Sugihiratake mushroom poisoning. The fact that hemodialysis was inefficient in preventing the encephalopathy in our series is probably because the elimination capacity was overwhelmed by the amount ingested. Alternatively, it may suggest that the molecular size of the toxin was not small enough to dialyze or that the toxin could have passed the blood-brain barriers, and hence became inaccessible for dialysis. This

may be an important contributing factor to its neurotoxic effect. The permeability of the blood brain barrier may have been increased by chemical mediators and cytokines (8). **Experiments to identify and isolate the specific toxin in the mushroom are still undergoing.**

In this report, we warn practicing nephrologists that mushroom poisoning must be considered when patients with chronic renal diseases present with conscious disturbances and unexplained neurological symptoms.

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Table 1: Clinical characteristics and outcome of the patients undergoing hemodialysis.

Patients	Age	Sex	Duration of HD (Years)	Onset of Symptoms (Days)†	Symptoms	Outcome*
1	69	F	5	1	1,2	Died
2	60	F	8	10	1,3	In hospital
3	62	F	8	11	1,2,4,7	In hospital
4	65	F	8	3	1,2,3	In hospital
5	70	F	15	14	1,2,3,6	In hospital
6	77	F	5	ND	1,3,5	Discharged
7	57	F	5	14	1,2,4,5	In hospital
8	66	F	10	ND	1,2,3	In hospital
9	58	F	4	14	1,2,6	In hospital
10	60s	F	0.3	12	1,2,3	In hospital
11	72	F	2	13	1,2,6	In hospital
12	71	F	11	ND	1,4,6,7	In hospital
13	72	F	3	4	1,2,4,6	Died
14	48	F	20	ND	1,2	Died
15	85	M	1	18	1,2,3	In hospital
16	68	M	6	12	1,2,4,5	In hospital
17	78	M	1	31	1,2,3	In hospital
18	66	M	3	14	1,2,3,5,6	Died
19	73	M	1.8	14	1,2,3,4	Died
20	64	M	7	ND	4,6	Discharged
21	50	M	0.3	1	1,2,3	Discharged
22	53	M	16	3	1,2	Died
23	83	M	1.5	ND	1,2	Died
24	60	M	2	7	1,2,3,4	In hospital

HD, hemodialysis; F, female; M, male; ND, not determined

1, disturbed consciousness; 2, convulsions; 3, myoclonus; 4, dysarthria; 5, ataxia; 6, paresis/paralysis; 7, parasthesias

* As confirmed by the end of October 2004.

† Time of symptom onset after Sugihiratake ingestion

Table 2: Clinical characteristics of the patients **with pre-end-stage renal disease.**

Patients	Age	Sex	Scr. (mg/dl)	Onset of Symptoms (Days) †	Symptoms	Outcome*
1	87	F	4.8	3	1,2,3,4,5	Discharged
2	68	F	5.6	ND	1,5	Died
3	71	F	5.5	7	1,2,5	Died
4	84	F	6.2	2	1,4	In hospital
5	80	F	1.5	1	1,2,3	In hospital
6	89	M	2.0	ND	1,2,5	In hospital
7	71	M	4.0	8	1,2	In hospital
8	67	M	8.0	20	3	Discharged

F, female; M, male; Scr, serum creatinine; ND, not determined

1, disturbed consciousness; 2, convulsions; 3, myoclonus; 4, dysarthria; 5, ataxia; 6, paresis/paralysis; 7, parasthesias

* As confirmed by the end of October 2004.

†Time of symptom onset after Sugihiratake ingestion

Figure 1