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ORIGINAL ARTICLE

Severe mushroom poisoning in one Macedonian family

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ABSTRACT

Background: Collecting and consuming wild mushrooms is a historical tradition in many European countries, including The Republic of Macedonia. This activity is predominantly performed in the period between June and October, when the weather is warm and humidity in the air and soil is at higher levels.
The *Amanita* genus consists of 500 different species of mushrooms; among these, *Amanita phaloides*, *Amanita virosa* and *Amanita verna* are most commonly found in oak forests in our country. These species are highly poisonous and because they can be similar to some edible mushrooms, they have often been misidentified. Their consumption causes severe intoxication.
Purpose: The aim of this case series report is to demonstrate a severe poisoning with *Amanita* mushrooms (*A. verna*) that occurred in 8 patients, all from 1 Macedonian family.
Results: We show the differences in the clinical appearance and status of these patients, the wide spectrum of symptoms as well as the treatment and outcome of this rare poisoning. One patient, an 8-month-old baby, was excluded from the study because the infant was immediately transferred to the pediatric clinic after admission to our clinic.
Conclusions: Despite modern therapy, poisoning due to ingestion of *Amanita* mushrooms is a serious clinical and health problem that may even be potentially lethal. The most efficient way for the general public to protect itself against potential poisoning is to avoid ingesting mushrooms that may not be edible.

Keywords: Mushrooms, Poisoning, *Amanita* genus

Introduction

Collecting and consuming wild mushrooms is a lifelong tradition in many European countries, including The Republic of Macedonia. This is particularly common in the period from June to October, when the weather is warm, with a high degree of humidity. Apart from Europe, various species of edible mushrooms can be found in the countries of North America. Different cases of mushroom poisonings are described in Africa, Asia, Australia, and South America (1-3). Although a lot of effort has been made to educate the public about the danger of consuming wild mushrooms, people continue to do so and as a result we often deal with these kinds of poisonings, some of which even have a fatal outcome (4).

There are about 5000 different species of wild mushrooms registered in the world; 100 of them are known to be poisonous and less than 10 are fatal (5, 6).

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According to the available literature, accidental mushroom poisonings are often reported in Europe, although mushroom poisonings are noted in the USA as well. Annually, 50 to 100 mushroom poisonings with fatal outcomes are recorded globally, and the majority of them are due to acute liver failure (7). Acute liver failure develops due to the toxic effect of the toxin known as hepatoxin that is found in wild mushrooms. It is an amatoxin, a cyclopeptide, that has a toxic effect on hepatocytes and in 90% of the cases it is responsible for the fatal outcome in these kinds of poisonings, especially those due to the ingestion of *Amanita* species. Poisonings are reported more among the adult population than in children. Poisonings in children are usually to a milder degree and with better outcomes (8, 9).

Amanita mushroom species can be found in the Macedonian woods, with *Amanita phaloides*, *Amanita virosa* and *Amanita verna* being the most commonly seen. These are extremely poisonous species that grow in oak forests and because of their similarities with some edible species, mistakes in collecting are easily made, resulting in severe poisonings with some occurrences of fatal outcomes.

This paper focuses on a severe poisoning incident from the consumption of *A. verna*, in 8 patients, all from the same family. We will describe the clinical features, the treatment, and the outcomes of this rare poisoning. One patient, an 8-month-old baby, was excluded from the study

because the infant was transferred to the pediatric clinic for further treatment.

Case series

Patient 1

The first patient was a 54-year-old man who was transferred to our clinic from the local hospital where he went for a medical examination due to nausea and vomiting following mushroom ingestion. The mushrooms that he collected and consumed were very similar to some edible mushrooms. He gathered the mushrooms together with his son, close to their house. They ingested them on 2 occasions. The first was when they prepared the mushrooms on a fire 24 h before the onset of the first symptoms. They tasted a couple of the mushrooms, which were not fully cooked. On the second occasion, the mushrooms were well cooked by sautéing in butter. He consumed the mushrooms together with the other members of his extended family, approximately 10 h before the onset of the first symptoms. The quantity consumed was approximately 800 g to 1200 g.

When he was admitted to the local hospital and when he arrived at our clinic, he complained of nausea, vomiting, frequent loose stools, weakness, and fatigue.

At admission, the laboratory results showed slightly increased glycemia (7.2 mmol/l), higher values for total proteins and albumins (90/53 g/l), increased values for bilirubin (total/direct/indirect 24/7/17 mmol/l) and higher ammonium (82 mmol/l). There were no pathogenic bacteria isolated from the stool. Coagulation status was normal. His health record did not show any previous diseases. Clinical examination at the time of admission revealed signs of abdominal tenderness; no hepatosplenomegaly or ascites were observed.

The patient was immediately hospitalized in the intensive care unit (ICU) and put on an intensive detoxification therapy protocol (a nasogastric tube was inserted, he received activated charcoal by mouth, n-acetyl cytokine, crystalloid solutions, vitamin therapy, crystalline penicillin, H_2 blocker, and ornicetil). Several hours later the patient underwent hemoperfusion with hemadsorption and a therapy using Legalon was started. Due to his severe clinical state, we also used plasma exchange.

During day 2 his condition started to deteriorate rapidly. He became confused, with depressed neurological reactions. The laboratory analyses indicated deterioration by disruption of the enzyme status and an increase in AST (2558 U/l), ALT (2656 U/l), AlkP (160 U/l); creatine phosphokinase (255 U/l); lactate dehydrogenase (4470 U/l); total bilirubin (146 mmol/l), direct bilirubin (69 mmol/l), indirect bilirubin (77 mmol/l). The coagulation status was disrupted, consumption coagulopathy with secondary activated fibrinolysis with a reduced platelet number and prolonged prothrombin, thromboplastin and thrombin index (>120 s) were noted. Liver encephalopathy grade II was also reported.

During day 3 of hospitalization his clinical condition became more severe, with additional changes in the laboratory tests. The value of the transaminases continued to increase (AST 4714 U/l, ALT 5824 U/l) and that of bilirubins (05/78/127) as well. His coagulation status also worsened.

Liver encephalopathy rose to grade III. Nonoliguric renal failure caused by acute tubular necrosis with urea (13.3 mmol/l) and creatinine (180 mmol/l) was recorded. The intensive therapy with crystal penicillin, ornicetyl, acetyl-cystein, crystalloid solutions, and plasmapheresis was continued. Over the course of days 4 and 5, his conditions worsened and hepatorenal syndrome developed. During day 5 the patient died with clinical features of severe hepatorenal syndrome.

Patient 2

The second patient is a case involving a 30-year-old male, the son of the patient described in the previous case. He was also referred to our institution from the local hospital, where he went for a medical examination following mushroom ingestion, described in the previous case. He gathered the mushrooms together with his father, near their house. They ate them on 2 occasions, also previously mentioned and described. The approximate quantity consumed was 800 g to 1200 g.

At the time of admission he complained of nausea, vomiting, frequent loose stools, weakness, and fatigue. His health record did not show any past conditions. At the time of admission the patient showed signs of abdominal tenderness. No hepatosplenomegaly or ascites were reported.

The laboratory analyses showed a higher value for glycemia and a protein status at the upper reference limit. His coagulation status was disrupted, with a reduced number of platelets (93 × 10/l), prolonged prothrombin time, and increased prothrombin index. Compensated disseminated intravascular coagulation was noted.

Immediately after admission, the patient underwent the intensive detoxification therapy mentioned above. Several hours later the patient was subjected to hemoperfusion with hemadsorption, and a therapy using Legalon was started.

On day 2, his condition deteriorated rapidly. The patient became confused, with depressed neurogical responses. The laboratory analyses indicated deterioration by disruption of the enzyme status and an increase in AST (2564 U/l), ALT (2763 U/l), AlkP (139 U/l), lactate dehydrogenase (3221 U/l), total bilirubin (84 mmol/l), direct bilirubin (64 mmol/l), indirect bilirubin (22 mmol/l), and higher ammonium (177 mmol/l). His coagulation status rapidly worsened; consumption coagulopathy with secondary activated fibronolysis with reduced prothrombin, thromboplastin, and thrombin time (>120 s) were noted. Liver encephalopathy grade II was diagnosed in this case as well. Due to the severe condition of this patient, we performed plasmapheresis as well.

During day 3, the patient's condition continued to decline. Transaminases increased (AST 3600 U/l, ALT 6025 U/l), bilirubin (152/81/71). His coagulation status did not improve. Grade III liver encephalopathy was diagnosed. Nonoliguric renal failure caused by acute tubular necrosis with a decreased value of urea (1.9 mmol/l), and increased creatinine (230 mmol/l) was recorded.

Despite the intensive therapy protocol and appropriate care in the ICU, during days 4 and 5, the condition of the second patient worsened and hepatorenal syndrome developed. On day 5 the patient died with the clinical features of severe hepatorenal syndrome.

Patient 3

The third patient who was admitted to our clinic was a 75-year-old female, the mother of the patient described in the first case. The mushrooms that she ingested were collected by her son. She consumed the mushrooms sautéed in butter together with the other members of the extended family approximately 10 h before the onset of the first symptoms. The quantity consumed was approximately 300 g to 400 g.

When she arrived at our emergency unit she was in a good clinical conditions, still complaining of the same symptoms as the previous 2 cases, but in milder forms. Her health records showed previous hypertension and diabetes.

The clinical examination went well and we did not detect any clinical signs of intoxication. At the time of admission, the laboratory findings showed a higher value of glycemia (10.2 mmol/l) and other results within the range of reference values. During the next few hours, the condition of this patient worsened and she was transferred to the ICU where she was put on the same detoxification protocol. Several hours later the patient was subjected to hemoperfusion with hemadsorption and a therapy using Legalon.

On day 2, the patient showed signs of clinical worsening. She complained of constant and severe abdominal pain and loose stools. The laboratory analyses indicated deterioration by disruption of the enzyme status and an increase in AST (307 U/l), ALT (321 U/l), lactate dehydrogenase (1012 U/l), total bilirubin (84 mmol/l), direct bilirubin (35 mmol/l), and indirect bilirubin (12 mmol/l). The coagulation status was disrupted and a hypercoagulable state ensued with a reduced platelet number (140 × 10/l) and a highly prolonged prothrombin time (16.3 s) and prothrombin index (1.57).

Over the course of day 3, the patient's state improved. The coagulation status showed signs of improvement by normalization of the platelet count and secondary activated fibrinolysis. The intensive therapy continued, including active detoxification, hemoperfusion and plasmapheresis therapy.

During day 4, there was significant improvement in the patient's state by normalization of the laboratory analyses. The intensive therapy continued without the active detoxification methods. The patient was discharged in a steady health condition after having spent 14 days in hospital. She was recommended for a clinical checkup after 7 days.

Patient 4

The fourth patient arrived at our clinic 1 day after the intoxication occurred. She was referred from the local hospital, after she had started to complain of severe abdominal pain. This patient was a 54-year-old female, the sister of the patient described in the first case. She ingested the mushrooms only on one occasion, together with her family, and the quantity consumed was approximately 300 g.

At the time of being admitted she complained of severe abdominal pain, nausea, vomiting, and frequent loose stools. Her health records showed only mild intestinal problems in the past.

At the time of admission the patient showed signs of abdominal tenderness. The other physical findings were normal. The laboratory findings were within the range of reference values.

Due to the worsening clinical condition of the first 2 patients described, we were aware of the risks and had this patient hospitalized in the ICU, putting her on the same intensive protocol. She also underwent a course of hemoperfusion with hemadsorption and a therapy using Legalon.

During day 2 there were no signs of deterioration. The patient complained of abdominal pain, cramping, and loose stools. The laboratory analyses indicated mild deterioration by disruption of the enzyme status and an increase in AST (44 U/l), ALT (60 U/l), lactate dehydrogenase (994 U/l), total bilirubin (28 mmol/l), direct bilirubin (20 mmol/l), and indirect bilirubin (18 mmol/l). The coagulation status was disrupted and a hypercoagulable state occurred with a prolonged prothrombin time (21.8 s) and prothrombin index (2.18). The other laboratory analyses were within the range of reference value limits.

During day 3 the patient's state improved, but due to the laboratory changes intensive therapy was continued, including active detoxification, hemoperfusion, and plasmapheresis therapy.

During day 4 there was significant improvement in the patient's state by normalization of the laboratory analyses. The intensive therapy continued without the active detoxification methods. After 12 days in hospital we discharged this patient in good conditions, with a recommendation for a follow-up after 7 days.

Patient 5

The fifth patient is a case involving a 31-year-old female, the niece of the patient described in the first case. She was also referred to our institution 1 day after the ingestion. She reported a quantity consumed of approximately 300 g.

At the time of admission she complained of nausea, vomiting, frequent loose stools, weakness, and fatigue. Her health records showed cholecystectomia in the past. On admission clinical and laboratory findings were all normal.

She was also admitted to the ICU. She received the intensive detoxification protocol and underwent 1 course of hemoperfusion.

During day 2 there were no signs of deterioration. The patient still complained of abdominal pains and loose stools. The laboratory analyses indicated deterioration by disruption of the enzyme status and an increase in AST (103 U/l), ALT (100 U/l), and lactate dehydrogenase (495 U/l). The coagulation status was disrupted with highly activated hypercoagulation with secondary activated fibrinolysis.

During day 3 we recorded improvement in both clinical and laboratory findings.

The intensive therapy continued, including active detoxification, hemoperfusion and plasmapheresis therapy.

The patient was discharged in good health conditions after having spent 10 days in hospital and she was recommended for a check-up after 7 days.

Patient 6

The sixth patient is a case involving a 34-year-old male, a nephew of the man described in the first case. He consumed the mushrooms, approximately 300 g, sautéed in butter together

with the other members of the extended family approximately 10 h before the onset of the first symptoms.

At the time of admission he complained of nausea, vomiting, frequent loose stools, weakness, fatigue, with signs of abdominal tenderness. The other physical findings were normal. The laboratory findings were within the range of reference values. He was hospitalized in our regular emergency unit, where he was also put on a detoxification therapy. Several hours later the patient underwent hemoperfusion with hemadsorption and a therapy using Legalon.

Over the course of day 2, there were no signs of deterioration. The patient complained of abdominal pains and loose stools. The analyses indicated deterioration by disruption of the enzyme status and an increase in AST (64 U/l), ALT (109 U/l), and lactate dehydrogenase (334 U/l). He also had disruption in the coagulation status, which improved over the next 5 days.

During day 4 there was significant improvement in the patient's state and control laboratory analyses showed better results. The intensive therapy continued without the active detoxification methods. The patient was discharged in good health conditions after having spent 7 days in the hospital.

Patients 7 and 8

The last 2 cases were patients who were transferred to our clinic after they had spent 2 days in the local hospital. The first was a 32-year-old woman, a niece of the man described in the first case, and the second was a 23-year old man, a close relative. Both of them consumed small amounts of cooked mushrooms during the above-mentioned family dinner. After being examined at the local hospital they were hospitalized there for immediate treatment. Two days later they were transferred to our clinic and admitted there in order to receive a better, specialized detoxification protocol. Both the patients only complained of mild abdominal pain and nausea. They were hospitalized at the regular emergency unit, nasogastric tubes were placed and they received activated charcoal, n-acetyl cysteine, crystalloid solutions, vitamin therapy, crystalline penicillin, and an H_2 blocker. Several hours later they underwent hemoperfusion with hemadsorption and a therapy using Legalon.

During the next 5 days they showed improvement in both clinical and laboratory terms. They were discharged after 7 days in quite a good state of health.

Discussion

Mycetism, or mushroom poisoning, is a pathological entity that requires the highest degree of urgency, since it can involve severe poisoning that usually puts patients into a grave clinical state. Mushroom poisoning is more frequent in Europe, and rather rare in the USA. The American Association of Poison Control Centers registers from 7000 to 9000 mushroom poisoning cases on an annual basis. In the year 2009 there were 5902 cases of *Amanita* poisoning in the United States, of which 2 had lethal consequences. *A. phalloides*, *A. verna* and *A. virosa* are all species of the genus *Amanita*. Even though the literature argues that more than 90% of fatalities due to mushroom poisoning are caused by the subgenera *A. phalloides*, according to the descriptions provided by the patients and comparing these to illustrations, in our cases it was a clear case of *A. virosa* poisoning. Mushroom poisoning occurs due to the ingestion of different types of toxins that may cause mild gastrointestinal disorders and even serious disorders of the function of the liver and kidneys (10-13).

The incidence of mushroom poisoning is not accurate, most probably due to the relatively small number of cases. In Europe approximately 50 to 100 cases with fatal consequences are recorded on an annual basis. Additionally, grave and fatal cases due to mushroom poisoning are registered in Africa, Asia, Australia, and South America (14).

Amanita species are generally common all over Europe, especially in oak forests. They can be found at the beginning and the end of summer when the weather is rainy and humid, and when the weather is changeable and characterized by excessive rainfall and frequent sunny periods.

There are 2 distinct groups of toxins with reference to *Amanita* species: phalloidin and amanitin (alpha-, beta- and gamma-amanitin). Phalloidin is a cyclic heptapeptide that consists of at least 7 different compounds that damage the membrane of enterocytes and cause the onset of gastrointestinal symptoms (the gastrointestinal syndrome) such as nausea, vomiting, and diarrhea, present in all patients. Even though it possesses high toxicity in hepatocytes, it does not damage them due to the fact that is not absorbed by the intestines and does not reach the liver at all.

Amanitin consists of 3 types of amatoxins, namely alpha-, beta- and gamma-amanitins. The alpha-amanitin is considered the most responsible for morbidity and mortality in the event of amanitin poisoning. The toxin is absorbed via the intestines, and 60% of the absorbed alpha-amatoxin is excreted through the bile and returned to the liver via enterohepatic circulation. Following the return to the liver, it is absorbed by the hepatocytes. It inhibits RNA polyremase II, thus causing reduction of mRNA, reduced synthesis of proteins, and cell death (15-17).

Food poisonings may be lethal. With reference to clinical features, the most dominant is hepatic failure, which is further complicated by coagulation, encephalopathy, hepatorenal syndrome, and death. The gravity of poisoning due to ingestion of *Amanita* mushrooms depends on the quantity of ingested mushrooms and may vary from not-so-serious, subclinical symptoms to fulminant cases with fatal outcomes. A full range of symptoms and complications was presented and observed in our cases. Massive hepatic necrosis was observed in 2 of our patients, indicating fulminant hepatic failure (18).

In addition to its grave liver toxicity, amatoxin is also toxic for the kidneys. Due to the fact that the link between the amatoxin and proteins is rather weak in the course of the first 48 h following ingestion, the amatoxin is filtered through the glomeruli and is reabsorbed through the renal tubules, thus demonstrating its toxic effect on the kidneys. This toxicity results in acute renal papillary necrosis and the occurrence of acute renal insufficiency (19, 20).

Clinical features

The clinical features in *Amanita* poisoning may vary from a mild subclinical form to a severe form that may even have a fatal outcome. However, all *Amanita* poisonings are not

characterized by severe clinical features and do not develop hepatic insufficiency (liver failure). The seriousness and severity of the poisoning depends on the quantity of ingested mushrooms and absorbed toxins, the time interval from ingestion to commencement of treatment, and probably some additional factors that have not been described in the literature. Therefore, one should point out that in addition to hepatic insufficiency, the poisoning may result in impairment of the coagulation status, encephalopathy, and hepatorenal syndrome (21, 22).

The clinical features are characterized by 4 stages that have separate characteristics and different symptomatology. The first one is a stage of incubation or a latent period lasting from 6 h to 40 h or an average period of approximately 10 h, when the patient experiences no difficulties. These data can be used in diagnosis because poisonings with amatoxin have a long latent period, unlike poisonings with other types of mushrooms that have a shorter latent period or period of incubation that lasts approximately 2 h to 3 h with clinical features that usually appear milder (23, 24).

The second stage of poisoning is characterized by the development of the clinical features of gastroenterocolic syndrome manifested by nausea, vomiting, strong abdominal pain, and frequent loose stools. If sufficient anamnestic and clinical data are not available at this stage, such a pathological image may be incorrectly identified as gastroenteritis or food poisoning and the investigation and the therapeutic approach may be wrongly directed.

Hence, intensive vomiting and diarrhea may lead to acid-base and electrolyte imbalance with the occurrence of hypoglycemia, dehydration, hypotension, weakness, and lassitude. This stage is not normally accompanied by hepatorenal involvement and if it was not a case of mushroom poisoning, the disease would end at this stage (25, 26).

The third stage is characterized by clinical improvement of the condition, occuring within 48 h following the ingestion of the mushrooms. This condition may mislead the doctor and result in wrong impressions, thereby complicating the condition even more. What is typical about this stage is that the clinical features show a period of improvement – unlike the biological status that shows sharp and drastic deterioration with an increase of the values of all relevant hepatic and renal parameters (27).

The third stage is clinically most severe and it consists of quick impairment of the patient's clinical features and conditions. It is characterized by quick and progressive development of acute hepatic insufficiency followed by hepatic encephalopathy, hyperbilirubinemia, hypoglycemia, and acute renal failure (hepatorenal syndrome). The neurological symptoms are a result of the hepatorenal syndrome and the expressed nephrotoxicity of amanitin. This stage ends with spontaneous recovery of the patient with normalization of all functions and laboratory parameters or death within a few days or weeks (28, 29). Detailed results collected from the laboratory test are summarized and showed in Table I.

Clinical approach

Mushroom poisoning does not have a distinctive therapeutic approach based on results from randomized clinical trials of a larger group of patients. Usually the recommendations for treatment are taken from studies of smaller groups of patients or isolated cases. The treatment consists of several specific measures and procedures that are normally applied in such poisonings (30).

Following the ingestion of poisonous mushrooms, patients do not usually experience any difficulties during the first few hours. However, if the obtained anamnestic data indicate ingestion of wild mushrooms, an attempt should immediately be made to remove the ingested mushrooms from the body. Placement of a nasogastric tube, stimulation of vomiting and administration of activated charcoal may help to eliminate the ingested mushrooms, thus reducing the possibility for absorption of the toxins from the ingested mushrooms and enabling enterohepatic circulation. These methods are more efficient if they are applied within the first 30 min to 1 h after the ingestion. Since most patients seek help 6 h to 15 h after the ingestion of mushrooms and the onset of the first symptoms, this method seldom has a full effect after its application. What is very useful at this stage, if possible, is to identify the toxins contained in the mushrooms from the material isolated from the stomach or the feces by means of toxin detection methods. At the beginning, it is vitally important to maintain the body's water-electrolyte balance and for this reason dehydration, electrolyte imbalance and metabolic acidosis, all resulting from the gastroenterocolic syndrome, require intensive treatment (31).

In order to protect the liver from the toxic effects of amanitin, active methods for extracorporeal detoxification are applied in practice. Good effects are obtained during treatment by applying hemoperfusion that uses filters containing activated charcoal. It is known that activated charcoal has a strong adsorption effect on aminitin and that the application of this method at the beginning, following the poisoning, provides good results, although this is not proven by studies involving a larger number of patients (32).

Recently, some of the applied methods have been used in practice for elimination of toxins from the mushrooms and to provide an opportunity to regenerate the damaged hepatocytes or to gain time until an attempt has been made for liver transplantation due to the fact that in some cases this is the only way to save a patient's life. One of the methods is plasmapheresis, whereby the toxins connected to the albumins from the plasma are replaced by fresh plasma in a procedure of extracorporeal dialysis. In recent years, the molecular adsorbent recirculating system (MARS) has been increasingly applied as an additional method of detoxification. This is actually a method of dialysis that mimics the biological characteristics of the hepatocytes. MARS is a modified dialysis method that mimics the biological features of the hepatocyte membrane by transferring protein-bound and water-soluble toxic metabolites from the blood stream into a dialysate compartment via a special membrane. The method was shown to be efficient in improving liver function by continuously removing protein-bound substances. These methods are more efficient if applied within the first 48 h after the poisoning (33, 34).

The patients were treated with charcoal hemoperfusion. The blood of the patients passed through an Adsorba 300 column with adsorptive properties on an AK 95 machine (both from Gambro, Lund, Sweden). The aim was to remove small-to- medium-sized molecules. The procedure lasted 6 h to

TABLE I - Laboratory analyses

Case		Day 1	Day 2	Day 3	Day 4	Day 5
1	Bilirubin (mmol)	24/7/17	146/69/77	205/78/127	(/)	(/)
	Ammonium (mmol/l)	82	(/)	(/)	(/)	(/)
	AST, ALT, AP (U/l)	(/)	2558/2656/160	4714/5824	(/)	(/)
	CPK, LDH (U/l)		255/4470			
	Coagulation	normal	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted DIC	(/)
	Urea, creatinine (mmol/l)	normal	normal	12,3/180	(/)	normal
2	Bilirubin (mmol)	normal	84/64/22	152/81/71	(/)	(/)
	Ammonium (mmol/l)	(/)	177	(/)	(/)	(/)
	AST, ALT, AP (U/l)	(/)	2564/2763/139	3600/6025	(/)	(/)
	CPK, LDH (U/l)	(/)	3221	(/)	(/)	(/)
	Coagulation	disrupted 93 × 10^9/l	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis
	Urea, creatinine (mmol/l)	normal	normal	1,9/230	(/)	Normal
3	Bilirubin (mmol)	(/)	84/35/12	22/6/11	(/)	(/)
	Ammonium (mmol/l)	(/)	(/)	(/)	(/)	(/)
	AST, ALT, AP (U/l)	(/)	307/321	276/263	(/)	(/)
	CPK, LDH (U/l)	(/)	1012	434	(/)	(/)
	Coagulation	140 × 10^9/l	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis
	Urea, creatinine (mmol/l)	normal	(/)	Normal	(/)	(/)
4	Bilirubin (mmol)	(/)	28/20/18	26/8/18		
	Ammonium (mmol/l)	(/)	(/)	(/)	(/)	(/)
	AST, ALT, AP (U/l)	(/)	44/60	42/63	(/)	(/)
	CPK, LDH (U/l)	(/)	994	400	(/)	(/)
	Coagulation	140 × 10^9/l	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis
	Urea, creatinine (mmol/l)	normal	(/)	(/)	normal	(/)
5	Bilirubin (mmol)	normal	(/)	normal	(/)	(/)
	Ammonium (mmol/l)	normal	(/)	(/)	(/)	(/)
	AST, ALT, AP (U/l)	(/)	103/100	306/293	(/)	(/)
	CPK, LDH (U/l)	normal	495	467	(/)	(/)
	Coagulation	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis
	Urea, creatinine (mmol/l)	normal	(/)	normal	(/)	(/)
6	Bilirubin (mmol)	normal	84/64/22	152/81/71	(/)	(/)
	Ammonium (mmol/l)	normal	177	(/)	(/)	normal
	AST, ALT, AP (U/l)	normal	64/109	64/108	(/)	normal
	CPK, LDH (U/l)	normal	334	324	(/)	normal
	Coagulation	93 × 10^9/l	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis	Disrupted, fibrinolysis
	Urea, creatinine (mmol/l)	normal	(/)	normal	(/)	(/)

AST = aspartate aminotransferase.
ALT = alanine aminotransferase.
CPK = creatine phosphokinase.
LDH = lactate dehydrogenase.
AP = alkaline phosphatase.

8 h, and was repeatedly used according to the patient's clinical conditions. The blood access was enabled through a temporary venous catheter, inserted into the femoral vein.

Plasma exchange was performed using TPE 2000 filters (Gambro, Lund, Sweden). During each plasma exchange session, approximately 50% of the patient's plasma was removed and simultaneously replaced by albumin, fresh frozen plasma, and saline solution. To enable the procedure, the blood access was secured through a temporarily inserted venous catheter into the femoral vein.

In addition to active methods, a symptomatic therapy, and water-electrolyte support in the treatment of mushroom poisonings, drug therapy is also used, consisting of specific medications indicated as antidotes in the literature. In the past antibiotics, antioxidants, hormones, etc. were used, which have now been abandoned. Lately, silibinin and N-acetylcysteine have mainly been used, and they are considered to be very useful in the treatment of patients who have ingested mushrooms of the genus *Amanita*.

Silibinin is a derivative of sylimarin, which prevents penetration of amanitin into the hepatocytes and the return of toxins to the liver through enterohepatic recirculation. Hence, its effect is hepatoprotective, which is particularly expressed immediately after the poisoning. It should be administered continuously for a few days.

Penicillin G breaks the link between amanitin and the plasma carrier proteins, that is, it prevents the connection of amanitin with the plasma proteins and its penetration into the hepatocytes. In this manner, it indirectly stimulates the excretion of amanitin.

N-acetylcysteine is also used in the therapy, which is an antioxidant applied in the treatment of poisonings with acetylcysteine. It has a strongly expressed hepatoprotective action. Due to these positive characteristics, it is increasingly used as a medicine of preference in cases of poisonings with amanita. High doses of ascorbic acid are also used in therapy, also considered to have a hematoprotective action (35, 36).

Despite all therapeutic measures, poisonings with amanita may end with acute liver failure, acute renal failure, and death. When such a life-threatening condition occurs, the only way to overcome the situation is to perform liver transplantation, which is not always possible and is very difficult to perform. Patients who develop acute liver failure should be treated in an ICU, and a liver transplant center should be contacted immediately. Two surgical options for liver transplantation are applied: orthotopic liver transplantation (OLT), and auxiliary partial orthotopic liver transplantation (APOLT) as an alternative approach (37, 38).

In the series of patients we have presented here, all members of an extended family, we have attempted to demonstrate the spectrum of clinical symptoms and signs and the strategy for treatment of these patients. Patients exposed to amatoxins develop liver complications that vary from a mild increase in liver enzymes to a severe form of acute liver failure that can only be treated with liver transplantation.

Conclusions

Despite modern therapy, poisoning due to the ingestion of *Amanita* mushrooms is a serious clinical and health problem that may even be potentially lethal. Avoiding the ingestion of mushrooms that may not be edible is the most efficient way for the general public to protect itself against any potential poisoning.

National poisoning control centers and poison information centers need to be fully engaged in the prevention and treatment of poisoning cases. Efforts need to be made on their part to identify ingested mushrooms more quickly, prior to their complete absorption. They are also responsible for comparing photographs as well as exchanging information with specialized treatment centers and with experts on mushrooms.

Additionally, the areas within the country where there is prevalence of mushrooms in the forests need to be identified and all available information sources must be taken advantage of for continuous education of the general public. Health workers should be educated on a continuous basis with reference to quick, accurate, and effective identification and treatment of mushroom-related poisonings.

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