Acute Liver Failure due to *Amanita phalloides* Poisoning: Therapeutic Approach and Outcome

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ABSTRACT

Introduction. *Amanita phalloides* poisoning is a potentially fatal cause of acute liver failure. The aim of this study was to analyze the impact of initial patients' characteristics and different treatment modalities on the outcome of patients with liver failure caused by *Amanita* poisoning.

Material and methods. We retrospectively evaluated 23 patients admitted to our center between July 2007 and August 2016.

Results. Mean time interval between *Amanita phalloides* ingestion and the onset of gastrointestinal symptoms was 12.48 ± 9.88 hours and the interval between ingestion and hospital admission 26.26 ± 15.14 hours. The treatment was intiated by oral decontamination using activated charcoal followed by intravenous rehydration and high doses of intravenous N-acetylcysteine and silibinin. Fourteen patients (61%) underwent extracorporeal elimination method. Ten patients had plasmapheresis, 1 patient had hemoperfusion, and 5 patients had fractionated plasma separation and adsorption. Seven patients who met King's College Criteria were listed for urgent liver transplantation; one of them died before transplantation. Six patients underwent liver transplantation; the mean waiting time was 6.5 ± 12.0 days (range, 1–31 days). One patient died 2 months afterward. All 16 patients who did not meet King's College Criteria and received conservative treatment survived.

Conclusion. Our results documented a good prognostic value of standard King's College Criteria for indication of urgent liver transplantation in acute liver failure caused by *Amanita phalloides* poisoning. Fractionated plasma separation and adsorption may contribute to low mortality on the waiting list. Intensive care and extracorporeal elimination methods seem to be crucial points of the conservative treatment.

AMANITA phalloides (AP; "death cap") is one of the most toxic mushrooms in the world, and, considering its hepatotoxicity, it is the most toxic mushroom species of all [1]. More than 90% of all fatal mushroom poisonings worldwide are caused by amatoxin-containing species (*Amanita, Galerina*, and *Lepiota*). However, the exact epidemiological data on mushroom poisoning, particularly with amatoxin-containing mushrooms, is missing. Poison control centers have only incomplete data because there is no report obligation, so the real incidence of AP intoxication remains unknown.

AP poisoning is a relatively rare but potentially fatal cause of acute liver failure (ALF). Mortality rate after AP poisoning ranges from approximately 10%–20%; in individuals younger than 10 years of age, it increases up to 50%. In the Czech Republic, AP intoxication occurs in 10–20 patients per year.

AP contains two different groups of toxins: phallotoxins and amatoxins. Phallotoxins damage the cell membrane of the enterocytes and are responsible for the initial

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gastrointestinal symptoms in the poisoned individuals. Amatoxins (α-amanitin and β-amanitin) interact with RNA polymerase II in the eukaryotic cells, inhibiting transcription, and causing deficient protein synthesis and cell death. The main places of their action are intestinal mucosa cells, hepatocytes, and proximal kidney tubules. Amatoxins are processed through enterohepatic cycle [2].

The lethal dose (LD50) of amatoxins is low. The LD of amanitin for humans is 0.1–0.3 mg/kg of body weight and may be contained in one single mushroom. The clinical picture of intoxication varies from mild subclinical manifestation to lethal fulminant course. The severity of intoxication depends on the ingested amount of toxin and on the length of time period between ingestion and treatment initiation.

AP poisoning has a typical time course that can be divided into four consecutive stages: an asymptomatic lag period (6–12 hours after ingestion) is followed by a gastrointestinal phase with nausea, vomiting, and severe diarrhea (cholera-like diarrhea; 12–24 hours), and a phase of apparent recovery (24–48 hours). In the last phase, liver and kidney damage occurs (4–7 days after ingestion). The clinical outcome ranges from complete recovery to fulminant organ failure and death. Some patients recover to their previous health condition, some patients survive with hepatic and renal impairment, and few patients develop ALF [3].

Standard medical treatment includes oral decontamination with activated charcoal, intravenous rehydration with balanced crystalloid solutions, N-acetylcysteine (NAC), and silibinin.

Many extracorporeal methods of toxin removal (hemodialysis, hemoperfusion, and plasma exchange) are used, but they seem to be effective only at the initial stage of poisoning (up to 48 hours after ingestion). Successful treatment with the Molecular Adsorbent Recirculating System (MARS®; Gambro, Stockholm, Sweden) (FPSA; Prometheus®; Fresenius Medical Care, Bad Homburg, Germany) and Fractionated Plasma Separation and Adsorption System (FPSA; Prometheus, Fresenius Medical Care, Germany) of patients who developed ALF due to AP intoxication has recently been described [4,5]. Nevertheless, these methods are available only in highly specialized centers. An alternative method in the therapy for ALF is high-volume plasma exchange. A recent prospective, randomized, controlled, multicenter trial showed its positive effect on the survival rate of nontransplanted, critically ill patients with ALF [6].

In selected patients with ALF and poor prognosis, urgent liver transplantation (LT) is indicated [7,8]. Decision for urgent LT in patients with ALF is usually based on King's College Criteria, however, in ALF due to amatoxin poisoning, specifically, the prognostic criteria proposed by Ganzert et al seem to be superior [9].

The aims of this study were to describe the baseline characteristics of the patients with ALF due to AP hospitalized in the transplantation center (TC), to analyze the results of their treatment, and to evaluate their outcome.

MATERIALS AND METHODS

Patients Cohort and Data Collection

Twenty-three consecutive patients with ALF due to AP poisoning admitted to TC intensive care unit (ICU) between July 2007 and April 2016 were studied retrospectively. Patients with mushroom poisoning other than AP were not included in the study. Demographic and clinical data, laboratory parameters, and therapeutic approach used were recorded. Standard medical treatment included oral decontamination with activated charcoal, intravenous rehydration with balanced crystalloid solutions, high intravenous doses of NAC, and silibinin. To remove toxins, an extracorporeal elimination method was perfomed in patients admitted less than 48 hours after mushrooms ingestion. The type of used elimination method corresponded to the standard recommendations at the time of patients' admission. Continuous veno-venous hemodialysis was initiated in cases with acute kidney injury (AKI) or hyperammonemia. One or more FPSA sessions was performed in selected patients awaiting LT. The indication for urgent LT was evaluated daily in respect to the ALF severity using the King's College Criteria.

The study was performed in accordance with ethical standards in compliance with the Helsinki Declaration, and patients' consents were not required because of the retrospective and observational nature of the study.

Statistical Analysis

Statistical analysis included mean, standard deviation, median, and range determination for continuous variables and count and percent quantification for categorical variables, as appropriate.

For intergroup comparisons, the Wilcoxon rank-sum test and the chi-square test were used. $P < .05$ was considered to be significant throughout the study. Survival analysis was performed using log-rank test. Kaplan-Meier survival curve is presented. Statistical analysis was performed using the R programming language v.3.2.0 (www.r-project.org).

RESULTS

Twenty-three patients with liver failure after AP poissoning were included in the study. The diagnosis of AP was based on the history of recent mushroom ingestion followed by gastrointestinal symptoms, laboratory markers of ALF, proven using mycological examination (positive mycological analysis of the stomach content or stool).

The cohort consisted of 12 males and 11 females. Their demographic and clinical characteristics on admission to TC are shown in Table 1; baseline laboratory parameters are shown in Table 2. All patients were referred to our center from regional hospitals, on average after 2.43 ± 1.20 days (range, 1–5 days; median, 2 days) after mushrooms ingestion. There were no important pre-existing diseases or dispositions found in any of the patients of the cohort, none of the patients had pre-existing chronic liver disease, except 1 male with hepatitis B virus (HBV) infection, who was hepatitis B surface antigen positive, but with negative viremia and no liver fibrosis.

On admission, hepatic encephalopathy (HE) was present in 8 patients; 2 patients required vasopressoric support and 1 patient was mechanically ventilated.