International Journal of Advances in Medicine
Parasher A et al. Int J Adv Med. 2020 May;7(5):875-880
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20201629

Review Article

Prognosis and treatment options in cases of acute liver failure caused by mushroom poisoning due to *Amanita phalloides*

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Received: 20 February 2020
Revised: 26 February 2020
Accepted: 20 March 2020

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ABSTRACT

Poisoning due to mushroom ingestion is a relatively rare but deadly cause of acute liver failure (ALF). Consumption of the poisonous mushroom Amanita phalloides, also known as 'death cap', is one of the most common causes of mushroom poisoning worldwide, being involved in the majority of human fatalities caused due to mushroom ingestion. A major portion of the liver damage due to Amanita phalloides is related to powerful toxins known as amanitins, which cause impairment in protein synthesis and subsequent cell necrosis by the inhibition of RNA polymerase II. Initially the presentation is that of an asymptomatic lag phase, followed by gastrointestinal symptoms and hepato-renal involvement. Amatoxin poisoning may progress into fulminant hepatic failure and eventually death if liver transplantation is not performed. It is based on a careful assessment of history of type and duration of mushroom ingestion, as well as the clinical manifestations. Diagnosis can be confirmed by laboratory tests measuring urinary amatoxin levels and identification of the mushroom. Although N-Acetyl Cysteine and Penicillin-G have proven to be effective therapeutic agents, Orthotopic Liver Transplantation (OLT) or Auxiliary Partial Orthotopic Liver Transplantation (APOLT) is the only treatment option for most of the cases carrying a poor prognosis.

Keywords: Amanita phalloides, Amatoxin, Hepatic failure, Liver transplantation, Mushroom poisoning

INTRODUCTION

Poisoning due to mushroom ingestion is a relatively rare but deadly cause of acute liver failure (ALF). Consumption of the poisonous mushroom Amanita phalloides, also known as 'death cap', is one of the most common causes of mushroom poisoning worldwide, being involved in the majority of human fatalities caused due to mushroom ingestion.[1] A major portion of the liver damage due to Amanita phalloides is related to powerful toxins known as amanitins, which cause impairment in protein synthesis and subsequent cell necrosis by the inhibition of RNA polymerase II.[2] Initially the presentation is that of an asymptomatic lag phase, followed by gastrointestinal symptoms and hepato-renal involvement. Amatoxin poisoning may progress into fulminant hepatic failure and eventually death if liver transplantation is not performed. The mortality rate after Amanita phalloides poisoning ranges from 10 to 20%.[2] Although there are a relatively high number of under-reported cases, amatoxin poisoning is a worldwide problem. Western Europe has reported an incidence of approximately 50-100 fatal cases every year, and cases of amatoxin poisoning from Africa, Asia, Australia, and Central and South America have been also described.[2-4]

Nearly 283 species of wild mushrooms are consumed by ethnic Indian tribes, out of 2000 species recorded world over.[5,6] About 100 species of mushrooms in India are known to be poisonous to humans, but hepatotoxicity is caused mainly by Amanita species and some members of the Galerina, Lepiota, and Conocybe genera by the

synthesis of amatoxin and gyromitrin toxins.[3,4,7] Although poisonous mushroom species identified from Hills in South India such as Omphalotus olivascens, Mycena pura and Chlorophyllum molybdites are commonly found, human poisonings are unusual as these ethnic tribes are experienced in identifying poisonous from non-poisonous mushrooms.[6,8,9] Fifteen cases of Amanita phalloides poisoning have been described in a case series from India with major clinical presentations as nausea, vomiting, diarrhea, jaundice and hepatic or renal failure seen after about two days from ingestion.[10] Prevalence of mushroom poisoning in children was found to be 3.2% out of all accidental poisonings in another Indian study.[5,11]

REVIEW OF LITERATURE

Toxins and pathogenesis

Acute liver failure (ALF) is caused by the ingestion of mushrooms containing extremely potent hepatotoxins.[3] Amatoxin ingestion is of primary importance because it accounts for about 90% of fatalities.[4] It is described as an asymptomatic incubation period followed by the gastrointestinal and hepatotoxic phases, leading eventually to multi-organ failure and death.[2] Two distinct groups of toxins i.e. phallotoxins and amatoxins are responsible for the toxicity of Amanita phalloides. The initial gastrointestinal symptoms of nausea, vomiting, and diarrhea exhibited by almost all the patients are caused by phallotoxin induced cellular membrane damage to the enterocytes.[2] Although highly toxic to liver cells, phallotoxins add little to the Amanita phalloides toxicity as they are not adsorbed from the intestine and do not reach the liver.[12]

Cooking does not destroy the amatoxins and neither does long periods of cold storage.[13] A dose of even as little as 0.1 mg/kg body weight may be lethal in adults and this amount can be adsorbed even by ingesting a single mushroom.[2] Amanitins bind weakly to serum proteins after their absorption from the intestinal epithelium and make their way initially to the liver, which is the first organ encountered after absorption in the gastrointestinal tract and the principal organ affected.[14] A non-specific transport system carries the amanitins into hepatocytes, causing extensive centri-lobular necrosis.[12,15] The enterohepatic circulation returns about 60% of absorbed α-amanitin to the liver, after it is excreted into the bile.[12,16-20] Aside from the hepatic damage, the kidneys are also susceptible to their toxicity.[2]

Amatoxins are cleared from plasma within forty eight hours of ingestion as they are not significantly protein bound.[21,22] They are filtered by the glomerulus and reabsorbed by the renal tubules, resulting in acute tubular necrosis.[23] Cellular damage also has been found in the pancreas, adrenal glands, and testes.[24,25] Amanitins inhibit the transcription process by directly interacting with the enzyme RNA polymerase II in eukaryotic cells, causing a progressive decrease in mRNA, deficient protein synthesis, and cell death. Thus, the metabolically active tissues, such as the cells of the gastrointestinal tract, hepatocytes and the proximal convoluted tubules of kidney, which are dependent on high rates of protein synthesis, are extensively damaged.[2]

Clinical features

The patient may remain asymptomatic for a while, which is known as the lag phase. The clinical picture after that is characterized by gastrointestinal symptoms with subsequent apparent improvement, followed by hepato-renal involvement and ultimately multi-organ failure.

Lag phase

The initial phase is characterized by the absence of any signs or symptoms as the toxins are not irritating by themselves. The incubation time is about 10 hours, and it is important to suspect amatoxin intoxication in any case of a relatively prolonged latency period between mushroom ingestion and onset of symptoms, since other toxic mushrooms that do not cause liver involvement usually induce gastrointestinal symptoms within a few hours after ingestion.[2-4,12]

Gastrointestinal phase

Nausea, vomiting and crampy abdominal pain dominate this phase, along with severe secretory diarrhea. Both diarrhea and emesis may become grossly bloody. This gastro-enteritic phase lasts for about a day and is severe enough to cause hypoglycemia, dehydration, electrolyte and acid-base abnormalities as well as hypotension. After few hours, the patient feels better if dehydration is corrected. Liver and kidney function tests are usually normal at this point of the illness. These patients may be wrongly diagnosed with gastroenteritis and discharged when stable, if the association with toxic mushroom ingestion is not made.[2-4,15,26]

Apparent convalescence

Despite the apparent improvement of gastrointestinal symptoms, the effects of toxins are damaging both the liver and kidneys, resulting in a progressive deterioration of liver function, seen usually 36 to 48 hours after ingestion. The liver enzymes are seen to be elevated with an increase of serum transaminases and lactic dehydrogenase. The onset of jaundice marks the clinical evidence of hepatic involvement.[2]

Acute liver failure: The last phase is marked by a dramatic rise in the serum transaminases and rapid deterioration of hepatic and renal function, resulting in hyperbilirubinemia, coagulopathy, hypoglycemia, acidosis, hepatic encephalopathy and hepato-renal syndrome.[27] Multi-organ failure, disseminated intravascular coagulation, mesenteric thrombosis,

convulsions, and death may result within 1-3 weeks after ingestion.[28] In contrast, in those patients later showing a favorable outcome, a rapid improvement in liver function tests occurs, followed by a full recovery and restoration of a normal quality of life.

Diagnosis

The most important step is to link the clinical presentation with the ingestion of mushrooms, as there may be a delay between symptom onset and the mushroom meal.[2] The history should include description of the eaten mushroom, whether it was cooked or eaten raw, the onset of similar symptoms in people who have eaten the same mushroom and the time frame between the mushroom ingestion and the onset of symptoms.[2] Amanitins are resistant to heat and are still active after long periods of storage, which differentiates it from poisoning due to other toxins or bacterial contamination. Thus, cooking or prolonged cold storage may exclude other causes of mushroom intoxication, but not poisoning due to Amanita phalloides.[15,29]

As the analysis of amatoxin levels in serum is not available for routine use in the clinical setting, the only specific laboratory test is the detection of amatoxins in the urine.[2] Different methods of analysis can be used (RIA, ELISA, HPLC), which are highly sensitive, without false negatives if performed in the first 48 hours after ingestion.[28,30] These procedures for detection of alpha-amanitins in urine are quite diffuse and the relationship between the urinary concentration of α-amanitin and the severity of the liver damage is very weak.[3] Apart from these scarcely available lab tests, the identification of any remaining mushrooms by a mycologist can be crucial for diagnosis.

Treatment options

The primary management of amatoxin poisoning consists of rehydration, supportive measures, specific therapies and liver transplantation. No specific amatoxin antidote is presently available.

Rehydration and supportive measures

Primary supportive care consists of rehydration of the patient along with gastrointestinal decontamination procedures. Necessary intravenous fluids should be started immediately and prompt correction of metabolic acidosis and electrolyte abnormalities should be done. Gastric lavage is most effective only when it can be performed early after ingestion.[4]

Specific therapies and detoxification

Detoxification procedures consist of two different approaches: reduction of intestinal absorption and enhancement of excretion.

Oral Detoxification - Gastro-duodenal aspiration through a nasogastric tube has been recommended as a sole technique or combined with repeated activated charcoal administration to remove bile fluids and interrupt entero-hepatic circulation, but the actual benefit of these procedures is not documented. The use of cathartics is recommended if the diarrhea has stopped.[1,4,26]

Urinary detoxification - A urinary output of 100-200 mL/hour for four to five days is sufficient to increase the renal elimination of amatoxins. Intense forced neutral diuresis is no longer recommended.[1]

Extracorporeal purification procedures - Treatment with the Molecular Adsorbent Recirculating System (MARS) has been recently described and may represent a potential additional option to treat patients with severe amanita poisoning.[1,31] MARS is a modified dialytic method that is similar to the biological action of the hepatocyte membrane, which acts by transferring protein-bound and water-soluble toxic metabolites from the blood stream into a dialysate compartment via a special membrane.[1] This method, although efficient in improving liver function by continuously removing protein-bound substances, is generally useful only if started very early after the gastrointestinal symptoms occur.[32,33]

Chemotherapy - Silibinin, Penicillin G and N-acetylcysteine (NAC) may be effective in the management of patients with Amanita phalloides poisoning.[1,3,4,12,26] Silibinin, a water soluble silymarin derivate, acts by competing with amatoxins for trans-membrane transport. By inhibiting the amanitin penetration into hepatocytes, it offers a direct hepato-protective effect.[1,34] It also appears to affect the secondary uptake of amatoxins in the liver mediated through entero-hepatic recirculation. Administration of silibinin is recommended if the patient is seen within 48 hours of ingestion. The doses are 20-50 mg/kg/day intravenously and treatment should be continued for 48-96 hours.[1] Silymarin capsules may also be given in dosage of 1.4 to 4.2 g/day orally.[1,35,36]

Penicillin G seems to have a similar mechanism of action, displacing amanitin from the binding to plasma protein and thus promoting its excretion and preventing its hepatic uptake.[1,34] Penicillin G is used in continuous intravenous administration of high doses of Na/K penicillin G (1,000,000 IU/kg for the first day, then 500,000 IU/kg for the next two days).[1,35] Combination therapy with silibinin and penicillin has not been shown to be superior to monotherapy with silibinin.[3]

Free radical scavengers such as N-acetyl cysteine (NAC) offer hepato-protection via their role as anti-oxidants, in the management of amatoxin intoxication.[1,37] N-acetyl cysteine is usually administered intravenously in 5% dextrose, but 0.9% saline may be also used. The suggested dosage is 150 mg/kg over 15 min intravenously, followed by 50 mg/kg over 4 hours

intravenously, followed by 100 mg/kg over 16 hours intravenously. Incidence of anaphylaxis may be reduced by infusion of the initial dose over 30 to 60 minutes rather than rapidly over 15 minutes.[1,38,39]

Liver transplantation

Liver transplantation (LT) is the only lifesaving option in complicated cases at the brink of fulminant hepatic failure and death.[1] On the basis of the available data, the mortality rate after Amanita phalloides poisoning ranges from 10 to 20%.[4,34,35] Patients with severe liver injury should be immediately admitted to an Intensive Care Unit connected to a liver transplant center. Both Orthotopic Liver Transplantation (OLT) and Auxiliary Partial Liver Transplantation (APOLT) are presently available. OLT is a well-established procedure requiring life-long immunosuppression to prevent graft rejection.[1] APOLT can represent an alternative approach in some patients whose native liver can recover well with partial hepatectomy and temporary support. In APOLT, only a portion of the native liver is removed and the remainder is left in situ; the transplant provides temporary assistance until the native liver recovers and the immunosuppression can be withdrawn.[1] The major dilemma in patients with Acute Liver Failure (ALF) is to find the right timing for transplantation. The patient can survive without impaired quality of life if the surgery can be performed in early stages. If the search for a liver graft starts too late, the patient may die before a suitable donor organ becomes available. Several sets of criteria to decide the timing of liver transplantation in patients with ALF have been proposed, although only Ganzert's criteria have been developed specifically for Amanita phalloides poisoning (Table 1).[1]

Table 1: Criteria for urgent liver transplantation in patients with Acute Liver Failure.

(Ganzert's criteria specific for *Amanita phalloides* poisoning.)

Clichy's criteria	**(a) Combination of a decrease in factor V below 30% of normal in patients over 30 years or below 20% of normal in patients below 30 years**
	(b) Grade 3-4 encephalopathy
King's College criteria for non-paracetamol causes of ALF	(a) Prothrombin time over 100 s (≈INR over 7) or
	(b) At least three of the following criteria:
	(i) Prothrombin time over 50 sec (INR over 3.5),
	(ii) Serum bilirubin over 300 µmol/L,
	(iii) Age below 10 years or over 40 years,
	(iv) An interval between jaundice and encephalopathy over 7 days,
	(v) Drug toxicity
King's College criteria for ALF due to paracetamol	(a) Arterial pH below 7.3 or arterial lactate above 3 mmol/L after adequate fluid resuscitation
	Or
	(b) Concurrently, serum creatinine above 300 µmol/L, INR above 6.5 and encephalopathy of grade 3 or more
Ganzert's criteria	(a) A decrease in prothrombin index below or equal to 25% of normal at any time between day 3 and day 10 after ingestion, along with,
	(b) Serum creatinine over or equal to 106 µmol/L within the same time period
Escudie's criteria	Prothrombin index below 10% of normal (INR of ≈6) 4 days or more after ingestion

The most widely used criteria for urgent Liver Transplant in patients with ALF are those of the King's College Hospital described by O'Grady et al, which include different parameters for paracetamol and non-paracetamol induced ALF.[40] In contrast, the Clichy criteria for urgent LT are based on Factor V, age and encephalopathy.[41] However, some of these criteria cannot be easily applied in patients with Amatoxin poisoning.

Ganzert et al retrospectively analyzed the outcome of a large series of amatoxin intoxication cases and found that predictors of death were the prothrombin index in combination with the serum creatinine level on 3-10 days after ingestion.[1,42] Thus, it was proposed that a patient with amatoxin poisoning should be listed for urgent Liver Transplantation regardless of the presence of hepatic encephalopathy, if the prothrombin index is less than 25% and serum creatinine greater than 106 µmol/L at the third day after ingestion.

Escudié et al, in a retrospective study including 27 patients admitted for Amanita phalloides poisoning, suggested that encephalopathy should not be an absolute prerequisite for deciding liver transplantation.[43,1]

Nonetheless, independently of any other variables, a decrease in prothrombin index below 10% of normal (INR >6) 4 days or more after ingestion should lead to consider urgent LT.[1]

It should be emphasized here that these prognostic criteria are only applicable in countries where donors are readily available and liver transplantation is a realistic option. However, the waiting time on any existing emergency transplant list may be very prolonged in other parts of the world and a liver transplant may never be performed in most others.[15,1,44] In such situations, the use of new therapies such as Molecular Adsorbent Recirculating System (MARS), and surgical options such as Auxiliary Partial Orthotopic Liver Transplantation (APOLT) could be extremely beneficial

DISCUSSION

Poisoning due to consumption of toxic mushrooms has become a very serious issue globally with an ever growing incidence; specifically in the northern and north-eastern parts of India.[1,5] Education regarding the proper identification of edible as well as poisonous mushrooms has become the need of the hour. Early diagnosis of Amanita phalloides poisoning with the background of history and timing of ingestion is crucial to begin prompt treatment in these cases.[7] As no antidote to amatoxins is currently available, immediate evaluation, rehydration with fluid support and correction of electrolyte imbalance and metabolic acidosis are essential for the initial recovery of such patients.[2-4] Although Silybinin, N-Acetyl Cysteine and Penicillin-G have proven to be effective therapeutic agents, Orthotopic Liver Transplantation (OLT) or Auxiliary Partial Orthotopic Liver Transplantation (APOLT) is the only treatment option for most of the cases carrying a poor prognosis.[34-37,41-44]

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Parasher A, Aggrawal A. Prognosis and treatment options in cases of acute liver failure caused by mushroom poisoning due to *Amanita phalloides*. Int J Adv Med 2020;7:875-80.