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MUSHROOM POISONING—NEED FOR OUR AWARENESS AND A TREATMENT PROTOCOL

Dr. A. K. Das*

There are over 10,000 species of mushrooms worldwide. Of these, only 50 to 100 are potentially toxic. 20–25% have been named, and 3% of these are poisonous.1 In this issue Dutta et al has reported an observational study of 48 cases of mushroom poisoning in a tertiary care hospital where treatment modalities were correlated with mortality.

There are many different types of mycotoxins, of which 14 distinctive types of mushroom poisoning found worldwide, and so far about 10 distinctive patterns of reactions to mycotoxins have been observed.

Among mushroom intoxications, the amatoxin syndrome is of primary importance because it accounts for about 90% of fatalities2. Although the exact incidence of mushroom poisoning is not precisely estimated due to a presumably relatively high number of underreporting cases, amatoxin poisoning is a worldwide problem. Approximately 50–100 fatal cases are reported every year in Western Europe, being less common in the United States; however, cases of amatoxin poisoning from Africa, Asia, Australia, and Central and South America have also been described3,4. It is characterized by an asymptomatic incubation period followed by the gastrointestinal and hepatotoxic phases, leading eventually to multiorgan failure and death.

About 35 mushroom species in three genera (Amanita, Galerina, and Lepiota) contain amatoxin2. The most important fact is that the fatality rate for Amanitin poisoning is about 50% without prompt, knowledgeable medical treatment, but is about 10% in the U.S. and Canada where good medical care is readily available. In the present study also, the fatality rate was 43.75%. Amatoxins are doubly dangerous due to the fact that the symptoms are delayed for 6 to 24 hours after ingestion, by which time the toxins have been completely absorbed by the body and after the initial state of gastric distress, the patient appears to recover and is sometimes sent home. Amanitins are a group of complex cyclic polypeptides which damage tissues by inhibiting RNA synthesis within each individual cell. Of the multiple amatoxins, alpha-amanitin appears to be most responsible for human toxicity4. Onset of symptoms manifests itself in four sequential stages.

- First stage is a latency period of 6 to 24 hours after ingestion, in which the toxins are actively destroying the victim’s kidneys and liver, but the victim experiences no discomfort.
- Second stage is a period of about 24 hours characterized by violent vomiting, bloody diarrhea, and severe abdominal cramps.
- Third stage is a period of 24 hours during which the victim appears to recover and is sometimes discharged from hospital.
- Fourth stage is a relapse, during which kidney and liver failure often occurs, leading to death. Patients may die as a result of extensive bleeding due to coagulopathy because of acute liver failure. Importantly, there may be more than one relapse. It is obvious that the patients report to the hospitals only after the 2nd stage.

The ‘deadly white Amanitas’ (eg, A. phalloides, A. bisporigera, A. virosa, A. ocreata, and A. verna) are most commonly involved in human exposures5. Physical characteristics of these mushrooms include a symmetric cap (pileus) and stem (stipe) with a bulbous base (volva) and free gills. They have no offensive taste or odor, most
often growing singly from the ground in moist, hardwood chestnut or oak forests. They mature throughout the mid-summer and fall in temperate regions. White spores may be detected if the cap is left on colored filter paper for one hour. Immature amatoxin-containing Amanita mushrooms are egg-shaped “buttons” that reveal developing structures when bisected. Not all Amanita mushrooms contain amatoxin, including several edible types.

Amatoxin is insoluble in water, so “parboiling” does not destroy the toxin which is confirmed by the observations made in this study that showed higher mortality in those who had parboiled mushrooms compared to fully cooked preparation. The overall severity of the intoxication depends on the amount of toxin ingested and the time elapsed between ingestion and initiation of treatment. This was not mentioned in detail in the present article by Dutta et al which could have been informative in regards to outcome measurement. They did not mention the species of mushroom precisely. The authors did not give a detailed treatment protocol in their cases, and due to logistic reasons neither did they try to triage the patients so that statistical differences between various clinical/biochemical factors could be absolutely pinpointed. However, they seemed to have followed a treatment pattern similar to any acute poisoning with organ support, which is justified under the circumstances, because mushroom identification is usually not readily available during the acute phase of care, and most mushrooms causing toxicity are never correctly identified.

The clinical efficacy of any modality of treatment in mushroom poisoning like Amanita phalloides is difficult to demonstrate since randomized, well controlled clinical trials have not been reported. In any case where ingestion of an amatoxin-containing mushroom species is highly suspected, either by expert mushroom identification or clinical manifestations, aggressive therapy is warranted. Therefore, it is important that we have some kind of treatment protocol in suspected mushroom poisoning since it is a worldwide problem, especially in the rural setting.

There are 14 described clinical syndromes due to mushroom poisoning. Defining which clinical syndrome (Toxidrome) predominates, initiating general supportive care, and administering any specific treatments for that syndrome are the key steps in the initial management for mushroom ingestion. This involves detailed knowledge about the different syndromes, which is beyond the scope of this editorial. Specific antidotes are available for some mushroom poisonings and may be helpful for patients with seizures and delayed gastroenteritis, methemoglobinemia, or cholinergic excess. The following line of management is presented which is based upon papers published till late 2012 by experts who have done studies specifically with evidence of efficacy in management of Amanita phalloides.

**CLINICAL APPROACH:**

Diagnosis of amatoxin-containing mushroom poisoning typically depends upon recognition of the clinical presentation and laboratory abnormalities that indicate hepatotoxicity. The clinical diagnosis should be confirmed, when possible, by amatoxin detection in the urine and/or mushroom identification. In our set up the latter should be tried. Amatoxins are characteristically undetectable in the blood or urine more than 4 days after consumption. If feasible, samples of all ingested mushrooms should be obtained. Whole mushrooms are preferred, but identification can be made on parts of the mushroom, especially the cap. Further storage is advised by wrapping the mushrooms in wax paper, placing them in a paper bag, and refrigerating the sample. Storage in plastic bags should be avoided. But, patients often ingest multiple mushrooms and have cooked, or otherwise damaged what they have ingested, making direct identification difficult or impossible. In these situations, a centrifuged gastric aspirate may be obtained for microscopic evaluation of spores by a professional mycologist (almost impossible in our part), although identification of the ingested mushroom or mushrooms is rarely possible from such specimens. However, treatment should not wait for these results. Clinical manifestations of amatoxin-containing mushroom poisoning may be categorized into three phases:

**a) Gastroenteritis** – Patients develop epigastric abdominal pain, vomiting, and severe, cholera-like diarrhea that may contain blood and mucous and typically starts between 6 and 24 hours after mushroom ingestion. Hepatomegaly may also be present, but liver enzymes and bilirubin are usually normal. Electrolyte abnormalities consistent with a secretory diarrhea (eg, hypokalemia and metabolic acidosis) may also occur. Earlier onset of gastroenteritis between 6 and 9 hours after mushroom consumption may correlate with severe hepatotoxicity
evidenced by elevations of liver enzymes at 24 to 36 hours. Profound GI fluid losses may lead to dehydration, acute renal failure, and circulatory shock.

b) Apparent recovery – With appropriate supportive care of the delayed gastroenteritis, patients appear to improve between approximately 24 to 36 hours after mushroom consumption. Elevations in the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are typically detectable between 24 and 36 hours after mushroom ingestion and typically peak by approximately 60 to 72 hours post-ingestion. In patients with severe poisoning, the patient may go directly from severe gastroenteritis into fulminant organ failure with hyperbilirubinemia, dramatic elevations in liver enzymes over 1000 to 2000 IU/L, prolongation of the prothrombin time, renal insufficiency, and disseminated intravascular coagulopathy.

c) Fulminant hepatic and multisystem organ failure – Approximately two to four days after mushroom consumption, severely poisoned patients develop hepatic failure, often complicated by acute renal failure. Massive simultaneous hepatocyte cell death disrupts hepatic venous and biliary flow. Peak transaminase elevations are typically seen between 48 and 72 hours post-ingestion and may be greater than 2000 IU/L. Direct nephrotoxic effects are seen in the proximal and distal convoluted renal tubules. Pancreatitis occurs in half of all severe cases. Loss of hepatic function over the following days causes hypoglycemia, coagulopathy, encephalopathy, and fluid shifts with progression to multi-organ failure. In up to 30 percent of patients, death occurs, typically within one to two weeks of mushroom ingestion. Patients who have evidence of liver toxicity or who develop signs of mushroom poisoning more than six hours after ingestion have a high risk of developing acute liver failure caused by amatoxin- or gyromitrin-containing mushrooms. Delayed renal insufficiency is associated with ingestion of mushrooms that contain orellanine or allenic norleucine. The major complications of renal failure include volume overload, hyperkalemia, metabolic acidosis, hypocalcemia, and hyperphosphatemia. The initial assessment therefore includes the careful evaluation of volume status and measurement of serum electrolytes, particularly potassium and bicarbonate, and evaluation of a complete blood count and serum phosphate, calcium, albumin and uric acid.

Asymptomatic patients with ingestion of amatoxin-containing mushrooms should undergo baseline assessment of the following:
- Serum electrolytes, calcium, and phosphate
- LFT (AST, ALT, total protein, albumin, total and direct bilirubin)
- Prothrombin time (PT), partial thromboplastin time (PTT)
- Complete blood count with pleatelets
- Blood urea nitrogen and serum creatinine
- Urinalysis

MANAGEMENT: The management of amatoxin poisoning consists of preliminary medical care, supportive measures, specific therapies, and liver transplantation. The specific treatments consist of detoxication procedures and chemotherapies. Let us examine the different treatment modalities available with evidence and then proceed to how to go about it. It is first important to realize that mortality rates of approximately 50 percent seen in series of amatoxin-containing mushroom poisoning can be reduced to below 10 percent with appropriate supportive care alone, primarily adequate fluid resuscitation, and administration of multiple dose activated charcoal.

In addition to careful assessment and support of airway, breathing, and circulation (A-B-C) as needed, treatment of amatoxin-containing mushroom poisoning consists of the following:
- Patients who ingest an amatoxin-containing mushroom do not undergo gastric emptying by gastric lavage in the emergency department. This recommendation is based upon randomized controlled trials showing minimal benefit and possible risk to patients who undergo gastric emptying after poisoning. Nasogastric aspiration in alert patients to obtain a sample for spore analysis may be appropriate in selected instances. Antispasmodic agents (eg, loperamide) should be avoided in patients with diarrhea.
- Perform gastrointestinal decontamination with activated charcoal (AC). The charcoal dosing regimen actually delivered is often dictated by patient tolerance. In patients with vomiting, smaller, more frequent doses or slow continuous nasogastric infusion may be better tolerated and effective. Antiemetics (eg, ondansetron 0.15 mg/kg, maximum single dose 8 mg)
may also be helpful. MDAC should not be used in patients with gastrointestinal ileus, perforation, obstruction, or in patients with depressed mental status and an unprotected airway.

Prevent enterohepatic circulation of amatoxins by administering multiple dose activated charcoal (MDAC). Optimum benefit is expected if MDAC is started within 24 hours of mushroom ingestion. It is recommended that alert patients with a suspected amatoxin-containing mushroom ingestion receive AC. Due to adverse effects like vomiting, diarrhea, and volume depletion, patients with mushroom poisoning should not receive a cathartic (e.g., sorbitol, magnesium citrate). Amatoxins bind well to AC in vitro. In patients with amatoxin-containing mushroom poisoning, multiple doses of AC are associated with improved survival compared with supportive care alone. The recommendation for AC also derives from indirect evidence of benefit in volunteers, animal studies, and evidence of benefit following ingestions of other poisonous substances. The dose is 0.5 grams/kg (maximum dose 50 g) every four hours and should be continued until four days after mushroom consumption. This recommendation is based upon the following observations:

1. Amatoxins are excreted in the bile and recirculated in humans. The duration of biliary excretion may be up to five days after mushroom consumption.
2. MDAC administration permits binding of amatoxins and elimination in the feces.
3. In one case series, MDAC administration alone without other specific therapies was associated with 9 percent mortality (2 out of 22 patients).
4. In a critical review of 2100 cases of amatoxin-containing mushroom poisoning, detoxification procedures alone, including MDAC, were associated with a mortality rate of 10 percent versus 47 percent when supportive care alone was provided.

- Aggressively manage fluid losses caused by vomiting and diarrhea. Patients with significant amatoxin-containing mushroom poisoning typically require aggressive fluid resuscitation to manage losses from severe vomiting and diarrhea.
- Intense forced neutral diuresis is no longer recommended, with urinary output of 100–200 mL/h for 4–5 days being sufficient to increase the renal elimination of amatoxins.
- Disrupt hepatocellular uptake of amatoxins with silibinin dihemisuccinate or if silibinin is not available, high-dose, intravenous penicillin G. No clear guidance for oral dosing of silymarin for amatoxin-containing mushroom poisoning is available. Oral absorption is approximately 20 to 40 percent in humans, and intravenous silibinin dihemisuccinate is superior to oral formulations and should be obtained if at all possible. Although silymarin has not been studied in a controlled fashion in humans, it has shown a protective effect in animal models of Amanita phalloides poisoning. Given the 50 percent concentration of silybin in most silymarin extracts and the low absorption, oral dosing of approximately 10 grams of silymarin capsules daily would be required to achieve plasma concentrations equivalent to the typical intravenous dose of silibinin (20 mg/kg/day). This dose is much higher than the usual silymarin dose of 150 to 360 mg three times daily that is used for other liver diseases. High doses of silymarin may produce significant diarrhea and may complicate management in some patients. Thus, the clinician may initially start with a trial dose of 50 to 100 mg/kg (maximum single dose: 2 grams) of oral silymarin in capsule form every eight hours and if tolerated, increase to a maximum of 200 mg/kg per dose (maximum single dose: 3 grams) for a duration of six days or until the patient shows signs of clinical improvement. In patients who do not tolerate the trial dose, lower doses may be attempted, but may not provide hepatic protection. Successful oral administration may require aggressive treatment of vomiting with antiemetics (e.g., ondansetron 0.15 mg/kg; maximum dose: 16 mg) and replacement of fluid losses caused by diarrhea. Studies indicate that IV silibinin therapy is safe and may have a significant impact on mortality in patients with amatoxin-containing mushroom poisoning, especially if initiated within 24 hours of mushroom consumption. Dilute liquid formulations of silymarin are of no value in amatoxin-containing mushroom poisoning because they contain low doses of silybin. Penicillin G may inhibit amatoxin uptake by organic anion transporting polypeptide (OATP) 1B3 located in hepatocyte membranes, may prevent cellular toxicity, and in animal experiments, appears to have a time and dose-dependent effect on survival.
Penicillin G is a much weaker inhibitor of human hepatocyte amatoxin uptake than silibinin in vitro. It is recommend that, when intravenous silibinin is not readily available, patients with amatoxin-containing mushroom poisoning receive a continuous intravenous infusion of high-dose penicillin G. Recommended dosing varies from 300,000 to 1,000,000 units/kg per day (maximum dose: 40 million units) given as a continuous infusion. Penicillin G is contraindicated in patients with a known penicillin allergy. However, the potential risk of this therapy is higher than for silibinin infusion. High-dose penicillin G infusion may be associated with coma, seizures, electrolyte imbalance (hyperkalemia or hypernatremia, depending upon excipient), severe granulocytopenia, acute interstitial nephritis, and/or renal tubular damage, although the frequency of these adverse effects are not known. Limited data suggest that IV ceftazidime 4.5 grams every two hours may be an alternative for such patients as it has some hepatoprotective effects. The use of other antibiotics, such as aminoglycosides (eg, gentamicin), macrolides (eg, erythromycin), or vancomycin, has not been shown to be beneficial. Experimental studies in isolated human hepatocytes indicate that cyclosporin A, paclitaxel, and rifampin are significant inhibitors of amatoxin uptake into liver cells, but their use in human mushroom poisoning has not been described.

The recommendation for Penicillin G is based upon the following evidence:

- In a case series of amatoxin-mushroom poisoning, mortality was 2% for 111 patients who received a continuous IV infusion of penicillin G in a dose of 1,000,000 units/kg for 24 hours followed by 500,000 units/kg for two days. In addition to aggressive supportive care, all patients also received multiple dose activated charcoal, dexamethasone, and glutathione.

- A systematic review of treatments given to 2100 patients with amatoxin-containing mushroom poisoning found that 1411 patients who received N-acetylcysteine had a mortality rate of 6.8 percent which was significantly lower than the average mortality rate of 11.6 percent among all patients.

- IV NAC is generally well-tolerated although anaphylactoid reactions have been described. L-ascorbic acid (vitamin C) and cimetidine have antioxidant and cytoprotective effects in animal models of amatoxin-containing mushroom poisoning. However, use in cases of human poisoning has been limited and beneficial effects on outcome have not been established. Some experts still recommend their use in combination with silibinin and N-acetylcysteine in the following doses:
  - Cimetidine: 300 mg IV every eight hours until clinical improvement
  - Vitamin C: 3 grams IV daily until clinical improvement
  - Anticipate and provide supportive care of fulminant hepatic failure, including intensive care in an institution with liver transplant capability if possible. Intensive supportive care of liver toxicity includes treatment of hypoglycemia, lactulose administration for hyperammonemia, vitamin K replacement, and infusions of
of fresh frozen plasma for significant coagulopathy. Other common comorbidities include acute renal failure, sepsis, metabolic disturbances, hepatic encephalopathy, and cerebral edema.

The optimal timing for the administration of MDAC, silibinin di-hemisuccinate or high-dose penicillin G, and N-acetylcysteine is within 24 hours of amatoxin-containing mushroom ingestion. Still, these therapies should still be initiated in patients with suspected amatoxin-containing mushroom poisoning who present for treatment after 24 hours. Certain therapies are associated with no benefit or worsening outcomes in animal models or clinical reports of amatoxin-containing mushroom poisoning and should be avoided e.g. glucocorticoids, vitamin E, amifostine, and amatoxin-specific Fab fragments.

Liver transplantation: The clinician should contact a medical toxicologist and a liver transplant center early on when managing patients with suspected amatoxin-containing mushroom poisoning. Transfer to a tertiary care center capable of performing liver transplantation (LT) or other bridging liver failure therapies (eg, molecular absorbent recirculating system [MARS], extracorporeal albumen dialysis) should occur if clinical signs of improvement are not evident by four days post-ingestion or, depending upon consultant’s advice, sooner. The major dilemma in patients with ALF is to find the right timing for transplantation. If the surgical procedure is performed too early, the patient could have survived without impaired quality of life. 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 they are not universally accepted. Since the number of patients with amatoxin poisoning evaluated for LT is quite small, the prognostic indicators are not clearly defined in this specific condition.

All patients with suspected or confirmed ingestion of a significant amount of amatoxin-containing mushrooms (eg, one to two whole mushrooms) based upon clinical findings, amatoxin detection, or mushroom identification warrant hospital admission with initiation of gastrointestinal decontamination, multiple dose activated charcoal, inhibition of amatoxin uptake (eg, IV silibinin dihemisuccinate), antioxidant therapy (IV N-acetylcysteine), and supportive care.

Children who are asymptomatic and ingested a small amount (eg, one bite) of a mushroom may receive a single dose of activated charcoal and be discharged if follow-up within 24 hours is assured.

IN OUR SETTING WHAT SHOULD WE DO?

The first task is to link the clinical presentation with mushroom ingestion, as the association may be obscured by the delay between symptom onset and the mushroom meal. When interviewing patients or the patient’s relatives suspected of suffering from mushroom poisoning, physicians must obtain a detailed history concerning the ingestion. Key questions include the description of the eaten mushroom, the environment from which it was harvested, the number of different types of mushrooms ingested, the storage before consumption, the preparation before ingestion, 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. Amanitins are resistant to heat and are still active after long periods of storage. Thus, in contrast to other toxins or bacterial contamination, cooking or prolonged cold storage may exclude other causes of mushroom intoxication, but not poisoning due to Amanita phalloides.

1. The onset of signs and symptoms >6 hours after mushroom consumption should increase suspicion for amatoxin-containing mushroom poisoning with the following temporal profile in the history and clinical manifestations, so that the patients can be triaged for ICU treatment when necessary:
   - Gastrointestinal illness (6 to 24 hours post-ingestion)
   - Latency (24 to 36 hours post-ingestion)
   - Fulminant hepatic failure (starting 48 to 72 hours post-ingestion)

2. The following patients warrant hospital admission:
   - Patients with delayed symptoms more than six hours after mushroom ingestion
   - Patients with early symptoms less than three hours after mushroom ingestion who remain symptomatic beyond six hours despite supportive care or who ingested more than one type of mushroom.
   - Patients with evidence of rhabdomyolysis, liver toxicity, or renal insufficiency
Asymptomatic patients in whom ingestion of amatoxin-containing mushrooms is strongly suspected

- Asymptomatic patients in whom follow-up at 24 hours cannot be assured.

3. All patients with strongly suspected or confirmed ingestion of a significant amount of amatoxin-containing mushrooms (eg, one to two whole mushrooms) based upon clinical findings, amatoxin detection (if possible), or mushroom identification warrant hospital admission. Children who are asymptomatic and have recently ingested a small amount (eg, one bite) of a mushroom may receive a single dose of activated charcoal and can be discharged, only if follow-up within 24 hours is assured. Asymptomatic patients must have baseline biochemical work-up for hepatotoxicity, admitted, and observed for 24-48 hours for complications like hepatocellular failure.

4. Supportive care of amatoxin-containing mushroom poisoning is a must with aggressive management of fluid losses caused by vomiting and diarrhea especially those in shock, and anticipation of hepatotoxicity and multisystem organ failure by appropriate lab tests. Gastric lavage or use of Loperamide is not recommended for treatment.

5. It is recommended that alert patients who have ingested amatoxin-containing mushrooms receive multiple dose activated charcoal (MDAC). The greatest benefit occurs if AC is given within one hour.

6. It is recommended that patients with amatoxin-containing mushroom poisoning also should receive intravenous silibinin dihemisuccinate, if available. If i.v. silibinin dihemisuccinate is not available, they should receive a continuous intravenous infusion of high-dose penicillin G. In addition to a continuous infusion of high-dose penicillin G, it is suggested that they also receive oral silymarin capsules. Liquid silymarin is useless.

7. In addition to amatoxin uptake inhibitor therapy such as intravenous silibinin or continuous infusion of penicillin G with oral silymarin, it is recommended that patients with evidence of hepatocellular injury due to amatoxin-containing mushroom poisoning receive intravenous N-acetylcysteine (NAC).

8. The optimal timing for the administration of MDAC, silibinin dihemisuccinate or high-dose penicillin G, and N-acetylcysteine is within 24 hours of amatoxin-containing mushroom ingestion.

9. Accepted indications for dialysis in patients with renal failure include:

- Fluid overload that is refractory to diuretics
- Hyperkalemia (serum potassium concentration >6.5 mEq/L) or rapidly rising serum potassium,
- Metabolic acidosis (arterial pH less than 7.10) in patients with volume overload, which will be made worse by the administration of sodium bicarbonate, or with lactic acidosis, which is generally not treated with bicarbonate.
- Signs of uremia, such as pericarditis, neuropathy, or an otherwise unexplained decline in mental status

10. If feasible contact a liver transplant centre when the patient deteriorates inspite of above mentioned treatment strategy. Because of the complexities involved, patients with acute liver failure should be managed in an intensive care unit in centers with an active liver transplant program. Patients admitted to hospitals without a transplant program should be transferred as soon as possible and ideally before the onset of the severe coagulopathy and increased intracranial pressure that may make later transfer dangerous.

11. Education of the public about the consumption of mushrooms and education of health personnel working in health centers regarding early treatment and transfer to hospitals with appropriate facilities are important for decreasing mortality.

In conclusion what we need in our set up, is a clear-cut approach to any suspected or confirmed case of mushroom poisoning regarding diagnosis, anticipation of serious toxicity, indications for hospitalization, the steps of treatment used (alongwith advanced therapeutic options which are available only in specialized centres). What was presented in this editorial was a practical approach and treatment protocol based on available information in the literature and most of these are based on Class IB or Class IC evidences.

REFERENCES


A Study Of Clinical Profile and Treatment Outcome of Mushroom Poisoning – A Hospital Based Study

A Dutta* , B C Kalita, A K Pegu**

Abstract

Introduction: The popular interest in gathering and eating uncultivated mushrooms has been associated with an increase in incidents of serious mushroom-related poisonings. This prospective study was conducted to observe the clinical presentations, laboratory data, histopathological findings, treatment modalities and prognostic factors in cases of mushroom poisoning coming to a tertiary referral center for treatment.

Materials and methods: All cases with a history of falling ill after ingestion of mushroom and coming to the departments of Medicine and Pediatrics of Assam Medical College and hospital were included in the study. A proper history was taken. Histopathological correlation was done in cases whenever possible. Course of the disease and treatment modalities were correlated with mortality data.

Results and observations: A total number of 48 cases were included in the study which came in 17 clusters. 27 (56.25%) were males and 21 (43.75%) were females. 8 (16.6%) cases were children below 12 years of age. 21 (43.75%) cases expired within hospital stay. It was seen that mortality was 83% in children below 10 years of age and 100% in those above 50 years of age. 10 (83%) out of 12 cases who took par boiled mushroom died whereas 11 (30%) out of 36 cases who took fully cooked mushroom died. Mortality was directly related to the four stages of presentation of the cases and increased from 0%, 30%, 54% and 100% respectively. The most common organ failures were acute liver failure or acute kidney injury, coagulopathy secondary to hepatic failure being a dangerous complication. Haemodialysis, forced diuresis showed significant benefit in management of patients. Fluid & electrolyte balance, Vit K & Fresh frozen plasma also had significant positive outcome in patients coming in stages 2 and 3.

Conclusion: Though mushrooms are commonly ingested, lack of proper knowledge about the poisonous and non poisonous varieties of the same, interest in growing and collecting wild mushrooms, lack of knowledge of the signs of such poisonings have led to frequent mortality, especially in the monsoon seasons in few districts of Upper Assam. Early detection and intervention are key to survival.

Keywords:- Mushroom poisoning, Acute liver failure, steatohepatitis, Toxic hepatitis, renal failure.

INTRODUCTION:

A mushroom is the fleshy spore-bearing fruiting body of a fungus, typically produced above ground on soil or on its food source. Typical mushrooms are the fruitbodies of members of the order Agaricales, whose type genus is Agaricus and type species is the field mushroom, Agaricus campestris. However, in modern molecularly defined classifications, not all members of the order Agaricales produce mushroom fruitbodies, and many other gilled fungi, collectively called mushrooms, occur in other orders in the class Agaricomycetes. Edible mushrooms are used extensively in many cuisines. Though mushrooms are commonly thought to have little nutritional value, many species are high in fiber and provide vitamins such as thiamine, riboflavin, niacin, biotin, cobalamin, ascorbic
acid. Mushrooms are also a source of some minerals, including iron, selenium, potassium and phosphorous.

The popular interest in gathering and eating uncultivated mushrooms has been associated with incidents of serious mushroom-related poisonings. This is very common in the monsoon seasons in our part of country in north east India where awareness about the poisonous mushrooms is less and this contributes to a great deal of morbidity and mortality. Alarming number of cases were reported in the spring of 2008 from a few districts of upper Assam including Golaghat, Sivsagar, Jorhat and Dibrugarh. This prospective study was conducted to observe the clinical presentations, laboratory data, histopathological correlation, treatment modalities and prognostic factors in cases of mushroom poisoning coming to a tertiary referral center, Assam Medical College and Hospital for treatment.

Methods and materials

All case with a history of falling ill after ingestion of mushroom and coming to the departments of Medicine and Pediatrics of Assam Medical College and hospital were included in the study. A proper history was taken. A sample of mushroom was collected from gastric lavage whenever it was possible and sent for analysis. Routine blood test including renal and hepatic function tests were done and recorded. Histopathological examination was done in cases whenever possible. Their progress was monitored and treatment modalities were correlated with mortality data. A rough estimate of the prognostic factors was sought after taking all the parameters into consideration.

Results and observations

A total number of 48 cases were included in the study which came in 17 clusters or incidents with one cluster including a family of 10 people. 27 (56.25%) cases were males and 21 (43.75%) cases were females. 8 (16.6%) cases were children below 12 years of age. 21 (43.75%) cases expired within hospital stay. Rest of the patients improved and was discharged. They were followed up for 6 weeks and were found to be in good health.

It was seen that Mortality was 83% in children below 10 years of age and 100% in elderly above 50 years of age. Moreover 10 (83%) out of 12 cases who took parboiled mushroom died whereas 11 (30%) out of 36 cases who took fully cooked mushroom died. This signifies the fact that probably parboiled mushroom had more toxic effects than fully cooked preparations. Quantity of mushroom taken was also directly related with the mortality of the patients. In 3 clusters, where they had taken more than one bowl full of mushroom, 13 (86%) out of 15 cases expired. In rest of the cases, 8 (24%) out of 33 cases had expired.

Chart 1 : Mortality (%) in relation to age of patients

There are 4 stages of presentation of mushroom poisoning. Stage 1 is the latent phase where the patient is mostly asymptomatic. It occurs from 1 hr to 6 hrs after ingestion of poisonous mushrooms depending on various types of species. Stage 2 is the gastrointestinal phase which starts within 6 to 12 hours and stays till approximately 24 hours. This stage is associated with nausea, vomiting, pain abdomen, cramps, diarrhea (cholera like), headache, dehydration, hypotension and if left untreated may lead to shock. Stage 3 is a late latency phase where the diarrhea improves and the patient seems to be improving. Stage 4 is where the hepatic and renal functions are deranged, coagulation factors drop drastically and eventually the patient may land up with acute liver failure and acute kidney injury.

Our study showed that 2 (100%) out of 2 cases who came in stage 1, 19 (70%) of 27 cases who presented in stage 2, 6 (46%) of 13 cases who came in stage 3 survived and none of the 6 cases who presented in stage 4 survived during the hospital stay. Hence the mortality was directly related to the stage of presentation of the cases and increased from 0%, 30%, 54% and 100% respectively in 4 stages.
The patients who expired had a higher bilirubin level (mean 7.17mg/dl) than those who survived (mean 2.58mg/dl). The prothrombin time was also higher (mean 16.5) in compared to patients who survived (11.85). Liver enzymes were also elevated (AST mean 1323, ALT mean 2435) in patients who expired in comparison to those who survived (AST mean 224, ALT mean 324). The mean serum creatinine was also elevated in patients who expired (9.7) in comparison to those who survived (3.8). This showed that deranged hepatic and renal function tests were directly related to mortality of the patients.

In patients who expired post mortem analysis was done and histopathological examination of tissues were done. There was severe gastric erosions and petechiae in stomach and intestines. Lung showed edema and necrosis. Heart showed petechiae and coronary artery obstruction.

Liver tissue showed fatty infiltration and enlargement. In one patient who died within 4 days of ingestion of mushroom, liver was enlarged and 1800 grams in weight. Whereas, in another patient who died 18 days after ingestion of mushroom, the liver was small, shrunken and weighed only 400 grams.

Macroscopic and microscopic picture of liver showed fatty infiltration, which can be seen even with naked eye. Microscopic study of the liver showed large fat globules and lymphocytic infiltration. There were focal signs of inflammation and ballooning of hepatocytes. The picture resembles with that of non-alcoholic seatohepatitis (NASH).

Figure 1. The 1800 gm liver in a patient who died 4 days after ingestion of mushroom(left) and small shrunken, 400 gm liver in a patient who died 18 days after ingestion of mushroom(right)
In relation to the treatment it depended on the stage of presentation to the hospital. If the patient had presented early to the hospital, gastric lavage was done and if any pieces of mushroom found they were sent for analysis. In early cases of presentation activated charcoal was also given. Vitamin K injection was given routinely in all cases intramuscularly for 3 days. In patients who presented in stage 2, they were adequately rehydrated and serum electrolytes were corrected whenever required. Silymarin 140mg in tablet or liquid form was given in patients showing signs of hepatic derangement. N-acetylcystine was also used in patients coming in stage 2 or later. In patients with bleeding manifestations, fresh frozen plasma was used along with vitamin K injections.

Patients coming in stage 3 and 4 with raised creatinine were subjected to forced diuresis and when indicated hemodialysis was done. Patients who presented with hepatic encephalopathy were treated with lactulose, L-ornithine-L-aspartate, mannitol, glucose, oxygen inhalation and supportive treatment. The following chart shows the percentage of patients receiving a particular treatment who improved or expired during their stay in hospital.

**Chart 6: (Percentage (%) of patients receiving a particular treatment who improved or expired)**

**Discussion**:

There are very few published case study reports of mushroom poisoning. In a study from northern California, nine persons required hospitalization after eating Amanita phalloides (i.e., “death cap”) mushrooms; two of these persons died. A study on circumstances of exposure and patterns of toxicity from Switzerland showed the mortality of confirmed amatoxin poisonings was high (5/32) compared to other reports.

In a study from Texas, 742 exposures occurred during the study period 2005-6. All exposures were acute and intentional. Of these exposures, 59 (7.9%) were admitted to the hospital, with 17 (28.8% of admissions) requiring admission to a critical care unit. Four cases required inpatient psychiatric admission. The average age of admitted exposures was 20.5 years, with a male-to-female predominance of 3.3:1. Eleven (22.9%) of the admitted exposures were identified, with Psilocybin being the most common agent (n = 10, 91%). Among the admissions, co-ingestions were identified with the mushroom ingestion in eleven patients (40.7%). The most common symptoms in admitted patients were vomiting (n = 34, 57.6%), nausea (n = 19, 32.2%), altered mental status (n = 17, 28.8%), abdominal pain (n = 13, 22%), and diarrhea (n = 10, 16.9%)

In a study from Pakistan, of the 18 patients with mushroom poisoning, fifteen were above five years of age. Fifteen patients developed hepatic failure and three patients developed renal failure. Thirteen patients expired. They concluded that to start timely management, Mushroom poisoning should be considered in the differential diagnosis in patients presenting with food poisoning particularly coming in groups. Delay in diagnosis is associated with high mortality.

We observed that children and elderly were more vulnerable to the toxic effects of mushroom. The amount of mushroom taken was also associated with increased mortality and so was the procedure of cooking. It was found that par boiled preparations were more deadly than fully cooked. This raises the question if the toxin is heat labile and should be studied further.

Early presentation and medical intervention had a significant effect on the outcome. Patients who presented in stage 1 and 2 had the best chance of survival compared to those who presented in stage 3 and 4. Hence the role of educating the primary care physician and early referral to a higher center plays a great role in preventing mortality and morbidity. Unfortunately most of the cases of mushroom poisoning are from rural or remote areas and their ignorance of medical science is as per with their unawareness of poisonous mushrooms coupled with poor communication and transport system.

 Elevated serum bilirubin, liver enzymes, serum creatinine and prothrombin time were associated with high
mortality rates and can be well used as a bad prognostic factors in hospitalized patients. Those with previous liver disease or chronic alcoholics were more likely to go into hepatic encephalopathy and had a bad prognosis.

Histopathological study showed signs of internal bleedings and petechies probably secondary to hepatic failure and raised prothrombin time. Liver showed fatty infiltration and inflammation similar to the picture in non-alcoholic seatohepatitis (NASH). Further study is required to know the mechanism and nature of hepatic injury in such patients.

Haemodialysis, forced diuresis had significant benefit in management of patients. Fluid & electrolyte balance, Vit K & Fresh frozen plasma had also significant positive outcome in patients coming in stage 2 and 3. Gastric lavage and activated charcoal were effective only in early stages of presentation, mostly within hours of ingestion of mushroom.

**Conclusion:**

Though often mushrooms are ingested, lack of proper knowledge about the poisonous and non poisonous varieties of the same, interest in growing and collecting wild mushrooms, lack of knowledge of the signs of such rare poisonings have led to frequent mortality, especially in the monsoon seasons in few districts of Upper Assam. This study was an observational case study report of 48 cases of such mushroom poisoning. Early detection and intervention was key to survival. The liver and kidney was the most affected organ and the nature of injury is mostly acute liver failure or acute kidney injury, bleeding disorder secondary to hepatic failure being a dangerous complication. Further research will help in formulating better management of such patients.

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A Clinical Study of the Spectrum of Complications of Cirrhosis

T Maitra* , A K Adhikari**

Abstract
Cirrhosis represents the final common histological pathway for a wide variety of chronic liver diseases and irrespective of its cause the clinical course of patients with cirrhosis is often complicated by a number of important sequelae. This study was conducted to determine the clinical spectrum of patients with chronic liver disease with reference to its etiology, clinical features, complications and causes of death. The mean age of presentation was 47.4±12.6 years and males constituted 80.5% of the cases. Alcohol was the most common cause of cirrhosis followed by hepatitis B. Easy fatiguability and abdominal distension were the most common presenting symptoms in 74.5% and 60% patients respectively and pallor followed by splenomegaly were the most common examination finding in 82% and 64% patients. 62% of the patients had ascites. Coagulopathy and esophageal varix were the most common complications encountered in 83% and 81% patients respectively. 13% patients died during hospital stay and worsening hepatic encephalopathy was the most common cause of death encountered.

Keywords:- Cirrhosis, Hepatitis B, Ascites, Coagulopathy, Esophageal varix, Hepatic encephalopathy.

INTRODUCTION
Cirrhosis of liver is defined anatomically as a diffuse process with nodule formation and fibrosis. It represents the final common histological pathway for a wide variety of chronic liver diseases. It can often be a silent disease, with patients remaining asymptomatic until decompensation occurs. Clinical features, are the result of the pathological changes, and they are the same irrespective of the cause. Decompensated disease can result in complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy and variceal bleeding from portal hypertension.

Established cirrhosis has a 10 year mortality rate of 34-66%, largely dependent on the cause of cirrhosis - Alcoholic cirrhosis has a worse prognosis than primary biliary cirrhosis and cirrhosis due to hepatitis.

Data regarding etiology and the spectrum of clinical manifestations and complications of cirrhosis is lacking from the North – East. Against this background, this present study was conducted with the following aims and objectives.

AIMS AND OBJECTIVES-
To determine the clinical spectrum of patients with chronic liver disease with reference to its etiology, clinical manifestations, complications and causes of death.

MATERIALS AND METHODS
• Study design- Single centre observational study
• Place of study- Department of Medicine and Gastroenterology, Gauhati Medical College and Hospital

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• **Duration** – August 2010 to July 2011
• **Study population** – 200 patients above 12 years of age of both sexes having features of cirrhosis

A detailed history, thorough clinical examination and relevant investigations were done in these patients to confirm the diagnosis and also to determine the presence of various complications in them.

**RESULTS AND OBSERVATIONS**

The results and observations of the study are presented below.

**AGE DISTRIBUTION OF PATIENTS**

**SEX DISTRIBUTION OF PATIENTS**

Fig 2: Sex distribution of patients

**ETIOLOGY OF CIRRHOSIS**

Fig 3: Etiology of cirrhosis

**PRESENTING COMPLAINTS**

Fig 4: Diagram showing the various presenting symptoms of the patients

**EXAMINATION FINDINGS**

Fig 5: Examination findings in the study patients
The present study “A clinical study on the spectrum of complications of cirrhosis” was conducted in 200 patients with cirrhosis of liver admitted to Gauhati Medical College and Hospital during the period of 1 year from August 2010 to July 2011.

In our study the age varied between 13 to 87 years. The mean age of presentation was 47.4±12.6 years and maximum number of patients were between 40-59 years (57.5%). This is in agreement with the findings of Ishaq SM et al who reported a mean age of 51.05 ±14.98 years in their study. Study conducted by Nepal N et al showed that 56% patients of cirrhosis were between 40-59 years.

Males constituted 80.5% of the cases of cirrhosis in our study, with a male to female ratio of 4.12:1. Kamal A et al in their study reported a male to female ratio of 6.14:1.

Alcohol was identified as the most common cause of cirrhosis in 62.5% of the patients followed by Hepatitis B in 11%, cryptogenic in 9.5%, NASH in 9% and hepatitis C in 3.5 % cases. Douds AC et al also reported alcohol as the commonest cause of cirrhosis (60.9%) followed by cryptogenic (14.9%) and post viral cirrhosis(12.1%). In our study, highest proportion of patients presented with easy fatiguability (74.5%) followed by distention of abdomen (60%). Kamal A et al reported ascites in 61% patients, generalised weakness in 55% and fatigue in 38% patients. Jaundice was observed in 42% of the patients in the present study. The incidence of jaundice in cirrhosis was reported to be between 20.3% to 67% by various workers. Patek et al found jaundice in 67% patients and Kamal A et al reported jaundice in 40% of the cirrhotic patients. 40% of the study patients complained of sleep disturbance which was comparable to 47.7% found by Juan C et al.

Alcohol was identified as the most common cause of cirrhosis in 62.5% of the patients followed by Hepatitis B in 11%, cryptogenic in 9.5%, NASH in 9% and hepatitis C in 3.5% cases. Douds AC et al also reported alcohol as the commonest cause of cirrhosis (60.9%) followed by cryptogenic (14.9%) and post viral cirrhosis (12.1%). In our study, highest proportion of patients presented with easy fatiguability (74.5%) followed by distention of abdomen (60%). Kamal A et al reported ascites in 61% patients, generalised weakness in 55% and fatigue in 38% patients. Jaundice was observed in 42% of the patients in the present study. The incidence of jaundice in cirrhosis was reported to be between 20.3% to 67% by various workers. Patek et al found jaundice in 67% patients and Kamal A et al reported jaundice in 40% of the cirrhotic patients. 40% of the study patients complained of sleep disturbance which was comparable to 47.7% found by Juan C et al.

In our study, pallor was the most common examination finding, present in 82% of patients. This was followed by splenomegaly in 64% cases, ascites in 62%, pedal edema in 44%, icterus in 40%, asterixis in 37%, hepatomegaly in 23% and abdominal tenderness in 15.5% of the patients. In the study conducted by Kamal A et al pallor and splenomegaly were present in 72% and 75% of the patients respectively, ascites was present in 65% of the patients, peripheral edema in 43% and icterus in 40% of
the patients respectively.

The Child Turcotte Pugh (CTP) score was calculated in all the patients and it was less than 7 in 6.5% patients (Child Pugh A), 7-9 in 41% (Child Pugh B) and more than 9 in 52.5% of the patients (Child Pugh C). This was in contrast to studies done by Atif Z et al and Varghese J et al who found majority of the patients having Child Pugh B cirrhosis.

13% patients died during the hospital stay and the most common cause of death was worsening hepatic encephalopathy in 50% followed by UGI bleed in 26.92% and sepsis in 11.53% of the patients. 7.69% patients died due to CLD unrelated causes. Schlichting P et al found liver failure as the most common cause of death in cirrhotic patients (24%) followed by cardiovascular disease in 22%, gastrointestinal bleed in 14%, liver failure with gastrointestinal bleed in 13%, infections in 7% and hepatocellular carcinoma in 9%.

CONCLUSION

Chronic liver disease is a condition with protean manifestations. Unfortunately, in this part of the country, patients present in a fairly advanced stage of the disease.

The present study revealed alcohol as the most common etiological factor for cirrhosis followed by Hepatitis B. Gastroesophageal varices, coagulopathy and ascites were found to be the most common complications and worsening hepatic encephalopathy and UGI bleed were the common causes of death in these patients. However larger studies with long duration follow up is necessary to throw more light on the exact trend in etiology, clinical features, complications and causes of death in patients with chronic liver disease.

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Study of Plasma Potassium Concentrations in pre-storage Gamma Irradiated blood units – AMCH experience

R Hazarika*, P Medhi**, S Ahmed, G Phukan***,

Abstract

Background & Objective: Irradiated blood and components are now-a-days very effectively used to prevent transfusion associated Graft Versus Host Disease (GVHD) in cases of bone marrow and solid organ transplantation. However, irradiation of blood components has received increased attention due to increased categories of patients eligible to receive such blood to prevent transfusion associated graft versus host disease. But significantly, irradiation also leads to enhancement of storage lesion i.e. high level of plasma potassium (one of the lesions) which could have deleterious effect in recipient when transfused. The aim of this study was to assess the extra cellular potassium concentrations during conventional preservation of irradiated and non irradiated whole blood units to evaluate the satisfactory and safe post irradiation expiry date for the blood bank of Assam Medical College & Hospital, Dibrugarh.

Materials & Methods: 22 (twenty two) units of whole blood collected (350ml in 49ml CPDA1 blood bags) from healthy donors and divided into two parts. One aliquot was subjected to gamma irradiation (25 Gy – Cobalt 60) and then stored under ideal conventional blood banking conditions at 2p C-6p C temperature. Sampling was done from irradiated and non-irradiated blood bags and estimations of plasma potassium were done on day 0, 7th & 21st. The statistical analysis of the parameters was done and significance evaluated.

Results: A progressive two fold increase in the mean values of potassium in both the groups was noted. The increment found is statistically highly significant (P<0.001). However, depending on the increment of potassium value, cold storage of irradiated blood upto day 7 is found to be acceptable for safe transfusion in this study.

Conclusion: The findings of this study indicated that gamma irradiation resulted in increased potassium level. Careful evaluation of potassium level in irradiated cold stored blood is essential for evaluation of a safe expiry date. However, further invivo studies to follow up the consequences of transfusion of irradiated blood in patients needs to be highlighted.

Keywords- Gamma irradiation, Potassium concentration, GVHD

INTRODUCTION:

Whole blood and cellular components are irradiated to reduce the risk of Graft Verses Host Disease (GVHD) induced by blood transfusion in a wide range of immunocompromised patients. Transfusion associated – Graft Verses Host Disease (TA-GVHD), a fatal alloimmune complication mediated by donor T-Cells in blood component, was first reported in 1960’s in individual with haematologic malignancies and in infant with congenital immunodeficiencies who developed “Runting Disease” after blood transfusion [1]. GVHD occurs when viable allogenic donor T lymphocytes in transfused blood and blood components engraft, multiply react against the tissue of the recipient. However, there are reports of GVHD occurring in apparently non-immunocompromised recipients, following transfusion of blood donated by family members when donor and recipient share genes for HLA determinants [2][3]. Irradiation of blood components has received increased attention due to increased categories of patients eligible to receive such blood to prevent transfusion associated graft versus host disease.
Although irradiation has been claimed to be harmless to red cells and neutrophil functions and to have little effect on platelet increment \(^{[4]}\)\(^{[5]}\)\(^{[6]}\), studies have reported raised potassium concentrations in irradiated blood \(^{[7]}\)\(^{[8]}\) due to leakage of intracellular potassium. The viability in vivo of irradiated RBC’s evaluated as the 24 hours recovery, is reduced during storage compare with that of non-irradiated RBC’s \(^{[9]}\)\(^{[10]}\). This reduced viability has raised questions concerning the maximum storage time for RBC’s after irradiation. The etiology of the RBC irradiation lesion has never been completely elucidated. Lipid peroxidation and RBC membrane protein assay appear unaffected whereas purine nucleotides decrease over time while the actual structural change that make RBC’s sensitive to irradiation-induced oxidative damage and result in potassium leakage are under consideration. There have been various studies with contrasting results \(^{[8]}\)\(^{[11-13]}\). Thus, the present study was undertaken to assess the storage lesion during conventional preservation of whole blood after Gamma Irradiation with the aim as follows –

1. To estimate the potassium level increment in pre storage irradiated as well as post irradiated stored blood units and compare with the non-irradiated stored (control) blood units.
2. To evaluate the safety of potassium level in stored blood units after being irradiated with Gamma Irradiation.

**Materials and Method:**

The study was carried out in Blood Bank, Assam Medical College & Hospital, Dibrugarh. 22 (twenty two) units of whole blood (350ml in 49ml CPDA1 blood bags) collected from normal voluntary donors were each divided under aseptic conditions in two equal parts. One part of each pair received 25 Gy irradiation (Source – Cobalt 60) in a gamma cell irradiator (BI-2000) installed in the blood bank, AMCH in 2009. All the samples were stored at 2p C-6p C under identical standard conditions. After mixing, aliquots were removed under aseptic conditions immediately after irradiation i.e. on day 0, then on day 7 & day 21 to determine plasma potassium concentration. Plasma potassium concentrations were also estimated in the non-irradiated samples (control group) of each pair on day 0, day 7 and day 21 of cold storage in the same way.

Statistical analysis of the data’s were performed. The potassium concentrations with its mean and standard deviation (SD) were calculated for each of the irradiated and non-irradiated groups on days 0, day 7 and day 21 and readings noted. t – test was used to evaluate the p-value of the corresponding groups to see the levels of statistically significant differences.(p<.05)

**Result and Observation:**

Plasma Potassium concentrations of both the irradiated and non-irradiated blood samples on day 0, 7 and 21 were recorded as per the protocol described. The mean values along with the standard deviations were also calculated out as shown in the table.

### Table-1

<table>
<thead>
<tr>
<th>Days Stored</th>
<th>K⁺ Range (m mol/L)</th>
<th>Mean (m mol/L) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Irradiated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.81 – 3.53</td>
<td>2.67 ± 0.35</td>
</tr>
<tr>
<td>7</td>
<td>6.02 – 14.81</td>
<td>9.88 ± 2.34</td>
</tr>
<tr>
<td>21</td>
<td>11.37 – 22.87</td>
<td>17.01 ± 3.15</td>
</tr>
<tr>
<td>Irradiated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2.36 – 3.92</td>
<td>2.85 ± 0.31</td>
</tr>
<tr>
<td>7</td>
<td>8.96 – 27.31</td>
<td>18.83 ± 4.35</td>
</tr>
<tr>
<td>21</td>
<td>19.09 – 38.64</td>
<td>29.28 ± 4.57</td>
</tr>
</tbody>
</table>

**Mean Potassium levels in Irradiated & Non-Irradiated blood units (22 blood units)-**

**Changes of Potassium level in non-irradiated & irradiated whole blood over a 21 day period (No. of samples = 22)**

![Graph showing changes of Potassium level in non-irradiated & irradiated whole blood over a 21 day period](image)
In this study no significant difference (P>0.05) has been found in the studied parameters between non-irradiated and irradiated blood samples on day 0. But a very highly significant difference (P<0.001) has been observed between non-irradiated and irradiated blood samples on day 7. Similar difference has also been observed on day 21 (P<0.001). In comparison with non-irradiated samples about two fold increase of potassium concentration has been recorded on day 7 & 21 in irradiated blood samples of this study.

**Discussion:**

Statistically significant progressive increase in the mean values of plasma potassium concentration in the irradiated blood has been observed in this study carried out in blood bank of Assam Medical College & Hospital, Dibrugarh. Increase of potassium permeability of red cell membrane during cold storage is one of the features of storage lesion. But gamma irradiation is found to cause greater increase in electrolyte permeability of RBC membrane during cold storage, though it is said to be reversible when RBC’s are warmed to 37°C [11].

The mean values of plasma potassium on day 0 in non-irradiated and irradiated samples have been found to be 2.67 mmol/L and 2.85 mmol/L respectively. But the differences in the control (non-irradiated) and irradiated groups on day 7 and 21 have been found to be highly significant (P<0.001). The mean value of potassium concentration of the irradiated blood samples on day 7 has been found to be equivalent to that of the control groups (non-irradiated) on day 21. Therefore, use of pre-storage irradiated blood upto 7 days of cold storage (i.e. at 2°C-6°C) can be considered safe for transfusion in our hospital though the general guide line permits transfusion upto 21 days of cold storage after irradiation depending on the potassium concentration.

Doubling values of extracellular potassium have also been recorded in other published studies. This sharp increment of potassium level is to be considered in certain cases – like exchange transfusion, neonatal cardiac surgery and massive transfusions. Unwilling use of blood with high potassium may be hazardous in patients with impaired renal function, pre-existing hyperkalaemia or both.

**Conclusion:**

1. Gamma irradiation can damage or impair the electrolyte pump mechanism of red cell membrane which is possibly responsible for significant increment in the extracellular potassium level in irradiated blood units. It is necessary that the clinicians and blood banks should be aware of the high potassium concentration in irradiated blood. Policies for safe use of irradiated blood and components should be made by blood banks authorities in association with clinicians and the centres responsible for irradiating blood.

2. Plasma potassium value of irradiated blood upto day 7 of cold storage is considered to be safe for AMCH, blood bank.

3. Physicians awareness of indications for requesting irradiated components is needed for prevention of serious post transfusion complications.

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Study of Correlation of Carcinoma Esophagus with Helicobacter Pylori infection - A Hospital Based Study

N P Pathak*, B K Jalan**, N Dutta***, R P Medhi****

Abstract

Objective - The role of Helicobacter pylori in progression to esophageal adenocarcinoma is still uncertain, but, on the basis of population data, it may carry a protective effect. This hospital based, analytical case control study was conducted with the aim to study the association of H. Pylori infection with Carcinoma of Esophagus.

Methods - Total number of subjects were 100. Of which, 68 were males and 32 were females. Age of these patients varied from 30 to 80 years. Study cases consisting of both urban and rural population coming to Aditya Diagnostics and Hospital, Dibrugarh. The final selection of cases rested on the positive biopsy reports. All the selected patients for the study were biopsy proved cases of Carcinoma of Esophagus. The study data was collected from personal interview.

Results - People from the age group of 41 to 50 and 61 to 70 years were found to be more commonly affected with Carcinoma of Esophagus. Regarding H. pylori, in total sample of 100 cases, 38 were H. pylori positive and 62 were H. pylori negative. Males were found to be more frequently affected with Carcinoma of Esophagus. (Male:Female Ratio is 2.33:1). Dysphagia was the most common presenting feature seen in 90% of cases. In 9 Adenocarcinoma cases, all were found to be H. Pylori negative. This negative association is statistically significant (p value 0.009).

Conclusion - The current study revealed that incidence of the squamous cell carcinoma is very much common than adenocarcinoma in this north east region. This study showed that there is a strong negative association between H. Pylori infection and esophageal adenocarcinoma, in the small number of cases done.

BACKGROUND:

Helicobacter pylori (H. pylori) is one of the most common bacterial pathogens in humans. H. pylori infection is now recognized as a worldwide problem. But H.Pylori infection is on a fast decline in most of the western countries, mainly due to the success of therapeutic regimens and improved personal and community hygiene that prevents re-infection. While H. pylori has been disappearing from the stomach of humans, the incidence of the related disorders like acid reflux disease, Barrett’s esophagus, and esophageal cancer have been rising dramatically1.

Globally the incidence of esophageal cancer is strikingly high. Globally the incidence of esophageal cancer is sixth and ninth among cancers in men and women, respectively, and is the fifth and ninth leading cause of cancer deaths2. In India Carcinoma of Esophagus (Ca Esophagus) is the commonest among all gastro-intestinal tract malignancies, varying from 42 % to 76% in several centers3. In Assam and in Northeastern Region as a whole, Ca esophagus is one of the commonest malignancies. In a surveillance carried out by Hospital Tumour Registry, Dibrugarh (including the patients of north eastern states) under the ICMR since 1982 to 1985, incidence was found to be 15.3% which was only next to hypopharyngeal cancer 16.4%. But the more recent studies reveal that Ca esophagus has emerged as the leading cause.4

The role of Helicobacter pylori in progression to esophageal adenocarcinoma is still uncertain, but, on the basis of population data, it may carry a protective effect.5,6. It is postulated that H. pylori prevents chronic gastritis, which is a risk factor for reflux, which in turn is a risk factor for esophageal adenocarcinoma. But the effect on squamous cell carcinoma is not certain yet.7 Possible
symbiotic relationships were debated since the discovery of this pathogen. However, the debate has been intensified since few years as some studies have posed the possibility that H. pylori infection may be beneficial in some humans.8

So this study is intended to see the association of H. pylori in Esophageal carcinoma.

AIMS AND OBJECTIVES OF THE STUDY –

This hospital based, analytical case control study was conducted with the aim to study the association of H. Pylori infection with Ca Esophagus.

This study evaluated the following features of Carcinoma Esophagus and H. Pylori infection:

- Age incidence of Ca Esophagus and H. pylori infection.
- Sex ratio of Ca Esophagus and H. pylori infection.
- Different modes of Clinical presentation of Ca Esophagus.
- Incidence of H. Pylori in two common types of Ca Esophagus.

MATERIALS AND METHODS:

The study was done in indoor and outpatient clinics of Department of Medicine and in Endoscopy Department in Aditya diagnostics and Hospital, Dibrugarh during the period of 1st December, 2009 to 30th November, 2009. In the present study, total number of patients were 100. Of which, 68 were males and 32 were females. Age of these patients varied from 30 to 80 years. Study cases consisted of both urban and rural population coming to Aditya Diagnostics and Hospital, Dibrugarh.

As study was focused on Ca Esophagus and its relation with H. pylori, patients presenting with signs and symptoms of carcinoma of esophagus were subjected to endoscopic and histopathological investigations. The final selection of cases rested on the positive biopsy reports. All the selected patients for the study were biopsy proved cases of Ca Esophagus.

The study data was collected from personal interview of the patients and recording the same in study proforma. Consistent with previous studies of upper gastrointestinal cancers, we considered age (years), sex (male vs. female), history of smoking and alcohol consumption (yes vs. no) as potential confounders.

Measurements used trained personnel, a systematic protocol, an established laboratory, validated questionnaires, direct review of pathology and endoscopic examinations.

Statistical Data analysis: Consistent with previous studies of upper gastrointestinal cancers, we considered age (years), sex (male vs. female), history of smoking and alcohol consumption (yes vs. no) as potential confounders.

- Mean and standard deviation of continuous variable (age), and numbers and percentages of categorical variables (sex, history of smoking and alcohol consumption) were calculated and reported for each cancer type.
- ANOVA method with paired ‘t-test’ was used to find whether the values were statistically significant or not. Throughout the thesis, all p-values are two-sided and p-values ≤ 0.05 were considered as significant and for comparison of proportions from 2 independent samples, p value was calculated with 2-proportion z-test.
- The analysis was carried out by using Graph Pad Quick Cals online calculator.

RESULTS AND OBSERVATIONS:

In this study, the range of the cases varied from 30 to 80 years. People from the age group of 41 to 50 and 61 to 70 years were found to be more commonly affected with Ca Esophagus. In the study, out of 50 cases, 41 are squamous cell carcinoma and 9 are adenocarcinoma. That means that number of squamous cell carcinoma cases were far more than adenocarcinoma. So squamous cell carcinoma appears to be commoner than adenocarcinoma of Esophagus. (Figure-1 and figure-2)
Regarding H. pylori, in total sample of 100 cases, 38 are H. pylori positive and 62 are H. pylori negative. So more common distribution of H. pylori is negative through cases and controls. (figure-3).

Figure-3. INCIDENCE OF H. PYLORI

Males were found to be more frequently affected with carcinoma esophagus compared to the females, almost twice commonly than females. (Male:Female Ratio is 2.33:1). Similar type of sexwise variation was seen regarding H. pylori status (Male:Female Ratio is 2.08:1). (Figure-4, figure-5)

While considering clinical presentation of Ca Esophagus, Dysphagia was the most common presenting feature. Dysphagia was seen in 90% of cases. Next common in presentation was found to be Betel Nut Chewing which was seen in 78% of cases. Comparing cases and controls, Weight loss was found to be 18% of cases as compared with only 2% of controls. Alcohol intake and Smoking were not statistically significant while compared with controls although smoking was found to be more common in cases. (Figure-6, table-1)

Figure-6. CLINICAL PRESENTATION OF CARCINOMA ESOPHAGUS

Table -1. CLINICAL PRESENTATION OF CARCINOMA OF ESOPHAGUS

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>CASES</th>
<th>%</th>
<th>CONTROLS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>45</td>
<td>90.00</td>
<td>5</td>
<td>10.00</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>18</td>
<td>36.00</td>
<td>1</td>
<td>2.00</td>
</tr>
<tr>
<td>Alcohol Intake</td>
<td>19</td>
<td>38.00</td>
<td>19</td>
<td>38.00</td>
</tr>
<tr>
<td>Tobacco Chewing</td>
<td>14</td>
<td>28.00</td>
<td>10</td>
<td>20.00</td>
</tr>
<tr>
<td>Smoking</td>
<td>19</td>
<td>38.00</td>
<td>14</td>
<td>28.00</td>
</tr>
<tr>
<td>Betel Nut Chewing</td>
<td>39</td>
<td>78.00</td>
<td>26</td>
<td>52.00</td>
</tr>
</tbody>
</table>

Regarding association of Ca Esophagus with H. pylori status, 38% cases and 36% controls are H. Pylori positive. There is inverse correlation between adenocarcinoma of esophagus and H. pylori infection. In 9 Adenocarcinoma cases, all were found to be H. Pylori negative. This negative association is statistically significant (p value 0.009). It means subjects with H. Pylori infections were less likely than uninfected subjects to develop esophageal adenocarcinoma. There is no statistically significant association found between squamous cell carcinoma of esophagus and H. pylori
DISCUSSION –

In the present study, 50 cases of Ca Esophagus were studied and association between Ca Esophagus and H. Pylori was obtained. Some other features were also seen. The patients were studied from the time of admission and followed up throughout their treatment period. The results and observations were analyzed and compared with available series in the literature.

Age Distribution of Cases: It was observed that the maximum number of cases were in the age group 41-50 years (28%) and 61-70 years (28%), followed closely by the age group 51-60 years (20%). And 12% of cases were in the age groups of 31-40 years. The present study includes cases ranging from 35 years to 77 years and the mean age of the cases of Ca Esophagus was found to be 57 ± 12 years, while in case of controls, it was 55 ± 12 years.

Sex Distribution of Cases:

In the present study of 50 cases with Ca Esophagus with similar number of healthy control, there was an overall male preponderance. 35 cases (70%) were males and only 15 cases (30%) were females with similar sex distribution in control. So there is clearly male preponderance in this present study.

Martel et al. (2005) in his study also documented male preponderance with 80.4% male and 19.6% female. Wu et al. (2009) in his study found male preponderance with 95% men and only 5% women. While Corley et al. (2008) study has 73% male cases showing more male sex distribution. (Table-3)

So, the present study is comparable to the above mentioned studies with clear male preponderance. The present study shows that incidence is much common in males probably explaining the role of causative agents like alcohol and smoking which is much more common among males.

Association between Carcinoma Esophagus and H. pylori:

In this study, out of 41 squamous cell carcinoma cases, 19 were found to be H. Pylori positive i.e 46.34% are positive. And out of 9 adenocarcinoma cases, none was found to be H. pylori positive i.e. 100% of adenocarcinoma cases were H. Pylori negative.

In the present study, there is inverse association between Adenocarcinoma of esophagus and H. Pylori.
infection as p value is 0.009. So it is very statistically significant. And odds ratio (OR) using the null hypothesis showing that 6.87 with 95% confidence interval [CI] is 1.578-29.936.

There is no association between occurrence of squamous cell carcinoma and a positive H. Pylori status. It means that squamous cell carcinoma is not related with the presence or absence of H. Pylori infection.

In Martel et al. (2005) study found that a strong negative association between H. Pylori infection and esophageal adenocarcinoma. The p value for association is 0.09.

Wu et al. (2009) in a study found that H. pylori infection, assayed by HP-CSA or CagA antibodies, was statistically significantly associated with a reduced risk for esophageal adenocarcinoma. They found p value to be <0.001. (table-5)

**Table-5. STUDIES FOR ASSOCIATION BETWEEN CARCINOMA ESOPHAGUS AND H. PYLORI**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>p Value</td>
<td>Not Available</td>
<td>Not Available</td>
<td>0.09</td>
<td>&lt;0.001</td>
<td>Not Available</td>
<td>0.009</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>0.16</td>
<td>0.3</td>
<td>Not Available</td>
<td>Not Available</td>
<td>0.42</td>
<td>6.87</td>
</tr>
</tbody>
</table>

**Mode of Presentation:**

In our present study, Dysphagia was the most common presenting feature of Ca Esophagus. It was seen in 90% of cases. Next was found to be Betel Nut Chewing, in 78% of cases. And least commonly seen was Tobacco chewing which was seen in only 28% of cases of Ca Esophagus. (Table-6)

**Table-6. COMMON RISK FACTORS OF CA ESOPHAGUS**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (%)</td>
<td>71.6</td>
<td>58.3</td>
<td>87.7</td>
<td>38.0</td>
</tr>
<tr>
<td>Alcohol intake (%)</td>
<td>20.3</td>
<td>26.5</td>
<td>81.1</td>
<td>38.0</td>
</tr>
<tr>
<td>Betel nut chewing (%)</td>
<td>Not Available</td>
<td>Not Available</td>
<td>53.0</td>
<td>78.0</td>
</tr>
</tbody>
</table>

From this table, it is clear that smoking and alcohol intake are common among cases in this present study and all other studies mentioned above. Betel nut chewing was also common in Wu et al. (2009) study and very much common in present study as betel nut is very commonly chewed and available in this part of Assam and north east region of India.

Future studies are needed to evaluate whether the absence of H. Pylori infection is associated with an increased risk of oesophageal adenocarcinoma.

**CONCLUSIONS :**

The present study showed that males are affected twice commonly in Ca Esophagus and also in H. Pylori infection than females. The current study revealed that incidence of the squamous cell carcinoma is very much common than adenocarcinoma in this north east region. This study also showed dysphagia as the most common presenting feature of Ca Esophagus. Dysphagia, Weight Loss and Betel Nut Chewing were significant findings in cases. Although smoking was found to be more common in cases, Smoking and Alcohol intake was not statistically significant findings while compared with controls.

This study concluded that there is a strong negative association between H. Pylori infection and esophageal adenocarcinoma. It means subjects with H. Pylori infections were less likely to develop esophageal adenocarcinoma. Whereas there is no statistically significant association found between squamous cell carcinoma and H. Pylori infection. In view of small number of cases, these conclusions may not be absolute but emphasize upon the need for later population based studies to unravel the association of H. Pylori infection with different types of esophageal cancers.

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Developing a Medical Referral Service Laboratory for Autoimmune Diagnostics: A need for The North East Region

V Pradhan*, K Ghosh**

The immune system possesses several properties that are of fundamental importance for its normal functions. These include specificity for different antigens, a diverse repertoire capable of recognizing a wide variety of antigens, memory for antigen exposure, specialized responses to different microbes, self limitation and the ability to discriminate between foreign antigens and self antigens. A common cause of hypersensitivity reactions which are the disorders caused as a result of various immune responses is mainly failure to self tolerance. Diseases caused by failure of self tolerance and subsequent immune responses against self, or autologous antigens are known as ‘autoimmune diseases’. Autoimmunity is defined as the humoral or cellular immune response that may be mounted against one’s own tissue antigens or cells due to breakdown of self tolerance. There may be diverse clinical manifestations that may include systemic dysfunction and/or destruction of particular organ or tissues. Autoimmunity is the cause for a number of collagen vascular disorders, in many of which specific serological autoantibody markers are now established and these markers along with clinical manifestations are helpful for proper diagnosis and prognosis of the disease. The autoimmune diseases have posed a challenge to clinicians and research scientists ever since the nineteenth century. Despite the recent acquisition of extensive information relating to the mechanisms of self tolerance, still our understanding of the mechanisms leading to pathogenic autoimmunity is very much fragmentary and incomplete, though the recent immunodiagnostic advances in this field have begun to assemble the missing pieces of the puzzle.

A wide spectrum of autoimmune, rheumatological as well and kidney diseases are characterized by autoantibodies to various nuclear components like double stranded DNA, single stranded DNA, other non histone nuclear proteins like ribonucleoproteins (nRNP) as well nucleoproteins like histones and also to some cytoplasmic components of the cells. These autoantibodies which are detected in patients’ sera are good diagnostic markers at early stages of disease and prognostic as well to monitor the treatment which is specially important in this era of improved therapy and overall management of the patients with new therapeutic approaches by detecting the changes in the levels of related autoantibodies at periodic time intervals as patients with autoimmune diseases mainly show episodes of unpredictable clinical exacerbations and remissions.

The detection and estimation as well as identification of various autoantibodies may help in the diagnosis of a particular disease of autoimmune origin and sometimes they may be quite helpful in monitoring the disease activity. Autoantibody test interpretation by determining its sensitivity, specificity along with the positive and negative predictive values will allow a calculation of how useful a positive test is in facilitating or negating a diagnosis of a particular autoimmune disease. Autoantibody profiling may serve purposes including classification of individual patients and subset of patients, examination of epitope spreading and autoantibody isotype usage, discovery and characterization of candidate autoantigens, and tailoring antigen-specific therapy. In the coming decades...

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proteomics technologies will broaden our understanding of the underlying mechanisms of and will further our ability to diagnose, prognosticate and treat autoimmune disease.

A variety of technologies for autoantibody profiling have been developed. The main techniques are line-blot immunoassays, bar-coded nanoparticle immunoassays, and bead-based assays with flow cytometry detection and antigen microarrays. Some of these technologies are only able to measure a limited number of autoantibodies, while others can detect elevated numbers. Assays for antinuclear antibody specificities using line-blot immunoassays and bead-based assays with flow cytometry detection are already commercialized. Antigen microarrays for autoantibody measurement are only in the development phase, although in the not too distant future these assays will probably appear on the market. Multiplexed testing in the autoimmunity laboratory appears to have a promising future. Forming a data bank from Eastern and Western Indian patients suffering from autoimmune diseases will enable us to answer specific questions that cannot be answered by the separate centers. Finally in order to improve the medical care of these patients and extend the basic and clinical research in India to establishment of ‘Autoimmune Diagnostic Center’ for detection of patients suffering from autoimmune diseases’ is valuable.

Due to the variability of symptoms and clinical course of the disease, up until now there is a need of developing a Medical Referral Service Laboratory for Autoimmune Diagnostics in the North East region with a sufficient number of patients that will enable a good documentation of the clinical course of these collagen vascular diseases. Similarly, there is a need of establishment of autoimmune diagnostic center in the North East region that would be able by itself to address the complicated clinical and diagnostic questions that will aid in early treatment and management of patients suffering from autoimmune disease from the North East region of our country. This joint effort will further help in getting clinical and laboratory information of patients suffering from autoimmune diseases from Eastern and Western part of India. The workshops and training programs will focus on issues related to recent research activities such as discovery of biomarkers and immuno genetic factors in autoimmune disease susceptibility will be helpful to create a collaborative network that will accelerate the discovery of new biomarkers, susceptibility genes, understanding possible environmental triggers for this disease and possible targeted immune therapeutic approach. As we learn more about the genetic and environmental factors contributing to these diseases, we will be able to develop effective prevention strategies that arrest the autoimmune process before it can irreversibly damage the body. In tandem, we must advance the training of researchers so that we can effectively translate the advances in biomedical research to clinical practice.

The implementation of such basic to advanced autoimmune diagnostics facilities can be possible approaching government funding agencies and by making funds available for infrastructure development, manpower, equipments and reagents required for the diagnostic testing facilities. As most of the states in the North East such facilities are not available. The detailed study about the space requirement for the laboratory set up, number of patients clinically and serologically each medical center can detect per year and number of suspected cases that will be tested serological in every reference laboratory needs to be evaluated. Hands on training to medical students, researchers need to be provided and training workshops should be conducted on regular basis. The data generated by each center should be compiled further for the genotype and phenotypic analysis and further networking in all the states of the North East can be done so as to get the overall clinical and serological makeup of autoimmune diseases from this region.

In recent years, extensive clinical and research activities are being conducted in research centers in India to better understand etiologies of autoimmune diseases. Now it is the time to develop more specific therapeutic modalities for patients suffering from various autoimmune diseases with joint national and International collaborative efforts. There is definitely a growing interest among Indian scientists to join efforts in the deciphering of these complicated and devastating diseases. The registry of clinical data of patients with autoimmune diseases, their family history, as well as a bank of serum and DNA samples will be maintained in this project. The DNA and serum bank together with the clinical registry will enable us to use the genetic material for DNA analysis and for genotype-phenotype analysis. In this era of the human genome project, such a ‘DNA bank’ from relatively closed
populations can serve as a unique tool for the deciphering of disease-associated genes and related epi genetics in the near future.

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Hairy Plexiform Neurofibromatosis and Spinal Deformity Presenting as Recurrent RTI

B C Kalita*, U K Nath**

Plexiform neurofibroma is an uncommon skin tumor. Plexiform neurofibromas (PNFs) are benign tumors of the peripheral nerves and connective tissue, which are usually associated with neurofibromatosis type 1. We present a case of 25 years-old boy with neurofibromatosis type 1 admitted in medicine ward with recurrent lower respiratory tract infection.

On Examination:

Revealed a soft, diffuse swelling measuring 3×5 cm over the dorsum of the distal end of the right forearm with growth of thick hair on its base. Another swelling seen over the left temporal region and over the left ear with displacement of the ear bellow. Excessive hair growth was seen around this swelling also and it extended up to the left submandibular region. The lesions were non-tender and freely mobile over the underlying tissues. In addition, he had multiple hyperpigmented macules with serrated margins over the trunk (cafe au lait macules) varying in size from 0.5 to 2 cm in diameter and left axillary freckle present since his childhood. He also had multiple soft nodules in the skin (mollusca fibrosa) which were widely dispersed over trunk and limbs. There was no h/o trauma or constitutional symptoms. The sensation over the swellings were normal. No family history of similar illness. Systemic examination was normal. Patient had thoracic vertebral scoliosis and localized bony depression of the

A clinical diagnosis of Neurofibomatosis type I with hairy plexiform neurofibromas over the right hand and left temporal region with LRTI was made.

Discussion:

Neurofibromatosis types 1 and 2 (NF1, NF2) are autosomal dominant disorders that primarily affect the development and growth of nerve cell tissues.
Neurofibromatosis type 1, also known as von Recklinghausen disease, is characterized by various skin lesions and peripheral or central nervous system neoplasms.\[1\]

Plexiform neurofibroma is considered an uncommon skin tumor it usually presents at birth or during the first several years of life \[4\]. One of the most noticeable characteristics of the disease is the development of neurofibromas, especially on the trunk and limbs. Four clinically and morphologically distinct variants of neurofibromas occur in neurofibromatosis type 1- Cutaneous lesions, localized intraneural tumours, plexiform neurofibromas and massive soft tissue neurofibromas. Cutaneous neurofibromas present as sessile and dome-shaped, sometimes pedunculated, flesh-coloured, and with soft papules or nodules. Patients with cutaneous neurofibromas are usually asymptomatic, but they can be pruritic. On the other hand, subcutaneous neurofibromas are usually larger than dermal lesions and consist of fusiform swelling that occurs along the sheaths of peripheral nerves. They do not infiltrate surrounding tissues but can grow to an enormous size.

About 95% of patients have discrete benign neurofibromas. These lesions do not usually develop before adolescence, may be quite variable in size, and may increase in number, as the patient grows older. The plexiform variant of neurofibromas involves single or multiple nerve fascicles that often arise from the branches of major nerves and form a mass of tangled, rope-like structures that feel similar to a “bag of worms” on palpation and can be associated with massive soft-tissue overgrowth, leading thus to functional impairment. Most plexiform neurofibromas are present at birth or become apparent during the first years of life in 30% of patients diagnosed with neurofibromatosis type 1 \[3\].

Although the clinical manifestations of NF1 are well known \[5\], the course of the condition in individual patients is largely unpredictable. This unpredictability and the general progression of the disease is a major concern for most patients with NF1 and their families \[6\].

NF1 primarily affects the peripheral nervous system and is often characterized by large numbers of neurofibromas.

NF2 causes a different kind of swelling involving the nerve sheath, called schwannoma. Schwannomas occur often around the nerve for hearing and balance: the acoustic nerve. So NF2 really doesn’t cause neurofibromatosis at all, although it used to be thought that it did. NF1 and NF2 generally do not happen in the same person, or even in the same family, and NF1 does not turn into NF2. They are totally separate conditions. NF1 is far more common than NF2.\[1\]

**Diagnostic Features of Neurofibromatosis**

<table>
<thead>
<tr>
<th>Table 1: Criteria for diagnosis of NF1:</th>
<th>Fulfilling at least two of seven criteria makes a diagnosis of NF1.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Six or more café-au-lait spots that are greater than 1.5 cm in postpubertal individuals or 0.5 cm or larger in prepubertal individuals</td>
<td></td>
</tr>
<tr>
<td>• At least two neurofibromas of any type or at least 1 plexiform neurofibroma</td>
<td></td>
</tr>
<tr>
<td>• Freckling in the axilla or groin (Crowe’s sign)</td>
<td></td>
</tr>
<tr>
<td>• Optic glioma</td>
<td></td>
</tr>
<tr>
<td>• At least two Lisch nodules (benign iris hamartomas)</td>
<td></td>
</tr>
<tr>
<td>• A distinct bony lesion including sphenoid wing dysplasia or thinning of the long bone cortex</td>
<td></td>
</tr>
<tr>
<td>• A first-degree relative with NF1</td>
<td></td>
</tr>
</tbody>
</table>


The problem with bone development can be characteristic of neurofibromatosis- and help in making the diagnosis is curvature of long bones, especially the tibia (shinbone). This is generally present at birth, and will not appear later in life if it is not present at birth. When it occurs, it can cause weakening—and even fracture.\[3\]

Plexiform neurofibromas are diffuse, elongated fibromas coursing along the nerves. These lesions frequently involve the trigeminal or upper cervical nerves. Plexiform neurofibromas often appear within the first 2 years of life\[2\]. There are two types of plexiform neurofibromas, nodular and diffuse\[3\]. Diffuse plexiform neurofibroma, also known as elephantiasis neurofibromatosa\[2\], has an overgrowth of epidermal and subcutaneous tissue associated with a wrinkled and pendulous appearance. Plexiform neurofibroma occurs in only 5 percent of patients with NF1 \[3\].

Plexiform neurofibromas need to be monitored frequently because 5 percent develop into malignant...
peripheral nerve sheath tumors \[3\]. Other complications include bleeding from trauma, neurological deficits, limited limb, and psychological disturbance because of abnormal anatomy. In each of the above complications surgery might be helpful.

**Conclusion:**

Large hairy pigmented lesion is a rare and atypical aspect of superficial and plexiform neurofibroma during neurofibromatosis type 1. The combination of thoracic spinal deformity with the plexiform neurofibromatosis may be the cause of repeated lower respiratory tract infection in this particular case. To the best of our knowledge this manifestation of von Recklinghausen’s neurofibromatosis has not been previously described. A biopsy may be useful if it is necessary for the diagnosis of the disorder.

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A Case of Autosplenectomy in Sickle Cell Disease


ABSTRACT:
A 22 year old male presented in Assam Medical College and Hospital with severe body ache following strenuous exercise. Laboratory parameters showed mild anemia and Hb typing revealed sickle cell anemia. The CT scan of abdomen had features suggestive of autosplenectomy. Sickle cell anemia is a common entity here and early diagnosis is important for proper management of the patients and prevention of the ‘vasoocclusive crisis’.

KEY WORDS: Sickle cell disease, Autosplenectomy, Hb.

Introduction: Sickle-cell disease is one of the most common severe monogenic disorders in the world. Hb polymerisation, leading to erythrocyte rigidity and vaso-occlusion, is central to the pathophysiology of this disease. Recurrent episodes of vaso-occlusion and inflammation result in progressive damage to most organs, including the brain, kidneys, lungs, bones, and cardiovascular system, which becomes apparent with increasing age.1

History: A 22 year old male presented in the casualty of Assam Medical College and Hospital with sudden onset of severe body ache for 3 days following swimming. On detailed history from the patient and his attendant we found the patient to have similar episodes in the past which were usually preceded by strenuous exercise like brisk walking, swimming, playing and also following excessive sweating. There were no significant symptoms other than pain associated with the episodes. The episodes were self limiting with relapses usually less than 3 per year. He has a past history of jaundice once, and trauma to the chest on separate occasions and on both the occasions he got admitted in local hospital.

Examination: The only significant finding on general examination was presence of Icterus and the vitals were stable. Pallor was absent. On systemic examination of abdomen we found tenderness over the epigastrium only. The examination of the other systems did not reveal any abnormality.

Investigation: The patient was admitted and evaluated as in-patient. His routine examination findings were Hb-9 g%. TC- 13,800/ cumm, DLC- Polymorphs-78, lymphocytes- 20, monocyte- 1, eosinophil -1 and basophil- 0. MCV-86 μ, MCH- 29 μg, MCHC- 34 %. PBS showed moderate degree of hypochromia and fair number of target cells. Urine routine examination did not reveal any abnormality. Liver function showed Total bilirubin- 6.4 mg/dl conjugated bilirubin- 0.4 mg/dl, unconjugated bilirubin 6.0 mg/dl. AST- 190 IU/L, ALT- 48 IU/L, GGT- 36 IU/L., Total serum protein- 6.2 g/dl, Albumin- 3.2 g/dl and globulin-3.0 g/dl, serum sodium-129 mmol/L and serum potassium- 4.2 mmol/L. Rapid test for Pf HRP – 2 antigen and Pv specific pLDH were negative. With this background we were prompted to investigate the patient in the line of haemolytic anemia, Hb typing was sent which showed sickle cell anemia with high fetal haemoglobin. His CXR showed a left sided hypoplastic cervical rib. USG findings were sludge in the gall bladder and the spleen could not be visualised. CT scan of the abdomen showed shrunken spleen and multiple punctuate calcifications suggestive of autosplenectomy as sequel of splenic infarcts, and the visualised vertebral
bodies showed marked sclerosis and central end plate depression leading to “H” shaped configuration as a sequelae of central vertebral body infarction (a section given below).

**Treatment:** After evaluating the patient we diagnosed the patient as a case of sickle cell disease in crisis and as per the guidelines we treated him with intravenous hydration and oral hydration and intravenous antibiotics. For pain he was prescribed intravenous tramadol. He was vaccinated against Pneumococcus. We counselled him regarding the disease and the possible measures for prevention of future ‘crisis.

**Discussion:** Sickle cell disease is prevalent in many parts of India, where the prevalence has ranged from 9.4 to 22.2% in endemic area.2

The sickle cell syndromes are caused by a mutation in the \( \alpha \)-globin gene that changes the sixth amino acid from glutamic acid to valine. Unlike normal and most abnormal Hb, deoxygenation of sickle cell Hb produces drastic alterations in the normally pliant erythrocytes’ shape and plasticity. The rigid, deformed erythrocytes may become trapped in the small blood vessels, resulting in the so-called “log-jam” occlusion. Chronic anemia, vascular stasis, and vasoocclusion combine to produce the many complications of sickle cell disease.3-6

Sickle cell anemia causes autosplenism by causing hypoxia and infarcts in the spleen. Since blood flow in the spleen is sluggish, the oxygen tension is low. When red blood cells with hemoglobin S are exposed to this low oxygen tension they tend to aggregate and polymerize. Sickled cells also express more adhesion molecules and appear more sticky. The sickle cells arrest in the hypoxic vascular bed in the spleen, resulting in a vicious cycle: decrease in O2, sickling and vascular obstruction from thrombus formation. Initially the spleen is enlarged, then progressively becomes smaller. The stasis of flow in the spleen causes hypoxic damage, thrombosis, infarction and fibrosis. In the end the spleen “disappears” completely (termed ‘autosplenectomy’).7-8

Babadoko A. A et al concluded anatomical autosplenectomy is not an uncommon finding in SCA patients. Usually in sickle cell disease autosplenectomy starts in childhood and complete autosplenectomy occurs by the age of 8. This may be related to inadequate clinical care due to the lack of good health education, ignorance, poverty, and poor standard of care, as well as the lack of newer therapeutic agents.9

This patient is a classical presentation of sickle cell disease where there is autosplenectomy.

**Conclusion:** Here in this part of India hemolytic anemia and hemoglobinopathy with various permutation and combination is a very common entity due to the mixed cultural and geographical background of people particularly among the tea garden working population. Many of these people with this Hb abnormality remain undiagnosed and remain deprived from proper treatment. This also deprives us from great knowledge of various presentations of this abnormality.

**Acknowledgement:** We are thankful to the Superintendent, Assam Medical College & Hospital for allowing us to publish the hospital records.

**REFERENCE:**


A Case of Sheehan’s Syndrome

G Kar, P Bhattacharjee*, D Deb, K Bhattacharjee**, B Thakuria***, K Chakraborty****, P Roy*****

ABSTRACT:
Sheehan’s syndrome is a well known cause of panhypopituitarism secondary to pituitary apoplexy, that generally occurs after an intra or postpartum bleeding episode characterized by severe hypotension or haemorrhagic shock. It is one of the most common causes of hypopituitarism in underdeveloped or developing countries. A 35 years old female patient presented with dizziness, fatigueability, amenorrhea, weight loss since 2007 following her childbirth. Serum Cortisol level was below normal range, free T3 and T4 level were below normal range, TSH level was inappropriately normal. She was diagnosed as a case of Sheehan’s syndrome and started on prednisolone and thyroxine.

KEY WORDS: Sheehan’s syndrome, Serum Cortisol, TSH, T3, T4.

Case Report
A 35 year-old lady, from Binbasti, Lakhipur, district of Cachar, presented to our hospital with lethargy, loss of weight and appetite, and alternating diarrhoea and constipation, amenorrhea for last six years. The patient had noticed progressively increasing weakness, skin pallor, cold intolerance and gradual loss of weight for the past several years before she came to our hospital. On further inquiry, the patient gave history of heavy vaginal bleeding following home delivery of a child on 2007. Immediately after the event the patient had become very sick and she was hospitalised to a nearest health centre where two units blood transfusion was given. The newborn baby died following delivery. The patient recalled that she never again had menstrual cycle and no breast milk discharge after that incident.

On examination, the patient looked sick, thin build, pale with sunken eyes. The pulse was 72/min and blood pressure was 70/50mmHg (supine). The skin was pale with absence of hair from skin, axillae, and groin. There was presence of wrinkles over forehead. There was generalised muscle wasting. She was dehydrated. Examination of the respiratory system, cardiovascular system, abdomen were normal. Examination of the central nervous system revealed depression, emotional lability and delayed relaxation of the ankle reflexes, the remaining examination was normal including fundoscopy.

Figure 1 : MRI of the brain showed partially empty sella with CSF entering inside sella.
Investigations revealed a haematocrit of 22% (with normocytic normochromic red cells), total WBC count was 4100/IL with a normal differential count, urea was 10 mg/dL, creatinine 0.8 mg/dL, Na+ 134 mEq/L, K+ 3.8 mEq/L, urinary specific gravity 1.004. Lipid profile was in normal range.

Other investigations showed free T3 .41 pg/mL, free T4 0.11 ng/dL, thyroid stimulating hormone (TSH)1.074I-lu/ mL, serum cortisol (at 8 am) 2.70l-lg/dL. Chest x-ray and abdominal ultrasound were normal.

MRI of the brain showed partially empty sella with CSF entering inside sella. There was no abnormality in hypothalamic, suprasellar, or para-sellar regions in the MRI.

Sheehan’s syndrome refers to postpartum hypopituitarism as a result of pituitary necrosis occurring during severe hypotension or shock secondary to massive bleeding during or just after delivery. Though first described by HL Sheehan in 1837, it was known as Simmond’s disease until 1939 when Sheehan described that the disease was due to postpartum necrosis of the anterior pituitary following postpartum haemorrhage. Owing to improved obstetric care and effective management of postpartum haemorrhage in more developed countries, the prevalence of Sheehan’s syndrome is decreasing. However, in a developing country like India, it is still encountered at times as postpartum bleeding is common and timely intervention is not possible in many remote and rural areas. The underlying process leading to Sheehan’s syndrome is the infarction of the physiologically enlarged pituitary gland, particularly anterior lobe, secondary to the grossly decreased blood supply during intrapartum or postpartum haemorrhage. The clinical presentation of Sheehan’s syndrome ranges from long-standing non-specific features such as weakness, fatigue, and anaemia to profound abrupt hypopituitarism resulting in coma and death. The mean duration between postpartum bleeding and the subsequent development of symptoms varies from 1 to 33 years; Clinical features are the result of the deficient hormones that may be single or many, but symptoms due to GH deficiency usually appear earliest. Our patient had clinical features consistent with GH, ACTH and TSH deficiency. Although failure of postpartum menstruation due to deficiency of FSH and LH is quite common, spontaneous pregnancies have been reported. This may be possible because of continual production of gonadotrophins, a little in amount but sufficient for ovulation.

The diagnosis of Sheehan’s syndrome is based on the features of hormone deficiency, a suggestive obstetric history, and decreased basal hormone levels (free T3, free T4, TSH, cortisol, ACTH, FSH, LH, oestrogen, prolactin and insulin like growth factor-1). The presenting symptoms, though vague, were suggestive of hypopituitarism in our patient. The delay in diagnosis as probably due to her vague symptoms, delayed reporting and inconsistent obstetric history. A dynamic pituitary function test like insulin tolerance test (ITT) is helpful to assess the pituitary reserve of GH and ACTH. MRI or CT of pituitary often shows an empty sella in the late stage of the disease. The treatment of Sheehan’s syndrome is replacement of the deficient hormones. ACTH and TSH deficiencies should be replaced with glucocorticoids and thyroxine respectively; mineralocorticoid replacement is usually not required. Our patient showed a remarkable improvement with steroid (prednisolone) and thyroxine within a few days. Sex hormone replacement is important in premenopausal patients and GH replacement has shown improved lipid profile and quality of life in these patients.

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 Childhood stroke is a neglected area of both professional and general population, lacking awareness of the problem and its consequences. Stroke is among the top 10 causes of death in childhood. More than half of the surviving children have long-term neurological sequelae. Ischemic stroke (IS) includes arterial ischemic stroke and cerebral venous thrombosis with venous infarction. Haemorrhagic stroke (HS) includes intracerebral haematoma or subarachnoid haemorrhage. Intracerebral haemorrhage (ICH) in children is relatively less common as compared to adults. Also there are limited studies about ICH in children. Although considered rare, stroke is more common in children than brain tumours. Stroke in children is rarely due to traditional stroke risk factors such as hypertension and diabetes mellitus, rather stroke in this age group typically results from simultaneous occurrence of multiple stroke risk factors, the presence of which necessitates a thorough evaluation to determine the cause of disorder. However, even after thorough evaluation one third cases remains undiagnosed; We are reporting a case of ICH in a 13 years old girl which remains of unexplained origin even after thorough evaluation.

CASE REPORT
 A 13 year old girl presented with sudden onset headache and vomiting followed by left sided hemiplegia, however there was no seizure or loss of consciousness at onset, also there was no history of any trauma or fever. On physical examination, her pulse rate was 76/min, regular and blood pressure was 110/70mmHg. On nervous system examination, she had left sided hemiplegia with left sided UMN type of seventh nerve palsy with extensor plantar response. However, patient was conscious and oriented. Other cranial nerves were normal and without normal. ANA was negative and serum homocysteine level was within normal limit.

 However after symptomatic and supportive treatment, she rapidly improved within a period of 15 days.

DISCUSSION:
 Stroke is an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause and stroke has

Unexplained Hemorrhagic Stroke in Thirteen years old Girl

CT brain showing acute intracerebral haemorrhage
occurred if neurological signs and symptoms last for more than 24 hours. Stroke is relatively less common in children as compared with adults. Cerebrovascular disorders are an important cause of mortality and chronic morbidity in children. The reported incidence of asymptomatic and symptomatic intracerebral haemorrhage varies from study to study probably due to differences in populations studied and differences in the sensitivity and timing of diagnostic imaging used. International incidence rates for childhood stroke have ranged from 1.3 to 13 per 100,000 children.

Ischaemic stroke is probably more common than haemorrhagic stroke in children. Clinical presentation of stroke in children varies accordingly age and location of stroke. Over 100 risk factors for stroke in children have been reported but in up to one-third of cases no cause is identified. Over half of children with stroke will develop lifelong cognitive motor disability and up to one-third will have recurrent stroke.

Intracerebral haemorrhage may be either traumatic or nontraumatic (spontaneous intracerebral haemorrhage). In the paediatric age group, intracerebral hemorrhage is not common. From the most frequent causes for spontaneous intracerebral haemorrhage (SICH) in children are vascular malformations. Other causes of SICH include: haematological diseases such as coagulopathies or thrombocytopenia, cerebral tumors and rare entities like Moyamoya disease, septicemia or drug abuse. Arteriovenous malformations (AVMs) account for 14% to 46% of hemorrhagic stroke in children and nearly 50% of intraparenchymal hemorrhage.

Hematologic abnormalities are reported to be the major risk factor in 10% to 30% of hemorrhagic strokes in most series. Hematologic causes of intraparenchymal haemorrhage include idiopathic thrombocytopenic purpura (ITP), acute lymphoblastic leukaemia (ALL), sickle cell anaemia (SCA), hemophilia, and coagulopathies. Brain tumors are also found to be one of the causes of ICH in children with a much lower incidence than previously mentioned include: motor deficit, sensory deficit, speech problems, cranial nerves palsies, cerebellar manifestations, visual abnormalities and pupillary changes. Irritability and fits may occur in about 6-9% of intracerebral hemorrhages.

The haemorrhage may expand within minutes or few hours and act as a solid mass, increasing the intracranial pressure. Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Conventional Angiography and Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) may be needed to establish the diagnosis of intracranial vascular anomalies. In cases of bleeding in children, the coagulation profile should be checked to exclude coagulation disorders and ole that may develop as a result of thromboplastin release from the damaged brain tissue.

Management of ICH in children depends on the location of haemorrhage, the volume of the hematoma, the presence of mass effect, the clinical condition of the patient as well as the etiological factors involved in the bleeding.

As already mentioned, even after thorough evaluation of ICH in children one-third cases remained of unknown etiology. In our patient as well even after excluding the common causes of ICH in children, etiology remains unexplained. More research and studies are required to find out those unexplained causes.

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