Elevated serum hyaluronic acid and interleukin–6 levels in patients with mushroom poisoning admitted to the emergency department

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ABSTRACT

الأهداف: تقييم الاستخدام الممكن لحمض الهيالرونيك (HA) وإنترليوكين6- (IL–6) معاً كمؤشر كيميائي حيوي لتلف الكبد بتسمم المشروم (MP).

الطريقة: أجريت دراسة شملت المرضى المصابين بتسمم المشروم (MP) والذين تم إدخالهم قسم الطوارئ بمستشفى مايس أوندوكوز الجامعي – سامسون – تركيا، خلال الفترة ما بين أبريل 2005م وحتى أبريل 2007م. شملت الدراسة 27 مريضاً مصاباً بتسمم المشروم (MP). تم تحديد مستوي مصل (HA) و(IL–6) لدى المرضى باستعمال طريقة الإنزيم المتصل المناعي يومياً لمدة ثلاثة أيام. احتوت مجموعة التحكم عشرة أفراد سليمين من أجل العمل كمجموعة تحكم. قُسم المرضى إلى ناجيين والغير ناجيين.

النتائج: لم يكن هنالك فرقاً ملحوظاً بين المرضى ومجموعة التحكم وفقاً لمستويات (HA) عند الدخول (p>0.05)، ولكن مستويات (IL–6) عند الدخول كانت أعلى بشكل ملحوظ لدى المرضى عن مجموعة التحكم (p<0.01). كانت مستويات مصل (HA) و (IL–6) عند الدخول وفي الأيام التالية أعلى بشكل ملحوظ لدى المرضى الغير الناجيين (عدد=5) من المرضى الناجيين (عدد=22) (p<0.05). كان هنالك علاقة ملحوظة بين مستويات (HA) و (IL–6) عند الدخول (r=0.42, p<0.05). كما كان تركيز (HA) متصل بشكل ملحوظ مع (AST)، (ALT) ومستويات الكرياتين خلال فترة الملاحظة. ازداد مستوى مصل (HA) و (IL–6) لدى المرضى الغير ناجيين خلال فترة الملاحظة.

خاتمة: إن زيادة مصل (HA) ومستويات (IL–6) مصاحبة لتلف الكبد في التسمم بالمشروم (MP). قد يكون (HA) مؤشراً مفيداً في تقييم فشل الكبد الحاد المحرض بواسطة (MP) في الممارسة السريرية.

Objectives: To assess the possible use of hyaluronic acid (HA) and interleukin–6 (IL–6) together as a biochemical marker of liver damage in mushroom poisoning (MP).

Methods: We prospectively studied patients with MP who were admitted to the emergency service, between April 2005 and April 2007, Samsun, Turkey. Twenty-seven patients with MP were included in the study. Serum HA and IL–6 levels of the patients were determined using enzyme-linked immunosorbent assay daily for a total of 3 days. Ten healthy adults were included in the study to serve as controls. The patients were divided into survivors, and non-survivors.

Results: There was no significant difference between the patients and controls with respect to serum HA levels on admission (p>0.05). However, IL–6 levels on admission were significantly higher in the patients than the control group (p<0.01). Serum HA and IL-6 levels on admission, and the following days were significantly higher in non-surviving patients (n=5) than in surviving patients (n=22) (p<0.05). There was a significant correlation between HA and IL–6 (r=0.42, p<0.05) on admission. The HA concentration was also significantly correlated with aspartate aminotransferase, alanine aminotransferase, and creatinine levels during the observation period. Serum HA and IL-6 levels increased in non-surviving patients throughout the period of observation.

Conclusion: Increased serum HA and IL-6 levels are associated with hepatic damage in acute MP. Hyaluronic acid may be a useful marker in the assessment of MP-induced acute liver failure in clinical practice.

Saudi Med J 2009; Vol. 30 (5): 656-661

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Received 17th January. Accepted 12th April 2009.

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Patients with mushroom poisoning (MP) have a spectrum of clinical presentations ranging from mild gastrointestinal symptoms to major cytotoxic effects resulting in organ failure and death.[1] The clinical outcomes range from complete recovery to liver transplantation (LT) requirement as a result of fulminant hepatic failure (FHF).[2,3] Therapeutic options employed to treat MP include: gastrointestinal decontamination, fluid resuscitation, oral activated charcoal, antiemetics, intravenous (iv) atropine, iv benzodiazepines for seizure control, hemoperfusion, or hemodialysis, mechanical ventilation for respiratory failure, silibinin, N-acetyl cysteine (NAC), iv benzyl penicillin and the molecular adsorbent recycling system (MARS).[1-4] When all of these treatment modalities fail, LT is the only option.[4] Serum transaminases, which are commonly used as markers in assessment of MP begin to increase 36-72 hours after ingestion of mushrooms that contain gyromitrin and amatoxin.[5] Unfortunately, these well known hepatic markers cannot provide enough information on the liver damage in the early phase of liver failure due to MP, such as amatoxin. Therefore, more useful biochemical markers are needed to help in assessment of the clinical status of the patients with MP in emergency clinical practice. Hyaluronic acid (HA) is an acidic polysaccharide with high molecular weight. It is detectable in body fluids and virtually all connective tissues, including the liver, where it is synthesized mainly by fibroblasts and hepatic stellate cells.[6] Elimination of HA from the circulation is achieved by a specific receptor-mediated mechanism on hepatic sinusoidal endothelial cells.[7] During liver disease, the removal of HA is impaired by the loss of hepatic sinusoidal cell function. As a result, it has been suggested that HA may be a useful marker of liver damage in primary biliary cirrhosis,[8] major hepatectomy,[9] and paracetamol-induced hepatotoxicity.[10,11] Interleukin–6 (IL–6) is a pro-inflammatory cytokine that plays an important role in the host defense mechanism. Serum IL–6 levels are low in physiological conditions, but increase considerably in pathological conditions such as trauma, inflammation, and neoplasia.[12] In the literature, it has been reported that serum IL-6 levels increase in various liver diseases, such as cirrhosis,[13] chronic hepatitis,[14] FHF and acute hepatitis.[15-17] Taken together, HA and IL-6 could be considered as a marker of hepatic damage in MP. To the aim of this study was to investigate the possible use of serum HA and IL-6 as biochemical markers of liver damage in patients with MP.

Disclosure. *This work was supported by Ondokuz Mayis University Research Fund, Samsun, Turkey.*

Methods. ***Patients.*** Various types of wild mushrooms containing amatoxins such as *amanita phalloides, galerina autumnalis*, grow in our region, and consumption by the local population is common. We prospectively studied patients with MP who were admitted to Ondokuz Mayis University emergency service between April 2005 and April 2007, Samsun, Turkey. Patients who had ingested wild mushrooms were included in the study. All patients received full liver intensive care, which included fluid resuscitation, gastric decontamination, administration of multiple doses of activated charcoal, iv benzyl penicillin, and NAC or hemodialysis in the emergency intensive care unit. Serum HA and IL–6 levels of the patients were studied for a 3-day period. In addition, blood was taken from[10] healthy adults to serve as the normal control group. Routine laboratory parameters of the patients were also recorded during the observation period. The local ethics committee approved the study protocol, and informed consent was obtained from all patients.

Measurement of serum HA and IL–6. Peripheral blood samples were collected daily from patients from indwelling catheters, with the first 1–2 ml being discarded, or else by venipuncture if no other access was possible. Blood samples were centrifuged at 3500 g for 15 minutes. After centrifugation, part of the sera was used to assess the main parameters of liver function by routine methods. The remaining 1 mL serum was stored at -80°C until the final analysis for HA and IL–6 assessments. Measurement of HA and IL–6 was performed by enzyme-linked immunosorbent assay (ELISA). The HA serum levels were assessed by a commercially available HA test kit (Corgenix Inc., Westminster, CO, USA). Serum IL–6 levels were determined using a commercially available kit (Quantikine, Human IL–6, R & D Systems, Minneapolis, MN, USA) in accordance with the manufacturer's instructions.

Statistical analysis. For the data obtained in our study were not normally distributed, we used median (minimal– maximal) as descriptive statistics and Mann-Whitney U test to compare the 2 groups, although it needs data to be normally distributed and it depends on mean ± 2 SEM (95% CI), we also performed the confidence interval test to compare the groups. Correlation analysis was performed with Spearman's correlation coefficient test. The daily differences in IL–6, and HA were evaluated using non-parametric Friedman variance analyses and Wilcoxon signed rank test. A p-value less than 0.05 was used to indicate statistical significance. All statistical calculations were carried out by using SPSS, for Windows 11.0 (SPSS Inc. Headquarters, Chicago, IL, USA) software program.

Table 1 - The initial laboratory tests on admission in patients with mushroom poisoning.

Parameter	Median (min-max)		Normal Range
AST (U/L)	26.0	(13.0 - 240.7)	8 - 46
ALT (U/L)	21.6	(9.4 - 184.1)	7 - 46
Total bilirubin (mg/dl)	0.7	(0.1 - 3.7)	0.1 - 1.5
Conjugated bilirubin (mg/dl)	0.8	(0.04 - 2.7)	0.0 - 0.4
Creatinine (mg/dl)	0.8	(0.5 - 2.6)	0.4 - 1.4
aPTT (second)	27	(23 - 48.1)	22 - 35
INR	1.1	(0.9 - 2.8)	0.8 - 1.1

AST - serum aspartate aminotransferase, ALT - serum alanine aminotransferase, aPTT- active partial thromboplastin time, INR- international normalized ratio

Results. Twenty-seven patients (median age 47 years, min-max 18–66 years; 8M:19F) were studied. The initial laboratory tests of the study population are shown in (**Table 1**). Although reliability of reporting is often questionable, the median admission time of the patients to our ED was 7 hours (2-16 hours) after mushroom ingestion. One patient died, and 4 patients were transferred to other centers for LT. These patients fulfilled the King's College Hospital criteria[3] for transplantation, and it was assumed that they would have died otherwise. So, for statistical analysis, they were grouped with the patients who died.[10] The remaining 22 patients survived to hospital discharge. There was

Table 2 - Serial measurement of serum HA (ng/ml) in patients with mushroom poisoning

Patients studied	Day 1		Day 2		Day 3	
	Mean	(range)	Mean	(range)	Mean	(range)
All patients (n=27)	34.6	(12.5 - 93.8)*	38.0	(11.9 - 275.3)	41.0	(15.1 - 484.0)
Survivors (n=22)	28.8	(12.5 - 69.1)*	31.5	(11.9 - 75.3)	33.0	(15.1 - 68.5)
Non-survivors (n=5)	61.2	(28.2 - 93.8)†‡	156.0	(139.8 - 275.3)‡	260.4	(169.8 - 484.0)‡
Controls (n=10)	19.2	(11.0 - 68.0)				

All patients on day one have a mean±SD of 35.7 ± 3.8§ (95% confidence interval of 28.1 - 43.3).
Controls on day one had a mean±SD of 18.2 ± 4.3§ (95 confidence interval of 9.6 - 26.8).
*p>0.05 compared to control values; †p<0.05 compared to control values; ‡p<0.05 compared to survivors.
§p<0.05 compared to control values

Table 3 - Serial measurement of serum IL–6 (pg/ml) in patients with mushroom poisoning.

Patients studied	Day 1		Day 2		Day 3	
	Mean	(range)	Mean	(range)	Mean	(range)
All patients (n=27)	6.2	(2.5 - 82.5)*	0.2	(3.6 - 199.5)	9.5	(3.1 - 141.5)
Survivors (n=22)	5.6	(2.5 - 29.6)*	8.1	(3.6 - 31.0)	9.0	(3.1 - 30.1)
Non-survivors (n=5)	25.5	(5.7 - 82.5)*†	46.5	(12.5 - 199.5) *	109.1	(54.0 - 141.5) *
Controls (n=10)	3.1	(2.5 - 12.1)				

All patients on day one have a mean±SD of 12.8 ± 3.2§ (95% confidence interval of 6.4 - 19.2).
Controls on day one had a mean±SD of 4.3 ± 0.9§ (95 confidence interval of 2.5 - 6.1).
*p<0.05 compared to control values; †p<0.05 compared to survivors. §p<0.05 compared to control values

Table 4 - Correlation between serum hyaluronic acid and other laboratory tests and in serial measurements.

Laboratory tests	Day 1	Day 2	Day 3
AST	0.468*	0.652*	0.523*
ALT	0.477*	0.589*	0.545*
Total bilirubin	0.254	0.328	0.445*
Conjugated bilirubin	0.291	0.342	0.490*
aPTT	0.182	0.482*	0.493*
Creatinine (mg/dl)	0.685*	0.584*	0.512*
INR	0.086	0.387*	0.346
IL–6	0.424*	0.228	0.289

AST - serum aspartate aminotransferase, ALT - serum alanine aminotransferase, aPTT - active partial thromboplastin time, INR - international normalized ratio, IL-6 - Interleukin–6. *p<0.05 by calculating Spearman's correlation coefficient

Table 5 - Correlation between serum IL–6 and liver function tests in serial measurements.

Laboratory tests	Day 1	Day 2	Day 3
AST	0.104	0.317	0.401*
ALT	0.206	0.402*	0.344
Total bilirubin	0.323	0.729*	0.505*
Conjugated bilirubin	0.084	0.257	0.485*
aPTT	0.601*	0.510*	0.588*
Creatinine	0.171	0.376	0.447*
INR	0.155	0.212	0.419*

AST - serum aspartate aminotransferase, ALT - serum alanine aminotransferase, aPTT - active partial thromboplastin time, INR - international normalized ratio. *p<0.05 by calculating Spearman's correlation coefficient

no significant difference between the patients and controls with respect to serum HA levels on admission. However, HA on admission was significantly higher in non-surviving patients than in the surviving patients and controls (p<0.05) Although no significant difference was found between the patients and controls with respect to serum HA levels on admission with Mann Whitney U test, a statistically significant difference was found with confidence interval test (**Table 2**). Serum IL–6 levels of the patients on admission were significantly higher than control group (median 3.1 pg/ml, range 2.5–12.1 pg/ml; p<0.01) in both of Mann Whitney U and confidence interval tests. Moreover, IL-6 levels on admission were significantly higher in non-surviving patients than in the surviving patients (p<0.05) (**Table 3**). There was a significant correlation between HA and IL–6 (r=0.42, p<0.05) on admission as well as between HA and aspartate aminotransferase (AST) (r=0.47, p<0.05), alanine aminotransferase (ALT) (r=0.48, p<0.05), and creatinine (r=0.68, p<0.05) (**Table 4**). There was a significant correlation between IL-6 and activated partial thromboplastin time (aPTT) (r=0.60, p<0.05), but not with any other parameters on admission (**Table 5**).

Serial measurements.

Serum HA: The HA concentration significantly correlated with AST, ALT, aPTT and creatinine levels throughout the period of observation, but not with IL-6 on days 2 and 3 (**Table 4**). There were significant differences in HA levels between the surviving and non-surviving patients on days 2 and 3. There was a statistically significant increase in HA on day 3 after admission in non-surviving patients (p<0.05) (**Table 2**). Serum HA levels increased continuously in non-surviving patients throughout the period of observation (**Figure 1**).

Serum IL–6: The IL–6 concentration positively and significantly correlated with total bilirubin and aPTT on days 2 and 3 (**Table 5**). There were significant differences in IL-6 levels between the surviving and non-surviving patients on days 2 and 3 (**Table 3**). There was a statistically significant increase in IL–6 on day 3 after admission in non-surviving patients (p<0.05). Serum IL-6 levels increased continuously in non-surviving patients throughout the period of observation (**Figure 2**).

Clinical course. All surviving patients were discharged from hospital in a median of 3 days (range 2–7 days). Non-surviving patients, despite exhibiting abnormal liver function tests, did not become encephalopathic. In the non-surviving group (n=5), one patient died due to massive gastrointestinal bleeding during the transfer to another center for LT on day 4. The other 4 patients were transferred on day 3. We have learned that one of them underwent LT and recovered, another 3 patients died because the appropriate liver was not available in another center.

Discussion. Mushroom poisoning may present varying degrees of digestive and hepatic involvement depending on the type and quantity of the mushrooms ingested.[18] Intoxication with mushrooms containing amatoxin (amanita, lepiota, and galerina species) may progress into acute liver failure and finally death.[19] The gold standard of treatment for liver failure is LT.[20] In the present study, determination of the exact type of mushroom was not available. Therefore, diagnoses were based on the patient's relevant history, symptoms and physical examinations. We think the 5 non-surviving patients in this study might have ingested mushrooms containing amatoxin.

The HA is cleared very rapidly by the normal liver with a half-life of 2-5 minutes; thus, very high levels measured up to 1000 times higher than normal indicate a profound failure due to impaired production and/or clearance of HA.[10] The HA clearance systems utilizing

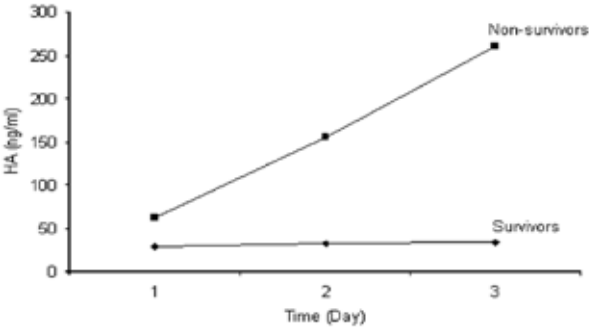

Figure 1 - Serial serum hyaluronic acid (HA) levels in survivors compared to non-survivors, median values are shown.

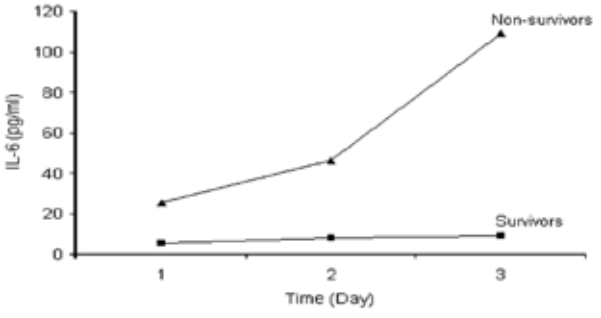

Figure 2 - Serial serum interleukin–6 levels in survivors compared to non-survivors, median values are shown.

the hyaluronan receptor for endocytosis (HARE) in lymph nodes and the liver keep the normal steady-state HA concentration in blood very low.[21] The impaired clearance of HA may therefore be due in part to defects and/or binding of the HA receptors to sinusoidal endothelial cells.[10] Decreases in HA uptake and degradation may be due to endothelial cell injury or to fibrosis-induced capillarization of sinusoids.[22] This may reflect the reduced cell numbers and/or the impaired liver cell function due to the effects of toxins in patients with MP. Another possible reason for the increase in HA is the local release from the liver itself. Ito cells have the capacity to synthesize large amounts of HA, but its production appears to be a slow process and is, therefore, unlikely to account for the rapid elevation of HA in acute liver failure.[11] Liver injury induces a wound-healing response characterized by hepatocyte proliferation, infiltration of inflammatory cells, and transformation of perisinusoidal stellate cells into myofibroblasts, which degrade the sinusoidal extracellular matrix by releasing matrix-degrading proteases. Sustained expression of matrix proteases may provoke the rapid influx of inflammatory cells.[23] Increases in HA production may be caused by the induction of Ito cell proliferation, and the synthesis of extracellular matrix components by inflammation via cytokines.[24] In the present study, serum HA increases at early stage of acute hepatic failure, rising continuously as a liver damage progress in MP. We showed that HA levels on admission and the following days were significantly higher in non-surviving patients compared to those who survived. There was a statistically significant increase in HA on day 3 after admission in non-surviving patients. In addition, during the observation, we found that the HA concentrations were significantly correlated with hepatic transaminases and creatinine, which are commonly used for clinical monitoring. Similar to our results, Williams et al[10] reported that HA was a marker of liver damage in patients who have ingested paracetamol, as it correlates with standard markers of liver function. They also reported that the admission time was 3 days after paracetamol ingestion and HA levels had peaked on day 2 after admission. Similarly, Bramley et al[11] indicated that HA levels in patients who had liver damage due to paracetamol intake could elevate up until the seventh day, thereafter decreasing. In our study, the median admission time to ED was 7 hours and HA levels were higher in day 3 in non-survivors. Therefore, it is possible that HA may have risen to even higher levels after the third day in non-survivors. Further, studies are needed to determine the serum HA levels in MP after the third day. Elevated HA levels in patients with hepatic encephalopathy due to acute hepatic failure in paracetamol overdose were previously reported.[11] However, Williams et al[10] were unable to show a relation between HA levels and grade of hepatic encephalopathy in paracetamol overdose. In our study, patients with acute hepatic failure had elevated HA levels without encephalopathy. The IL–6 is a pleiotropic cytokine that stimulates a variety of cell types, including hepatocytes, and also modulates the hepatic expression of acute-phase proteins during inflammation. The IL–6 increases in patients with FHF, acute hepatitis,[14-16] and alcoholic liver disease.[25] Apart from its role in inflammation, IL–6 is an essential cytokine involved in liver regeneration.[26] It is considered to be a hepatoprotective factor by stimulating hepatocyte proliferation.[22] In our study, IL–6 was used as a marker of inflammation. We found that serum IL-6 levels were increased continuously in non-surviving patients. However, no correlation was observed between IL-6 and standard parameters except for aPTT throughout the observation period. Furthermore, there was no significant correlation between increased HA and IL-6 in the patients on days 2 and 3, suggesting that a number of factors are involved in the production and clearance of HA. Thus, IL-6 can not be used as an early prognostic marker in MP. However, almost all the parameters were correlated with IL-6 on day 3. It is possible that the increased serum IL–6 levels observed in patients with severe MP represent a protective response to severe hepatic injury. The relationship of HA to increased IL-6 production due to MP needs to be investigated in larger series. According to our results, HA is clearly a marker of liver damage in patients with MP as it correlates with standard markers of liver function. In patients who have developed liver damage due to MP, immediate preparations should be made to transfer patients to the closest facilities equipped for LT. This is especially important for MP with late admission to the ED. The life-saving role of LT in FHF secondary to MP should be considered as soon as possible.[3] This preliminary study needs to be extended to a large group of patients to evaluate the potential value of HA as a criterion marker for LT in MP–induced FHF. In their study, Williams et al[10] observed a considerable decrease in the post-transplant serial HA levels of the patients who had undergone LT due to hepatic failure caused by paracetamol poisoning. We think that determination of HA levels may also be beneficial in the follow-up of patients after LT in MP. Further evaluation is needed.

Study limitation. In patients who developed acute hepatic failure because of MP, a progressive increase in HA, and IL–6 levels up to 3 days was observed. Unfortunately, we could not determine the serum levels of HA and IL-6 thereafter. Thus, serum levels of these markers on the following days should be evaluated. The prognostic value of HA levels in patients with MP was found to be limited, and is unlikely to have any advantage over standard markers of liver function. Our

study was limited by the small sample size; prospective and controlled studies involving larger numbers of mushroom-poisoned patients are needed.

According to the presented data, serum HA increases at an early stage of acute liver failure, rising continuously as liver damage progresses in MP. Additionally, because of its significant correlation with the conventional markers of liver function, serum HA concentrations should be considered an important marker for clinical monitoring of liver damage in patients with MP admitted to the ED or intensive care unit.

Acknowledgment. *The authors thank Dr. Ahmet Tevfik Sunter for his valuable statistical advice.*

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