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Research Article

Retrospective Evaluation of Patients with Toxic Liver Disease and Fungal Intoxication: A University Hospital Experience

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Abstract

Objectives: The liver has an important place in toxin and drug metabolism. However, the diagnosis of liver damage due to chemicals, fungi, herbal toxins and drugs can rarely be detected. In our study, it was aimed to retrospectively evaluate the laboratory values, liver biopsy, treatment, mortality and morbidity rates of patients diagnosed with mushroom poisoning or toxic liver disease.

Methods: The data of 303 patients diagnosed with fungal intoxication or toxic liver disease, who admitted to Departments of Internal Diseases and Gastroenterology of Necmettin Erbakan University Faculty of Medicine between 2006 and 2016, were evaluated retrospectively by using the hospital automation system. The treatments applied to the patients, pathology results, laboratory results and mortality rates were analyzed.

Results: Of the patients; 52.5% (n=159) were female and 47.5% (n=144) were male. The average age of the patients was 50.9±19.7 years. Drugs were the most common cause of toxic hepatitis cases (48.8%), other causes were followed by fungi, herbal medicines, unknown cases and narcotic toxins (20.8%, 18.8%, 8.6%, 3.0% respectively).Drugs causing toxic hepatitis were most commonly NSAIDs (31.1%), followed by antibiotics, antiepileptics, antituberculosis drugs and paracetamol (21.6%, 6.8%, 6.8%, 6,1%, respectively). In histopathological examination, 92.9% of the cases had liver necrosis, 60.7% eosinophilia, 67.9% hydropic liver degeneration, and 28.6% bile obstruction. In addition to supportive treatments during the therapeutic process, plasmapheresis was applied in 13.2% of the patients and hemodialysis was applied in 13.2%, while liver transplantation was performed in 2.3% of the patients due to a fulminant course. While 20 patients died for various reasons, the overall mortality rate was calculated as 6.3%. The mean age of the deceased patients was 66.5±16.8 years and the mean age of the survivors was 49.9±19.5 years, and that of deceased patients was statistically significantly higher ($p<0.001$). The mortality rate was 9.0% in men and 3.8% in women, with no statistically significant difference ($p=0.060$). Histopathological findings were not associated with mortality. The mortality rate in toxic hepatitis was caused by mushroom, narcotics, drugs, herbs and unknown causes (12.7%, 11.1%, 4.7%, 3.5% and 3.8%, respectively).

Conclusion: Toxic hepatitis is a common health problem that can result in serious morbidity and mortality. In this thesis study, various drugs, mushroom poisoning and use of herbal medicines were determined as the causes in most of the toxic hepatitis cases diagnosed in our hospital. Based on these findings, we believe that in order to prevent toxic hepatitis cases in our country, it would be beneficial to take measures to prevent unnecessary use of drugs and herbal products, to regulate the marketing and usage conditions of herbal products and to carry out studies to inform the public about this issue.

Keywords: Drug-induced toxicity, hepatic injury pattern, herbal toxicity, mushroom toxicity, narcotics toxicity

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Toxic hepatitis is responsible for less than 1% of acute liver injury. It is the most common cause of acute liver failure in the Europe and the USA.[1] It is also the most common reason for withdrawal of drugs from the market.[2,3] Toxic hepatitis is grouped under three main headings as liver damage prompted by drugs, chemicals and herbal products. Drug-induced liver injury (DILI) represents the prototype of toxic hepatitis.

Toxic hepatitis cases could be asymptomatic or present in a wide clinical spectrum that can result in acute fulminant liver failure and even death. In acute DILI, asymptomatic elevation in liver function tests (LFT), cholestasis and pruritus are common, and the clinical presentation may mimic acute liver failure and viral hepatitis. This disease can be confused with chronic liver diseases. For example, it can be confused with autoimmune hepatitis, primary biliary cirrhosis, and alcoholic liver diseases.

Drug-induced liver injury (DILI) occurs by dose-related intrinsic and non-dose-dependent idiosyncratic mechanisms. Toxic hepatitis or DILI is classified as cholestatic, hepatocellular and mixed type according to laboratory findings and clinical examination. It can be classified as predictable and idiosyncratic type when evaluated in terms of hepatotoxicity mechanism, and as hepatitis type, cholestatic type and steatosis when liver histological findings are considered.[4] While toxic hepatitis constitutes 10-20% of fulminant hepatitis and approximately 10% of acute hepatitis, it is responsible for only 1% of chronic hepatitis and cirrhosis.[5]

In the diagnosis of toxic hepatitis, detailed anamnesis, liver function tests, liver ultrasonography and histopathological examination are used. With the results of the examination, the possible causes were excluded and toxic hepatitis was diagnosed. The diseases that should be considered in the differential diagnosis vary according to the liver damage pattern. Biliary obstruction, primary sclerosing cholangitis and primary biliary cirrhosis should be considered in cholestasis pattern; viral infections, autoimmune hepatitis, and alcoholic liver damage in the hepatitis pattern. In case of steatosis, non-alcoholic fatty liver injury disease should also be considered in the differential diagnosis.[6]

Elimination of the causative factor is a priority in treatment. Early detection of drug toxicity is important in terms of preventing complications that may lead to mortality. Self -improvement is achieved when the active agent is eliminated in most of the DILI patients. However, in some patients, various supportive treatments are needed and even in severe cases, the need for liver transplantation may arise. DILI can be mortal in some patients. Various factors including advanced age, multiple drug use, jaundice, comorbid diseases, and dose and duration of exposure to toxic substances are crucial factors determining the prognosis of disease.[7]

In this presented study, various clinical and laboratory findings of cases which admitted to our hospital and were diagnosed with toxic liver damage or fungal intoxication were evaluated. It was aimed to evaluate retrospectively the liver biopsy results and applied treatments, to determine mortality rates, and to investigate conceivable risk factors that may affect clinical outcomes.

Methods

Ethics Committee Approval

This study was carried out with the approval of Clinical Research Ethics Committee (Date: 01.09.2015 and Approval Number: 1068).

The Study and its Characteristics

The study is descriptive, retrospective and analytical. The cases who admitted to Necmettin Erbakan University Faculty of Medicine Outpatient Clinics of Internal Diseases and Gastroenterology between 2006 and 2016 were included. As inclusion criteria, patients were required to have a diagnosis of toxic liver disease or mushroom poisoning.

Study Method

Hospital automation and information recording system was used to determine the patients to be included in the study, retrospective scanning was performed based on the diagnoses "Toxic Liver Disease" with the diagnosis code K71.0-K71.9 ICD-10 and "Toxic Effect of Fungus Ingestion" with the diagnosis code T62.0. As a result of this screening, 327 patients with the aforementioned diagnoses were reached, but due to missing data, 24 patients were excluded from the study. 303 cases with sufficient data were included in the study.

Sociodemographic parameters (age/gender) of the cases whose records were accessed were included in the analyses. The etiology of toxic hepatitis was obtained from the patient records. The data involved in the analysis included white blood cell count (WBC), neutrophil count, biochemical parameters such as alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), INR, albumin, total and direct bilirubin levels were included. In addition, biopsy findings were examined in patients who underwent liver biopsy for histopathological examination. Exposure times to the toxic substance were obtained from their anamnesis. The treatments applied to the patients (hemodialysis, plasmapheresis, liver transplantation, etc.) and the final post-treatment status of the patients (survival, deceased) were included in the analysis.

The etiology of the cases included in the study was classified as drugs, mushrooms, herbal products, narcotics and unknown. Drugs were grouped as NSAIDs, antibiotics, antiepileptics, anti-tuberculosis drugs, paracetamol, antipsy-

chotics, oral contraceptives, anti-hyperlipidemics, anti-thyroid drugs, anti-neoplastics, corticosteroids, proton pump inhibitors and oral antidiabetics.

For liver damage, ALT/ALP and AST/ALT ratios were used for classification. The AST/ALT rate, which was first defined by Fernando De Ritis in 1957, is used to determine the etiology. The AST/ALT rate is less than 1 in viral etiologies, usually between 0.5 and 0.7.[8] The De Ritis ratio, which provides important information in the diagnosis of acute hepatitis, was used in this study.

The classification by Verma et al.[9] was used to classify the liver injury pattern: hepatocellular ICHD: LOWER ≥3 times the upper limit of normal (ULN), cholestatic ICHD: ALP ≥ 2 NULES, mixed type: LOWER >3 NULES and ALP >2 NULES.

Liver biopsy findings of the cases, if any, were also included in the study. In histopathological examinations, hydropic balloon-like degeneration, necrosis, eosinophilia, and presence of biliary plug were evaluated.

Exclusion Criteria

- Being under 18 years of age and having any comorbidity affecting liver functions
- Presence of viral, bacterial and other infectious agents of hepatitis
- Presence of primary and metastatic cancers of the liver

Statistical Analysis

SPSS version 20.0 (IBM®, Chicago, USA) package program was used for data analysis. Descriptive statistics are summarized as number, percentage, mean, median, and standard deviation. The conformity of the variables to the normal distribution was examined using visual (probability plots and histogram) and analytical methods (Kolmogrov Smirnov test). The numerical variables determined according to the normal distribution were compared between the two groups using the independent samples t test, between the three groups using and the One-Way ANOVA test. Pearson correlation test was used for the correlation analysis. A Pearson correlation coefficient of 0.05-0.30 indicated a low or insignificant correlation, 0.30-0.40 a low-moderate correlation, 0.40-0.60 a moderate correlation, 0.60-0.70 a good correlation, 0.70-0.75 a very good correlation, and 0.75-1.00 a perfect correlation. Homogeneity of variances was evaluated with Levene's test. Post hoc analyzes with Tukey and Bonferonni tests were performed in cases of a significant difference. Numerical variables that did not show normal distribution were compared between two groups using the Mann Whitney U test and between three or more groups using the Kruskal Wallis Test. Nominal data were obtained using the Chi-square test between the two groups. In the statistical analyzes of the study, comparisons with a p value below 0.05 were considered statistically significant.

Results

Of the 303 patients in the study with a mean age of 50.9±19.7 years (median 50 years,); 144 patients male (47.5%) and 159 patients female (52.5%).

The most common etiological agent causing toxic hepatitis was drugs (48.8%). This was followed, in descending order of frequency, by mushroom (20.8%), herbal product use (18.8%) and drug intoxication (3.0%). The etiological factor could not be determined in 8.6 % of the cases. In 148 patients with toxic hepatitis caused by drugs, the drugs causing intoxication were found to be NSAIDs, antibiotics, antiepileptics, antituberculosis, and paracetamol in descending order of frequency of frequency (31.1%, 21.6%, 6.8%, 6.8%, 6.1%, respectively) (Fig. 1). The antibiotic molecule responsible for the etiology was unknown in the vast majority (62.5%) of 32 patients whose toxic hepatitis was caused by antibiotics. These patients stated in their anamnesis that they used antibiotics for various reasons, but they did not know the type of antibiotic molecule they used. In addition, the types of antibiotics in cases diagnosed with ICHD due to antibiotic use and the antibiotics they used could be identified are given in Figure 2.

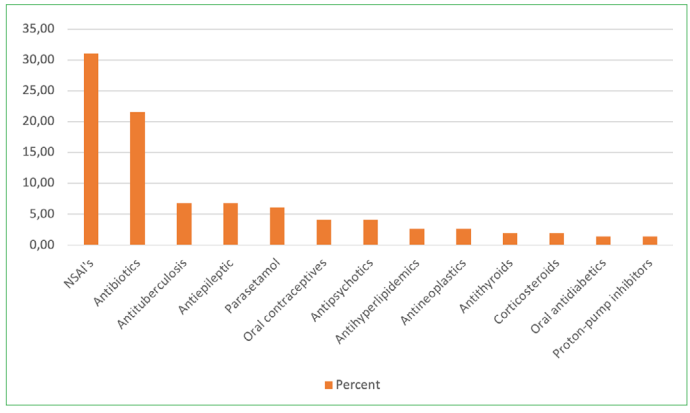

Figure 1. Drugs that cause toxic hepatitis.

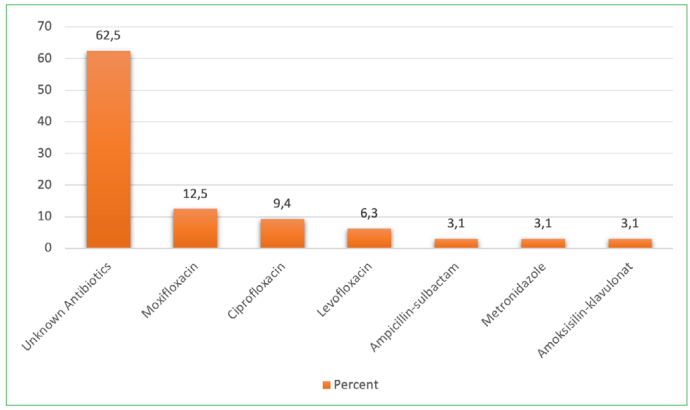

Figure 2. Types of antibiotics that cause toxic hepatitis.

Data concerning various laboratory results of patients are given in Table 1. The mean ALT/ALP ratio was 8.9±13.1 (median 4.3). Accordingly, when the cases were evaluated according to the ALT/ALP ratio, ALT/ALP ratio was determined to be 5 and above in 46.2 % of the patients (hepatocellular type), 2 and below in 25.1% (cholestatic type), and between 2 and 5 in 28.7% of the patients (mixed type). When the patients were evaluated according to the AST/ALT ratio, AST /ALT ratio was found to be 1 and below in 54.1% of the patients, between 1-2 in 35.6%, and 2 and above in 10.2%. The findings are summarized in Table 2.

Table 1. Laboratory values related to liver functions of patients

	Mean±SD	Median	Min	Max
WBC (10^3/µL)	9.0±4.5	8.1	1.2	32
Neutrophil count (10^3/µL)	6.5±4.3	5.6	0.5	27
ALT (U/L)	1069±1144	608	13	6874
AST (U/L)	1106±1578	602	23	11129
ALP (U/L)	179±125	149	32	974
LDH (U/L)	751±1359	422	140	17865
INR	1.6±1.6	1.2	0.8	18
GGT (U/L)	211±205	151	10	1493
Albumin (g/dL)	3.4±0.6	3.4	10	1493
Total bilirubin (mg/dL)	6.6±7.2	3.3	0.2	36
Direct bilirubin (mg/dL)	4.0±4.8	1.8	0.1	24

Table 2. ALT/ALP and AST/ALT ratios of the patients

	Percent (%)	Mean±SD	Median	Min	Max
ALT/ALP ratio		8.9±13.1	4.3	0.1	105.7
≤2 Cholestatic	25.1				
2-5 Mixt	28.7				
≥5 Hepatocellular	46.2				
AST/ALT ratio		1.1±0.7	0.9	0.1	5.3
≤1	54.1				
1-2	35.6				
≥2	10.2				

Mean albumin, INR, total and direct bilirubin values according to liver damage pattern are given in Table 3. Accordingly, it was determined that total bilirubin (p=0.120) and direct bilirubin (p=0.112) levels did not differ between cholestatic, mixed and hepatocellular liver damage types, although albumin and INR values showed statistically significant differences among the all types of liver damage (p=0.035 and p=0.001, respectively). In the post - hoc analyzes performed, the albumin level decreased more in hepatocellular type than in the mixed type (p=0.049), and the INR was determined to be higher in hepatocellular type, mixed type (p=0.025) and cholestatic type (p=0.001).

A liver biopsy was performed in 56 (18.5 %) patients. Histopathological biopsy revealed liver necrosis in 92.9 % of patients, hydropic liver degeneration in 67.9%, eosinophilia in 60.7 %, and bile occlusion in 28.6 %.

Regarding supportive treatments, dialysis was applied in 13.2% and plasmapheresis in 13.2% of the patients, whereas liver transplantation was performed in 7 patients (2.3%). The survival rate in the study group was calculated as 93.7%, with 2 patients (6.3%) had deceased due to complications of toxic hepatitis. The effects of various factors on mortality are given in Table 4. 9.0% of male patients and 3.8% of female patients deceased. However, this difference was not statistically significant (p=0.060). The mean age of the deceased patients (66.5±16.8) was significantly higher than the survivors (49.9±19.5) (p<0.001). The mortality rate was higher in patients treated with hemodialysis and plasmapheresis (p<0.001).

12.7% of the patients with toxic hepatitis caused by fungi, 11.1% of those with drugs, 4.7% of those with drugs, 3.5% of those with herbal products and 3.8% of patients with no identified cause of toxic hepatitis were found to be deceased. The difference between groups in mortality rates was not statistically significant (p=0.13).

Table 3. Albumin, INR and bilirubin levels in biochemical liver damage patterns

Liver damage pattern	Albumin (g/dl)	INR	T.Bilirubin (mg/dl)	D.Bilirubin (mg/dl)
Hepatocellular	3.3±0.6	2.0±2.1	7.0±7.9	4.2±5.3
Cholestatic	3.3±0.6	1.2±0.6	7.3±6.6	4.7±4.6
Mixt	3.5±0.5	1.4±0.9	5.2±6.2	3.1±3.9
p	0.035	0.001	0.120	0.112
Comparison of groups	**p**	**p**	**p**	**p**
Hepatocellular-mix	0.049	0.025	0.204	0.335
Cholestatic-mix	0.100	0.964	0.225	0.135
Cholestatic-hepatocellular	1.000	0.001	1.000	1.000

*Data are expressed as mean±standard deviation; **One-Way ANOVA test was used. Bonferroni test was preferred in post-hoc analyses.

Table 4. Factors affecting mortality

	Deceased		Survivor		p
	n	%	n	%	
Demographic information					
Gender					
Male	13	9.0	131	91.0	0.060
Women	6	3.8	153	96.2	
Liver histopathology					
Liver necrosis					
Yes	2	3.8	50	96.2	0.690
None	0	0	4	100	
Eosinophilia					
Has	2	5.9	32	94.1	0.247
None	0	0	22	100	
Hydropic degeneration					
Yes	1	2.6	37	97.4	0.582
None	1	5.6	17	94.4	
Bile plug					
Yes	1	6.2	15	93.8	0.495
None	1	2.5	39	97.5	
Treatment administered					
Plasmapheresis					
Yes	9	22.5	31	77.5	<0.001
None	10	3.8	253	96.2	
Hemodialysis					
Yes	8	20.0	32	80.0	<0.001
None	11	4.2	252	95.8	
Liver transplantation					
Yes	1	14.3	6	85.7	0.376
None	18	6.1	278	93.9	

*Chi-square test.

When liver damage was evaluated in regard to mortality, the mortality rate was hepatocellular type, mixed type and cholestatic type (8.6%, 5.7%, 2.6%, respectively). Mortality seen in hepatocellular type liver damage was found to be higher than that observed in cholestatic type (p<0.001) (Table 5).

The deceased patients had lower albumin and INR values than the survivors. LDH, GGT and ALT levels were found to be similar in both groups (Table 6).

Exposure times of the cases to the toxic agent were known in most of the patients (n=277). The mean exposure time to the toxic substance was determined to be 16.7±28.3 days (median 7 days). The mean exposure time of to the toxic substance was 16.9±28.5 days in the survivors and

Table 5. Mortality rates by liver injury patterns

	Deceased		Survivor		p
	n	%	n	%	
Hepatocellular type	12	8.6	128	91.4	0.001
Mix type	5	5.7	82	94.3	
Cholestatic type	2	2.6	74	97.4	

*Chi-square test.

Table 6. Biochemical parameters affecting mortality

	Deceased		Survivor		p
	Mean	SD	Mean	SD	
WBC	11.3	7.5	8.9	4.2	0.024
Neutrophil	9.1	7.0	6.4	4.0	0.008
AST	1957	1821	1049	1548	0.015
ALT	1456	968	1043	1151	0.127
ALP	175	77	179	128	0.872
GGT	169	110	214	210	0.353
LDH	929	852	739	1387	0.557
Albumin	2.9	0.7	3.4	0.5	<0.001
Total Bilirubin	13.1	11.3	6.1	6.6	<0.001
Direct Bilirubin	8.2	6.9	3.7	4.5	<0.001

*T-test in independent groups.

13.3±24.1 days in the deceased patients. There was no difference among deceased and survived patients in regard to exposure time to toxic substances (p=0.601).

6.2 % of those with bile occlusion, 5.9% of those with eosinophilia, 3.8% of those with liver necrosis and 2.6% of those with hydropic balloon degeneration were found to be deceased. No statistical significance was found in the relationship between liver biopsy findings and mortality (p>0.05).

Discussion

Toxic hepatitis, the majority of which is caused by drug-induced liver disease, can have an acute or chronic course and can progress in a clinical spectrum ranging from asymptomatic disease to liver failure and even death.[10]

It does not often have a specific treatment and current treatments should focus on early diagnosis and prevention of the disease before it occurs. For this reason, recognition of the parameters causing the manifestations of toxic hepatitis beforehand and defining the variables that have an effect on the clinical results will contribute to the clinical feedback of these patients. In this study conducted with patients diagnosed with toxic hepatitis in our hospital, It is aimed to analyze our regional data on this subject by evaluating the etiology, laboratory results and clinical conditions, thus to guide the studies that may be carried out in our region in order to reduce the morbidity and mortality, and to prevent toxic hepatitis associated with toxic hepatitis.

The first striking finding of our study was that various drugs (48.8%) were responsible as the etiological agent in most of the toxic hepatitis patients admitted to our hospital. In our study, the drugs causing toxic hepatitis, in descending order of frequency, were NSAIDs (31%), antibiotics (21.5%), antiepileptics (7%), antituberculosis drugs (7%) and paracetamol (6%). In terms of the etiology of toxic hepatitis, the findings of our study are consistent with various studies conducted in our country and all over the world. It is known that access to certain drugs without a prescription is easy in our country and that over-the-counter drug use is common. In a study by Yapıcı et al.[11], it was reported that the use of over-the-counter drugs was common (31.3%) in patients who admitted to primary health care institutions, and NSAIDs were the most commonly used drugs. Non-prescription access to drugs and the low frequency of rational drug use may have caused NSAIDs to be the most widespread agent in our study. Various studies have reported that antimicrobial drugs are among the most common causes of ICHD. Antibiotics were found to be the responsible agent at a rate of 32% and 45.5% in the studies by Andrade RJ et al.[12] and Chalasani et al.,[13] respectively. In addition, the same investigators reported that the most common agent among antibiotics was amoxicillin clavulanate. In our study, antibiotics ranked first among the drugs causing toxic hepatitis, and moxifloxacin (12.5%) was the most commonly used antibiotic, which was followed, in descending order of frequency of frequency, by ciprofloxacin, levofloxacin, ampicillin-sulbactam, amoxicillin-clavulanate and metronidazole (3.1%). Differences in the causative antibiotic in studies may be related to national differences (availability of antibiotics, reimbursement conditions, etc.) or regional differences related to antibiotic preference (microorganism types, antibiotic resistance rates, etc.). In addition, it should be taken into account that the etiological antibiotic could not be determined in the vast majority (62.5%) of antibiotic-induced ICHs in our study. In our study, it was observed that antituberculosis drugs were responsible for 6.8% of ICHD cases. In regions where tuber-

culosis is common, antituberculous drugs continue to play a significant role in the etiology of ICHD. India, where the prevalence of tuberculosis is high, reported antituberculosis drugs as the most common cause of ICH.[14] Tuberculosis continues to be an important health problem in our country. Therefore, ICHD cases due to antituberculosis drugs are frequently encountered in our country as well.

Another result of our study is the high frequency of toxic hepatitis cases due to herbal product use. In our study, it was observed that the cause of toxic hepatitis in 18.8% of the cases was the use of herbal medicines. Our findings are in line with the scientific literature in this respect. Herbal products are used in the world for the treatment of different diseases or for non-disease purposes such as body building and weight loss. It is known that the habit of using herbal products is also significantly affected by ethnicity and geography. A study in Asia reported that herbal products were more common in the etiology of ICHD, unlike Western countries.[15] Herbal products are used frequently, especially in Asian countries. For this reason, especially in these countries, a significant part of the GKKs are related to herbal products. This rate was reported as 24.2% in a study by Li et al.[16] 19% in a study by Zhou et al.[17] from Public Republic of China, and 30.7 % in a study by Suk et al.[18] from Korea. Toxic hepatitis has been reported due to the increase in the use of herbal products as a result of cultural interaction in the world, and due to an increase in the frequency of use of these products observed in western countries. Navarro et al.[19] reported in their study that herbal products accounted for 20% of IKKDs in 2013. Various herbal products can easily be put on the market without supervision.[20] In addition, since they are not evaluated in the drug category, they do not contain posology information and can be put on the market without the control of the health authority in terms of content. In some studies, it has been reported that various herbal products may contain high doses of active substances in their compositions.[20,21] It may be possible to prevent many health problems related to the use of herbal products by imposing restrictions on the use and sale of these products, making the necessary legal regulations, ensuring that they can be recommended only by experts, and informing the public about the possible harms of unconscious use of herbal medicines.

According to the classification of the International Councils of Medical Sciences Organizations,[22] 46.2% of the ICHD patients in this study were of hepatocellular type, 28.7% of mixed type, and 25.1% of cholestatic type. In a study conducted by Bjornsson and Olsson in which 784 drug-induced hepatitis cases diagnosed in Sweden between 1970 and 2004 were examined, ICHD patterns were reported as follows: 52.1 % hepatocellular type, 26.2% cholestatic type, and 21.5% mixed type, similar to our data.[23]

In this research, the mortality rate of cases with toxic hepatitis was calculated as 6.3 %. In the literature, varying rates of mortality due to toxic hepatitis have been reported. The mortality rate was reported as 8% by Chalasani et al.[13] 9.2% by Bjornsson et al.[23] and 4.7% by Mani et al.[24] In conclusion, the mortality rate found in our study was close to or slightly below the mortality rates reported in other studies in the literature. According to the data of our study, advanced age; hepatocellular-type liver damage; high WBC, bilirubin and INR; and low albumin were determined as parameters correlate with the increased risk of mortality. In the literature, advanced age[25] high bilirubin[13,26] hepatocellular-type liver damage[13] coagulopathy[24] diabetes[25] obesity[25] and high serum creatinine[24] are factors reported to negatively affect the prognosis. In addition, environmental factors such as smoking or alcohol consumption, drug-related features such as drug interaction, multiple drug use, metabolic profile of the drug and the dose used have also been shown to be effective in the course of ICHD.[25] In studies evaluating mortality according to liver biopsy patterns, Bjornsson et al.[23] found it to be 2.4% in mixed pattern, 7.8% in cholestatic pattern and 12.7 % in hepatocellular pattern, whereas Chalasani et al.[13] reported them to be 14.3% in the cholestatic pattern, 7.5% in the hepatocellular pattern and 2.1% in the mixed pattern. Chalasani et al.[13] stated in their study that mortality due to the cholestatic type was also dependant on causes other than acute liver failure, therefore the mortality rate was higher than that in the literature. In the present study, the mortality rate was hepatocellular pattern 8.6 %, cholestatic pattern 2.6%, and mixed pattern 5.7%. In patients with hepatocellular-type ICHD, mean serum albumin levels were lower and INR values were higher than other types. This suggests that liver failure is more severe in patients with hepatocellular-type ICHD in our study group and explains the high mortality rate in this type. Although the association of ICH symptoms such as jaundice with clinical findings and mortality could not be evaluated owing to the retrospective manner of our research, it was found that patients with higher serum bilirubin levels (13.1 mg/dl vs 6.1 mg/dl) had a higher mortality rate. Bjornsson et al.[23] also reported in their study that age, AST, ALT, AST/ALT, and bilirubin levels were higher in deceased patients. There are other studies reporting that advanced age is a risk parameter for ICHD.[25,27] As a matter of fact, it was observed that the mean age of the deceased cases was greater than the survivors.

Liver biopsy is not necessary for diagnosis of idiosyncratic ICHD or for assessment of its severity. However, when performed, it provides important data about the histological classification, pathogenesis and prognosis of liver injury. In

addition, it is useful for excluding the differential diagnoses of ICHD. In the study conducted by Andrade et al.,[23] it was stated that hepatocellular-type damage and the existence of necrosis indicated a poor prognosis. Other studies have confirmed that the presence of necrosis is associated with a poor prognosis.[28] It has also been reported that the presence of eosinophilia and granuloma indicates a good prognosis.[29] In our study, liver biopsy was performed in 18.5 % of the patients. In our study, no correlation of histological findings such as necrosis, eosinophilia, hydropic degeneration and the presence of bile occlusion in liver biopsy with mortality was found. The possible reason for this may be the small number of patients who had undergone biopsy (n=56) and the results were not statistically significant.

Liver transplantation is a survival-enhancing treatment method for patients with ICHD in whom recovery is not expected/not seen. Acute liver failure has been reported to develop in 10% of ICHD patients.[27] It has been reported that the MELD (Model for End-Stage Liver Disease) score is the strongest predictor of the need for liver transplantation, especially in patients with acute liver failure.[26,30] In our study, liver transplantation was performed in 2.3 % (n=6) of ICHD patients, of which 5 (83.3%) survived while 1 (16.7%) deceased. In the study performed by Russo et al.[31] it was stated that 7% of the patients who developed liver failure due to ICHD underwent liver transplantation. The results of our study and literature data clearly demonstrate that liver transplantation is life-saving in patients with fulminant ICHD. Practices regarding liver transplantation in ICHD cases may show intercountry and intercenter variations. The biggest problem in liver transplantation in our country is insufficient amount of cadaver organ donor. For this reason, the majority of liver transplants in our country are made from living donors.

The results obtained from our study showed that fungal intoxication remains to participate an important role in the etiology of toxic hepatitis in our region. Although there has been a decrease in the frequency of mushroom poisoning in our country, owing to various studies carried out to raise public awareness, and the ease of accessibility of information sources such as the internet and social media, it is seen that mushroom intoxication still continues to be an important health problem. As a matter of fact, in our study, fungal intoxication was observed to be the second most common cause of toxic hepatitis. An increase in transaminases is observed within 2-3 days in fungal intoxications, and if not treated early, liver failure and death may result. In this study, the mortality rate of the patients whose toxic hepatitis was caused by fungi was 12.7%. While the mortality rate of fungal intoxications was reported to be up to 80% in the 1970s, which has decreased below 20% today with the development of early diagnosis and advanced treatment options.[32,33]

There are some limitations in our study. The most significant restriction of our study is the retrospective design. For this reason, ICD10 codes associated with ICHD were scanned using the hospital automation system to identify ICHD patients, and the patient group was formed by considering the medical history, clinical symptoms and findings, as well as liver function tests recorded in the automation system of the patients after the scan. Due to the retrospective study design, it is possible to use standardized diagnostic methods such as Digestive Disease Week-Japan (DDW-J), Naranjo Adverse Drug Reactions Probability Scale (NAD-RPS), Roussel Uclaf Causality Assessment Method (RUCAM) or Maria and Victorino scale (MV) in the diagnosis of ICHD. In addition, histological findings could not be standardized because the biopsy materials were not re-examined in patients who underwent liver biopsy. It is possible that this affected the results of the examination of the histological findings.

Conclusion

Toxic hepatitis is an important health problem all over the world and in our country. In our study, it was seen that the most common cause of toxic hepatitis cases admitted to our hospital was drugs, with NSAIDs and antibiotics taken the first place. Since tuberculosis continues to be an important health problem in our country, antituberculosis drugs are also among the causes of toxic hepatitis at a significant rate. The results of our study show that mushroom intoxication also ranked 2nd in the etiology of toxic hepatitis in our region, followed by the use of herbal products and drugs. Considering all the etiological reasons, it is clear that one of the most important steps in the prevention of toxic hepatitis is to increase the awareness level of the society about the risks of using unnecessary drugs and herbal products and consuming natural mushrooms. In addition, taking measures to prevent access to over-the-counter drugs and strict control of the marketing and usage conditions of herbal products will also contribute to the prevention of the development of toxic hepatitis and many other health problems associated with these products.

Toxic hepatitis can be encountered in a broad spectrum ranging from asymptomatic disease and abnormal liver function test results to death. In our study, the mortality rate among patients was found to be approximately 6.3%. Liver transplantation was performed in 2.3% of the patients due to the fulminant course. Due to the risk of mortality and the possibility of liver transplantation, it would be appropriate to follow-up patients with toxic hepatitis, their

risk factors and comorbid diseases, and rapid progression in experienced centers where liver transplantation can be performed, with availability of supportive treatments such as hemodialysis and plasmapheresis.

Disclosures

Ethics Committee Approval: This study was carried out with the approval of Clinical Research Ethics Committee (Date: 01.09.2015 and Approval Number: 1068).

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