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Acute liver failure in Turkey: A systematic review

LIVER

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Original Article

ABSTRACT

Background/Aims: To present the causes of acute liver failure in Turkey.

Materials and Methods: International and national medical research databanks were searched for publications related to acute liver failure and originating from Turkey. Patients in the databank of acute liver failure of our center were also added to this literature search. Patients were evaluated for age, gender, etiology, treatment modality, and outcomes.

Results: A total of 308 patients were analyzed. Hepatitis A (20.9%) for children and hepatitis B (34.7%) for adults were the most common causes of acute liver failure. Cryptogenic (18%) and metabolic (14%) reasons were the followings. Wilson's disease was the most common cause of metabolic diseases. Mushroom intoxication was the most frequent factor of toxic liver failure for both adults and children (13%). Firework intoxication, including yellow phosphorus, is an indigenous factor. Anti-tuberculosis agents (3.2%) were the main cause of drug-induced acute liver failures (9%). Paracetamol was responsible for only 0.7% of all acute liver failures. Survival of the transplanted patients (n=118) was better than the non-transplanted patients (n=178) (65% vs. 36% respectively, $p<0.001$)

Conclusion: Preventable causes of acute liver failure in Turkey include hepatitis viruses and intoxication. Active vaccination and public awareness can decrease the number of acute liver failures. Paracetamol is not an emerging reason for acute liver failure in Turkey now, but selling it over the counter may increase the risks.

Keywords: Acute liver failure, hepatitis viruses, transplantation, systematic review, epidemiology

INTRODUCTION

Acute liver failure or fulminant hepatic failure is liver failure in a patient who has not had a previously known liver disease for the last two months. It has a high mortality rate, and its causes vary according to country and time interval. There is no comprehensive study on the etiologic factors for acute liver failure in Turkey. We systematically compiled data from published studies that were originated from Turkey, and our clinical data were included in those databases as well. The purpose of this study is to investigate the causes of acute liver failure in Turkey and, if possible, to predict prevention and treatment methods.

MATERIALS AND METHODS

We investigated this topic from several medical research databases in January 2011. We used all reported studies of Turkey both from national and international publications. Systematic review was performed by two independent investigators (CK & VE). We searched PubMed, ISI Web of Science, Ovid-Medline, Ebsco-Host, Science Direct, and Google Academic as international medical databases, and our search keywords were [(acute OR fulminant) AND (liver OR hepatic) AND failure*] in the titles of the studies. For national research, we used [(akut VEYA fulminan*) and (karaciğer VEYA hepatik) VE yetmezli*] keywords in the study titles, and

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Table 1. Age and gender distribution of the patients

	Pediatric (n=210)	Adult (n=98)*	Total (n=308)*
Male	119 (57%)	35 (42%)	154 (52%)
Female	91 (43%)	48 (68%)	139 (48%)
Age (mean)	6.3 years	36.0 years	15.7 years
Age (range)	1 month - 16 years	17-75 years	1 month - 75 years

*The gender of 15 patients was not available.

Turkishmedline, Google-Turkiye-Akademik, and ULAKBIM Turk Tip Dizini were searched. We eliminated duplicate studies from the same origin, unrelated articles, experimental studies, reviews, and editorial letters. The remaining publications were analyzed for trials, and the references of all these articles were cross-checked to decrease the possibility of missing relevant publications.

Data in the studies were stratified in terms of study type (clinical series or case report), patient age (adult or child) and gender, etiologic factors, treatment (transplantation and others), and outcome (death or recovered). For missing data, we contacted with the authors of articles of the studies via e-mail or phone. We added data on our patients with acute liver failure who were referred to us for follow-up or transplantation in this systematic research. The final data were tabulated in tables, and the sum of the colons in the tables and the means were calculated. Chi-squared test and student-t test (SPSS 13.0, Inc., Chicago, IL, USA) were used for statistical analysis.

RESULTS

We found 3489 related studies overall in the databases. We evaluated their title and/or abstract for origin in Turkey and found a total of 72 studies. Thirty-one studies were excluded (eleven duplicated, seven experimental, five unrelated studies, four reviews, and four editorial letters), and the remaining 41 (1-41) studies were evaluated for analysis. Of the 41 studies, 27 were in international refereed journals, 12 were in national refereed journals, and two studies were presented as papers in international congresses. Publication dates were between 1998 and 2010, and the series of patients included were from 1987 and 2007. There were a total of 234 cases from the published studies, and we added our 74 patients to the database, which reached a total of 308 acute liver failure patients.

The age and sex of the patients are summarized in Table 1. The overall age range of the patients was large (1 month and 75 years), but most of the patients (68%) were of pediatric age. In the pediatric age group, there was a slight male predominance, contrary to adults, where female patients were more frequent (p=0.035).

Table 2. Etiologies of acute liver failure in Turkey

Etiology	Pediatric n=210	Adult n=98	Total n=308
Viruses	72 (%34)	39 (%40)	111 (%36)
Hepatitis A	44	4	48
Hepatitis B	5	34	39
Hepatitis A and B	1	0	1
Hepatitis Non A-Non E	4	0	4
Hepatitis NonA-NonB-NonC	1	0	1
Epstein Barr Virus	3	0	3
Parvovirus	1	0	1
Cytomegalovirus	0	1	1
Adenovirus	1	0	1
Viral (not specifically defined)	12	0	12
Intoxications	29 (%14)	11 (%11)	40 (%13)
Mushroom intoxication	19	6	25
Toxic (not specific mentioned)	2	3	5
Firework intoxication	7	0	7
Datura stramonium intoxication	1	0	1
Ecstasy	0	2	2
Drug-induced	10 (%5)	19 (%20)	29 (%9)
Paracetamol	2	0	2
Tuberculosis drugs	5	5	10
Aspirin	1	0	1
Diphenylhydantoine	1	0	1
Drug-induced (not mentioned)	0	6	6
Imatinib	0	1	1
Propycil	0	1	1
Levofloxacin	0	1	1
Nimesulide	0	1	1
Pantanzaprole	1	0	1
Nonsteroid anti-inflammatory	0	2	2
Carbamazepine	0	1	1
Multiple myeloma treatment	0	1	1
Metabolic	41 (%19)	2 (%2)	43 (%14)
Wilson	31	1	32
Galactosemia	3	0	3
Tyrosinemia	4	0	4
Hemachromatosis	1	0	1
Niemann-Pick	1	0	1
Yellow nail syndrome	1	0	1
Citrullinemia	0	1	1
Autoimmune	7 (%3)	3 (%3)	10 (%3)
Cryptogenic	46 (%22)	8 (%8)	54 (%18)
Others	5 (%2)	16 (%16)	21 (%7)
Budd-Chiari	3	2	5
Postoperative	0	3	3
Tumors (lymphoma, hepatoma)	0	3	3
Hemophagocytic syndrome	0	3	3
Postpartum	0	4	2
Hypoxic hepatitis	2	0	2
Amyloidosis	0	1	1
Age (range)	1 month - 16 years	17-75 years	1 month - 75 years

Table 3. Causes of acute liver failures of countries (%)

	Drug induced		Hepatitis viruses				
Country	**Paracetamol**	**Others**	**HAV**	**HBV**	**HEV**	**Cryptogenic**	**Others**
United States	39	13	4	7	-	18	19
England	57	11	2	5	1	17	7
Australia	36	6	4	10	-	34	10
Canada	15	12		30		27	16
Germany	15	14	4	18	-	21	28
Scandinavia	17	10		12		43	17
France	7	21		33		18	21
Spain	2	17	2	32	-	35	12
Pakistan	-	2	7	20	60	7	4
India	-	1	2	15	44	31	7
Sudan	-	8	-	22	5	38	27
Chile*	-	7		37		44	11
Turkey**	1	8	16	13	-	18	44

Adopted from references 42 and 43
* Only pediatric patients
**Results of this study
HAV: hepatitis A virus; HBV: hepatitis B virus; HEV: hepatitis E virus

Viruses, especially hepatitis viruses, were the most common cause of acute liver failure in Turkey (30%). The types of hepatitis viruses were different for pediatric and adult patients (Table 2). The main cause of acute liver failure in children was hepatitis A virus (21%), but the most prominent in adults was hepatitis B virus (35%) (p<0.001). In addition, Epstein Barr virus, parvovirus, adenovirus, and other viruses were reported as a cause of acute liver failure, particularly in children.

Cryptogenic causes were the second most common etiology (18%), and it was more frequent in children (22% vs 8%, p=0.005) (Table 2). Metabolic diseases and intoxications were the next most frequent causes. Metabolic disorders in the etiology of acute liver failure were significantly more frequent in children (19% vs 2%, p<0.0001), and Wilson's disease was the most common reason. The most common type of intoxication was mushrooms for both adults and children. Fireworks, including inorganic phosphorus poisoning in children, was the second reason of intoxication. Drug-induced acute liver failure was more common in adults than children (20% vs 5%, p<0.0001) (Table 2). The most important cause of drug-induced acute liver failure in Turkey was anti-tuberculosis drugs (34% of all drug-induced acute liver failures). Paracetamol-induced acute liver failure was less than 1% (0.6%) of all acute liver failures.

When we evaluated the treatment methods of the patients, we could not obtain enough information for 12 patients. The remaining 296 patients were treated by liver transplantation (n=118, 40%) or by conservative methods (n=178, 60%). A total of 77 (65%) patients survived after liver transplantation, and only 64 (36%) patients survived after conservative treatments (<0.001).

DISCUSSION

Causes of acute liver failure vary among countries (Table 3) (42,43). While the viral causes in developing countries are frequent, drug-induced causes are the main etiological factor in North America and Western Europe. We have no comprehensive data about the reasons and the incidence of acute liver failure in Turkey. We examined the causes of acute liver failure in Turkey for the first time by a systematic analysis.

Hepatitis viruses

In the United States, the incidence of acute liver failure due to hepatitis A and B viruses is significantly decreased by vaccination programs (44). Similarly, hepatitis viruses cause less acute liver failure in the United Kingdom and Sweden. In Germany and Spain, hepatitis B virus-related acute liver failure is not uncommon. In the Far East (India, Pakistan), water-related hepatitis E virus is the main reason of acute liver failures. In Turkey, the main causes of acute liver failure were hepatitis A virus for children and hepatitis B virus for adults. Hepatitis E virus does not look like an important risk factor for Turkey. However, hepatitis E virus surveillance should be done routinely for all acute liver failure patients. As is well known, hepatitis C virus rarely causes acute liver failure (45). Active vaccination programs are proven and effective methods for prevention of hepatitis A and

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B infections. In Turkey, hepatitis B and A vaccination programs for children started in 1998 and 2012, respectively. We believe that extending the vaccinated population by longstanding programs will provide a significant decrease in the numbers of acute liver failures.

Drug induced

Anti-tuberculosis drugs can be the main cause of drug-induced acute liver failure in Turkey (10 of 29 reported cases). Treatment of acute liver failure in a patient with active tuberculosis has lots of difficulties. If the patient requires liver transplantation, postoperative immunosuppression with steroids can aggravate the tuberculosis, and non-standard treatment protocols become mandatory (13). The most common cause of acute liver failure in the United States (39%) and United Kingdom (57%) is paracetamol, which is usually unprescribed. In Turkey, paracetamol is responsible for only 1% of all acute liver failures, but selling it over the counter may increase the risks.

Intoxication

Mushroom intoxication was the most prevalent reason of toxic liver failures both for adults and children in Turkey. Mushroom poisoning is a preventable factor for acute liver failure, and public awareness constitutes the mainstay of precautions. Early diagnosis and intervention is another factor to avoid deterioration of mushroom poisoning. Another noteless but highly fatal reason of acute liver failure for children was ingestion of fireworks containing yellow phosphorus (called çat-pat) (46). This hepatotoxic, neurotoxic, and cardiotoxic agent particularly jeopard children with its easy accessibility from local stores and with its sweet taste. At 2011, our clinic sent a criminal complaint for this material to the Security General Directorate of the Interior Ministry.

Others

We particularly outlined the main preventable causes (hepatitis viruses, intoxication, and drugs) of acute liver failure. Other reasons include metabolic disorders (usually Wilson's disease for children) and cryptogenic, autoimmune, postoperative, and postpartum liver failures. The reason of the high percentage of other causes in this study might have originated from the design of this study. This systematic review included lots of extraordinary reasons of acute liver failure that were valuable for publication. Because rare reasons are more prone for publication, this may result with those rare causes being a bit higher than their normal percentage.

Incidence and treatment

The incidence of acute liver failure can be predicted by two ways. Generally it is accepted that 1-6 persons per million of the population per year result in acute liver failure. We can estimate 70-420 acute liver failure cases per year in the 70-million-person population of Turkey. Again, it is generally accepted that liver transplantation requirement for acute liver failure constitutes 5-10% of all liver transplantations. The total liver transplantation requirement of Turkey is 2500-3000 cases per year, and we can estimate that Turkey comes up against almost 200-250 acute liver failure cases per year. When indicated, the most effective treatment of acute liver failure is transplantation. Therefore, all acute liver failure patients should be followed in hospitals with liver transplant programs. The recent cadaveric liver donation rate in Turkey is nearly 250 per year. It is clear that some patients with acute liver failure can not find any cadaveric livers and need living donor livers (47). We believe that pediatric patients should be hospitalized in centers with active split or living donor liver transplantation programs.

CONCLUSION

Preventable causes of acute liver failure in Turkey include hepatitis viruses and intoxication. Active vaccination and public awareness can decrease the number of acute liver failures. Paracetamol is not an emerging reason for acute liver failure in Turkey now, but selling it over the counter may increase the risks.

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