



# Evaluation of Geriatric Patients Hospitalized for Toxic Hepatitis in a University Hospital

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## Abstract

**Introduction:** Toxic hepatitis is a common condition that causes impaired liver function. In the geriatric population, factors that further increase the existing risk of toxic hepatitis include an age-related physiological decline in liver function, polypharmacy and the use of herbal products as natural remedies for health problems. This study aims to investigate the causes of toxic hepatitis and comorbid clinical conditions in patients aged 65 years and over who were hospitalized for toxic hepatitis.

**Methods:** Data were collected by retrospective analysis of the medical records of 15 patients aged 65 years and older who were treated for toxic hepatitis in the geriatric ward of a university hospital between January 2019 and December 2019.

**Results:** The mean age of the patients was  $69.53 \pm 7.22$ , and 73.3% (n=11) were women. The most common chronic comorbidity was hypertension (46.7%). The most common suspected etiological factor for toxic hepatitis was an edible plant from the genus *Ferula* that is cultivated in the wild in Erzurum and its vicinity (locally known as *çaşır otu*). None of the patients developed fulminant hepatic failure or acute tubular necrosis during follow-up. All 15 patients in this study recovered and were discharged.

**Discussion and Conclusion:** The geriatric population is at risk for toxic hepatitis due to age-related physiological changes, polypharmacy, higher rates of chronic disease, and more frequent use of herbal medicines.

**Keywords:** Herbal medicine; elderly; toxic hepatitis.

Toxic hepatitis is a common problem that causes liver dysfunction. It may cause a mild biochemical abnormality and lead to severe acute liver failure<sup>[1]</sup>. Causes of toxic hepatitis are divided into three groups as drugs, natural toxic agents and chemicals. It has been, stated that besides medicines, vitamins, alcohol and similar substances, some of the medicinal plants can cause toxic hepatitis<sup>[2]</sup>. Besides, the risk of toxic hepatitis also increases concerning

genetic factors, various diseases, chemical content of the drug, chronic alcohol use, and sex and older age<sup>[3–5]</sup>.

As is known, the geriatric population carries risks in many conditions and is considered as a special age group. One of the conditions that pose a risk in old age is toxic hepatitis. Increasing aging of the population and the proportion of the elderly individuals in the total population, and incidence of chronic diseases, especially non-communicable

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chronic diseases, and symptoms that impair quality of life; and consequently, increasing drug use increases the risk of toxic hepatitis in elderly individuals<sup>[6, 7]</sup>.

Depending on the age, the physiological decline of liver functions, use of herbal products as a result of multiple drug use, as well as search for natural remedies for health problems are other factors that support the increase of the current risk<sup>[6, 8]</sup>.

An inverse relationship has been reported between liver volume and blood flow with age. It has also been indicated that hepatic perfusion decreases and liver weight decreases with age<sup>[9–11]</sup>. In addition, due to the increase in age, some changes in the cellular size and deterioration in activities are manifested by the decline in the metabolism of some drugs and products, together with a decrease in the hepatic blood flow, even if it is not at large rates. Hydroxylation, dealkalization, reduction reactions occur with phase I metabolism in drug metabolism in the liver, mainly provided by microsomal cytochrome p450 enzyme. This phase enables the transition of drugs or toxins to phase II. Conjugation, acetylation and methylation steps are also provided in the phase II step<sup>[12]</sup>. It has been shown that cytochrome p450 level decreases with aging and there is a decrease in excretion of many drugs and toxins<sup>[13]</sup>.

In animal studies, it has been shown that pseudocapillarization increases with aging, the sinusoidal endothelial cell decreases, the hepatic sinusoidal endothelium thickens, and collagen accumulation increase in the Disse space<sup>[14,15]</sup>. In addition, the toxic levels of drugs increase in the elderly due to decreased hypoalbuminemia, d biliary secretion and glutathione levels<sup>[15]</sup>. Considering the literature, it is seen that studies on toxic hepatitis in the geriatric population are limited. This study aims to investigate the causes and clinical conditions of toxic hepatitis in individuals aged 65 years and older who were diagnosed with toxic hepatitis.

## Materials and Methods

The data of the study were obtained by retrospective analysis of the data of 15 patients aged 65 and over who were followed up in a geriatric ward of a university hospital between January 2019 and December 2019 with the diagnosis of toxic hepatitis. All patients were tested for hepatitis A, B and C. In addition, ANA, AMA and SMA antibodies were evaluated for autoimmune hepatitis. These diagnoses are excluded.

The data were evaluated in SPSS 21.0 statistical package

program. The descriptive data were categorized with frequency distribution and percentage, and continuous variables were presented as means ( $\pm$ ) standard deviation and median (maximum, minimum) values. Spearman correlation analysis was performed to evaluate the relationship between the laboratory variables measured at the beginning and during hospitalization, and the time interval between hospital admission, and the contact with the suspected etiologic agent and the value of statistical significance was accepted as  $p < 0.05$  in statistical analyzes.

## Results

The mean age of the patients included in this study was  $69.53 \pm 7.22$ , years, and 73.3% (n=11) of them were women. When the current chronic diseases were examined, it was observed that hypertension was the most common (46.7%) one, followed by diabetes and heart valve diseases (13.3%), coronary artery diseases and malignancy (6.7%) (Table 1). Alcohol and drug addiction were not detected in the patients' history.

Laboratory and clinical findings of the patients when they apply to the hospital due to toxic hepatitis are presented in Table 2. It was found that nausea, vomiting and abdominal pain (60%) were the most common findings, and the baseline median ALT (alanine aminotransferase), and AST (aspartate aminotransferase) values were more than 10 times normal. Among the suspicious factors thought to be responsible for toxic hepatitis, most frequently the wild herb grow in in Erzurum and its surroundings, and known among local residents of Erzurum as giant fennel (*fennula communis*) was detected (Table 3).

The correlation between the duration of hospitalization and the time elapsed between admission to the hospital after contact with the suspect factor and the laboratory variables at baseline was evaluated (Table 4). A statistically significant, and strongly positive correlation was found between day of hospitalization and total bilirubin levels ( $p = 0.006$ ,  $r = 0.674$ ). The median time interval between hospital admission and contact with the suspected agent was

**Table 1.** Current chronic diseases of elderly individuals

Chronic Disease	n (%)
Hypertension	7 (46.7)
Diabetes mellitus	2 (13.3)
Cardiac valve disease	2 (13.3)
Coronary artery disease	1 (6.7)
Malignancy	1 (6.7)

**Table 2.** Baseline clinical and laboratory findings of the patients with toxic hepatitis

Clinical Findings	n (%)
Nausea	9 (60.0)
Vomiting	9 (60.0)
Abdominal pain	9 (60.0)
Lassitude	5 (33.3)
Jaundice	3 (20.0)
High fever	2 (13.3)
Skin rash	1 (6.7)
Laboratory Findings	Median (minimum–maximum)
Creatinine (mg/dL)	0.70 (0.35–2.70)
AST (U/L)	638 (147–4441)
ALT (U/L)	698 (184–4629)
ALP (U/L)	185 (63–760)
GGT (U/L)	220 (22–856)
INR	1.15 (0.95–2.45)
Total Bilirubin (mg/dL)	1.44 (0.45–15.27)
Direct Bilirubin (mg/dL)	0.40 (0.09–7.64)
Eosinophil (%)	0.90 (0–7.70)

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; INR: International Normalized Ratio.

**Table 3.** Presumptive causes of the toxic hepatitis in study patients

Suspected factors	n (%)
Giant fennel	5 (33.3)
Fungi	2 (13.3)
Coriander seed or a medication not known by the name	1 (6.7)
Black sesame	1 (6.7)
Green tea	1 (6.7)
Thyme tea	1 (6.7)
Methotrexate disodium	1 (6.7)
Ciprofloxacin and nitrofurantoin	1 (6.7)
Unknown healing herb	1 (6.7)
Deltamethrin	1 (6.7)

**Table 4.** Correlation between the length of hospital stay and laboratory variables

	Creatinine	AST	ALT	ALP	GGT	INR	Total Bilirubin
Length of hospital stay (days)	r=0.189	r=0.322	r=0.288	r=0.463	r=0.118	r=0.237	r=0.674*
p	0.500	0.242	0.298	0.082	0.676	0.396	0.006
Time passed after contact with the suspected agent (hours)	r=-0.310	r=-0.101	r=-0.207	r=-0.004	r=0.324	r=-0.196	r=-0.026
p	0.261	0.721	0.460	0.990	0.239	0.483	0.927

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; INR: International Normalized Ratio.

48 (3-720) hours and the median length of hospital stay was 5 (3-34) days. In the follow-up of the patients, fulminant liver failure and acute tubular necrosis did not develop. All 15 patients included in the study were discharged with complete recovery.

## Discussion

Toxic hepatitis is a pathology that often causes hepatic dysfunction. It has a wide clinical spectrum<sup>[1]</sup>. In our study, it was observed that the majority of patients presented with nonspecific symptoms, such as nausea, vomiting and abdominal pain. The elderly population is mostly exposed to over-the-counter drugs (OTCs) and herbal medicines. In a study conducted in Germany with 466 people aged 70 and above, it was observed that 3.7% of the elderly used prescription and 1.4% of them OTC drugs<sup>[16]</sup>. In a study involving 271 individuals aged 50 and over in the UK, it was observed that the average use of prescription drugs was 2.26 and the use of herbal medicine was 5.91<sup>[17]</sup>. In a study conducted by Karaman et al.<sup>[8]</sup> in our country, 15.7% of the patients reported that they used at least one of herbal supplements. In the literature, herbal treatment was observed to be more than 1 in 3 in two case series performed on people with an average age of 50<sup>[18]</sup>. In our study, it was observed that people who were hospitalized for toxic hepatitis mostly used herbal supplements. Toxic hepatitis cases have been reported in the literature for nitrofurantoin and ciprofloxacin that we have also used in our study.

Generally, an age-independent relationship between duration of medication use and toxic hepatitis was also emphasized in cases<sup>[19, 20]</sup>. Methotrexate disodium, whose hepatotoxicity was frequently reported, was detected in one of our patients., *F. communis*, which is known as "giant fennel" among people, may cause bleeding in cats and humans<sup>[17]</sup>. Although this plant is known to have an antibacterial effect, the substance ferulenol it contains has toxic effects,

disrupts the interaction between microtubules, causes mitochondrial dysfunction, and also impairs oxidative phosphorylation<sup>[21, 22]</sup>. Although animal studies have shown that it significantly reduced the level of coagulation factors, its effect on bleeding has not been fully understood<sup>[17, 21]</sup>. Previously, cases of toxic hepatitis that developed in our region with that herb were reported in the literature<sup>[23]</sup>. In our study, it was observed that the most common indication of hospitalization in patients was related to toxic hepatitis that arises from giant fennel.

Generally, the time between the development of liver damage after the use of a drug or herbal supplements is between one week and three months. The regression of laboratory findings after cessation of the drug or herbal supplement is pathognomic<sup>[1]</sup>. In the literature, it has been observed in some cases that the symptoms of toxic hepatitis occur months after exposure to the agent, and in some cases, develop within hours after exposure to the toxin<sup>[24]</sup>. In our study, the median time to hospital admission was found to be 48 hours after contact with the suspected agent, but none of these patients developed fulminant liver failure.

The limitation of our study is that it was performed in a single center and only among hospitalized geriatric patients. To our knowledge, the strength of our study is that this was the first study to examine toxic hepatitis in the elderly population.

In conclusion, the geriatric population is at risk of toxic hepatitis due to physiological changes, polypharmacy, increasing chronic diseases and increasing frequency of herbal medication use.

**Ethics Committee Approval:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: P.T.T., H.D.; Design: P.T.T., O.K.; Data Collection or Processing: M.F.V.; Analysis or Interpretation: O.K.; Literature Search: P.T.T., O.K.; Writing: P.T.T., O.K.

**Conflict of Interest:** None declared.

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