Drug-Induced Acute Liver Failure

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KEYWORDS

• Drug hepatotoxicity • Liver failure • Cerebral edema • Encephalopathy
• Liver transplantation

KEY POINTS

- Drug-induced acute liver failure (ALF) disproportionately affects women and nonwhites. It is predominantly caused by antimicrobials, complementary and alternative medications, antimetabolites, antiepileptics, nonsteroidals, and statins.
- It presents as severe hepatic dysfunction characterized by jaundice, encephalopathy, and coagulopathy, in a patient without prior liver disease.
- Cerebral edema and intracranial hypertension are the most serious complications, which require intensive monitoring and therapy.
- Although advances in intensive care have improved survival, ALF has significant mortality without liver transplantation.

INTRODUCTION

Although advancements in intensive care management have considerably improved the outlook of patients with acute liver failure (ALF), it remains a diagnosis that has grave prognostic implications.[1] ALF or fulminant hepatic failure is severe hepatic dysfunction that is characterized by rapid onset, hepatic encephalopathy, and coagulopathy, in the absence of preexisting liver disease.[1,2] Fortunately, it is a rare disease with 2000 to 3000 reported cases in the United States per year.[3] Among 6199 adult liver transplant recipients in the United States in 2014, 239 (3.9%) had ALF.[4] ALF is a syndrome of varied causes, including acetaminophen, idiosyncratic drug-induced liver injury (DILI), viral hepatitis A, B, and E, Epstein-Barr and herpes simplex hepatitis, autoimmune hepatitis, Wilson disease, shock liver, and acute fatty liver of pregnancy.[5]

Disclosures: The authors have nothing to disclose.
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http://dx.doi.org/10.1016/j.cld.2016.08.003

1089-3261/16/Published by Elsevier Inc.

DILI is a major cause of ALF. In a retrospective population-based study, 62 patients were deemed to have definite or possible ALF, and among them, 32 (52%) had acetaminophen or DILI cause.[6] Acetaminophen was implicated in 18 events (56%), dietary/herbal supplements in 6 events (19%), antimicrobials in 2 events (6%), and miscellaneous medications in 6 events (19%). Acute liver failure study group (ALFSG) is a consortium of major liver centers in the United States that has prospectively collected data from ALF subjects since 1998. Among 1198 patients enrolled at 23 sites over a period of 10 years, acetaminophen toxicity was responsible for 46% of cases, whereas DILI was noted in 11%.[5,7] Sixty-one unique agents were implicated in the causation of DILI, alone or in combination. Antimicrobials were the commonest cause, in particular isoniazid, trimethoprim-sulfamethoxazole, nitrofurantoin, and antifungal agents. Other offending drugs included complementary and alternative medications, antiepileptics, antimetabolites, nonsteroidals, and statins. The implicated DILI ALF agents were taken from 1 to 2 weeks, up to 8 months, and most subjects (65%) did not stop the drug until or after jaundice developed.

CLINICAL FEATURES

Jaundice, hepatic encephalopathy, and coagulopathy are the cardinal manifestations of ALF.[8] However, the syndrome often presents with nonspecific symptoms such as fatigue, malaise, anorexia, nausea, abdominal pain, and fever.[9] These symptoms progress to the development of encephalopathy and coagulopathy, although the rates of progression are somewhat variable. Coagulopathy often precedes the onset of encephalopathy. There are no characteristic features that differentiate DILI ALF from other causes. Nevertheless, DILI can be distinguished from other causes of ALF by the drug history and subacute course. Typical allergic signature drug reactions are less frequently noted in DILI ALF patients than suggested by a survey of common causes of DILI.[7,10]

DILI-associated ALF tends to occur in younger adults and more commonly in women than men. In the ALFSG study, the average age of subjects was 44 years; only 15% were older than 60 years, and the majority was women (71%).[7] In addition, compared with the US general population, nonwhites were overrepresented (43% vs 25%). On admission to the tertiary site, 68% had grade 2 or higher encephalopathy, 25% had clinically detectable ascites, and jaundice was typically noted. Most patients with DILI ALF have hepatocellular pattern of liver injury. In the ALFSG study, 78% had hepatocellular injury, 13% had cholestatic injury, and 10% had mixed pattern. About one-half of patients depicted some degree of renal impairment with serum creatinine greater than or equal to 1.5 mg/dL. Drug injury from herbal medications, traditional therapeutic preparations, and dietary supplements was more commonly associated with hepatocellular liver injury than prescription medications. Skin rash and eosinophilia were noted in a minority (8%), whereas autoantibodies were positive in 63% of the patients tested.

Encephalopathy

Hepatic encephalopathy may vary from subtle changes in affect, insomnia, and difficulties with concentration (grade 1) to deep coma (grade 4).[11] Cerebral edema (CE) is a common neurologic accompaniment of ALF unlike encephalopathy associated with chronic liver disease. It occurs in most patients who progress to grade 4 encephalopathy and is the most commonly identifiable cause of death in autopsy studies. The pathogenesis remains unclear but both vasogenic and cytotoxic mechanisms play a role.[12] CE may be recognized by the development of systemic hypertension,