MINI REVIEW

Epidemiology of liver failure

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Summary The etiology of fulminant hepatitis varies in different countries and at different times. The main causes of fulminant hepatitis are viruses, paracetamol, drugs (other than paracetamol), poisons and 15–30% remained of undetermined origin. The prevalence of these etiologies varies according to the geographic region and has changed over the past 10 years. Paracetamol has now overtaken viruses (particularly hepatitis B virus) as the leading cause of fulminant hepatitis. Establishing the cause of fulminant hepatitis is an important step in the management of acute liver failure, so that specific therapy can be initiated and any contraindications to liver transplantation be eliminated.

Fulminant hepatic failure is characterized by a deterioration in liver function and hepatic encephalopathy. Three main definitions have been proposed for fulminant hepatitis (FH) including acute hepatitis complicated by acute liver failure (ALF) with hepatic encephalopathy occurring less than 8 weeks after the onset of jaundice. The definition of FH is important because of its implications to the prognosis. Likewise, there are many causes of ALF and various definitions have been proposed [1–3]. The common points of these definitions are the occurrence of encephalopathy during the course of FH in a patient without previously known hepatopathy and the spontaneous poor prognosis with a mortality rate of 85%.

The main causes of FH are viral infection, drugs, or indeterminate. Early elucidation of the cause of ALF is one reason to refer patients to a specialist center as quickly as possible so that its consequences can be established promptly and appropriate treatment initiated. Another important reason to refer patients is so that they can be considered for emergency liver transplantation. It is only in this setting that the different available prognostic scores can be applied.

Etiology of fulminant hepatitis

There are many causes of FH, which vary with geographic region. The most frequent causes worldwide include viral hepatitis (particularly hepatitis A (HAV) and B (HBV)), medication overdose (in particular paracetamol), idiosyncratic drug reactions, ingestion of toxins and metabolic disorders. In addition to these known etiologies, indeter-
Epidemiology of liver failure

Indeterminate causes accounted for 30% [5]. From the Euro-Liver (1.5%), Budd-Chiari syndrome (5%) and others (1%). Autoimmune (2.5%), pregnancy related (2.5%), Wilson’s disease (56.5%) from non-paracetamol causes. The non-paracetamol patients (43%) had ALF resulting from paracetamol and 178 Bernal et al., including 310 patients from 1994 to 2004, 132 cellaneous etiologies in 14% [4] (Fig. 1, Table 1). In a study by paracetamol or toxins in 18%, unknown origin in 17% and mis-

HCV antibodies), autoimmune (autoantibody titers, gamma globulin levels), metabolic (serum caeruloplasmin level, 24-
hour urinary copper, cupriuria).

In a survey in the USA carried out between 1998 and 2008, the major etiologies of ALF in 1147 patients were paracetamol overdose (46%), followed by indeterminate cause (14%), drug-related ALF (11%), HBV (7%), other (7%), autoimmune hepatitis (AIH) (5%), ischemic hepatitis (4%), HAV (3%), and Wilson’s disease (2%). In UK, the first cause of FH is paraceta-
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Pregnancy related ALF is more frequent in the UK than in North America. In the UK, ALF or fulminant hepatic failure is more often due to an intentional paracetamol overdose whereas in the USA paracetamol hepatotoxicity is usually secondary to an accidental overdose (ingestion of multiple doses of parac-
tamol for pain relief without suicidal intent). A comparison of 122 subjects with intentional overdose and 131 subjects with unintentional overdose shows many differences [16]. Overall, unintentional overdose subjects were signifi-
cantly older (median, 38 years) than those who attempted suicide (median, 32 years) (p = 0.002), and used multiple paracetamol-containing preparations more frequently (38% vs. 5%, p = 0.0001). Accidental overdose patients were less likely to report depression (24% vs. 45%, p < 0.0001), have severe (grade 3 and 4) hepatic encephalopathy on admission compared to intentional overdose subjects (55% vs. 39% respectively, p = 0.002). In these two groups of patients, the number listed for transplantation and time to transplanta-
tion did not differ. Paracetamol dose was significantly lower in accidental overdose victims (median, 12 g) than in those with a suicidal intent (median, 20 g) (p = 0.009). Chronic alcohol consumption, malnutrition probably played a role in the occurrence or worsening of liver injury. In addition, several studies strongly suggested that therapeutic doses

With antiviral therapy, the incidence and overall morbidity of HBV reactivation decreases significantly. HBV represented around 50% of the cases of ALF until the early 1990s. Since then, there has been a decline in HBV FH in Europe. France has also seen a sharp decline in the number of cases of HBV-

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Table 1  Incidence of different etiologies of fulminant hepatitis in various countries according to year.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Ref</th>
<th>Years</th>
<th>No. of patients</th>
<th>Main etiologies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Paracetamol</td>
<td>Drug-induced, not paracetamol</td>
</tr>
<tr>
<td>Williams R</td>
<td>London</td>
<td>[12]</td>
<td>1973–1993</td>
<td>1257</td>
<td>765 (60.9%)</td>
<td>77 (6%)</td>
</tr>
<tr>
<td>Shakil AO</td>
<td>Pittsburgh</td>
<td>[51]</td>
<td>1983–1995</td>
<td>177</td>
<td>33 (19%)</td>
<td>21 (12%)</td>
</tr>
<tr>
<td>Brandsaeter B</td>
<td>Nordic countries</td>
<td>[21]</td>
<td>1990–2001</td>
<td>315</td>
<td>52 (17%)</td>
<td>31 (10%)</td>
</tr>
<tr>
<td>Ostapowicz G</td>
<td>USAa</td>
<td>[19]</td>
<td>1998–2001</td>
<td>308</td>
<td>120 (39%)</td>
<td>40 (13%)</td>
</tr>
<tr>
<td>Farmer DG</td>
<td>UCLA</td>
<td>[52]</td>
<td>1984–2001</td>
<td>204</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Gow PJ</td>
<td>Australia</td>
<td>[20]</td>
<td>1988–2001</td>
<td>80</td>
<td>29 (36%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Samuel D</td>
<td>France</td>
<td>[4]</td>
<td>1986–2006</td>
<td>363</td>
<td>26 (7%)</td>
<td>75 (21%)</td>
</tr>
<tr>
<td>Escorsell A</td>
<td>Spain</td>
<td>[15]</td>
<td>1992–2000</td>
<td>267b</td>
<td>6 (2.2%)</td>
<td>36 (13.5%)</td>
</tr>
<tr>
<td>Areia M</td>
<td>Portugal</td>
<td>[14]</td>
<td>1992–2006</td>
<td>61</td>
<td>1 (2%)</td>
<td>13 (21%)</td>
</tr>
<tr>
<td>Miyake Y</td>
<td>Japan</td>
<td>[22]</td>
<td>1990–2001</td>
<td>80</td>
<td>0</td>
<td>15 (18.7%)</td>
</tr>
<tr>
<td>Mudawi HMY</td>
<td>Sudan</td>
<td>[53]</td>
<td>2003–2004</td>
<td>37</td>
<td>0</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Bernal W</td>
<td>London</td>
<td>[5]</td>
<td>1994–2004</td>
<td>310</td>
<td>132 (42%)</td>
<td>26 (8%)</td>
</tr>
</tbody>
</table>

a 17 tertiary care centers.

b 20 /267 children.

c B: 77, B-Delta: 16, HBV reactivation: 7.
d hepatitis B and D.
e HCV: 2.
f HEV 2.
of paracetamol might be associated with an increased liver injury in patients with liver failure form other causes liver disease [11,17,18].

Drug-related ALF (not due to paracetamol) is a frequent cause of hepatitis. The incidence varies with geographic country. The incidence is of 2.5% in the UK [12], 13% in the USA [19], 6% in Australia [20], 19.5% in Spain [15], 21% in Portugal [14] 10% in Nordic countries [21], 22% in Japan [22] and 15% in France [8]. In Scottish series, non-paracetamol drugs were implicated in 4.8% (30/625 cases of ALF) of cases. The most common drugs related to ALF were antibiotics (23%) followed by ecstasy (3,4 methylidioxymethamphetamine, MDMA) (20%), antituberculosis antibiotics (13%), non-steroidal anti-inflammatory drugs (7%), and aminosalicylates (7%) [23]. Ecstasy is a common cause of FH consumed mainly by young people and taken for its amphetamine-like stimulatory effect, increasing energy and reducing awareness of fatigue [24]. The clinical presentation is hypothermia, hypotension, fits, disseminated intravascular coagulation and rhabdomyolysis associated with severe hepatic damage. Young people with severe hepatitis of unknown origin should be investigated thoroughly.

Table 2 Rare causes of fulminant hepatic failure.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Year</td>
<td>N</td>
<td>315</td>
<td>308</td>
<td>80</td>
<td>363</td>
<td>61</td>
</tr>
<tr>
<td>Total miscellaneous cause</td>
<td>48 (15%)</td>
<td>59 (19%)</td>
<td>8 (10%)</td>
<td>77 (22%)</td>
<td>14 (23%)</td>
<td>31 (11.6%)</td>
</tr>
<tr>
<td>Ischemic hepatitis</td>
<td>1 (0.3%)</td>
<td>17 (6%)</td>
<td>—</td>
<td>21 (6%)</td>
<td>—</td>
<td>6 (2.2%)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>7 (2%)</td>
<td>13 (3%)</td>
<td>—</td>
<td>16 (4.6%)</td>
<td>2 (3%)</td>
<td>13 (4.9%)</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>5 (2%)</td>
<td>8 (3%)</td>
<td>6 (7%)</td>
<td>15 (4%)</td>
<td>3 (5%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>16 (5%)</td>
<td>5 (2%)</td>
<td>2 (3%)</td>
<td>1 (0.3%)</td>
<td>4 (6.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Pregnancy-related liver failure</td>
<td>2 (0.6%)</td>
<td>6 (2%)</td>
<td>—</td>
<td>6 (2%)</td>
<td>—</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Neoplastic infiltration</td>
<td>2 (0.6%)</td>
<td>4 (1%)</td>
<td>—</td>
<td>5 (1.5%)</td>
<td>2 (3%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Heat stroke</td>
<td>6 (2%)</td>
<td>—</td>
<td>1 (0.3%)</td>
<td>—</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mushroom ingestion</td>
<td>6 (2%)</td>
<td>—</td>
<td>—</td>
<td>5 (1%)</td>
<td>3 (5%)</td>
<td>—</td>
</tr>
<tr>
<td>Viral other (EBV, HCV, HGV, parvovirus B19)</td>
<td>3 (1%)</td>
<td>—</td>
<td>—</td>
<td>7 (2%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Post-surgery liver failure</td>
<td>5 (2%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Metabolic liver failure</td>
<td>1 (0.3%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
due to the relatively high number of causes of ALF or FH in these individuals. In a large US retrospective cohort study performed from 1987 to 2006, 661 patients were transplanted for drug-induced acute liver failure. The 4 leading implicated drug groups were acetaminophen (n = 265; 40%), antituberculosis drugs (n = 50; 8%), antiepileptics (n = 46; 7%), and antibiotics (n = 39; 6%). The survival probabilities after liver transplantation were significantly lower in patients with antiepileptics induced acute liver failure compared to the others drugs [25]. More recently, in a multicenter, prospective study, drug-induced acute liver failure accounted for 11.1% (133 patients) among 1198 subjects enrolled at 23 sites in United States. 81.1% were considered highly likely by expert opinion, 15.0% probable and 3.8% possible. Over 60 individual agents were implicated and the most common were antimicrobials (46%). Transplant-free (3 weeks) survival was poor (27.1%), but transplantation was successful in 42.1% [26]. Among the patients with drug-induced liver injury, the risk of progressing to death or transplantation was calculated at 11.7% in the series of Andrade RJ et al. The anti-infective group of drugs was the more frequently incriminated and amoxicillin-clavulanate accounting for the 12.8% [27].

Despite intensive investigations and the use of the most modern techniques (PCR methods, molecular techniques, genomic DNA, biochemical), the causes of most cases of FH or ALF remain unknown: 26% in Portugal [14], 12% in Australia [28], 43% in Nordic countries [21], 18% in France. In addition to viral, drug/toxin (paracetamol or other), and indeterminate causes of ALF or FH, a large number of cases are classified as other causes (Table 2). The main "other causes" include rare viruses (HSV-1 and -2 infection, varicella zoster virus (VZV) infection, parvovirus B19), a fulminant course of Wilson’s disease, Budd-Chiari syndrome, Reye’s syndrome, autoimmune hepatitis, acute autoimmune hepatitis (AIH), massive malignant infiltration of the liver (liver metastasis, leukemia, lymphoma), hypoxic hepatitis due to cardiac failure, heatstroke, fatty infiltration of the liver, and HELLP syndrome. Overall, the incidence of these rare cases varies from 11—23%. In France, miscellaneous causes included hypoxic hepatitis, Autoimmune Hepatitis (AIH), heatstroke, Wilson’s disease, Budd-Chiari syndrome, Reye’s syndrome, HELLP syndrome, neoplasia, and acute fatty pregnancy. In Nordic [21] countries between 1990 and 2001, the etiology of the majority of cases could not be established. These indeterminate cases of FH represented 43% of patients, followed by paracetamol (17%), viral hepatitis (10.2%), and non-paracetamol drug-induced (10%) [21].

HSV-related hepatitis is a rare cause of FH, and is included most of the time in different reports under "miscellaneous causes". The spontaneous prognosis of HSV-related hepatitis is poor, in spite of the existence of antiviral treatment [29]. Despite the rarity of HSV-1 and -2 related ALF or FH, the diagnosis should always be considered in immunocompetent or immunocompromised patients with high fever, with or without leukopenia, with or without skin or genital lesions, and with or without marked elevations in aminotransferase levels after exclusion of other common causes. HSV hepatitis can follow both recurrent and primary HSV infection in immunocompromised hosts. In immunocompetent hosts, however, only primary infections have been associated with hepatitis. Both HSV types can induce severe or fulminant acute hepatitis although HSV-2 is more frequent. Serological assays are of very limited value for establishing an early diagnosis. Thus, molecular methods (real time PCR) in particular appear the most reliable for diagnosis [30].

As well as HSV, diagnosis of VZV infection must be considered when the classical etiologies have been eliminated in the presence of severe abdominal pain, fever, chills, malaise, fatigue, mild elevation of aminotransferase levels and skin lesions. A definitive diagnosis can be established rapidly by VZV DNA detection in serum by PCR [31]. In the above two cases, histology and immunostaining of transjugular liver biopsy specimens can help to establish or confirm a diagnosis of HSV or VZV hepatitis, which shows nuclear inclusion.

The hepatitis E virus (HEV) is an enterically transmitted RNA virus responsible for large waterborne epidemics of acute liver failure or fulminant hepatitis in developing endemic regions (India, Central America, Africa, Asia) [32]. Traditionally, North America and Europe have been considered as non-endemic countries. Recently, a rising incidence of acute hepatitis E have been reported in these industrialized regions [33,34]. The disease in endemic regions is caused by genotype 1 HEV; in autochthonous countries, HEV is caused by HEV of genotype 3 or 4. The symptoms include: abdominal pain with vomiting and diarrhea, arthralgia, myalgia, fever, asthenia, jaundice, hepatomegaly. Jaundice can persist for many weeks. The diagnosis of HEV infection is made on presence of anti-HEV IgM antibodies and HEV RNA (in serum and/or feces during the acute phase). However, hepatitis E serological tests have limitations and final diagnosis is HEV RNA. The overall mortality due to Hepatitis E fulminant liver failure in endemic regions varies from 0.5% to 4% [35], but in pregnant women with HEV fulminant hepatitis, mortality is higher (20%). Peron JM et al. showed that acute sporadic hepatitis E in France can appear as fulminant hepatitis. All hepatitis E virus sequences evaluated were of genotype 3. Severity of the prognosis was related to the age at diagnosis and presence of underlying chronic liver disease [36]. In a long-term prospective study from Italy, 20.6% of patients with non A, non C hepatitis (134/651) had acute hepatitis E and 109 of them (81.3%) developed the disease traveling to endemic areas (Indian subcontinent) by viral genotype 1, 3 (2.3%) acquired intra-familial infection, and 22 (16.4%) patients an autochthonous acute hepatitis E caused by genotype 3. In all cases, patients improved within 3—6 weeks [37,38]. Recently, several studies have reported some cases of chronic progression of hepatitis E [39]. Thus, patients with unexplained causes of acute liver failure, with or without travel in endemic countries, should be screened for HEV infection.

Severe forms of autoimmune hepatitis (AIH), and particularly inaugural severe forms of AIH, are a rare cause of FH, which most often affects young women. After eliminating the common causes of FH, diagnosis is based on the presence of gamma globulin levels greater than 20 g/L, significant titers of autoantibodies, the presence of a marked lymphoplasmocytic infiltrate on histological examination of transjugular liver biopsy specimens [40]. The standard initial treatment of AIH for the induction of remission is either prednisone monotherapy or combination therapy with prednisone and azathioprine. With this conventional treatment, remission, defined as a complete biochemical and histolog-
Epidemiology of liver failure

In the fulminant presentation of Wilson’s disease, diagnosis is based on a combination of a young adult or child, with a familial history of liver disease, Coombs-negative hemolysis, significant ratio of alkaline phosphatase/total bilirubin and aspartate aminotransferase, alanine aminotransferase, rhodanine test positive and/or the presence of arguments from liver histology of transjugular liver biopsy specimens, and the absence of other causes of FH. Other arguments favoring a diagnosis of Wilson’s disease include the following: presence of Kayser-Fleischer rings on slit lamp examination, low serum caeruloplasmin level (< 0.21/L), elevated 24-h urinary copper excretion (> 1.6 μmol/24-h). Diagnosis of Wilson’s disease is confirmed by quantitative hepatic copper measurement (> 250 μg/g dry weight) and by genetic analysis.

At the FH stage, chelator therapy is ineffective [43]. Hemolysis syndrome, elevated liver enzymes and low platelets (HELLP syndrome) is a rare complication of pregnancy (1 to 6/1000 deliveries). Fulminant hepatic failure is one of the complications of HELLP syndrome. With other morbidities such as subcapsular liver hematoma, major intraabdominal bleeding, disseminated intravascular coagulation, acute renal failure, intracerebral hemorrhage, and pulmonary edema, these complications occur in 2–3% of patients. The cause of HELLP syndrome is unclear, but endothelial cell dysfunction probably plays an important role. HELLP syndrome is usually associated with preeclampsia. The majority of cases of liver rupture occur in multiparous patients more than 30 years of age. Immediate delivery is the definitive treatment for HELLP syndrome. The prognosis depends on the early recognition of HELLP and can be improved by prompt treatment. Management of patients with HELLP syndrome is multidisciplinary. In series from the literature and from the UNOS database of 17 patients, the main indications for liver transplantation in HELLP syndrome were liver necrosis and subsequent liver failure following rupture and uncontrolled bleeding. The maternal survival rate is over 80%. Shames et al. proposed an algorithm for the management of complicated HELLP syndrome [44–46].

Hyponic hepatitis is a relatively common cause of ALF or FH (6% in our series) [8]. The most frequent underlying conditions, in the series of Henrion et al., were cardiac failure (70%), congestive heart failure (56%), circulatory shock (septic, toxic, traumatic, hemorrhagic, hypovolemic), and chronic respiratory failure [47]. Shock state is not a prerequisite for the occurrence of hypoxic hepatitis. Hyponic hepatitis results from an association of several hypoxic mechanisms depending on the underlying condition. In a few cases, hypoxic hepatitis is inaugural and occurs in patients without prior history of cardiac or respiratory disease [48].

Diagnosis of Budd-Chiari syndrome must be suspected in patients with acute liver failure or fulminant hepatic failure, with ascites and evidence of hepatic congestion. Diagnosis of hepatic vein occlusion is made by ultrasonography and confirmed by hepatic MRI or angio CT-scan or hepatic venography. Fulminant form of Budd-Chiari can only be treated by liver transplantation [49].

Changes in etiology over time

In a recent Spanish study of 267 patients, Escorsell et al. found significant changes in the causes of ALF over time. Between 1992 and 1995, viral infections were the predominant cause of ALF (61/145 cases, 42%). However, between 1995 and 2000, viral etiology decreased to 30% (37/122 cases). In the same period of time, toxic substance or drug-related ALF increased (27% vs. 13% before 1995). However, paracetamol had the lowest increase among these drugs [15]. The same evolution was observed in our experience and in Europe. In 500 patients referred in our department for ALF, the main causes of ALF, until 1996 were acute viral hepatitis in 42%, drug- or toxin-related FH in 25%, other etiologies in 11% and indeterminate origin in 22%. After 1996, HBV decreased significantly (15%, p < 0.0001), whereas paracetamol overdose increased significantly (15%) [8].

The USA has followed the same evolutionary trends. In the series of 459 patients reported by Detre et al. [50], between 1987 and 1991, roughly one-third had HBV-related fulminant hepatitis (22.9%), one-third had NANB hepatitis (22.9%), followed in frequency by drug- or toxin-induced liver injury (paracetamol: 4.6%; others drugs: 10.7%); HCV and HAV, respectively. More recently, in another North America series of 308 patients with ALF, paracetamol was the most common cause (39%), followed by indeterminate cause (17%), idiosyncratic drug reactions (13%), HBV and HAV infection (7%), and other causes (24%) [19].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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