# SEVERE ACUTE LIVER FAILURE RELATED TO VIRAL, TOXIC OR AUTOIMMUNE HEPATITIS : A REVIEW OF 27 CASES

# INSUFFISANCE HEPATIQUE AIGUE SEVERE SECONDAIRE A UNE HEPATITE VIRALE, TOXIQUE OU AUTO-IMMUNE : ETUDE RETROSPECTIVE DE 27 ENFANTS

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**Résumé**

Introduction: L'insuffisance hépatique aigue sévère (IHAS) peut être secondaire à une hépatite aigue virale, toxique ou auto-immune partageant un tableau clinique similaire.

Patients et méthodes : Etude rétrospective menée de 2006 à 2013 colligeant tous les patients hospitalisés pour une IHAS secondaire à une hépatite aigue virale, toxique ou auto-immune.

Résultats : vingt sept patients ont été colligés. L'âge moyen est de 6 ans (extrêmes : 16 jours à 13 ans). La présentation clinique a été marquée par une asthénie et une anorexie (85%), un ictère (66%) et une fièvre (37%). Une encéphalopathie hépatique est survenue dans 44%. L'hépatite virale était l'étiologie la plus fréquente (74%) suivie de l'hépatite auto-immune (18,5%) puis l'hépatite toxique (7,5%). L'évolution était marquée par la guérison dans 74%. Une issue fatale a été notée dans 26% des cas.

Conclusion : L'enquête étiologique doit être urgente avec une prise en charge précoce et adaptée afin d'améliorer le pronostic.

**Mots clés :** insuffisance hépatique aigue ; encéphalopathie hépatique ; hépatite ; enfant.

**Abtract**

Introduction: Numerous etiologies of hepatitis may lead to acute liver failure. Viruses are the most common cause of hepatitis. Other causes include toxins and autoimmune liver disease. These forms of hepatitis share the same clinical and biological features.

Patients and methods: Retrospective study between 2006 and 2013 of children diagnosed with acute liver failure secondary to infection with viruses, hepatotoxic drugs and toxins or autoimmunity.

Results: Twenty-seven children were included in the study. The mean age was 6-year-old (range: 16-day-old to 13-year-old). The common symptom at diagnosis was weakness and anorexia in 85% followed by jaundice (66 %) and fever (37%). Hepatic encephalopathy occurred in 44 %. Viral hepatitis was the commonest etiology in 74 % of cases followed by auto-immune hepatitis (18,5%) than by toxic hepatitis (7,5 %). The outcome was good in 74 % of cases with normalization of hepatic tests. A fatal outcome was found in 26 % of cases.

Conclusion: The search for causes of acute liver failure should be done urgently. Early and well-conduced management may improve the outcome.

**Key words :** acute liver failure; hepatic encephalopathy; hepatitis; children.

**ملخص:**

المقدمة: قد يكون قصور الكبد الحاد ناجما عن التهاب الكبد الفيروسي الحاد، أو ناجم عن تسممات كبدية أو اعتلال الكبد المناعي الذاتي و تقاسم كل منها صورة سريرية مشابهة.

المرضى والطرق: دراسة استعادية لوجود قصور الكبد الحاد الناجم عن التهاب الكبد الفيروسي الحاد أو السمي أو المناعي الذاتي.

النتائج: تم جمع سبعة وعشرين مريضا. وكان متوسط عمر مجموع الأشخاص 6 سنوات (من 16 يوما إلى 13 عاما). وقد تميزت العلامات السريرية من الوهن وفقدان الشهية (85٪)، واليرقان (66٪) والحمى (37٪). حدث اعتلال الدماغ الكبدي في 44٪. كان التهاب الكبد الفيروسي المسبب الأكثر شيوعا (74٪)، يليه التهاب الكبد المناعي الذاتي (18.5٪) والتهاب الكبد السام (7.5٪). وقد تميز تطور المرض نحو البرء في 74٪. ولوحظ وجود نتائج قاتلة في 26٪ من الحالات.

الخلاصة: يجب أن يكون مسح خاص لأسباب هذا المرض بصفة عاجلة مع الرعاية المبكرة.

**الكلمات المفاتيح:** قصور الكبد الحاد; التهاب الكبد ; اعتلال الدماغ الكبدي ; الطفل.

## 1/Background

Acute liver failure (ALF) is a severe and sudden onset of hepatocyte dysfunction leading on to synthetic and detoxification failure, which could progress to multi-organ failure and death [1].
Common causes vary with age and geographical location [2]. Identification of the etiologic factors must be done urgently in an aim to apply the adequate therapy, and to manage the patient within a specialized hepatology reanimation unit in close contact with a liver transplantation center [1,3].
The purpose of our study is to describe clinical and biological features and the outcome in a cohort of patients with acute liver failure due to acute severe viral, toxic or autoimmune hepatitis.

## 2/ Methods

The medical records of all children younger than 14 years of age admitted to our department, with ALF secondary to infection with viruses, hepatotoxic drugs or autoimmune attack of hepatocytes in over a period of 8 years, from January 2006 to December 2013, were reviewed.
Severe ALF was defined as the presence of prothrombin time (PT) < 50 % without preexisting liver disease. Time to hepatic encephalopathy (HE) was defined as time from first symptom to onset of encephalopathy.
The medical records of patients were analyzed by precising their demographic data, past or personal history, biochemical parameters at admission and the initial time when encephalopathy occurred, clinical manifestations, ultrasonographic findings, and hospital course to access the predicting factors for mortality in ALF children.

## 3/ Results

Twenty-seven children were included in the study. Clinical Characteristics and biological features are summarized at table I.

The mean age was 6-year-old (range: 16-day-old to 13-year-old). Females were more predominant than males (15*vs*12). Consanguinity was found in 7 cases.

The common symptom at diagnosis was weakness and anorexia in 85% followed by jaundice (66 %) and fever (37%). Digestive signs were present in 17 cases and nasal bleeding was the first symptom in 4 cases.

Physical examination showed jaundice in 23 cases associated with hepatomegaly in 13 cases. HE occurred in 44 % with irritability (2cases) and unconsciousness (10 cases).

High transminases was ten times more than the normal levels in 23 cases with a mean level of AST 2048 IU/L (extreme: 312-5548 IU/L) and ALT 1562 IU/L (extreme: 218-4822 UI/L). High total bilirubin level was observed in 20 cases with a mean level of 237 µmol/l (extreme: 30-574 µmol/l). The mean level of direct bilirubin was 180 µmol/l. The mean level of PT was 20% and was lower than 20% in 6 cases.

Symptomatic treatment was instituted in all cases in intensive care unit with use of plasma, glucose and mannitol.

None of the patients had a liver transplantation which was impossible in our country for lack of available liver transplant centers.
Viral hepatitis was the commonest etiology in 74 % of cases (hepatitis A virus infection in 18 cases; non-A-E hepatitis virus (unknown viruses) in 2 cases). Viral hepatitis was followed by auto-immune hepatitis (18,5%) than by toxic hepatitis (7,5 %) secondary to Tars and herbs in one case and to treatment with sodium valproate in the other case.

Complications such as digestive bleeding, respiratory distress, status epilepticus and hypoglycemia were observed.
The outcome was good in 74 % of the cases with normalization of hepatic tests. A fatal outcome was found in 26 % of the cases.

**Table I:** Clinical and biological features of children with acute liver failure secondary to acute severe viral, toxic or autoimmune hepatitis

| | Total number (sex: F/M) | Mean age (years) | Jaundice (case) | Hepato-megaly (case) | HE (case) | Transaminases level | | TB (µmol/l) | DB (µmol/l) | PT (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | <10 N | >10N | | | |
| **hepatitis A virus infection** | 18 (8/10) | 7,5 | 15 | 8 | 7 | 3 | 15 | 358 | 300 | 24,5 |
| **non-A-G hepatitis virus (unidentified viruses)** | 2 (2/0) | 6 | 2 | 1 | 2 | 0 | 2 | 197 | 140 | 16 |
| **auto-immune hepatitis** | 5 (3/2) | 2 | 3 | 0 | 3 | 0 | 5 | 200 | 165 | 21.5 |
| **toxic hepatitis** | 2 (2/0) | 4,5 | 1 | 0 | 0 | 1 | 1 | 194 | 115 | 18 |

**Abbreviations :** Hepatic encephalopathy; **TB :** mean level of total biluribin; **DB :** direct level of total biluribin; **PT:** mean level of prothrombin time.

## 4/ Discussion

ALF is a rare syndrome, the result of rapid hepatocyte injury occurring over days or few weeks. Numerous etiologies of hepatitis lead to ALF and have a similar clinical and biological features [2,3].
As the onset of disease might be in utero and difficult to establish, Bhaduri and Mieli-Vergani [4] defined ALF in children as “a rare multisystem

disorder in which severe impairment of liver function, with or without encephalopathy, occurs in association with hepatocellular necrosis in a patient with no recognized underlying chronic liver disease”.
The Paediatric Acute Liver Failure study group [2] used the following criteria: i) Hepatic-based coagulopathy defined as a PT greater than or equal to 15 seconds or international normalized ratio (INR) greater than or equal to 1.5 not corrected by vitamin K, in the presence of clinical HE, or a PT greater than or equal to 20 seconds or INR greater than or equal to 2.0 regardless of HE, ii) Biochemical evidence of acute liver injury, iii) No known evidence of chronic liver disease.

Patients usually present with icterus and markedly raised serum transaminase levels. HE usually is a late feature and is not essential for the diagnosis [2,4,5].

The determination of etiology of ALF is very important to plan the management strategy and to predict outcome [6,7]. Viral hepatitis is the most common cause of ALF in the developing countries, while drug-induced ALF is more common in developed world [8,9].
Proportion of liver failure attributable to hepatitis virus infection is different from region to another [6,8].

Hepatitis A virus (HAV) infection is the most common cause of ALF in developing countries [10,11]. The diagnosis of acute hepatitis A is made by the detection of the anti-HAV immunoglobulin M antibody in serum. In 95% of cases, the anti-HAV immunoglobulin M antibody is present at the time of presentation, and the remaining 5% become positive while repeating test [10]. In our Study, eighteen patients had ALF due to hepatitis A which is the predominant etiology in our series and in our country. Hepatitis B virus as a cause of ALF is less common in children than in adults as the perinatal

infection in most of the infants leads to a chronic state; however, infants born to mothers positive for the antibody to hepatitis Be antigen are a special group that can present with ALF around 3 weeks to 3 months of age [11]. Hepatitis E virus infection, a water-borne infection like hepatitis A and a well-recognized cause of ALF, is common in the Indian subcontinent and in Africa [8,11]. Numerous studies showed that pediatric LAF is most frequently caused by hepatitis without an identifiable specific viral agent called Non-A-G hepatitis. In our series, two out of 27 cases of ALF were due to unidentified hepatitis virus or non-A-G hepatitis virus [12].

Although viruses are the most common cause of hepatitis, other causes include toxins. Drug-induced injury is the second main cause of acute liver failure and predominates in much of the developed world [6]. Drugs and toxins are well known to cause liver failure in children [13]. In general, risk factors for drug-induced hepatotoxicity are age (very young children or adolescents), abnormal renal function, concurrent use of other hepatotoxic agents, drug interactions and preexisting liver diseases. Drug-induced hepatoxicity can be a dose-dependent response, an idiosyncratic reaction, or a synergistic reaction. In our series, one patient presented with sodium valproate hepatotoxicity and the second had ALF due to toxic plants.

Autoimmune hepatitis (AIH) is an uncommon cause of ALF and is usually associated with second type autoimmune hepatitis, particularly in children [14]. The diagnosis may be difficult as some cases were seronegative and do not show auto-antibody response at presentation. Many pathogenic events occur; for instance, an important loss of homeostasis with multiorgan failure as the main outcome includes an uncontrolled immune response. Most of these patients have liver/kidney microsome antibody positive which was the case of three patients of our series [15].

Management of ALF is especially symptomatic [18]. Causal treatment is not available for many types of acute liver failure. Liver transplantation offers the best chance of long term survival in children with severe ALF. It's the only definite treatment. An INR >4 or factor V concentration of <25% is considered the best available criteria for listing for liver transplantation [17,18]. It is important to exclude genetic multisystem disorders before considering liver transplantation [6]. The molecular adsorbent recirculating system (MARS) has been proposed in children with severe ALF awaiting liver transplantation [19,20]. The MARS treatment improved the clinical status and can lead to improvement of hepatic tests without liver transplantation [20].

Severe ALF carries a high mortality [1-3,8]. Predictors of poor outcome were advanced encephalopathy, peak bilirubin >220 µmol/l and INR >4 [7,16]. The magnitude of transaminase elevation and the rate of decline do not predict prognosis. In patients who spontaneously recover, serum bilirubin, the INR, and serum transaminases gradually decline, whereas continued increases in bilirubin levels and INR, despite declining serum transaminase levels, indicate massive hepatocyte necrosis and poor prognosis [6,16,17].

## 5/ Conclusion

Recent advances in extracorporeal liver support and hepatic transplantation have provided an opportunity to convert fulminant hepatic failure from an enigmatic, often fatal syndrome to a manageable medical emergency. Progress in this area and the benefits to children and families will come only with a carefully designed, coordinated, multicenter, collaborative effort among multiple pediatric hepatology to promote creation of liver transplant centers in our country.

## REFERENCES

[1] Dhawan A. Acute liver failure in children and adolescents. Clin Res Hepatol Gastroenterol 2012: 36, 278-283

[2] Squires RH Jr, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the Pediatric Acute Liver Failure Study Group. J Pediatr 2006; 148:652-658.

[3] Devictor D, Tissieres P, Durand P, Chevret L, Debray D. Acute liver failure in neonates, infants and children. Expert Rev Gastroenterol Hepatol. 2011;5:717-29

[4] Bhaduri BR, Mieli-Vergani G. Fulminant hepatic failure: pediatric aspects. Semin Liver Dis 1996;16:349—55.

[5]Datar S, Wijdicks EF. Neurologic manifestations of acute liver failure. Handb Clin Neurol 2014;120:645-59

[6] Dhawan A. Etiology and Prognosis of Acute Liver Failure in Children.Liver Transpl 2008;14:S80-S84.

[7] Rajanayagam J, Coman D, Cartwright D, Lewindon PJ. Pediatric acute liver failure: etiology, outcomes, and the role of serial pediatric end-stage liver disease scores. Pediatr Transplant 2013;17:362-82.

[8] Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet 2010; 376:190-201.

[9] Lee WM. Recent developments in acute liver failure. Best Pract Res Clin Gastroenterol 2012; 26: 3–16

[10] Shah U, Habib Z, Kleinman RE. Liver failure attributable to hepatitis A virus infection in a developing country. Pediatrics 2000;105:436-438.

[11] Arora NK, Nanda SK, Gulati S, et al. Acute viral hepatitis types E, A, and B singly and in combination in acute liver failure in children in north India. J Med Virol 1996;48:215-221
[12] Whitington PF, Alonso EM.Fulminant hepatitis in children: evidence for an unidentified hepatitis virus. J Pediatr Gastroenterol Nutr. 2001;33:529-36.
[13] Amathieu R, Levesque E, Merle JC, et al. Severe toxic acute liver failure: etiology and treatment. Ann Fr Anesth Reanim 2013;32:416-21.
[14] Stravitz RT, Lefkowitch JH, Fontana RJ, et al. Acute Liver Failure Study Group. Autoimmune acute liver failure: proposed clinical and histological criteria. Hepatology 2011;53:517-26
[15] Czaja AJ. Acute and acute severe (fulminant) autoimmune hepatitis. Dig Dis Sci 2013;58:897-914.
[16] Cicocca M, Ramonet M, Cuarteola M, et al. Prognostic factors in paediatric acute liver failure. Arch Dis Child 2008;93:48-51.
[17] D'Agostino D, Diaz S, Sanchez MC, Boldrini G. Management and prognosis of acute liver failure in children. Curr Gastroenterol Rep 2012;14:262-9
[18] Bhatia V, Bavdekar A, Yachha SK. Management of acute liver failure in infants and children: consensus statement of the pediatric gastroenterology chapter, Indian academy of pediatrics. Indian Pediatr 2013;50:477-82.
[19] Tabata S, Cavarocchi NC, Hirose H. Successful management of severe liver failure on venoarterial extracorporeal membrane oxygenation using molecular adsorbent recirculating systeme. J Heart Lung Transplant 2012;31:1322-3
[20] Novelli G, Rossi M, Morabito V, et al. Pediatric acute liver failure with molecular adsorbent recirculating system treatment. Transplant Proc 2008;40:1921-4