

Subacute Hepatic Failure

Kora S A, Doddamani G B, Doddamani Usha, Biradar Satish

ABSTRACT

Subacute hepatic failure (SAHF) had been recognized and reported from India in 1982, but until now, there has been no precise definition of the disease or the description of its nomenclature, clinical and pathological factors, aetiology, diagnosis and its management.

So, we have analyzed all the material which was available for over 30 years and have summarized a few points.

- a) Poor regeneration of hepatocytes is the main pathogenesis of this disease.
- b) Viral hepatitis, including hepatitis 'E', is the main aetiology of SAHF.

- c) Ascites is the cardinal feature of this disease and it occurs in the 4th or 5th decade.
- d) Liver biopsy shows submassive or bridging necrosis and plasma fibronectin levels are low.
- e) The mortality is upto 70% when treated medically and the best available treatment is liver transplantation.
- f) Renal failure indicates a bad prognosis.

It can be concluded that it requires further case studies and research to define the disease and to describe its nomenclature, aetiology, pathogenesis, clinical features, prognostic factors, investigation and management in the coming years.

Key Words : Subacute hepatic, Onset hepatic, Subfulminant hepatic failure.

MAIN ARTICLE

The liver is the largest organ of the body, weighing 1 to 1.5 kg and representing 1.5 to 2.5% of the lean body mass. A majority of the cells in the liver are hepatocytes, which constitute two-thirds of the mass of the liver. Inflammation of the hepatocytes leads to hepatitis. Hepatitis can be caused by drugs and toxic agents as well as by numerous viruses. Hepatitis can further be classified into acute and chronic hepatitis.

Hepatic failure is defined as the occurrence of the signs or symptoms of hepatic encephalopathy in a person with severe acute or chronic liver disease. In fulminant hepatic failure, encephalopathy occurs in less than 2 weeks of the onset of jaundice.

Sub acute hepatic failure (SAHF) had been recognized and reported from India in 1982 as a clinical entity which was distinct from fulminant and chronic hepatic failure and was characterized by progressive or persistent jaundice, 8 weeks after the onset of hepatitis, with unequivocal evidence of ascites in the absence of pre-existing liver diseases. Various western researchers, by using different names, have reported similar clinico-pathological entities.

DEFINITION AND TERMINOLOGY

Tandon et al 1982 [1],[2] coined the term SAHF and proposed that its diagnosis was made on the basis of

1. Persistence or progressive jaundice, 10 weeks after the appearance of icterus in a patient with acute hepatitis.
2. Development of unequivocal ascites and or encephalopathy, 10 weeks after the appearance of the icterus.
3. Biochemical evidence of hepatocellular necrosis.
4. Sub-massive or bridging necrosis on liver biopsy whenever the tissue is obtained.

Within the next 4 years, various European, Asian and American workers proposed different terms for similar syndromes which occurred in patients with acute liver diseases.

Gimson et al (King's College Group) [1],[3] used the term, Late Onset Hepatic Failure (LOHF), when encephalopathy and other evidences of hepatic decompensation occurred between 8 to 24 weeks after the first symptoms of illness.

According to O'Grady JG et al [4], LOHF is diagnosed when encephalopathy occurs later than 4 weeks after jaundice and when the cut off for encephalopathy [5] is 8 weeks.

Bernau et al [1],[6] preferred the term, Sub-Fulminant Hepatic Failure (SFHF), when acute liver failure was complicated by encephalopathy, 2 weeks to 3 months after the onset of jaundice. An American study (Peleman et al) [1],[7] considered the term SAHF when irreversible liver failure developed 8-28 weeks after the onset of symptoms in an individual without prior evidence of hepatic decompensation.

It is clear therefore, that there is an ongoing debate about the following points:

1. Nomenclature of the condition- subacute hepatic failure, late onset hepatic failure or sub-fulminant hepatic failure.
2. Which first symptom (Jaundice or any other non-specific symptom of acute illness) should be considered as the starting point of the original disease?
3. What should be the period between the onset of jaundice or hepatic illness and the onset of later symptoms which are suggestive of SAHF (2 to 12 weeks)?
4. Last, but not the least, whether ascites or encephalopathy should be the symptoms which are suggestive of SAHF.

According to the International symposium on SAHF, March 1993, there are several inclusion and exclusion criteria. [8],[9]

A) Inclusion Criteria:

- I) Jaundice persisting for more than 8 weeks after its onset, with the development of unequivocal ascites with or without encephalopathy.
- II) SGPT (ALT) levels twice the upper limit of the normal.

B) Exclusion Criteria:

- I) Presence of dilated biliary radicals on sonography.
- II) Evidence of varices larger than Grade-I on endoscopy.
- III) Alcoholism.
- IV) Chronic renal failure.
- V) Kayser Fleischer ring or low ceruloplasmin level.
- VI) Liver biopsy (either ante-mortem or post-mortem); histological evidence of established cirrhosis.

AETIOLOGY

The most common aetiology of SAHF is viral hepatitis and its incidence ranges from 60 % to 90% of all hepatic diseases. In various series, the distribution of different viruses in cases of SAHF due to viral hepatitis [10],[11] is shown in [Table/Fig 1].

Name of Virus	Shah.et al	D.Amarapurkar. et al	U.Zacharisah. et al
'A' Virus	00	04%	03%
'B' Virus	18	34%	19%
'C' Virus	17	58%	00%
'D' Virus	00	04%	00%
'E' Virus	00	00%	16%

[Table/Fig 1]: Distribution of different viruses in cases of SAHF due to viral hepatitis

The role of the hepatitis 'E' Virus is yet to be established because the prognosis of hepatitis 'E' Virus SAHF is very good [12] as compared to the prognosis of other viruses, drug toxicities (eg: troglitazone) [13] and autoimmune diseases [5] are other causes of SAHF. The history of herbal medicines is important, as these drugs are used routinely in the Asian sub-continent for the treatment of jaundice and it could be a possible aetiological factor.

PATHOGENESIS

In viral hepatitis, continuing liver cell necrosis with poor regeneration of the liver cells may lead to SAHF. [10] Impaired hepatic regeneration may probably be related to age, which explains the frequent occurrence of SAHF in the 4th and 5th decades.

In experimental liver injury which was produced by galactosamine, submassive hepatic necrosis was prevented by hepatopietin (a low molecular weight peptide which promotes hepatic regenerations) in Wister rats. This probably explains the failure of the regeneration of hepatocytes as the main pathogenic event in SAHF.

Hepatopietin has a trophic and an antiapoptotic effect on hepatocytes and multiple cell lines. (The levels of hepatopietin, measured by ELISA, are elevated both in fulminant and chronic liver diseases as compared to those in the normal controls). No data on the hepatopietin levels in SAHF is available as yet.

The mechanism of ascites (Lebree et al) [14] in case of SAHF, is the increased wedged hepatic venous pressure which is secondary to the collapse of the sinusoids, which means that the intrahepatic block is the cause of portal hypertension in SAHF which leads to ascites.

PATHOLOGY

Submassive or bridging necrosis is characteristic of SAHF. Histology shows the features of viral hepatitis with bridging necrosis, which may be portal to portal, central to central, or portal to central. Regenerating activity is conspicuous by its absence. Necrotic areas contain a large amount of polymorphonuclear infiltration and a significant number of plasma cells.

Other features like the ballooning degeneration of the hepatocytes, lobular inflammation, cholestasis and the ductal proliferation of the bile ducts can be seen.

CLINICAL FEATURES

Age: SAHF is commonly encountered in the 4th and 5th decades; less than 2% patients were below the age of 20 years in a series of patients in Delhi. Other researchers who have described comparable entities under different terminologies as LOHF, SFHF, impaired regeneration syndrome and subacute hepatic necrosis, have observed a similar preponderance. The only exception was a report from USA where the mean age of the patients with SAHF, who underwent liver transplantation, was 28.7. A series from Vellore (TamilNadu) reported 32 cases with SAHF, with a mean age of 36±15 years.

Jaundice and ascites were the cardinal features and encephalopathy was the terminal event. [Table/Fig 2].

	Shah et al [8]	Tandon et al [2]	Gimson et al [3]	U.Zacharisah et al [11]	Pruti HS et al [15]
Jaundice	100%	100%	100%	100%	100%
Ascites	80%	80%	60%	100%	100%
Encephalopathy	40%	60%	80%	31%	27%

[Table/Fig 2]: Distribution of Clinical features of Sub acute hepatic failure in various studies

The main clinical difference in FHF and SAHF was the slower tempo of the illness with ascites as a major manifestation in SAHF, in contrast to the rapid progression to encephalopathy in patients of FHF. Cerebral oedema was present in 80 to 100 % of the cases of FHF and was uncommon in SAHF (Gimson et al – 9%) [3]

Hepatomegaly was present in 40 to 60 % and splenomegaly was present in 10 to 30 % of the SAHF cases. Other clinical features like nausea, vomiting, abdominal pain, and fever have been reported in 20 to 80 % of the cases. Cerebral oedema was uncommon in patients with SAHF as compared to FHF and renal failure and SBP occurred more in SAHF cases. The incidence of bacteraemia, sepsis and GI bleeding was similar in acute and subacute hepatic failure cases. When these cases were treated medically, the mortality ranged from 70 to 90 %. Renal failure accounted for upto 50 % deaths, while GI bleeding and infection accounted for 30% of the deaths. All the survivors developed chronic liver diseases within 1 to 2 years. [Table/Fig 3].

	Shah et al [8]	Tandon et al [2]	Gimson et al [3]
GI Bleed	10%	20%	40%
Renal Failure	30%	40%	50%
Infection	10%	10%	15%

[Table/Fig 3]: Complications of Sub acute hepatic failure in various studies

INVESTIGATIONS

Liver function tests suggested hepatocellular necrosis. Predominantly, conjugated S.Bilirubin was elevated, SGPT levels were increased, but they did not rise above 6 times the normal [8] [Table/Fig 4].

	Shah et al [8]	Tandon et al [2]	Gimson et al [3]
S.Bilirubin	16	17	16
SGPT	200	150	250

[Table/Fig 4]: Liver function tests Sub acute hepatic failure in various studies

The prothrombin time was markedly prolonged [8]

- S. Albumin levels were also decreased mildly. (In the Naik et al series, the mean Albumin level was 3.0 gm / dl)
- Ascitic fluid was transudative in nature,
- The coagulation factors II, V, VII, IX and X were decreased below 50% of the normal. The estimation of the factor 5 levels was shown to have a diagnostic, prognostic and therapeutic role in SAHF according to some series [8].
- The plasma fibronectin concentration was significantly low in SAHF cases as compared to the normal and uncomplicated acute viral hepatitis cases. [10],[16]. This may be the cause for impaired kupffer cell function and the consequent susceptibility to endotoxaemia and bacterial infections. The opsonisation activity was markedly impaired and it correlated well with secondary infections.
- Serum alpha fetoprotein levels were normal or low.
- Liver biopsy showed sub-massive or bridging necrosis.

MANAGEMENT

Aims of therapy

Logically, the therapeutic formulations should be based on pathogenesis. Based on the available information about the pathogenesis, the desired therapeutic aims of SAHF are [8]:

- I) Control of liver cell necrosis.
- II) Acceleration of liver cell regeneration.
- III) Replacement of necrosed liver tissue.
- IV) Supportive therapy for liver failure.

I) Control of liver cell necrosis:

Today, at present, there are no standard drugs to prevent liver cell necrosis. Many controlled trials have shown that corticosteroids are not useful in FHF cases and that it is same for SAHF also. The role of other immunomodulators have not been studied in SAHF cases. The role of interferons was proved in case of chronic hepatitis and these did not show any good results in FHF. The role of these drugs in SAHF has to be studied. The role of antivirals like acyclovir, adenosine arabinose and interleukins is yet to be studied. The available studies do not [8],[18] show any good results with any of the drugs.

II) Therapy to accelerate liver cell regeneration:

There is no effective treatment for liver cell regeneration as yet. This is because we still do not know about the specific hepatocyte growth factors and the "Stem cells" which possibly repopulate the liver after massive hepatic necrosis.

PROSTAGLANDINS

In one series, Sinclair et al[19] treated 17 patients with FHF and SAHF by PGE-1 at a rate of 0.2 to 0.6 microgram / kg / h, for upto 28 days. Two of these patients underwent liver transplantation

and 12 of the remainder (80%) survived. But the other two series failed to reproduce the same amount of results. These drugs acted by maintaining the integrity of the micro vascular circulation and cytoprotection. So, the role of prostaglandins is yet to be established [8].

HEPATOCTE GROWTH FACTORS

Historically, there are two main theories for the growth factor control of hepatic regeneration. The first is that the reduction in the liver mass stimulated the production of positive growth factors and the second theory is that the normal liver mass decreases the local inhibitor and that the liver starts to regenerate until the normal inhibitor tone is restored. [17] Now, a recent theory has combined both these theories and has suggested that it is a complex interaction between stimulatory and inhibitor influences on growth.

Hepatocyte growth factors are capable of inducing hepatocyte replication by inducing the synthesis of DNA in hepatocytes. However, these are not organ specific. Epidermal growth factor (EGF), insulin, glucagon, norepinephrine, hepatocyte growth factor (HGF) and transforming growth factor (Alpha and Beta) are the known growth factors. EGF is the growth factor for several epithelial tissues and it induces DNA synthesis in hepatocytes. Its activity (in vivo) is markedly increased by the actions of Insulin and glucagon.

In one series, insulin and glucagon had promoted liver regeneration, but the results were not satisfactory in other series. So, the role of these hormones needs to be further evaluated in SAHF.

Transforming growth factor alpha and beta are stimulators and inhibitors respectively in the DNA synthesis of hepatocytes. TGF alpha has a 30 to 40 % sequence homology with EGF and can also bind to the EGF receptor and initiate hepatocyte replication. TGF alpha is more potent than EGF.

Recently, the hepatocyte growth factor (HGF) (hepatotrophin, probably identical with hepatopietin A) was identified and it was found to be specific for hepatocytes. The non-parenchymal cells of the liver secrete it. So, further research on these factors can help us to treat SAHF by regenerating the liver cells.

(iii) Replacement of necrosed liver tissue:

(a) Liver support systems and bio-artificial liver [8]:

Now- a -days – the ex vivo linear support which is generated by developing the bio-artificial liver, is becoming a reality. Now, two such devices are being used in clinical evaluation.

- One- this uses pig hepatocytes and is perfused with the plasma by a technique which is similar to plasmapheresis.
- Second - extra-corporeal liver assist device (EALD).

The EALD is still in the stages of early development and it may be useful. This device uses C-3A hepatoblastoma cells which are grown in hallow fiber cartridges. When EALD is used, blood passes through the porous channels between the cell chambers and the removal of bilirubin and the synthesis of S. albumin with the clotting factors is observed.

The device which is used currently contains 200 gm of hepatocytes as compared to 2000 gm of hepatocytes in normal adult liver . However, there are no accessory cells such as the bile duct epithelial cells, the kupffer cells and the endothelial cells which contribute substantially to the function of the liver. In recent reports

from several, small, uncontrolled studies, these devices were found to improve encephalopathy, intracranial pressure and several biochemical measures. But controlled trails are needed and these will act as a bridge to transplantation in several patients.

(b) Liver transplantation:

The curative treatment for FHF is orthotopic liver transplantation and survival rates of 50 to 70 % have been reported. It may prove to be useful in SAHF, but some points have to be noted here. One exact status of viral replication is not known in SAHF and it is difficult to assess the chances of the recurrence of viral replication in transplanted livers.

Further, at least 20 to 30 % of the patients with SAHF do survive the illness. Until the prognostic factors are known, it would be difficult to predict as to which patient would die and which one would benefit from transplantation.

U.Zachariah et al[11], concluded from their study, that the worsening renal failure in hospitals could be used as markers for liver transplantation. In a study by Bruno et al [18] the survival rate after transplantation was found to be 75%. Selection criteria for liver transplantation is same as for fulminant hepatic failure, example the Kings or the Clichy criteria which are used in Berne for LOHF:

- Factor V < 20 % in patients who were less than 30 years old.
- Factor V < 30 % in patients who were more than 30 years old.

At some centers, auxiliary liver transplantation is suggested for FHF/ LOHF, in which the native liver has to be left in place. Such patients have a survival rate of 65 %; in these series, the native liver was found to recover its function by 70 to 80 %, thus allowing the discontinuation of immunosuppression. The long-term effect of immunosuppression in these patients is not known. So, the available information indicates that liver transplantation is one of the best available treatments for SAHF and that it needs thorough evaluation.

(c) Hepatocyte transplantation:

This is one of the most important things that have emerged in the field of hepatology. Here, hepatocytes which were transplanted on the spleen were shown to survive for more than one year, they showed sinusoidal structures and bile canaliculi and possessed several liver specific enzymes. Thus, this procedure is a potential replacement for a more complex and expensive liver transplantation.

(iv) Supportive therapy:

The patients should be admitted to the ICU, with the maintenance of nutrition by either the oral or the parenteral route (about 1500 Kcal with low sodium diet). Fluid and electrolyte balance is a must. Diuretic therapy with spiralanolactone and frusemide may be

useful. Complications like GI bleeding, infections and hepatorenal syndrome should be treated.

CONCLUSION

Further case studies and research regarding the definition, nomenclature, aetiology, pathogenesis, clinical features, prognostic factors, investigation and the management of this disease is essential in future.

REFERENCES

- [1] S.R.Naik, Subacute hepatic failure, post-graduate medicine 1994; 8: 105-8.
- [2] Tandon. B.N., Joshi.Y.K., Krishnamurthy et al, subacute hepatic failure; is it a distinct entity ? J. clin. Gastroentero. 1982; 4: 362-4.
- [3] Gimson AE, 'O' Grady, Ede RJ et al, Late onset hepatic failure, clinical, serological and histological features, Hepatology. 1986; 6: 288-94.
- [4] 'O' Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993; 342 (8866) : 273-275.
- [5] Fujiwara K, Mochida S, Matsui A, et al. Fulminant hepatitis and late onset hepatic failure in Japan. Hepatol Res. 2008;38 (7): 646-657
- [6] Bernau J, Rueff B, Benhamou P, Fulminant and sub-fulminant liver failure, Definition and causes, Seminar liver diseases. 1986; 6: 97-106.
- [7] Peleman R.R, Gavler JS, Van Thiel DH et al, Orthotopic liver transplant for acute and subacute hepatic failure in adults, Hepatology 1987; 7: 484-489.
- [8] Sharad Shah, Subacute hepatic failure, Medicine Update – 1995; 9: 220-224
- [9] Shah S.R., Shah SC (ed) Proceedings of the international symposium on subacute hepatic failure, Indian. J. Gastroenterology 1992; 2 (suppl-2): 1-28.
- [10] D.M. Amarapurkar, Shah SC, Shah SR, Subacute hepatic failure, JAPI 1993; 41/ 6: 381-382.
- [11] U Zachariah, S Choudhury, C Eapen. et al – Prognostic factors in subacute hepatic failure: An Indian perspective; The Canadian. J. Gastroenterology 2009, 23(supplement A), (<http://www.pulsus.com/cddw2009/abs/063.html>)
- [12] Ramachandran J, Ramakrishna B, Eapen CE, et al. Subacute hepatic failure due to hepatitis E. J.Gastroenterol Hepatol. 2008; Jun23(6): 879-882.
- [13] Miya Fukano, Shigeru Amano, Jin Sato, et al. Subacute hepatic failure associated with a new antidiabetic agent, troglitazone: A case report with autopsy examination, Human Pathology. 2000; 31/ 2: , 250-253
- [14] D.Lebree, O.Nouel, J.Bernau et al, Portal hypertension in fulminant viral hepatitis, Gut 1980; 21: 962-964.
- [15] Pruthi HS, Anand AC, Singh B et al, Subacute hepatic failure a clinical profile, Medical J. Armed Forces India, 1998; Oct 54(4): 335-336.
- [16] Fibronectin in Acute and subacute hepatic failure, Journal of Clinical Gastroenterology;1989; Jun3 11/ 3 (http://journals.lww.com/jcge/Abstract/1989/06000/Fibronectin_in_Acute...)
- [17] A.C.Selden, HJF Hodgson, growth factor and the liver, Gut 1991; 32: 601-603.
- [18] Bruno Strelbel , Jurg Reichen; Late onset hepatic failure; Institute of clinical pharmacology and Visceral research, University Bern, Switzerland, 2008; 09,(<http://www.ikp.unibe.ch/lab2/loh.html>)
- [19] Sinclair, Abecuss M, Falk M et al. Treatment of fulminant hepatic failure with a continuous infusion of prostaglandins. Hepatology. 1987; 7: 109.

AUTHOR:

1. KORA S A
2. DODDAMANI G B
3. DODDAMANI USHA
4. BIRADAR SATISH

NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr.Kora.S.A,'Shailaja Nilaya', Mahaveer Road, BAGALKOT- 587 101, (Karnataka-India), E-mail: shreeramkora@yahoo.co.in

DECLARATION ON COMPETING INTERESTS: No competing Interests.

Date of Submission: **12/9/2010**
Peer Review Completion: **12/27/2010**
Date of Acceptance: **12/28/2010**
Date of Online First Publication: **1/7/2011**
Date of Final Publication: **02/06/2011**