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Hepatic Failure after Injury – A Common Pathogenesis with Sclerosing Cholangitis?*

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Abstract

Objective: Hepatic failure after trauma occurs in about 5 – 10 % of multiple injured patients. Mortality rate remains high and liver dysfunction might deteriorate to complete liver failure and contribute to multi organ failure (MOF). Pathogenesis is multifactorial and distinct mechanisms are unknown.

Methods: To get further knowledge about pathogenesis of posttraumatic liver failure we investigated clinical course, inflammatory mediators, ERCP and histologic findings in 7 patients [6 male, 1 female, mean age 45.7 ± 12.1 years, mean ISS 38.4 ± 10.8 pts. (range 25-58 pts.)] that evolved hepatic failure after major trauma. Mortality rate was 14 %.

Results: All patients presented with a prolonged shock period after trauma and severe respiratory failure requiring differentiated ventilatory support and prone positioning. Onset of significant bilirubinemia (> 2.0 mg/dl) was day 3 to 16 days (median 11 days) after trauma. Past medical history did not reveal any underlying liver disease in all patients. Pro-and anti-inflammatory parameters like WBC, Procalcitonin, IL-4, IL-10, IL-11, IL-12, and IL-18 remained close to healthy control values. CRP was elevated but did not correlate with Bilirubin. Transaminases (ALT, AST) remained close to normal values but increased during the further course, whereas alkaline phosphatase (aP) and gamma-glutamyl transpeptidase (γGT) were already significantly elevated even before Bilirubin (γGT: 394 ± 317 U/l; controls: < 56 U/l; aP 557 ± 311 U/l; controls: < 127 U/l). Although no cholestasis was proven in ultrasound and CT investigations, all patients underwent ERCP and liver biopsy. Here, all patients presented uniform signs of multiple strictures of the intrahepatic bile ducts and sclerosing cholangitis.

Conclusions: Our data provide evidence that sclerosing cholangitis contributes to liver failure after trauma. The pathomorphologic picture can not distinguish between shock liver and sclerosing cholangitis. Ischemia during posttraumatic shock might be an early trigger of hepatic failure, supported by further contributing factors such as catecholamines, parenteral nutrition, and bacterial translocation. As specific therapy for sclerosing cholangitis does not exist yet, prevention of triggers is central to avoid progressive hepatic failure in those patients. Further prospective studies have to prove whether sclerosing cholangitis is commonly involved in the pathogenesis of liver failure after trauma and shock. If so, one might speculate that early therapy with ursodeoxycholic acid might be effective thus reducing incidence and/or severity of hepatic failure in the future.

Key words: sclerosing cholangitis, trauma, hepatic failure, vanishing bile duct, ICU

Short Introduction

Cholestasis with subsequent hepatic failure after trauma is a well known entity that occurs in about 5 – 10 % of multiple injured patients [1, 2]. Mortality rate remains high and liver dysfunction might exacerbate to complete liver failure. The pathogenesis is multifactorial and distinct mechanisms remain unknown. Among others, hepatic hypoxia, mass transfusions, total parenteral nutrition and inflammation are held responsible [3-5].

A number of cholestatic syndromes with chronic cholestasis, cholangiocyte proliferation and consecutive cholangiocyte loss, ductopenia, fibrosis and portal inflammation are summarized as "vanishing bile duct" disorders with a variety of underlying etiologies [6].

Reports on patients with secondary sclerosing cholangitis after trauma or burn injury and consecutive treatment on intensive care units with and without sepsis and septic shock are rare [3, 7-10]. Benninger describes posttraumatic sclerosing cholangitis with the following six characteristic features: absence of former liver disease, severe injury with temporary severe arterial hypotension, slowly increasing signs of cholestasis, secondary moderate rise of aminotransferases, primary sclerosing cholangitis (PSC) -like appearance of intrahepatic bile ducts (multifocal strictures and dilatations) and exclusion of other liver injury [3].

To get further knowledge about pathogenesis of posttraumatic liver failure we investigated clinical course, inflammatory mediators, ERCP and histologic findings in 7 patients that developed hepatic failure after major trauma.

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Patients and Methods

In a retrospective study we analyzed a database of 190 patients that were treated between 01/2001 and 05/2005 at our surgical intensive care unit (Level I trauma center, BG-Kliniken Bergmannsheil, Ruhr University of Bochum, Germany) due to major injury after blunt trauma. 32 patients (16.8 %) developed liver failure during their stay at the ICU and retrospectively we were able to identify 7 patients (6 male, 1 female; mean age 45.7 years, range 32 – 62 years) of which data about clinical course, inflammatory mediators, ERCP and histologic findings after biopsy were available. For the remaining 25 patients, a complete data set including ERCP and histologic findings was not available.

Statistical analysis was limited due to the small number of patients. For data interpretation, no normal distribution of data was observed using the "Kolmogorov-Smirnov-test". Therefore data is not presented as mean ± standard deviation but rather as median ± range. For statistical analysis, SPSS software package (version 12.0, SPSS® Inc., Chicago, IL) was used.

Results

Patient clinical data and injury pattern is shown in Table 1. All patients presented with severe trauma (ISS 38.4 ± 10.8 pts., range 25 – 58 pts.) and had a positive shock index on admission (systolic blood pressure on admission: 80 mmHg, range 75 – 90 mmHg). In all patients, pelvic injury was present. All patients suffered a prolonged shock period after trauma and severe respiratory failure requiring differentiated ventilatory support and prone positioning for acute lung injury or ARDS. Mean duration of ventilation was 29 days (range 13 – 82 d). All patients required total parenteral nutrition over extended periods of time. Mean ICU stay was 37 days (range 21 – 82 d); mean total stay in hospital was 78 days (range 48 – 96 d).

Trauma pattern did not involve liver injury in any of the patients. No other liver diseases or thrombosis of hepatic arteries or veins were found in the further course. Past medical history did not suggest any preexisting hepatobiliary impairment such as haemochromatosis, Wilson´s disease, viral or autoimmune hepatitis or alcohol abuse.

Table 1. Clinical data and Injury pattern of the patients.

No	Sex	Age	Trauma	ISS (pts)	Blood pressure systolic (mmHg)	Stay on ICU (d)	Ventilator support (d)	Stay in hostpital (d)	Outcome	Injury pattern
1	F	55	Fall from height	32	80	21	13	59	s	Instable pelvic ring # type C
2	M	49	Fall from height	43	90	24	19	96	s	Craniocerebral trauma, # os petrosum, # vertebrae C VI, Th XII, L II, incomplete paraplegia, thorax trauma, # ribs 9-12, lung contusion, # femur, blunt pelvic trauma, stable pelvic # type A
3	M	42	Motocycle accident	58	75	82	82	82	n	Lung contusion, haemato/pneumothorax, # femur, # fibula, instable pelvic ring # type B, traumatic amputation lower leg, multiple # forearm and hand
4	M	62	Fall from height	32	80	28	14	48	s	Lung contusion, # ribs 2-11, # clavicula, # scapula, # vertebra Th VI, blunt pelvic trauma, stable pelvic # type A
5	M	50	Fall from t heigh	25	80	32	26	95	s	# vertebrae Th VIII and IX, subluxation vertebra Th VIII, complete paraplegia, blunt pelvic trauma, stable pelvic # type A, haemato/pneumothorax, # ribs 3-10
6	M	32	Traffic accident	43	80	44	37	76	s	Mesenterial rupture, instable pelvic ring # type C, pneumothorax
7	M	28	Fall from height	36	80	30	11	89	s	Lung contusion, atelectasis upper lobe, laceration thigh and pelvis, stable pelvic # type A, luxation and # D V Hand, intestine necrosis

s-survivor; n-nonsurvivor;

Table 2. Systemic parameters of inflammatory response.

median (range) l pg/m	Cholangitis (n = 7)	Healthy controls (n = 35)	Major trauma w/o liver failure (n = 172), ISS 30 pts. (14-66 pts.)
IL-4	9 (0 - 99)	5 (1 – 70)	5 (0 – 1826)
IL-10	15 (0 - 129)	12 (0 – 187)	26 (0 – 3000)
IL-11	43 (0 - 120)	3 (0 – 10)	16 (0 – 5000)
IL-12(p70)	4 (0 - 83)	4 (0 – 191)	6 (0 – 2502)
IL-18	47 (0 - 73)	23 (0 – 284)	90 (0 – 3311)

All patients developed hyperbilirubinemia ranging from 4.9 to 37.7 mg/dl (mean 8.2 mg/dl). Onset of significant bilirubinaemia (> 2.0 mg/dl) was after 3 to 16 days (median 11 days) after trauma. Upon discharge from ICU, Bilirubin levels remained elevated at 8.2 mg/dl (1.1 – 34 mg/dl).

Transaminases (ALT, AST) remained initially close to normal values but increased during the further course, whereas alkaline phosphatase (aP) and gamma-glutamyl transpeptidase (GGT) were already significantly elevated even before Bilirubin (GGT: 394 ± 317 U/l; controls: < 56 U/l; aP 557 ± 311 U/l; controls: < 127 U/l). Pro-and anti-inflammatory parameters like WBC, Procalcitonin, IL-4, IL-10, IL-12, and IL-18 remained close to healthy control values (Table 2). Elevation of IL-11 (43 pg/ml [range 0-120 pg/ml]) above average values (3 pg/ml [range 0-10 pg/ml]) did not reach statistical significance ($p > 0.05$). C reactive protein (CRP) was elevated but did not correlate with Bilirubin. Multidirectional analysis of systemic immune response by analyzing a broad range of pro- and anti-inflammatory mediators in the blood serum did not reveal any statistical relevant difference between those patients who underwent hepatic failure and those who did not.

Although no cholestasis was proven in ultrasound and CT investigations, all patients underwent ERCP which comprised sphincterotomy. All patients presented uniform signs of multiple strictures of the intrahepatic bile ducts and attenuation of the peripheral branches consistent with the clinical picture of sclerosing cholangitis (Fig. 1).

Needle biopsies of the liver were available from all patients. Uniformly, bile duct proliferation and portal lympocytic inflammatoric infiltration could be observed (Fig. 2).

One patient died 82 days after trauma due to multi organ failure. During follow-up after 6 months, all six remaining patients had recovered from liver damage, some with remaining elevated Bilirubin. None went into cirrhosis.

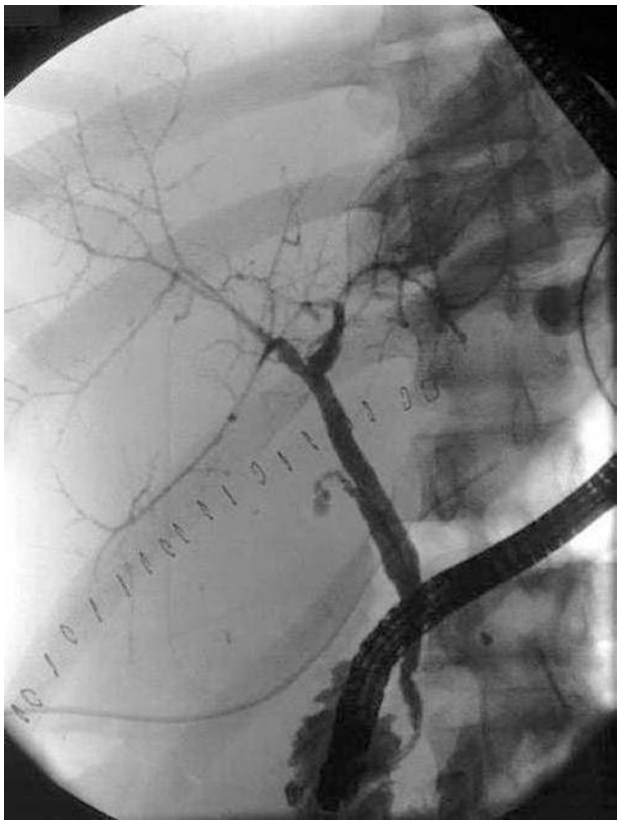

Fig. 1. ERCP of patient No. 3 showing multiple strictures and dilatations of the intrahepatic bile ducts.

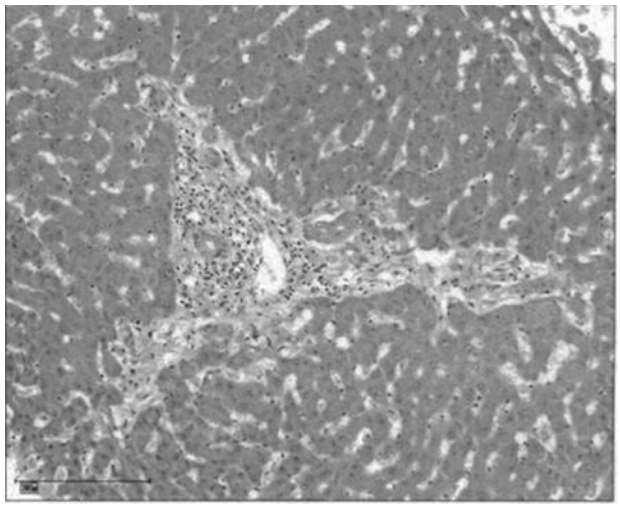

Fig. 2. Liver biopsy of patient No. 4 Immunohistochemical staining showing bile duct proliferations and lymphocytic infiltration of a small bile duct.

DISCUSSION

Despite the fact that a relevant number of patients succumbs liver failure after trauma, our knowledge about precise pathomechanisms remains poor [5, 11, 12]. Thirty years ago Champion described three different phases of liver injury after trauma [1]: during the first phase of "profound posttraumatic hemorrhage", hepatocyte damage is reflected by changes in serum enzymes, transaminases, and lactic acid dehydrogenase. In the second phase, serum Bilirubin and cholestatic enzymes, alkaline phosphatase, and gamma glutamyl transpeptidase rise progressively, beginning at about the 5th post injury day and peaking around the 10th or 12th day and demonstrating chronic inflammatory changes. The third phase reflects hepatic recovery with gradual return to normal of the serum Bilirubin, alkaline phosphatase and gamma glutamyl transpeptidase. Today, it seems that the cause of liver failure is multifactorial and preexisting liver conditions as well as injury pattern have to be taken into account. A common factor seems to be a reduced or absent oxygen delivery causing primary (hypoxic) or secondary (ischemia and reperfusion) hepatocellular injury [1, 13-15].

The incidence of liver dysfunction in patients admitted after major trauma ranges in amounts up to 20 % [15, 16]. The clinical course after liver failure ranges from restitutio ad integrum to long term liver dysfunction [15]. In our study, liver disease did not progress into cirrhosis in any of the patients. One patient died of multi organ failure. The other 6 patients were transferred to peripheral hospitals in good general condition and without further severe liver compromise and were lost to follow up after about 6 months.

After initial liver damage, mild to moderate transaminasemia and hyperbilirubinemia can deteriorate due to sepsis or systemic inflammatory state. Sepsis and shock cause endothelial and bile duct injury also through translocation of bacteria and endotoxins into the portal blood and into the bile ducts [4, 17, 18]. Although it is known that the release of proinflammatory cytokines can cause destruction of the mucosal wall, in our group of patients we could demonstrate, that cytokines are not helpful in diagnosing and monitoring hepatic failure and sclerosing cholangitis.

Our data provide evidence that sclerosing cholangitis contributes to liver failure after trauma. The pathomorphologic picture can not distinguish between shock liver and sclerosing cholangitis. Ischemia during posttraumatic shock might be an early trigger of hepatic failure, supported by further contributing factors such as catecholamines, parenteral nutrition, or bacterial translocation. Common risk factors in our patients include severe trauma, shock on admission, pelvic trauma, prone positioning and high ventilatory pressure for ARDS.

The clinical image of sclerosing cholangitis that develops over decades and often waxes and wanes and the changes seen in our patients is apparently very similar. The mechanism of the disease, however, might be a distinct one and is not described in the presented retrospective study but will have to be subject for further investigation.

One weakness of the presented retrospective clinical study is the fact, that neither the gastroenterologists who performed the the ERCP on ward on a routine basis, nor the pathologist, who evaluated the biopsies, were blinded to the clinical course of the patients. Both, however used objective criteria and stated that the clinical picture of their finding was consistent with the appearance of sclerosing cholangitis. Neither the gastroenterologist nor the pathologist were aware of their interpretation being subject to a retrospective clinical trial.

So far, there is no proven specific therapy for liver failure after trauma or for sclerosing cholangitis. Ursodeoxycholic acid (UDCA) and papillotomy might attenuate clinical deterioration of sclerosing cholangitis. Several randomized double – blinded placebo-controlled studies have shown that UDCA-therapy improves biochemical parameters including serum Bilirubin levels [19-24]. UDCA treatment in combination with repeated endoscopic interventions has been shown to improve the survival of patients with sclerosing cholangitis [25, 26]. Most effective in the treatment of liver failure after trauma, however, is prevention of triggers: underperfusion damage and ischemia-perfusion-damage by the time of trauma and following trauma might be prevented by adequate resuscitation and subsequently adequate trauma management.

Further prospective studies will have to prove whether or not sclerosing cholangitis is commonly involved in the pathogenesis of liver failure after trauma and shock. If so, one might speculate that early therapy with ursodeoxycholic acid might be effective thus reducing the incidence and severity of hepatic failure in the future

In summary our data suggest, that sclerosing cholangitis contributes to liver failure after trauma. This represents a new entity of vanishing bile duct disorders in a liver in which an ischemia-perfusion-damage occurred. The clinical course varies considerably, but in most cases, liver disease does not progress into early cirrhosis. Best therapy known so far is prophylaxis by adequate trauma management. An ongoing prospective study has to proof our results and evaluate the preventive efficacy of UDCA and papillotomy.

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