

## Liver – surgery

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## PERI-OPERATIVE RENAL TUBULAR DYSFUNCTION IN PATIENTS WITH OBSTRUCTIVE JAUNDICE AS INDICATED BY URINARY ENZYMOLOGICAL STUDIES

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Surgical intervention in obstructive jaundice has a significant post-operative mortality (13-37%), predominately attributed to the development of acute renal impairment (6-50%) which carries a mortality of 25-80%. The true incidence of this proximal tubular failure may be underestimated or undiagnosed in the early post-operative period by conventional serum creatinine measurements.

The peri-operative urinary activities of the proximal renal tubular brush border enzymes gamma-glutamyl transferase (GGT) and alanine aminopeptidase (AAP), and the intracellular lysosomal hydrolase N-acetyl-B-D-glucosaminidase (NAG) were measured in 14 jaundiced patients (group 2), 45 patients undergoing laparotomies (group 1), and in 20 patients having infra-renal aortic surgery (group 3).

Surgical intervention in group 1 had little effect on the urinary activities of NAG, GGT and AAP (24±16 vs 30±28, 3.8±1.3 vs 4.1±3.8 and 1.1±0.7 vs 1.3±1.2 U/mmol creatinine respectively), yet in the jaundiced patients (group 2) both pre- and post-operative levels were significantly elevated: NAG 236±153 vs 328±182 p<0.01, GGT 6.6±2.5 vs 11.5±5.0 p<0.05 and AAP 5.8±4.1 vs 10.1±6.1 p<0.01. No correlation existed between the duration or degree of hyperbilirubinaemia, and the detected enzymuria. Urinary NAG was elevated following aortic surgery, 45±38 vs 128±98 U/mmol creatinine p<0.05, though less significantly than in the jaundiced group. Serum creatinine remained static following surgery in the jaundiced (92±32 vs 89±20 umol/l) and aortic (92±49 vs 90±47 umol/l) groups. Urinary enzymology highlights a proximal tubular dysfunction in patients with obstructive jaundice, augmented by surgical intervention. Serum creatinine measurements lack this sensitivity and are of limited value.

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## IMMUNOSUPPRESSION FOLLOWING MAJOR LIVER RESECTION.

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Systemic infection accounts for a high percentage of the morbidity seen following major hepatic resection. Since an intact cellular immune responsiveness is required for adequate resistance to infection, we evaluated the effects of a major liver resection on ex vivo immune function.

Male Wistar rats (220-230 g.) were randomized to receive a sham operation (SHAM, n=6) or 70% partial hepatectomy (PHx, n=14). A third group received no operation and functioned as a normal control group (CON, n=8). After twenty-four hours the spleen was removed and freshly harvested splenocytes (macrophages and lymphocytes) were cultured. Mitogenic responses of splenocytes to the T-cell mitogen phytohemagglutinin (PHA) and the B-cell mitogen lipopolysaccharide (LPS) were determined by measurement of <sup>3</sup>H thymidine incorporation. In the presence of LPS, TNF and IL-1 levels were determined in the supernatants of separate splenocyte cultures.

Partial hepatectomy resulted in significant depression of proliferative responses to PHA and LPS stimulation of resp. 55.1% ± 14.1% (p<0.005) and 62.7% ± 7.7% (p<0.0001) compared to CON rats; mitogenic responses were not significantly influenced by a sham operation. LPS-stimulated TNF and IL-1 levels of SHAM rats were significantly higher than those for CON and PHx rats. In addition, TNF production following PHx was significantly decreased compared to CON rats (Table).

	CON	SHAM	PHx
TNF (pg/ml)	51.8 ± 6.5	472.3 ± 137.6 <sup>1)</sup>	27.2 ± 4.0 <sup>2)</sup>
IL-1 (units/ml)	1.24 ± 0.18	2.26 ± 0.23 <sup>3)</sup>	1.08 ± 0.13 <sup>4)</sup>

Expressed as means ± SEM. <sup>1)</sup> p<0.0005 vs CON; <sup>2)</sup> p<0.01 vs CON and p<0.0001 vs SHAM; <sup>3)</sup> p<0.01 vs CON; <sup>4)</sup> p<0.001 vs SHAM (ANOVA).

In conclusion: major liver resection results in a severe depression of immune function, as demonstrated by a decreased mitogenic response of both B- and T-cells and impaired TNF and IL-1 production by splenocytes. These results indicate that physiological immune responses to injury, as seen in sham operated rats, are disturbed after liver resection. This immunosuppression may well explain the postoperative infections seen in patients undergoing liver surgery.

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## FAMILIAL AMYLOIDOTIC POLYNEUROPATHY: A NEW INDICATION FOR ORTHOTOPIC LIVER TRANSPLANT.

The objective of this paper is to present the long-term results of seven patients undergoing OLT with a diagnosis of FAP.

The FAP diagnosis was based in all cases on:

1. Compatible neurological symptoms and electromyography.
2. Family history.
3. Location of amyloid in abdominal fat and sural nerve and
4. Presence of a biochemical marker (TTR-met-30) of the disease in serum.

The mean follow-up is 6.4 months (max. 18 months; min. 4 months) with a patient survival rate of 100%.

## RESULTS.

1. The biochemical marker of the disease (TTR) disappeared from plasma in all cases.
2. The neurological situation showed a discrete improvement in the two patients receiving transplant more than 10 months previously, and
3. Electromyography neither improved nor worsened in any of the cases.

In conclusion, we believe that whilst we await less aggressive solutions, a liver transplant may be useful in the treatment of certain cases of familial amyloidotic polyneuropathy, in order to stop the neurological deterioration of the disease.

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## INFECTION BY THE HEPATITIS C VIRUS AFTER LIVER TRANSPLANTATION: ANALYSIS THROUGH PCR. M. Prieto, S. Siles, R. Benages, D. Carrasco, M. Berenguer, J. Cordoba, J. Mir, J. Berenguer, Depts of Gastroenterology, Surgery and Microbiology, Hospital La Fe, Valencia, Spain.

Infection with the hepatitis C virus (HCV) represents an important etiology of liver disease in patients undergoing liver transplantation (LT). Recent studies have showed the postliver transplant recurrence of HCV infection. However, its incidence, and clinical course remain to be determined.

**Aim:** To define the frequency and consequences of HCV infection after LT by means of a HCV-RNA PCR analysis of sera.

**Patients:** Group 1: eighteen liver transplant patients with evidence of HCV infection at the time of liver transplantation. All these patients tested positive for anti-HCV and/or HCV-RNA by PCR of sera. Group 2: twenty-five liver transplant recipients without evidence of HCV prior to LT. All of these subjects tested negative for both anti-HCV and HCV-RNA. The mean follow-up after LT was similar for both groups (12.7 ± 5.7 vs 12.3 ± 5.2 months).

**Methods:** Stored serum was tested for HCV-RNA by PCR using primers derived from the 5' noncoding region of the genome. Anti-HCV was tested by EIA 2.

**Results:** HCV infection recurred in 100% of the subjects with evidence of HCV infection prior to LT; 17 (94%) of these patients were positive for both anti-HCV and HCV-RNA. One patient was positive only for HCV-RNA. By contrast, HCV-RNA was positive after LT in only 2 (8%) out of 25 subjects without HCV infection prior to LT (p<0.0001). Graft reinfection resulted in acute hepatitis in 4 (22%) group 1 subjects with a median delay of 3 months (range: 2-6 months) until onset of hepatitis. At the time of their latest follow-up, serum ALT levels were within the normal range in 22% of group 1 patients compared with 68% of group 2 subjects (p<0.005). Progression to chronic hepatitis was noticed in 3 out of 5 group 1 patients with a follow-up after LT longer than 1 year. Hepatitis has not developed in any of the two subjects with "de novo" HCV infection after LT. The one-year survival rate after LT was similar for both groups (77% vs 79%).

**Conclusions:** (1) Acquired HCV infection after LT is a rare event. (2) Recurrent HCV infection is universal in patients with active HCV infection at the time of LT and, (3) a significant number of these patients develop liver dysfunction and chronic hepatitis after LT.

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**EPSTEIN-BARR RELATED LYMPHOPROLIFERATIVE DISORDERS IN PEDIATRIC LIVER TRANSPLANT RECIPIENTS**  
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Pediatric liver transplant recipients (PLTR) are in high risk of developing Epstein-Barr virus (EBV)-related B-cell lymphoproliferative disorders (LPD). In this study a prospective approach of EBV serology evolution is reported in 270 PLTR's among which 10 developed EBV-related LPD. EBV infection was monitored by regularly performed serologic evaluation (IgM VCA, IgG VCA, IgG EA, IgG EBNA) and culture. Documentation and analysis of specific characteristics for each case of LPD was assessed by histological, immunohistochemical and cytogenetic studies.

**Results:** During 6-12 months after transplantation EBV serology changes revealed a marked elevation of the percentage of reactivation (from 10 to 62%) among patients with past immunity. Non immune population dropped from 41 to 8% during the same period. The overall incidence of LPD was 3.7%. Only in 5/10 it was following primary infection. Evidence of EBV implication was demonstrated by EBV culture and/or in situ hybridization on resected tissues. Histologically monomorph LPD was found in 1 case. Monoclonality and oligoclonality was documented in 4/10. Cytogenetic abnormalities were detected in 1 case. Based on clinical criteria LPS patients were divided into four groups. Group I: lymphadenopathic B-cell proliferation with or without tonsillitis (1 case). Group II: Same as group I, plus digestive tract involvement (2 cases). Group III: Disseminated B-cell proliferation, with multiorgan involvement (3 cases). Group IV: Pseudotumoral mass or B-cell lymphoma (4 cases). Treatment included immunosuppression reduction, antiviral chemotherapy (in 7), tumor resection (in 4), anti B-cell monoclonal antibodies (in 2) and retransplantation (in 3). Group III patients had the most unfavourable outcome.

**Conclusion:** Following liver transplantation, EBV infection is related to a wide spectrum of LPD, especially in children. Early detection, and use of multiple therapeutic modalities can improve outcome.

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**IMPACT OF CYTOMEGALOVIRUS AND EPSTEIN BARR VIRUS INFECTION IN CHILDREN FOLLOWING LIVER TRANSPLANTATION**  
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The high seroprevalence of CMV and EBV in adults is well known. In contrast, most children are seronegative for these viruses at transplantation, and are at greater risk of subsequent disease. The incidence of CMV and EBV infection and associated morbidity were studied prospectively in 92 paediatric OLT recipients (median age 2.1 years, range 0.13 to 14.8 years).

At OLT 69 (75%) were seronegative for CMV and 44 (46%) children received CMV positive grafts. 51% of CMV negative children received a positive graft. Of 70 survivors, 24/55 CMV seronegative recipients seroconverted to CMV. 18/24 had received seropositive grafts and despite Acyclovir prophylaxis 14/18 developed significant disease. Seroconversion was asymptomatic in 6 patients who had received seronegative grafts. Median time to CMV seroconversion was 51 days (range 8-872). All children with CMV disease responded to treatment with Ganciclovir and hyperimmune globulin.

EBV serology was available in 86 patients at transplantation 54 (63%) being seronegative. 43/68 survivors were seronegative at OLT and 26/43 seroconverted to EBV at a median of 203.5 (range 12-746) days. Reactivation occurred in 9/25 seropositive recipients at a median of 577 (range 306-861) days. There was significant morbidity in 7 patients, one of whom developed lymphoproliferative disease and in addition 1 patient with EBV and Hepatitis C co-infection developed acute hepatic failure requiring retransplantation.

**CONCLUSION:** As most children undergoing OLT are seronegative for CMV and EBV, subsequent infection is frequent and has a significant morbidity. Effective antiviral prophylaxis or vaccination in this high risk population is essential.

OX/6 1004

**HCV INFECTION IN LIVER TRANSPLANT RECIPIENTS.**  
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Transplanted patients may have chronic end-stage liver disease attributed to hepatitis C virus (HCV) infection and are also at risk of becoming infected perioperatively by HCV because of blood transfusions and immunosuppression.

**MATERIAL AND METHODS:** 31 consecutive liver transplant recipients (from January 91 to August 92) were considered, with a follow-up of at least 4 months. Serological tests included second generation enzyme immunoassays (Elisa II, Abott\*) and second generation recombinant immunoblot assays (Riba, Ortho\*); serum samples were taken before liver transplantation (OLT), 1 month after OLT and there after every 6 months.

#### **RESULTS:**

\* **The 10 patients** having HCV markers before OLT remained positive: 6 of these developed chronic active hepatitis within 5 months (2 --> 7) after OLT, leading to cirrhosis in 2 cases (at 15 and 22 months). The 4 other patients have normal hepatic enzymes and their liver biopsies do not show any sign of chronic hepatitis after a mean delay of 15 months (4 --> 24).

\* **Among the 21 patients** without HCV markers prior to transplantation, 16 remain negative and have normal liver histology at 13 months (4 to 25). 5 patients had no detectable antibodies against HCV prior to OLT but acquired them 3 months (2 --> 10) after the procedure. One patient suffered from acute hepatitis C which went on to chronicity. The 4 others have normal liver tests and normal liver histology.

**CONCLUSION:** Patients with HCV infection at the time of OLT keep their antibodies against HCV and 60% of them develop rapidly liver dysfunction and histopathologic abnormalities. Acquired hepatitis C after OLT seems to seldom occur (3%).

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**DIAGNOSTIC AND OPERATIVE ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY AFTER LIVER TRANSPLANTATION.**

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Biliary complications occur in 10 to 30% of the cases after liver transplantation. This report extends our experience of endoscopic diagnosis and treatment in 15 patients out of 84 (92 transplantations) who presented with cholestasis (10 cases) or suspected bile leakage (5 cases).

#### **Cholestasis**

Mean time between transplantation and endoscopic retrograde cholangiography (ERC) was 8 months (2 --> 17 months). In 4 patients, ERC revealed a stricture of the choledoco-choledocal anastomosis, which benefitted from plastic stents. Recalibration of the stenosis was maintained in 3 cases after 3 to 10 months stenting. Cholangitis due to rapid (6 weeks) and recurrent clogging of the stents led to Roux-en-Y biliary reconstruction. Two patients had biliary calculi, easily removed with a balloon after endoscopic sphincterotomy (ES). Two patients presented with intrahepatic strictures, attributed to histologically proven severe rejection.

One patient had hepatic artery thrombosis and a stricture of the hilar bifurcation with contrast medium extravasation.

In the last case the cholangiogram was normal.

#### **Bile leakage.**

In 3 patients, bile leak occurred through the T-tube orifice immediately after T-tube removal. They developed clinical peritonitis and were treated by ES followed by insertion of a nasobiliary catheter allowing drainage of the bile. Surgical abdominal drainage was mandatory but surgical bile duct repair was unnecessary. In the 2 remaining patients, malposition of the T-tube was responsible for impaction of one of the limbs into the common bile duct wall. Their removal provoked bile leakage at the site of impaction, easily managed by ES and insertion of a nasobiliary tube.

ERC, when performed for biliary complications of liver transplantation, reveals the site and nature of biliary strictures and the precise level of leakage. This diagnostic examination may immediately be followed by a therapeutic procedure, decreasing the need for repeated surgery.