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Clinical hepatology

OP01 ALCOHOL AND LIVER DISEASE DETECTION STUDY ALDDES: EARLY RESULTS AND IMPLICATIONS

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Introduction Liver deaths have increased 5—8 fold in 30 years and the majority are alcohol related. Cirrhosis develops silently and presents late; around 25% of subjects die before they have a chance to stop drinking. Blood tests in routine use do not stage fibrosis and diagnosis often requires a liver biopsy—impractical for the 2 million UK residents drinking at levels that may result in cirrhosis. Newer blood tests detect cirrhosis and progressive fibrosis at an earlier stage and, combined with alcohol screening, could greatly improve detection and management of these patients, reducing morbidity and mortality.
Aim Assess feasibility of screening a primary care population for hazardous drinking using the AUDIT questionnaire, practicality of screening heavy alcohol users for liver disease using a non-invasive test and resource implications of assessment and follow-up.
Method We offered postal screening to 10 000 adults age 25—55 randomly selected from general practice lists using the AUDIT questionnaire. An offer of liver fibrosis tests was made to those screening positive. Those with marked elevation of fibrosis markers are referred on for liver health checks markers. Participants were followed up after 1 year.
Results 10 000 AUDITs were dispatched from 9 primary care sites. Response rate was 3677 (37%) Of these responders 907 were hazardous/harmful drinkers (18.5%), of whom 207 (4.2%) were dependent drinkers. Audit positive subjects were invited to attend a research clinic of whom 290 (32%) attended and were screened using our traffic light algorithm (HA, P3NP, PTS, albumin, INR) of whom 28 (9.6%) were red (cirrhosis/severe fibrosis) and 121 (41%) amber (50% likelihood of progressive fibrosis in a secondary care population).
Conclusion Postal screening for hazardous drinking followed by non-invasive liver assessment is feasible in the primary care setting. Ten percent of hazardous drinkers had good evidence of significant liver disease and a half had equivocal serum fibrosis markers, with these results fed back to subjects to encourage behaviour change. Further details and follow-up results will be available.

OP02 PREVALENCE AND SEVERITY OF NONALCOHOLIC FATTY LIVER DISEASE IN A LARGE PROSPECTIVE PRIMARY CARE COHORT WITH ABNORMAL LIVER FUNCTION TESTS

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Introduction An unexpected finding of abnormal liver function tests (ALFTs) is common in primary care. Currently there is a lack of data for determining the severity of liver disease, in particular nonalcoholic fatty liver disease (NAFLD), in the primary care setting.
Aim To determine the causes of unexpected ALFTs in a large primary care cohort. To determine the prevalence and severity of NAFLD in this cohort.
Method We analysed patients presenting with ALFTs, in the absence of known liver disease, to 8 primary care practices in Birmingham between 2006 and 2008. NAFLD was diagnosed in subjects with fatty liver on ultrasound (USS), negative liver aetiology screen, and alcohol consumption of =21 & =14 units/week in males and females, respectively. As a sub-study we calculated the NAFLD Fibrosis Score (NFS) (Angulo, Hepatology 2007) to estimate the presence of advanced liver fibrosis (F3/F4 Kleiner classification) in subjects who met the diagnostic criteria for NAFLD.
Results Data from 1118 adult patients were analysed: 56% male; 83.9% white race; Age 60 years (48—70); 23.5% type 2 diabetes; 52.2% hypertension; body mass index 28.7 kg/m^2 (25.5—33.1) (values expressed as median (IQR) or %). Regarding alcohol consumption, 42.5% were non-drinkers, 32.2% drank within UK guidelines (male=21, female=14 units/week) and 26.3% drank in excess.

Liver aetiologies identified included alcohol-induced liver disease (25.7%), haemochromatosis/carrier (1.1%), viral hepatitis B/C (0.91%), primary biliary cirrhosis (0.8%), alpha-1-antitryspin deficiency (0.18%) and primary sclerosing cholangitis (0.18%). Aetiology remained unexplained (normal USS, negative liver aetiology screen and alcohol consumption within UK guidelines) in 479 subjects, although at least 18% of this group had 2+ factors of the metabolic syndrome.

NAFLD was diagnosed in 26.4% (295/1118) of cases. A high NFS (>0.676) was found in 7.6% of these cases indicating the presence of advanced liver fibrosis. The presence of advanced fibrosis could not be confidently excluded in 35.2% of NAFLD patients who had an "indeterminate" NFS (−1.455 to 0.676), indicating the need for further investigation. Although NFS was validated in a secondary care cohort and may over-read severity in primary care, it is currently the best validated non-invasive method of assessing liver fibrosis in patients with NAFLD.
Conclusion NAFLD accounts for over a quarter of patients with ALFTs in primary care (26.9%). Of the patients with NAFLD a significant proportion either have advanced fibrosis (7.6%) or require further investigation (35.2%). This highlights the growing burden of NAFLD, and the need for validated methods of assessing NAFLD disease severity in primary care.

OP03 EFFECTS OF TWO YEARS OF LIRAGLUTIDE TREATMENT ON FATTY LIVER DISEASE IN PATIENTS WITH TYPE 2 DIABETES: ANALYSIS OF THE LIRAGLUTIDE EFFECT AND ACTION IN DIABETES-2 EXTENSION TRIAL

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Introduction Currently there are no established treatment options for fatty liver disease. Glucagon-like peptide 1 (GLP-1) analogues have been shown to reduce hepatic steatosis and markers of liver inflammation in rodents.
Aim To determine the efficacy of 2 years treatment with 1.8 mg liraglutide, a once-daily human GLP-1 analogue, on fatty liver disease and body composition in patients with poorly controlled type 2 diabetes (T2D).
Method Analysis was performed on the "Liraglutide Effect and Action in Diabetes-2" (LEAD-2) study cohort. LEAD-2 was a 26-week, double blind phase III trial with a 1.5-year open-label extension. Patients were randomised (2:2:2:2:1) to liraglutide 1.8, 1.2 or 0.6 mg/day, glimepiride 4 mg/day or placebo, all in combination with metformin 1.5—2 g/day. DEXA (n=160) and computerised tomography (CT) (n=154) sub-studies were performed to measure body fat composition and hepatic steatosis (defined by a liver-to-spleen attenuation ratio <1), respectively.

Repeated measure and ANCOVA analysis was performed using last observation carried forward on the intention-to-treat population to estimate change from baseline. Values expressed as mean (SD).

Results 529/1091 patients (58% male; 87% white; age 56.7 years (9.5); body mass index 31 kg/m^2 (4.7); HbA1c 8.4% (0.9); male alanine aminotransferase (ALT) 32.0 IU/L (17.9); female ALT 27.3 IU/L (14.9)) completed 2 years treatment. Of the subjects enrolled in the sub-study 75% had the metabolic syndrome (ATP III classification) and 65.7 % (90/137) had hepatic steatosis on CT at baseline.

Patients with elevated ALT levels (53%) at baseline (males >30, female >19 IU/L) had a significant reduction of ALT with liraglutide (−8.53 from baseline 40.9 IU/l, p<0.0001). This was a significant improvement vs glimepiride (p<0.05). 37% of patients normalised their ALT with liraglutide in comparison to 21% on glimepiride.

Liver-to-spleen attenuation ratio significantly increased with liraglutide (+0.10, p<0.05) indicating reduced hepatic steatosis. Reductions in trunk fat tissue mass, trunk lean tissue mass and % total body fat with liraglutide were significantly different vs increases with glimepiride (−3.0 kg, −1.3 kg, −2.05%, respectively; p<0.05). Greater improvements were seen in liver-to-spleen attenuation ratio (+0.05), trunk fat mass (−1.6 kg) and % total body fat (−0.63%) with liraglutide vs placebo.

Conclusion Two years treatment with liraglutide significantly improves liver enzymes and hepatic steatosis in patients with T2D and associated fatty liver disease. Significant improvements in % body fat, in particular central adiposity support the role of liraglutide in reducing hepatic steatosis and cardiovascular morbidity.

OP04 CIRCULATING LEVELS OF THE LONG PENTRAXIN PTX3, BUT NOT HEPATOCYTE DERIVED C-REACTIVE PROTEIN, CORRELATE WITH SEVERITY FOLLOWING HUMAN ACUTE LIVER INJURY

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Introduction The innate immune response may underpin the development of multiorgan failure following acute liver injury, particularly following paracetamol overdose (POD). Pentraxin 3 (PTX3) is a long pentraxin induced by interleukin (IL)-10, and produced by vascular endothelium, macrophages, and myeloid dendritic cells. PTX3 has diverse effector functions including opsonisation, clearance of apoptotic debris, and tissue repair.

Aim To measure levels of PTX3 and C-reactive protein (CRP), a hepatocyte derived short pentraxin involved in the acute phase response, in patients with acute liver injury.

Method Consecutive patients admitted to the Royal Infirmary of Edinburgh with acute liver injury (ALT>1000 IU/l and coagulopathy) were enrolled. PTX3 and CRP levels were measured by ELISA and turbimetry, respectively.

Results A total of 60 patients (48 POD, 12 non-POD) were enrolled. 28/48 (58.3%) of POD and 8/12 (66.7%) non-POD patients developed hepatic encephalopathy (HE), and therefore acute liver failure. As expected, admission PTX3 levels correlated strongly with IL-10 (Spearman's r=0.641, p<0.001), but also correlated with INR (r=0.728, p<0.001) and ALT (r=0.554, p<0.001), but not with CRP (r=-0.124, p=0.35). Admission PTX3 levels were significantly higher in POD patients with HE (median (interquartile range) 329.4 (77.7–738.1 ng/ml)) compared with POD patients without HE (46.1 (6.1–172.4) ng/ml, p=0.0005), or with non-POD patients (23.7 (9.1–40.0) ng/ml, p=0.004). PTX3 levels in POD patients who died or required emergency liver transplantation (LT) (772.9 (268.2–848.7) ng/ml) were significantly higher compared with spontaneous survivors (81.1 (12.0–437.1), p<0.0001), with an area under the receiver operator characteristic curve of 80.3 (95% CI 67.1 to 93.4). Admission PTX3 levels in POD patients correlated with admission APACHE II (r=0.398, p=0.006) and SOFA (r=0.536, p<0.001) scores, and were higher in POD patients who developed the systemic inflammatory response syndrome (SIRS 306.4 (113.9–764.7) ng/ml, no SIRS 50.5 (6.66–297.7) ng/ml, p=0.001). Conversely, admission CRP levels were significantly decreased in POD patients (6.05 (3.93–15.38) mg/l) compared with non-POD patients (17.6 (3.9–15.4) mg/l, p=0.011). There were no significant differences in CRP levels between POD patients who died/required LT (5.2 (4.3–15.9) mg/l) and survivors (7.9 (3.5–15.7) mg/l, p=0.820).

Conclusion These data suggest that the humoral arm of the innate immune system plays an important role in the pathogenesis of multiorgan failure following POD. PTX3 may have a role as a novel prognostic marker in this condition.

OP05 MEDIUM TERM OUTCOME OF DE NOVO AUTOIMMUNE HEPATITIS AFTER LIVER TRANSPLANTATION IN CHILDREN; A SINGLE CENTRE EXPERIENCE

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Introduction Post-transplant de novo autoimmune hepatitis (dn-AIH) is a cause of late graft dysfunction characterized by hypergammaglobulinemia, elevated titres of serum auto-antibodies, histological features of chronic hepatitis with portal and periportal inflammation with lymphocytes and plasma cells, and clinical response to the treatment for classical autoimmune liver disease with steroids and azathioprine (aza) or mycophenolate mofetil (MMF).

Aim To establish the prevalence and the medium term outcome of dn-AIH.

Method Retrospective review of case notes of patients who were diagnosed with dn-AIH since the initial case description in 1995 to date.

Results Thirty children (17, 57% female) were diagnosed using the above criteria. Overall incidence was around 5 %. The aetiologies leading to liver transplant (LT) were: biliary atresia (16), Alagille syndrome (3), alpha 1-antitrypsin deficiency (3), progressive familial intrahepatic cholestasis (2), glycogen storage disease type 1b (2), familial hypercholesterolemia (1), non-A-E hepatitis (1), Crigler-Najjar syndrome type 1 (1) and cryptogenic end-stage liver disease (1). Four (13.3%) patients received whole grafts, while the remainder received segmental grafts, including 2 (6.7%) auxiliary and 4 (13.3%) living-related grafts. The median age at diagnosis of dn-AIH was 11.2 years (range, 2.6–19.3). The median post-LT interval to develop dn-AIH was 4.1 years (range, 0.2–11.0). The median follow up after diagnosis of dn-AIH was 8.2 years (range, 0.3–14.8). Auto-antibodies detected included ANA (n=21), SMA (n=20), anti-mitochondrial antibody (n=4), anti-LKM (n=2) and anti-liver cytosol-1 (n=1). Immunosuppressive regimens at the time of dn-AIH diagnosis included: CyA/aza/pred (9), Tac/aza/pred (6), Tac/MMF/pred (6), CyA/MMF/pred (4), and Tac/pred (5). Dn-AIH was treated with increased dose of steroids and increased dose or addition of aza or MMF. Eleven (36.7%) patients did not adhere to medications during follow up. Of these, 10 (33.3%) developed chronic liver failure (CLF) and 6 (20%) required re-LT, after a median period of 5.8 years. Two (6.7%), including a non-adherent child, died with multiorgan failure after re-LT for CLF. Of 4 further children with CLF, 3 (10%), all with history of non-adherence, are currently listed for re-LT, while one (3.3%) is stable. Twenty patients (66.6%) have no evidence of graft dysfunction.

Conclusion The medium-term prognosis of dn-AIH is severe in a considerable proportion of patients and is determined by adherence to medications.