Posters

Clinical hepatology

P01 UDCA RESPONSE CRITERIA IDENTIFY A SUB-GROUP OF PBC PATIENTS WITH AN INHERENTLY GOOD PROGNOSIS RATHER THAN A SPECIFIC DISEASE RESPONSE

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Introduction Recent follow-up cohort studies have identified biochemical parameters in UDCA-treated patients which identify "responders" with survival identical to normal control populations, in contrast to "non-responders" who have survival indistinguishable from that predicted by the Mayo Risk Score for untreated patients. The most widely accepted criteria for UDCA "response", proposed by Corpechot, consist of alkaline phosphatase (ALP) <3× uln, alanine transaminase (ALT) <2× uln and bilirubin <1× uln. However, Bilirubin and ALP levels are independent predictors of outcome in PBC irrespective of UDCA treatment. ALT, in addition, is a biomarker for overlap syndrome, a prognostic feature itself.
Aim UDCA response criteria identify a group of patients with an inherently low risk rather than UDCA response per se.
Method In a comprehensive cohort of patients, geographically defined in 1999 followed up for 10 years, a group of patients (n=94) not treated with UDCA were identified. This cohort, matched prospectively to individual community case controls, represents an opportunity to study the natural history of non-UDCA treated PBC.
Results In the whole cohort (including UDCA treated patients), survival was significantly better in the UDCA-responding patients (defined using the Corpechot criteria) than in the non-UDCA-treated patients ($p<0.05$ log-rank test) although as in other studies survival was not the same as in age and sex match controls ($p<0.05$). Of the 94 non-UDCA receiving patients, 80 and 14 had, after 1 year of follow-up, biological features which, if they had received UDCA, would have been compatible with UDCA-response and UDCA-non response, respectively. Un-transplanted survival was significantly better in the non-UDCA patients meeting response criteria (58/80 (72%) at 10 years follow-up) than in non-UDCA treated patients meeting non-response criteria (5/14 (36%), $p=0.01$; χ^2 9.4, $p<0.01$ log-rank test). The magnitude of this effect was similar to that associated with UDCA response in other series. The absence of UDCA treatment precludes, of course, this being a phenomenon of actual UDCA response.
Conclusion UDCA response criteria identify a group of patients who, at the time of criterion measurement, have a good prognosis. It does not appear to matter whether attainment of these parameters is a natural feature of untreated disease or a consequence of treatment. These criteria therefore have an important role in identifying high and low risk patients, and a sub-group of PBC patients with poor prognosis for whom additional therapies should be sought. They do not, however, provide specific information about the actions of UDCA.

P02 IMPAIRED SUBENDOCARDIAL MYOFIBRE FUNCTION IN PRIMARY BILIARY CIRRHOSIS

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Introduction A follow-up study[1] of 770 PBC patients found that their survival was much poorer than an age- and sex-matched population (standardised mortality ratio for PBC patients was 2.87). Excluding deaths from hepatic causes, the standardised mortality ratio for PBC patients was 1.73: the balance of the risk was of a cardiac-related death the mechanism by which the disease could affect cardiac tissue was unclear. 50% of PBC patients suffer systemic fatigue, and in these the risk of cardiac-related death has been shown to be higher than in non-fatigued patients.[2]
Method 15 proven PBC stage I–II patients were recruited (age: 48±6 y) and 8 age, weight and height- matched female subjects were recruited as controls (age: 52±11 y). MRI short axis cardiac tagging was used to measure circumferential strain and torsion throughout the cardiac cycle.[3] Patient and control subject fatigue severity was assessed by means of a validated questionnaire, the Fatigue Impact Score (FIS), where 0 indicates no fatigue to a maximum of 160. Patients were divided into two groups: those without significant fatigue (defined as FIS<25) and those with severe fatigue (FIS>50). All controls had FIS <25.
Results In fatigued PBC patients, cardiac torsion was increased and circumferential strain significantly decreased compared to controls and non-fatigued PBC patients, indicating impaired subendocardial myofibre function, which is characteristic of advanced ageing.[3] Anatomical MRI showed no morphological or functional alteration in the hearts of either group of PBC patients compared to controls.

Abstract P02 Table 1 Results

	Control	PBC non-fatigued	PBC fatigued
Torsion to endocardial strain ratio	0.46±0.14	0.44±0.12	0.70±0.13*
Peak torsion	6.3±1.9	5.6±1.4	7.9±1.4*
Peak endocardial circumferential strain	18.9±1.6	19.0±2.0	16.5±2.4*

*p <0.05 by ANOVA.

Conclusion In PBC patients with severe fatigue we have found changes in the relationship between peak torsion and circumferential strain indicating that these patients may have suffered effective ageing of their hearts. This is in alignment with previous findings that PBC patients with substantial fatigue had a greater risk of cardiac-related death.

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P03 THE USE OF BRUM1 RESEQUENCING MICROARRAY TO IDENTIFY MUTATIONS IN PATIENTS WITH NEONATAL CHOLESTASIS

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Introduction Neonatal cholestasis is the presenting clinical feature of serious and potentially life limiting liver diseases such as progressive familial intrahepatic cholestasis (PFIC), arthrogryposis-renal-cholestasis (ARC) syndrome and Niemann Pick C (NPC) disease. A single rapid molecular test to confirm the diagnosis would reduce the delay from molecular genetic investigation at multiple diagnostic centres thus facilitating optimal clinical management and counselling. We have designed a resequencing microarray (BRUM1) capable of simultaneously sequencing multiple genes associated with neonatal cholestasis.

Aim To assess the utility of BRUM1 as a first-line molecular investigation for patients with neonatal cholestasis in whom an inherited causes is suspected.
Method DNA from 95 infants with neonatal cholestasis in whom an inherited cause was suspected was amplified by PCR and hybridised to BRUM1 (validated against reference sequencing with 98.9% agreement (CI 0.97 to >0.99)) for simultaneous sequencing of the main causes of inherited disease in this group which included ATP8B1, ABCB11, ABCB4, VPS33B, VIPAR, NPC1 and NPC2. Children with known α-1 antitrypsin deficiency or Alagille syndrome were not included.
Results 30 infants had pathogenic mutations, which cause neonatal cholestasis. 23 of the mutations were novel.

Abstract P03 Table 1 Results

Gene	Total number of mutations	Novel mutations
ATP8B1	6	1
ABCB11	11	10
ABCB4	2	1
VPS33B	5	4
VIPAR	2	2
NPC1	17	4
NPC2	1	1

In this cohort of patients, 30.5% of infants with neonatal cholestasis had a genetic diagnosis confirmed by BRUM1. The average time to diagnosis was 5–25 days.
Conclusion A specific and rapid genetic diagnosis in infants with a phenotype of neonatal cholestasis can be made using a single resequencing microarray, to optimise clinical management and facilitate appropriate counselling of families.

P04 ADMISSION SERUM LACTATE IS A STRONG PREDICTOR OF OUTCOME IN CIRRHOTICS ADMITTED TO INTENSIVE CARE UNIT, AND WHEN ADDED TO THE LIVER-SPECIFIC SCORES OF MODEL FOR END-STAGE LIVER DISEASE OR UK MODEL FOR END-STAGE LIVER DISEASE, IMPROVES THEIR RESPECTIVE PREDICTIVE VALUE

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Introduction Accurate prognostic indicators of patient survival in an intensive care unit (ICU) help guide clinical decision-making. Factors known to portend poor prognosis in acutely ill cirrhotics in ICU include the need for mechanical ventilation, development of shock, renal failure and sequential increase in the number of failing organs. While serum lactate is now an established marker of survival and/or the need for transplantation in fulminant liver failure, its impact on critically ill cirrhotics is less well known.
Method We retrospectively studied 133 consecutive acutely ill cirrhotics admitted to the ICU between 2005 and 2008 at the Royal Free Hospital, a tertiary referral centre in liver diseases and transplantation. Data were collected on demographic variables, aetiology of liver disease, liver-specific prognostic scores (Child–Turcotte–Pugh (CTP), model for end-stage liver disease (MELD), UK model for end-stage liver disease (UKELD)), and acute illness scores (acute physiological score and chronic health point (APACHE II), sequential organ failure assessment score (SOFA)). In addition, serum lactate levels at 0, 24 and 48 h were also recorded. Multivariable logistic regression analysis was performed, and the discrimination ability of each of the above-mentioned scoring models in predicting ICU and hospital survival of these patients was evaluated using the area under the receiver operating characteristic (ROC) curve.
Results The ICU and hospital non-survivors—43/133 (32.3%) and 57/133 (43.4%) respectively—had similar demographic features as the survivors, but had significantly higher mean admission MELD, UKELD, SOFA and APACHE II scores, as well serum lactate levels on admission. Serum lactate at admission and particularly at 24 h had a better discriminative accuracy for mortality (AUC=0.737 and 0.764) compared with liver-specific prognostic scores, MELD (AUC=0.732 and 0.720), MELD-Na (AUC=0.338 and 0.554) and UKELD (AUC=0.698 and 0.695). Acute illness scores exhibited a rather poorer predictive power, both APACHE II (AUC=0.632 and 0.571) and SOFA (AUC=0.688 and 0.716). Adding lactate to MELD and UKELD scores further improved their outcome prediction potential (AUC MELD-lactate=0.737 and UKELD-lactate=0.717).
Conclusion Serum lactate is a powerful independent tool in predicting survival of acutely ill cirrhotics on ICU. Persistent hyperlactataemia after aggressive resuscitation for 24 h may reflect native liver's inability to metabolise it. In that case, should lactate not be incorporated in the liver function scoring models such as CTP, MELD or UKELD?

P05 B-CELL EPITOPE MAPPING OF ANTI-RO-52 RESPONSES IN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

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Introduction Up to 40% of patients with primary biliary cirrhosis (PBC) show reactivity against Ro-52 (*Hepatology* 2009), a Sjögren's syndrome (SS)-associated autoantibody. Previous studies have shown that anti-Ro-52 in SS targets the central, coiled-coil sequence of the 475-aa of the antigen. No study has dissected anti-Ro-52 reactivity in PBC.
Aim To investigate anti-Ro-52 B-cell responses in patients with PBC and compare them with those obtained in patients with SS.
Method Human recombinant full-length Ro-52 and 3 constructs spanning the whole protein were expressed in *E. coli* and tested for reactivity by a line immunoassay. Construct 1 (C1: aa1–129) contained the RING finger and the B-Box domains, construct 2 (C2: aa125–268) contained the coiled-coil domain and construct 3 (C3:aa 268–475) contained the B30.2/SPRY domain. Twenty-three 18-mer peptides overlapping by 12aa were synthesised and tested by an in house ELISA to better define the core epitopes within the highly immunogenic C2 region. Overall, 122 serum samples (68 from Ro-52 positive PBC patients, 39 from Ro-52 positive SS patients without liver disease and 15 from Ro-52 negative healthy blood donors) were tested.
Results Reactivity to the C2 construct of Ro-52 was present in all Ro-52 positive sera from PBC and SS patients and in none of the controls ($p<0.001$). Reactivity to the C3 construct was virtually absent in PBC (3%) and SS (0%) while reactivity to C1 was equally present in PBC (15%) and SS (10%). Within the immunodominant C2 sequence, 2 novel epitopic regions were identified using peptide mapping: the first sequence (aa 175–192: 1 peptide) was recognised by the great majority of patients with PBC (86%) and SS (69%), the second sequence (aa235–258: two overlapping peptides) was recognised by 35% PBC and 54% SS patients (p=NS, for both).
Conclusion This is the first systematic B-cell mapping approach of anti-Ro-52 responses in PBC patients showing that the antigenicity