as in this case has not been described to best of our knowledge.

Conflict of interest statement. None declared.

P.D. Hinduja National Hospital and Medical Research Centre Mumbai India

Email: dr_rirsat@hindujahospital.com


doi:10.1093/ndt/gfh790

Advance Access publication 5 April 2005

**Liver disease vs systemic inflammation in haemodialysis patients**

Sir,

The direct association between elevated liver enzymes and serum C-reactive protein (CRP) was recently reported in subjects with metabolic syndrome [1]. This indicates that even mild liver disease contributes to generalized low-grade inflammation and, in consequence, may enhance cardiovascular risk. Chronic inflammation is common in patients undergoing maintenance haemodialysis (HD) therapy, and deleteriously underlies the progression of malnutrition and atherosclerosis [2]. Renal failure is also an instructive model of the metabolic syndrome, with its harmful effects on both the cardiovascular system and liver [2]. In addition, chronic viral hepatitis may affect up to 70% of HD patients [3]. The hypothesis that liver disease also contributes to generalized inflammation in the HD population has not been tested so far.

We retrospectively studied 237 patients (42% females) with a median age of 61 years (full range: 16–83 years) who had been treated in our unit between 1996 and 2002. At data collection, all subjects were clinically stable, dialyzed for at least 4 weeks, without HIV infection, had not suffered from any acute infectious and inflammatory diseases or cardiovascular events in the preceding month, were not treated with statins or regularly with NSAIDs, were not suffering from alcohol abuse, and did not have liver cirrhosis. Ninety-one (38%) patients were seropositive for either hepatitis B virus surface antigen (HBV), antibodies against hepatitis C virus or hepatitis C virus RNA (HCV); none were on antiviral therapy. One hundred and five (44%) patients had cardiovascular disease. In all subjects, pre-dialysis serum alanine aminotransferase (ALT) activity and concentrations of five acute-phase reactants (APR) such as CRP, α1 acid-glycoprotein (AGP), α1-antitrypsin (AT), fibrinogen (FBG) and endothelial marker von Willebrand factor (vWF) were simultaneously measured. Definitions, methods and assays were as described previously [4,5]. Data were expressed as means±1 SD or medians (full range) depending on their distribution; all CRP values <6 mg/l were treated as 5 mg/l. For statistical analysis, several complementary approaches were used. First, the associations between ALT and the APRs were tested, by non-linear Spearman regression, in five groups: (i) the whole cohort; (ii) patients positive for HCV or HBV markers; (iii) patients negative for both hepatitis markers; (iv) seropositive subjects with increased serum ALT; and in (v) seropositive patients with normal ALT activity. Next, the comparisons were performed, by non-parametric Mann–Whitney *U* test, in three sub-groups: (i) patients with ALT activity in the top vs the lowest quartile; (ii) subjects with hepatitis markers vs those without; and (iii) in seropositive patients with elevated ALT vs seronegative subjects with normal ALT activity. The cut-off value for serum ALT activity was set at 29 IU/l, which was the upper limit of its 95% confidence interval in the seronegative patients. This ALT value was very close to 27 IU/l, which was determined in (v) seropositive subjects with normal ALT activity. The cut-off value for serum ALT activity was set at 29 IU/l, which was the upper limit of its 95% confidence interval in the seronegative patients. This ALT value was very close to 27 IU/l, which was determined in a similar manner by Espinosa et al. [6] and found to reliably indicate liver damage in maintenance HD patients.

In our whole group, the variables were as follows: ALT, 19 (5–256) IU/l; CRP, 8 (5–280) mg/l; AGP, 1.08 (0.48–3.90) g/l (reference value 0.30–1.30 g/l); AT, 1.49 ± 0.39 g/l (reference 1.10–2.30 g/l); FBG, 314 (164–568) mg/dl (reference 1.10–2.30 g/l). In (v) seropositive patients with normal ALT activity, the ALT value, in the top (34 IU/l) vs the lowest quartile (9 IU/l), was found to reliably indicate liver damage in maintenance HD patients.

Liver disease as a risk factor and independent predictor of cardiovascular events was tested with Pearson χ² test; for inflammatory markers analysis was adjusted for demographic and clinical variables.

### Table 1. Characteristics and inflammatory markers in HD patients with and without evident liver disease

<table>
<thead>
<tr>
<th></th>
<th>HCV- or HBV-positive and ALT ≥291 IU/l (n=61)</th>
<th>HCV- and HBV-negative and ALT &lt;291 IU/l (n=123)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 (22–72)</td>
<td>64 (16–77)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Females (n, %)</td>
<td>24, 39.3</td>
<td>53, 43.1</td>
<td>0.63</td>
</tr>
<tr>
<td>Dialysis vintage (months)</td>
<td>32 (8–100)</td>
<td>7 (1–64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiovascular disease (n, %)</td>
<td>20, 32.8</td>
<td>61, 49.6</td>
<td>0.03</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>9 (5–55)</td>
<td>7 (5–280)</td>
<td>0.45</td>
</tr>
<tr>
<td>α1 Acid-glycoprotein (g/l)</td>
<td>1.12 (0.57–1.98)</td>
<td>1.02 (0.48–3.90)</td>
<td>0.79</td>
</tr>
<tr>
<td>α1-Antitrypsin (g/l)</td>
<td>1.43 (0.80–2.68)</td>
<td>1.49 (0.65–2.64)</td>
<td>0.24</td>
</tr>
<tr>
<td>Fibrinogen (mg/d)</td>
<td>333 (185–491)</td>
<td>313 (164–568)</td>
<td>0.63</td>
</tr>
<tr>
<td>von Willebrand factor (%)</td>
<td>125 ± 25.6</td>
<td>128 (76–246)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

aDifferences in gender and cardiovascular disease prevalence were tested with Pearson χ² test; for inflammatory markers analysis was adjusted for demographic and clinical variables.
150–350 mg/dl), and vWF, 130 ± 27.4% of normal value (reference 60–150%). In 160 (67%) patients at least one inflammatory marker was found to be increased. Serum ALT did not show significant correlations with any of the APRs studied in either of the above five groups (all $P > 0.075$), including patients with active liver disease (seropositive with ALT ≥ 291 U/l). On the other hand, the APRs were consistently and notably associated with each other (all $P < 0.0003$) as already reported [4,5]. None of the APRs differed between patients with ALT activity in the top quartile vs the lowest quartile (all $P > 0.119$). Patients with the HCV or HBV marker had almost 3× higher median ALT activity than subjects without [42 (6–192) U/l vs 15 (5–256) U/l, $P < 0.0001$]; it is noteworthy that the ALT level in the hepatitis-free patients was comparable to those of 15.6 U/l and 16.3 U/l reported in previous studies [6,7].

Our hepatitis marker-positive patients presented with slightly lower vWF levels than patients without the markers ($124 ± 25.1$% vs $133 ± 28.3$%, $P = 0.017$); the other APRs did not differ between the positive and negative subjects (all $P < 0.093$). The variation in vWF became non-significant when adjusted for cardiovascular disease prevalence. Finally (Table 1), there were no differences in inflammation markers in HD patients with serologically and biochemically evident viral hepatitis compared to subjects without obvious liver pathology.

Our study shows that liver disease does not clearly contribute to systemic inflammation in HD patients. The disparity between this and previous investigation [1] may be due to methodological limitations as well as conditions that are specific for HD therapy. Namely, our cohort was apparently undersized compared to 1740 subjects with metabolic syndrome [1], and serum CRP was not quantified with the high-sensitivity method. However, the advantage of the present report could be the variety of APRs studied, including not only CRP but also the long-lived reactants and endothelial injury marker vWF. The specific condition that probably masks the association between hepatic and systemic inflammation is repeated stimulation of the inflammatory response by HD procedures themselves [2]. Another potential confounder is the unusual presentation of liver disease in HD patients, in whom serum aminotransferases are inexplicably lower [6,7], while liver damage caused by hepatitis C virus is significantly less severe than in subjects without renal failure [8].

Finally, the link between liver disease and systemic inflammation, although not directly evident, is biologically plausible and of potential importance in maintenance HD patients. Further studies are needed before this new trait is definitely excluded.

Conflict of interest statement. None declared.

Department of Nephrology and Transplantology with Dialysis Unit
Medical University
Białystk
Poland
Email: jborawski@post.pl

doi:10.1093/ndt/gfh804

Advance Access publication 19 April 2005

Gabapentin for uraemic pruritus

Sir,

Gunal et al. [1] reported that gabapentin is effective in the treatment of uraemic pruritus. In previous years, we used gabapentin therapy in haemodialysis (HD) patients for restless leg syndrome, chronic pain and peripheral diabetic neuropathy. In our clinical experience, diverse patients suffered from drowsiness when treated with gabapentin 300 mg after each HD session, thus the dose had to be consistently reduced or the drug had to be stopped. Accordingly, previous studies [2,3] have reported the appearance of somnolence/lethargy in some HD patients receiving gabapentin at the same dosage, and there are a number of case reports highlighting the risk of gabapentin-induced neurotoxicity and coma due to its narrow therapeutic window [4–6].

Similarly to the study of Gunal et al., after having observed the spontaneous remission of uraemic itch in a HD patient receiving gabapentin therapy for peripheral diabetic neuropathy, we started a pilot evaluation aimed at testing the effectiveness and safety of low doses of gabapentin in HD patients with uraemic pruritus [7]. We began this evaluation by cautiously administering gabapentin 100 mg after every HD session and observed no side effects. In addition, the clinical response was as impressive as in the work of Gunal et al. in all of the five treated patients [7]. Importantly, we administered gabapentin under nurse surveillance after HD in order to avoid erroneous extra doses of this medication.

In conclusion, we agree with Gunal et al. that gabapentin is an effective therapy for uraemic pruritus, but we would suggest that administering a lower gabapentin dose (i.e. 100 mg thrice weekly, after each HD session) under nurse surveillance and slowly titrating it up- or downward may lessen the risk of neurotoxicity and gabapentin-induced coma in HD patients.