Association of uraemic pruritus with inflammation and hepatitis infection in haemodialysis patients

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Abstract

Background. Chronic inflammation and hepatitis C virus (HCV) infection have been implicated in the pathogenesis of uraemic pruritus in haemodialysis (HD) patients. However, each one's independent roles have not been previously studied.

Methods. A total of 321 HD patients diagnosed with end-stage renal disease with maintenance HD for >3 months were included. A visual analogue scale (VAS) was used to subjectively measure the severity of itching. Based on the VAS score, patients were divided into three groups: Group 1, no pruritus (VAS = 0); Group 2, mild to moderate pruritus (VAS 0–5) and Group 3, severe pruritus (VAS >5).

Results. There were 120 (37.4%) patients without any pruritus, 141 (43.9%) with mild to moderate pruritus and 60 (18.7%) with severe pruritus. Forty-six (14.3%) had hepatitis B virus (HBV) infection and 37 (11.5%) had hepatitis C virus (HCV) infection. The average serum high-sensitivity C-reactive protein (hsCRP) level was 0.58 mg/dl. Patients with severe pruritus had a significantly higher serum hsCRP level and more HBV or HCV infection (all P < 0.05). In the multi-variable logistic regression model, higher levels of hsCRP (OR = 3.54, P = 0.008) and HCV infection (OR = 2.77, P = 0.014) were both significant independent predictors for severe pruritus.

Conclusion. Our study demonstrated the heavy burden of pruritus in HD patients and corroborated the role of inflammation in the pathogenesis of uraemic pruritus. HCV infection is associated with severe uraemic pruritus but is independent of the serum hsCRP level in HD patients.

Keywords: hepatitis C; inflammation; uraemic pruritus

Introduction

Uraemic pruritus is strongly related to lower quality of life scores in haemodialysis (HD) patients and is frequently a cause of sleep disturbance [1,2]. Yet there is still a limited understanding of its pathophysiology and many hypotheses have been raised in previous years. Factors such as xerosis [3], parathyroid hormone [4], precipitated calcium phosphate crystals [5], iron deficiency anaemia [6], µ-receptor alteration [7] and neuropathy [8] have all been suggested to cause uraemic pruritus.

However, controlling these factors generally has had only limited success and the pathophysiology of pruritus in dialysis patients remains poorly understood. For example, µ-receptor alteration is presumed to be involved because several µ-receptor agonists are known to induce pruritus and the administration of opiate antagonists can alleviate cholestatic pruritus [9,10]. Moreover, reports about the effects of naltrexone, a µ-receptor antagonist, on uraemic pruritus in HD patients are extremely conflicting [7,11].

Systemic inflammation has likewise been proposed as an important mechanism for uraemic pruritus [12], and two small studies have observed increased inflammatory parameters in HD patients with severe pruritus compared to those without it [13,14]. However, in these studies, factors that were potentially related to inflammation, such as age and dialysis vintage, were not controlled. Chronic hepatitis C virus (HCV) infection, a presumed chronic inflammatory status, was also associated with severe pruritus in the multinational DOPPS study [1].

We believe that establishing the pathophysiology for uraemic pruritus is important. We therefore conducted this cross-sectional study in a large cohort of HD patients to clarify the effects of inflammation and hepatitis infection on uraemic pruritus.

Methods

Patients

This is a single-centre, cross-sectional study performed in the Far-Eastern Memorial Hospital HD unit. The inclusion criteria were (1) diagnosis of end-stage renal disease (ESRD), (2) regular maintenance HD for >3 months in the unit and (3) patient's informed consent. The exclusion
criteria were (1) active infection, (2) recent hospitalization within 3 months, (3) psychotic illness and other communication problems, (4) primary skin disorder, (5) cholestatic liver disease or acute hepatitis and (6) active malignancy.

From a total of 374 patients, 321 were enrolled. All were using reverse osmosis purified water and bicarbonate-containing dialysate. In 71.3% patients, high-flux polysulfone membrane was used as a dialyzer while the remaining 28.7% used a synthetic membrane low-flux dialyzer.

**Pruritus treatment and assessment**

In the unit, all of the patients received only oral anti-histamine and topical moisture agents for pruritus. A visual analogue scale (VAS) measuring the general severity of pruritus was reported from 0 to 10 (0 = no pruritus to 10 = intolerable pruritus) as described in previous studies [1]. The VAS for each patient was completed between March and April 2007 with the help of study nurses. The study period was chosen to minimize the potential confounding effect of humidity on pruritus. The average relative humidity of the study months was 72.3%, which is close to the annual average of Taiwan (75%).

**Laboratory data**

All of the blood samples were collected immediately before the patient’s mid-week HD treatment and all laboratory tests were performed at the Far-Eastern Memorial Hospital’s central lab. High-sensitivity CRP (hsCRP) was used to assess systemic inflammation because of its higher reliability than other biomarkers [15]. hsCRP levels were assayed by an Immage autoanalyser with the nephelometric method (Beckman Coulter, Inc., CA, USA). Biochemistry data were determined using the Hitachi 747 autoanalyser.

Serum anti-hepatitis C virus and anti-hepatitis B virus antibodies were measured with third-generation ELISA kits using an AxSYM analyser purchased from Abbott Laboratories (Abott Park, IL, USA). Patients with positive hepatitis B surface antigen (HbsAg) and negative anti-HBsAg antibody were considered to have HBV infection. Patients with positive anti-HCV antibody were considered to have HCV infection. The Kt/V and normalized protein catabolic rate were calculated using a single-compartment model.

**Statistical analysis**

The patients were divided into three groups according to their VAS scores: Group 1 had no pruritus (VAS scores: 0); Group 2 had mild to moderate pruritus (VAS scores: 0–5); and Group 3 had severe pruritus (VAS scores: > 5).

Normally distributed continuous variables were presented as mean (SD) while non-normally distributed continuous variables were presented as median (1st and 3rd quartile). Categorical data were presented as percentages. Chi-square analysis was used to test the differences of categorical variables between different VAS groups. For normally distributed variables, the one-way ANOVA test was used. For non-normally distributed continuous variables, the non-parametric Kruskal–Wallis test was used. Post hoc Dunnett’s test was used to compare Groups 1 and 3.

All of the possible predictor variables (P < 0.1) were subsequently used in a multi-variable-adjusted logistic regression model using severe pruritus as the dependent variable. The effects of sex, age and vintage of dialysis were further adjusted in the model because these might influence the inflammatory status in the ESRD population. The non-parametric Mann–Whitney U-test was used to compare VAS scores and hsCRP levels between patients with and those without hepatitis. The statistical analyses were performed with SPSS 13.0 and a P-value < 0.05 was considered significant.

**Results**

A total of 321 patients completed this study. Of these, 37.4% had no pruritus, 43.9% had mild to moderate pruritus (VAS 0–5) and 18.7% had severe pruritus (VAS >5). Demographic and laboratory data are presented in Table 1. The mean age was 59.7 years; 49.5% were males and 43.6% were diabetic. Forty-six (14.3%) had HBV infection while 37 (11.5%) had HCV infection. The median time for dialysis was 2.9 years and the median serum hsCRP level was 2.55 mg/l.

By non-parametric ANOVA analysis, patients with severe pruritus had a significantly higher serum hsCRP level (P = 0.017) and more HBV (P = 0.004) or HCV infection (P = 0.020). The use of a low-flux dialyzer tended to be associated with severe pruritus (P = 0.083).

In the multi-variable-adjusted logistic regression model, the higher hsCRP level (OR = 3.536, P = 0.008) and HCV infection (OR = 2.773, P = 0.014) were both significantly independent predictors of severe pruritus after adjustment for sex, age, duration on dialysis and type of dialyzer used (Table 2). However, HBV infection was not a statistically significant predictor of severe pruritus in this model (OR = 1.658, P = 0.213). The Nagelkerke R-square of the model was 0.103.

Table 3 shows the comparison of VAS scores and hsCRP levels between patients with and those without hepatitis infection. Patients with either HBV or HCV infection had significantly higher VAS scores (P = 0.002 and 0.009, respectively) but not hsCRP levels (P = 0.245 and 0.840, respectively).

**Discussion**

This study reinforces previous observations about the role of inflammation in uraemic pruritus. After controlling for potential confounding factors, a significant association between the hsCRP level and severe pruritus is shown in this large, unselected population of HD patients. Hepatitis C infection is also associated with severe pruritus, independent of the serum hsCRP level. Hepatitis B infection tends to be associated with severe pruritus but not statistically significant in the multi-variable model.

Chronic inflammation had been found to be the culprit of various clinical diseases, including obesity, diabetes, malnutrition, cardiovascular diseases, psychiatric illness and even ageing [16]. It is also well established that
For non-normally distributed continuous variables, values shown as median (1st and 3rd quartiles); for normally distributed continuous variables, values shown as mean (SD).

have both higher blood cytokines and other inflammatory and erythematous skin changes [19]. Since uraemic patients with ESRD is also associated with many important clinical complications, including atherosclerosis, malnutrition and mortality, even in patients with pre-dialysis chronic kidney disease [17].

Furthermore, inflammation has been an important cause of skin itching. Intra-dermal injection of complement-activating products or interleukin-2 induces itching both in atopic dermatitis patients and in healthy controls [18]. Interleukin infusion in cancer patients also causes itching and erythematous skin changes [19]. Since uraemic patients have both higher blood cytokines and other inflammatory factors that are associated with severe pruritus, it can be postulated that an aggravated inflammatory status directly or indirectly leads to uraemic pruritus. In this regard, Virga et al. first studied 68 Italian HD patients to assess the effects of inflammation, iron deficiency and other serum parameters on uraemic pruritus [13]. Compared with patients with moderate or no pruritus, patients with more severe pruritus tended to have higher serum C-reactive protein (P = 0.057) and lower serum albumin levels.

Another study conducted by Kimmel et al. indicated that uraemic pruritus is a result of a Th1-dominant immune activation, with more cytotoxic and inflammatory cytokine patterns present [14]. However, in their study, patients with severe pruritus had been on dialysis for significantly longer periods than patients without pruritus, which might have directly led to higher serum inflammatory cytokines in the former. Other evidence supporting the immune hypothesis includes certain effective immunological treatments. Concomitant attenuated Th1 differentiation and improvement of pruritus were noted after ultraviolet B exposure [20]. Successful treatment had also been reported using oral thalidomide [21] and cyclosporine-A therapy [22].

All of these findings, including ours, are consistent with a significant role of inflammation in the pruritus of HD patients. In fact, like inflammation, pruritus is also associated with poorer survival of HD patient after adjustment for other significant clinical risk factors for mortality [23].

The association of HCV infection with uraemic pruritus is rarely reported. Our group first reported that HCV infection is related to pruritus in peritoneal dialysis patients [24]. Two other studies performed on HD population, including inflammatory indexes are frequently elevated in individuals with ESRD. This may be due to decreased renal cytokine excretion, multiple co-morbidities and the dialysis procedure. Persistent inflammation in ESRD is also associated with many important clinical complications, including atherosclerosis, malnutrition and mortality, even in patients with pre-dialysis chronic kidney disease [17].

Table 1. Demographic and laboratory data of all patients, with comparisons among groups of different pruritus severity

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n = 321)</th>
<th>No pruritus (VAS = 0) (n = 120)</th>
<th>Mild to moderate pruritus (VAS = 0–5) (n = 141)</th>
<th>Severe pruritus (VAS &gt;5) (n = 60)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>49.5</td>
<td>45.0</td>
<td>55.3</td>
<td>45.0</td>
<td>0.177</td>
</tr>
<tr>
<td>Age (year)</td>
<td>59.6 (11.9)</td>
<td>60.1 (11.6)</td>
<td>58.6 (11.9)</td>
<td>61.1 (13.0)</td>
<td>0.351</td>
</tr>
<tr>
<td>Use of high-flux dialyzer (%)</td>
<td>71.3</td>
<td>78.8</td>
<td>70.9</td>
<td>63.3</td>
<td>0.083</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>43.6</td>
<td>40.0</td>
<td>47.5</td>
<td>41.7</td>
<td>0.398</td>
</tr>
<tr>
<td>Hepatitis B (%)</td>
<td>14.3</td>
<td>5.8</td>
<td>19.2</td>
<td>20.0</td>
<td>0.004*</td>
</tr>
<tr>
<td>Hepatitis C (%)</td>
<td>11.5</td>
<td>9.1</td>
<td>9.2</td>
<td>21.7</td>
<td>0.024*</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>72.1 (18.3)</td>
<td>71.2 (17.6)</td>
<td>72.8 (19.1)</td>
<td>72.3 (18.0)</td>
<td>0.792</td>
</tr>
<tr>
<td>WBC (10⁹/L)</td>
<td>6.53 (5.37, 7.85)</td>
<td>6.56 (5.34, 7.84)</td>
<td>5.37 (6.44, 7.80)</td>
<td>6.58 (5.20, 8.26)</td>
<td>0.792</td>
</tr>
<tr>
<td>Haemoglobin (10⁹/L)</td>
<td>10.9 (1.4)</td>
<td>10.8 (1.3)</td>
<td>11.0 (1.4)</td>
<td>10.9 (1.5)</td>
<td>0.637</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>41 (39, 43)</td>
<td>42 (39, 43)</td>
<td>41 (40, 43)</td>
<td>41 (38, 43)</td>
<td>0.290</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>13.0 (10.0, 20.0)</td>
<td>12.0 (9.0, 13.0)</td>
<td>14.0 (10.0, 21.5)</td>
<td>14.0 (11.0, 21.8)</td>
<td>0.260</td>
</tr>
<tr>
<td>Total bilirubin (µmol/L)</td>
<td>0.3 (0.2, 0.4)</td>
<td>0.3 (0.3, 0.4)</td>
<td>0.3 (0.2, 0.4)</td>
<td>0.3 (0.2, 0.4)</td>
<td>0.970</td>
</tr>
<tr>
<td>Intact PTH (ng/L)</td>
<td>245</td>
<td>244.5</td>
<td>249.0</td>
<td>222.0</td>
<td>0.451</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.27 (2.20, 2.39)</td>
<td>2.26 (2.18, 2.41)</td>
<td>2.30 (2.19, 2.39)</td>
<td>2.28 (2.18, 2.43)</td>
<td>0.330</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.61 (1.35, 1.96)</td>
<td>1.55 (1.32, 1.93)</td>
<td>1.67 (1.38, 2.03)</td>
<td>1.64 (1.38, 1.95)</td>
<td>0.173</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>508.3</td>
<td>492.7</td>
<td>508.7</td>
<td>549.5</td>
<td>0.377</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>2.55 (1.11, 6.62)</td>
<td>2.11 (0.99, 6.48)</td>
<td>2.55 (1.05, 6.40)</td>
<td>4.10 (1.56, 9.54)</td>
<td>0.005*</td>
</tr>
<tr>
<td>K/Cl urea</td>
<td>1.29 (1.21, 1.43)</td>
<td>1.31 (1.19, 1.44)</td>
<td>1.27 (1.16, 1.40)</td>
<td>1.30 (1.19, 1.45)</td>
<td>0.425</td>
</tr>
<tr>
<td>NPCR (g/kg/day)</td>
<td>1.10 (0.25)</td>
<td>1.10 (0.25)</td>
<td>1.12 (0.25)</td>
<td>1.11 (0.24)</td>
<td>0.688</td>
</tr>
</tbody>
</table>

Table 2. Predictors for severe pruritus (VAS > 5) in multi-variable adjusted logistic regression analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.326</td>
<td>0.724–2.431</td>
<td>0.361</td>
</tr>
<tr>
<td>Age (year)</td>
<td>0.985–1.037</td>
<td>0.583</td>
<td>0.165</td>
</tr>
<tr>
<td>Duration of dialysis (year)</td>
<td>0.773</td>
<td>0.307–1.945</td>
<td>0.584</td>
</tr>
<tr>
<td>High-flux dialyzer use</td>
<td>1.025</td>
<td>0.956–1.098</td>
<td>0.486</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>0.643</td>
<td>0.331–1.249</td>
<td>0.192</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>2.773</td>
<td>1.225–6.280</td>
<td>0.014*</td>
</tr>
<tr>
<td>HsCRP (mg/dl) &lt; 1st quartile</td>
<td>2.249</td>
<td>0.952–5.313</td>
<td>0.065</td>
</tr>
<tr>
<td>&gt; 3rd quartile</td>
<td>3.536</td>
<td>1.398–8.944</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

*P < 0.05.
the prestigious DOPPS study, also observed this association [1,25]. The authors postulated that chronic inflammation secondary to hepatitis C infection aggravates pruritus. Actually, HBV and HCV infections are implicated in the elevation of oxidative stress and plasma pro-inflammatory and chemo-attractant cytokine levels in uraemic patients [26]. Serum-soluble cellular adhesion molecules, which are also related to inflammation, are elevated in HCV-positive HD patients [27].

In the present study, patients with hepatitis infection do not have higher hsCRP levels and hepatitis infection is associated with the severity of pruritus independent of the hsCRP level. Because CRP is produced in the liver, the serum hsCRP level may not accurately reflect the status of inflammation in HCV infected patients as suggested by previous studies [28,29]. It is not known whether hepatitis C infection may lead to pruritus through other inflammatory pathways or mechanisms. Anti-HCV antibody positivity only denotes prior infection and active infection can only be demonstrated by HCV RNA testing [30]. Further study should focus on the relationship between viral load and pruritus, as well as the effect of anti-viral treatment on the severity of uraemic pruritus.

In our study, there is no association between serum parathyroid hormone and pruritis severity. Improvement of uraemic pruritus after parathyroidectomy has been reported [31], but there has been subsequent reports questioning the direct role of parathyroid hormone in pruritus [32,33]. We could not find a significant association of serum ferritin and albumin levels with pruritus, although both are indirect markers of systemic inflammation. We found a tendency of patients with severe pruritus to have higher serum ferritin and lower albumin levels. Because serum albumin and ferritin levels are confounded by nutritional status and intra-venous iron therapy, these may not correctly reflect the inflammation status.

Our study corroborates previous studies about the persistent burden of uraemic pruritus in HD patients [1,2,34]. In the present study, only 37.4% patients did not suffer from pruritus. This study is the first to establish the relationship between inflammation and pruritus in a large and unselected HD cohort while carefully adjusting for other clinical and laboratory factors. This is the main strength of our study. Because this study was unable to prove a causal relationship between elevated C-reactive protein level and uraemic pruritus, a carefully designed study that applies anti-inflammatory agents and follows up both inflammatory parameters and severity of pruritus is warranted. A longitudinal follow-up of HD patients with pruritus and their inflammation status will also help determine the independent role of pruritus on survival.

In conclusion, immune function is becoming more and more important in maintaining a good health status for HD patients. Accumulating evidence, including ours, indicates that uraemic pruritus is related to a systemic inflammatory condition rather than a solitary skin disorder. Hence, the importance of uraemic pruritus should not be neglected. While there is still no definite effective treatment for uraemia-related inflammation, further study on the interplay between contributing factors for inflammation should help establish an optimal treatment strategy.

Conflict of interest statement. None declared.

References


