Plasmapheresis improves chronic fatigue in patients with primary biliary cholangitis

Authors: Ewa Wunsch, Beata Kruk, Emilian Snarski, Grzegorz Basak, Marcin Krawczyk, Piotr Milkiewicz

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Title: Plasmapheresis improves chronic fatigue in patients with primary biliary cholangitis

Short title: Plasmapheresis improves fatigue in PBC

Authors: Ewa Wunsch*¹, Beata Kruk², Emilian Snarski³, Grzegorz Basak³, Marcin Krawczyk*²,³,⁴, Piotr Milkiewicz¹,⁵,⁶

Affiliations:

1. Translational Medicine Group, Pomeranian Medical University in Szczecin, Szczecin, Poland.
2. Laboratory of Metabolic Liver Diseases, Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland.
3. Department of Hematology, Medical University of Warsaw, Warsaw, Poland.
4. Department of Medicine II, Saarland University Medical Center, Homburg, Germany.
5. European Reference Network.
6. Liver and Internal Medicine Unit, Medical University of Warsaw, Warsaw, Poland.

*Contributed equally

CORRESPONDENCE:

Piotr Milkiewicz MD, MRCP (UK)
Liver and Internal Medicine Unit, Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland
Banacha 1A, 02-097 Warsaw, Poland
Tel. +48225991662, Fax. +48225991663
E-mail: p.milkiewicz@wp.pl

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**Introduction**

Chronic fatigue remains an untreatable and incapacitating symptom occurring in various autoimmune conditions exerting dramatic effects on a patient’s health-related quality of life (HRQoL) [1]. Its origin remains unclear however increasing evidence indicates that it is centrally mediated with evident autonomic dysfunction. Moreover it has been recently postulated that resistin and transforming growth factor β (TGF-β) may play a role in its pathogenesis [2]. Primary biliary cholangitis (PBC) may manifest itself with chronic fatigue [3] which does not depend on the stage of the disease. Unlike pruritus, fatigue persists after liver transplantation [4]. Plasmapheresis remains a valid option in the treatment of intractable pruritus in PBC when other modalities fail [5]. Here we analyzed the effect of plasmapheresis on chronic fatigue in a group of 13 patients with PBC suffering from intractable pruritus.

**Methods**

**Patients**

Thirteen clinically stable patients with PBC: 12 (92.3%) females, 6 (46.1%) patients with cirrhosis, median age 60 years, range 40-69 years; treated in our centre (Medical University of Warsaw), and intractable pruritus not responding to medical therapy were prospectively enrolled. In these patients plasmapheresis was performed as a part of medical therapy. Additionally, in order to investigate the potential role of resistin and TGF-β in fatigue of cholestatic disease, these cytokines were analyzed in 103 patients with PBC: 99 (96.1%) females, median age 52 years, range 28-83 years; and correlated with their Fatigue score from
The diagnosis of PBC was based on EASL criteria [6]. All were treated with ursodeoxycholic acid (UDCA) in the dose of 13-15mg/kg b.w.

**Procedures**

Plasmapheresis was performed in 13 patients with intractable pruritus as previously described using COBE Spectra LRS Turbo Version 7.0 (Caridian BCT, Lakewood, CO, USA) [5]. Three procedures, usually every other day, were performed during one admission (e.g. Monday-Wednesday-Friday). Liver biochemistry, measurements of serum resistin and TGF-β using ELISA (Thermo-Fisher Scientific US) and HRQoL questionnaires were performed before and one month after the procedure.

**HRQoL questionnaires**

PBC-40 is a disease-specific HRQoL questionnaire, designed for self-completion in patients with PBC [7]. It consists of 40 questions in 5 domains: Cognition, Itch, Fatigue, Social-Emotional and Other Symptoms, marked with a five-point scale (1=never to 5=always), with higher scores denoting greater symptoms impact and poorer HRQoL. The possible range of each domain is: Other Symptoms domain 7-35, Itch 3-15, Fatigue 11-55, Cognitive 6-30, Social and Emotional 13-65 points. Patient Health Questionnaire-9 (PHQ-9) is a self-administered screening tool for depressive symptoms as they are defined in the Diagnostic and Statistical Manual IV. The PHQ-9 score ranges from 0 to 27 points. Scores ≥ 10 have sensitivity and specificity of 88% for major depression, with scores of 5, 10, 15, and 20 points correlate with mild, moderate, moderately severe and severe depression, respectively [8].

Hospital Anxiety and Depression Scale (HADS) originally developed by Zigmond and Snaith is commonly used self-administered questionnaire to determine respondent’s levels of anxiety and depression [9]. The scale consists of 7 items related to anxiety and 7 related to depressive
symptoms, each scored from 0-3 points with higher scores indicating greater symptoms severity. The possible range of both domain is 0-21 points.

Pruritus was also assessed by Numbering Rating Scale (NRS), a 10-point self-report scale, where 0 points indicates “No pruritus at all”, 10 points - “Intractable pruritus”.

Statistical analysis

The Shapiro-Wilk normality test and visual inspection of histograms were used to examine the distribution of quantitative variables. Continuous data were presented as median and interquartile range (IQR) and categorical data as numbers and percentage. Statistical analysis was performed using Wilcoxon rank sum test and correlation-coefficient assessed with Pearson’s or Spearman rank correlation tests, as appropriate (Statistica 13.0, TIBCO Software Inc. 2017). P values < 0.05 were considered significant.

Ethics

Appropriate informed consent was obtained from each patient included in the study. The study protocol was approved by the ethics committee of Medical University of Warsaw and conforms with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

Results

In the plasmapheresis group there was a significant amelioration of chronic fatigue after the procedure measured by Fatigue score of PBC-40. The plasmapheresis also reduced pruritus measured with both PBC-40 and NRS, caused improved in Other symptoms domain of PBC-40 and in Depression domain of HADS (Table 1). Fatigue and pruritus did not show a significant correlation after plasma exchange (Rho=0.36; p=0.22). Plasmaphereses had no significant effect neither on liver biochemistry nor on analyzed cytokines (Table 1). There was no correlation between chronic fatigue and resistin or TGF-β neither before nor after
plasma exchange (Figure S1). Analysis of the control cohort of 103 patients with PBC also showed no correlation between chronic Fatigue score of PBC-40 and analyzed cytokines (r=0.15, p=0.29 for resistin and r=-0.167, p=0.24 for TGF-β).

**Discussion**

Chronic fatigue exerts dramatic effect on HRQoL and may lead to long time sickness absence [10]. It remains untreatable and may occur in various, usually autoimmune conditions such as rheumatoid arthritis or multiple sclerosis. In the latter it is considered by patients as the most debilitating symptom affecting everyday life more than spasticity or bladder dysfunction [11].

Plasmapheresis provides a long term relieve of pruritus associated with cholestatic liver conditions [5]. Here we report a beneficial effect of plasmapheresis on chronic fatigue in PBC. This effect did not correlate with the observed improvement of pruritus caused by the procedure. This suggests that the decrease of fatigue induced by plasma exchange could be independent from the reduced pruritus. This is a novel and original finding.

Plasmapheresis was implemented in 13 patients with PBC as a treatment of their intractable pruritus. The impact of this procedure on patients’ well-being was assessed with questionnaires assessing both disease-specific HRQoL (PBC-40) as well as depression (HADS and PHQ-9). In order to gain more insight into pathogenesis of chronic fatigue in cholestasis we measured serum levels of two cytokines, resistin and TGF-β, which showed the strongest link with chronic fatigue of non-cholestatic origin in previous studies [2]. These two cytokines were not only analyzed in patients who underwent plasmapheresis but also in a large groups of patients with PBC and various degrees of chronic fatigue: both showed resistin and TGF-β no link with chronic fatigue in our patients.

It can be inferred that plasmapheresis, by virtue of its mode of action, eliminates unknown factor(s) responsible for chronic fatigue in PBC. In turn, this may offer a treatment option to
those patients most affected by this devastating symptom. Notwithstanding, our findings require validation in a larger group of patients with chronic cholestatic liver conditions.

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**REFERENCES**


**TABLES**

**Table 1.** Study parameters at baseline and after plasmapheresis in a group of 13 patients with PBC.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemical parameters</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total bilirubin, mg/dl</td>
<td>1.1 (0.5—4.5)</td>
<td>0.7 (0.5—3.3)</td>
<td>0.02 (-0.1—0.04)</td>
<td>0.67</td>
</tr>
<tr>
<td>ALP, IU/l</td>
<td>196 (105—315)</td>
<td>265 (109—387)</td>
<td>29.5 (-25.5—69.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>GGT, IU/l</td>
<td>105 (55—198)</td>
<td>115 (76—169)</td>
<td>26 (-3—66)</td>
<td>0.24</td>
</tr>
<tr>
<td>ALT, IU/l</td>
<td>59 (35—94)</td>
<td>65 (37—92)</td>
<td>-3 (-9—24)</td>
<td>0.70</td>
</tr>
<tr>
<td>AST, IU/l</td>
<td>75 (41—98)</td>
<td>65 (35—93)</td>
<td>-6.5 (-19—20)</td>
<td>0.81</td>
</tr>
<tr>
<td>Resistin, ng/ml</td>
<td>10.8 (9.4—13.5)</td>
<td>9.4 (7.4—13.7)</td>
<td>-0.8 (-6.0—3.2)</td>
<td>0.48</td>
</tr>
<tr>
<td>TGF-β, ng/ml</td>
<td>2.0 (1.4—2.8)</td>
<td>2.6 (1.1—3.0)</td>
<td>0.2 (-0.6—0.9)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

**PBC-40**
<table>
<thead>
<tr>
<th>Other Symptoms, points</th>
<th>21 (18—22)</th>
<th>17 (14—21)</th>
<th>-2 (-4— -1)</th>
<th>0.02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itch, points</td>
<td>12 (3.3)</td>
<td>8 (7—11)</td>
<td>-4 (-4— -1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Fatigue, points</td>
<td>38 (32-42)</td>
<td>30 (17—34)</td>
<td>-6 (-11 — -4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cognitive, points</td>
<td>18 (14—19)</td>
<td>16 (13—18)</td>
<td>-1 (-3— 1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Social Emotional, points</td>
<td>39 (26—49)</td>
<td>38 (29—45)</td>
<td>-4 (-5— 3)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>NRS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS, points</td>
<td>8 (8.0—8.0)</td>
<td>5 (3.5—7.5)</td>
<td>-3 (-5.5— -0.5)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>PHQ-9</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHQ-9, points</td>
<td>10 (6—15)</td>
<td>9 (4—13)</td>
<td>0 (-7— 3)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>HADS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression, points</td>
<td>6 (5—8)</td>
<td>6 (2—7)</td>
<td>-1 (-4— 0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Anxiety, points</td>
<td>7 (6—9)</td>
<td>7 (5—11)</td>
<td>1 (-1— 3)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Data presented as median (IQR). The Wilcoxon rank sum test, p value <0.05 is significant.

**Abbreviations:** alanine aminotransferase, ALT; alkaline phosphatase, ALP; asparaginian aminotransferase, AST; gamma glutamyltransferase, GGT; Hospital Anxiety Depression Scale, HADS; Numering Rating Scale, NRS; Primary biliary cholangitis, PBC; Patient Health Questionnaire-9, PHQ-9.