Case Report

A New Approach Using Nanomembrane-Based Therapeutic Plasmapheresis for Treatment of Patients with Multiple Sclerosis. A Case Report

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Abstract

We present for the first time treatment of patients with multiple sclerosis by minimally invasive therapeutic plasmapheresis using a nanomembrane (EC Certificate No CQ102011-ll). Plasmapheresis was carried out in accordance with the sixth revised edition of the “Guidelines on the use of Therapeutic Apheresis in Clinical Practice” [1], published in 2013, and the National consensus for intensive treatment of diseases by therapeutic apheresis in Bulgaria [2]. Four procedures of plasmapheresis were applied every other day with separation of plasma out of the circulation. The plasma separated from the patient was substituted with saline. This separated plasma contained immunoglobulins A, G and M, among others. Oxygen saturation was improved in the course of the plasmapheresis procedure. The observed reversal of the pathological process in the treated MS patients was not only based on subjective opinion of the patients, but also on objective research based on the scale of Kurtzke. During the plasmapheresis procedures we did not observe hemodynamic disturbances associated with the cardiovascular or the respiratory system.

The obtained results gave us ground to assume that the removal of pathogenic autoantibodies along with the application of a modern immunosuppressive therapy can change the prognosis, associated with invalidization of these patients.

We believe that this new, low-invasive plasmapheresis based on the use of nanomembrane, combined with modern immunosuppressive therapy would provide a good perspective for the quality of life and the prognosis of the treated patients.

ABBREVIATIONS

MS: Multiple Sclerosis; TNF: Tumor Necrosis Factor; IL: Interleukins; NGF: Nerve Growth Factor; HDL: High Density Lipoproteins

INTRODUCTION

Multiple sclerosis [MS] is an autoimmune, inflammatory, neurodegenerative, demyelinating, chronic fluctuating disease of unknown etiology with a possible genetic predisposition. This autoimmune disease with diverse symptoms and clinical manifestations often leads to serious damage of the motor activity, paresis and/or paralysis, decreased vision, disorders in the function of the pelvic organs, etc.

It has been reported that the titers of antibodies to various viruses [measles, influenza, herpes simplex, Epstein-Barr virus, papilloma virus] are increased in the plasma and cerebrospinal...
fluid in patients with MS, but there is no clear scientific evidence for the detection of RNA or viral antigens in the brain tissue of these patients. However, there is evidence of the possible role of retroviruses in the development of multiple sclerosis [3].

It is assumed that MS is accompanied by development of protein mimicry, as the antigenic structure of individual proteins of the viruses is close or similar to proteins in the white matter of brain tissue. These disturbances might be related to the possible mechanisms, underlying the pathogenesis of MS [4].

S. Sriram et al. [5] suggest that the major cause of multiple sclerosis are T lymphocytes that penetrate into the microglia, activate the secretion and the release of myelin- toxic factors, and damage directly myelin in the oligodendrocytes. Autoantibodies against myelin basic protein [MBP] are involved in the process of demyelination at later stages of development of multiple sclerosis [6]. The activation of microglia cells further induces the production of pro inflammatory cytokines, chemokines, which in turn additionally activate the T lymphocytes. These processes are accompanied by release of tumor necrosis factor [TNF], nitric oxide, oxygen free radicals and interleukins [IL] 1 and IL12. Cytokines are also found in the cerebrospinal fluid. In these patients the contents of IL12 increases continuously [for about 4-6 weeks] before the onset and aggravation of a new outbreak of the disease [7]. In a number of patients with multiple sclerosis were detected antinuclear autoantibodies that are specific for systemic lupus erythematosus, which also suggests the systemic nature of the disease [8].

At the beginning, the process of demyelination is not irreversible, due to the presence of the nerve growth factor [NGF], which enables regeneration of myelin and recovery of the nerve cells [9]. The appearance of antibodies against this protein [NGF] in multiple sclerosis slows down or even stops the process of regeneration of myelin and of the axons of nerve cells [10].

The application of therapeutic plasmapheresis was started in the last 10 years as an element of a complex therapeutic approach, involving corticosteroids and cyclophosphamide [11].

Our scheme of nanomembrane-based plasmapheresis produced very good results, allowing 7 patients to reach remission of multiple sclerosis. Success has been achieved with the use of serial plasmapheresis. Performed in four sessions one procedure per month.

In the present study we carried out a course of 4 sessions of plasmapheresis with subsequent performance of 1 procedure each month, with a very favorable result for the patient.

We present here one patient with MS, who underwent therapeutic plasmapheresis on the background of conservative treatment with immunosuppressive drugs. We carried out 4 procedures of plasmapheresis every other day with separation out of the circulation of antibodies-containing plasma in a volume of about 0.8 l (Figure 1). Substitution of the separated plasma was performed only with saline. Plasmapheresis was carried out in accordance with the sixth revised edition of the “Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis”, and the rules developed for plasmapheresis in Bulgaria [2] with nanotechnology membranes (Figure 2). We used nanomembrane with EC Certificate No CQ102011- II produced by “Trackpore Technology Corporation”, 141980 Dubna, Moscow region, Russian Federation. After the last [fourth] procedure was observed an apparent clinical improvement, which was assessed also according to the international scale of Kurtzke EDSS.

CASE PRESENTATION

The patient was 61 years old female with initials M.P.K. The diagnosis of multiple sclerosis has been specified in 2000. The
The patient has been treated with corticosteroids during relapses. However, a gradual deterioration of neurological symptoms [irrespective of therapy] has been observed and she was admitted to the hospital for treatment with therapeutic plasmapheresis on July/22/2013.

The clinical examination before plasmapheresis revealed the following parameters:

- Patient was 165 cm tall with weight 70 kg. Circulating blood volume - about 5 liters.
- Volume of circulating plasma - about 3.2 liters.
- Kurtzke EDSS score - 6.0

Table 1: Alterations in the level of proteins, immunoglobulins and cholesterol before the initiation of the procedures and after each separate plasmapheresis.

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Before plasmapheresis</th>
<th>After 2-nd plasmapheresis</th>
<th>After 3-rd plasmapheresis</th>
<th>After 4-th plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>65 g/l</td>
<td>56 g/l</td>
<td>48 g/l</td>
<td>67 g/l</td>
</tr>
<tr>
<td>Albumin</td>
<td>36 g/l</td>
<td>31 g/l</td>
<td>28 g/l</td>
<td>44 g/l</td>
</tr>
<tr>
<td>IgA</td>
<td>1.37 g/l</td>
<td>1.38 g/l</td>
<td>1.28 g/l</td>
<td>1.05 g/l</td>
</tr>
<tr>
<td>IgG</td>
<td>10.12 g/l</td>
<td>8.74 g/l</td>
<td>7.79 g/l</td>
<td>8.01 g/l</td>
</tr>
<tr>
<td>IgM</td>
<td>1.02 g/l</td>
<td>0.94 g/l</td>
<td>0.87 g/l</td>
<td>0.92 g/l</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>7.51 mmol/l</td>
<td>5.91 mmol/l</td>
<td>5.3 mmol/l</td>
<td>5.6 mmol/l</td>
</tr>
<tr>
<td>Cholesterol/HDL</td>
<td>7.42</td>
<td>6.42</td>
<td>6.88</td>
<td>7.03</td>
</tr>
</tbody>
</table>

**Abbreviations:** IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; HDL: High Density Lipoproteins

Table 2: Alterations in the level of proteins, immunoglobulins and cholesterol before and after the performance of plasmapheresis one month after the completion of the four initial procedures.

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Before plasmapheresis</th>
<th>After plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>63 g/l</td>
<td>57 g/l</td>
</tr>
<tr>
<td>Albumin</td>
<td>37 g/l</td>
<td>32 g/l</td>
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<tr>
<td>IgA</td>
<td>1.47 g/l</td>
<td>1.3 g/l</td>
</tr>
<tr>
<td>IgG</td>
<td>10.93 g/l</td>
<td>9.3 g/l</td>
</tr>
<tr>
<td>IgM</td>
<td>1.06 g/l</td>
<td>0.96 g/l</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>8.13 mmol/l</td>
<td>6.98 mmol/l</td>
</tr>
<tr>
<td>Cholesterol/HDL</td>
<td>7.46</td>
<td>6.98</td>
</tr>
</tbody>
</table>

**Abbreviations:** IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; HDL: High Density Lipoproteins
Imperative urge to urinate. Diseased cannot retain more than 5 minutes.

Treatment: Four sessions of plasmapheresis have been performed every other day.

During each single procedure was separated 0.8 l autoantibodies-containing plasma, which makes a total of 3.2 liters of plasma as a result of the four sessions. The separated plasma was substituted with saline.

Before the initiation of the procedures and one hour after the completions of each plasmapheresis were determined the following blood parameters: total protein, albumin, immunoglobulins, cholesterol, cholesterol/ HDL (Table 1). It is evident from the obtained values that all parameters under investigation, including the immunoglobulins and cholesterol, were reduced at a different degree. In this table are presented the values obtained after the 2-nd, 3-rd and 4-th sessions of plasmapheresis, because we did not measure these values after the first procedure.

One month after the completion of the cycle of the first four procedures of plasmapheresis, we performed one more therapeutic plasmapheresis (Table 2) which showed similar alterations of the measured values to the ones obtained after the initial procedures (Table 1). In addition, the monitoring of SatO₂ showed a gradual increase during the performance of the plasmapheresis procedure (Figure 2).

Ten days after completion of the plasmapheresis sessions we observed alterations in the patient’s condition as follows:

- Improvement of the mobility in the right eye bulb and a lack of diplopia.
- A significant reduction of the horizontal nystagmus.
- Significant improvement of the left leg quadriparesis
- Reduced spasticity in the 4 extremities.
- Walking became possible without attendant or solely with unilateral assistance up to 100 meters
- Significant improvement in the coordination
- There was no imperative urge to urinate.
- Normalization of the speech
- Total assessment of Kurtzke EDSS score - 5 points.

DISCUSSION

The reported results in this study imply that the application of nanomembrane-based therapeutic plasmapheresis can contribute significantly for improvement of the clinical symptoms, accompanying the development of MS. We suggest that this method can be used successfully for treatment of MS and most importantly, it does not show the side effects of most of the currently used therapeutic approaches. For example, it has been shown that injection of MS patients with recombinant interferon β-1b induces binding and neutralizing of antibodies in some patients with multiple sclerosis, although its endogenous production and the level in these patients was elevated [12,13]. The body begins to synthesize antibodies against the introduced interferon-β-1b, which reduces the effectiveness of this drug and for 6-12 months it becomes ineffective [14]. Furthermore, a number of serious side effects have been reported during treatment with interferon-β-1b - formation of subcutaneous abscesses in places of application, hepatic dysfunction, flu-like reaction, asthenia, stomatitis, anorexia, decreased hemoglobin (anemia), neutrophils and thrombocytopenia. Selective inhibitors of molecule adhesion are considered as promising in the treatment of MS, a representative of which is the recombinant monoclonal antibody natalizumab. A major drawback of this treatment is that it produces a progressive multifocal leukoencephalopathy, urinary tract inflammation, chills, fever, fatigue and others. [15]. Therapeutic plasmapheresis removes the complications associated with natalizumab and stops the development of progressive multifocal leukoencephalopathy.

We performed a continuous monitoring the of patient’s condition during the last year. After the series of four therapeutic apheresis we observed that there were no new relapses of the disease. Maintaining treatment with therapeutic apheresis every 3 months stabilized the outcome and resulted in regression of the symptoms of the patient. This gave us grounds to recommend nanomembrane-based therapeutic apheresis as a reliable component in a complex MS therapeutic approach besides medications, physiotherapy and diet. The reported conclusions have been confirmed by additional otoneurological functional...
investigations and image observations using nuclear magnetic resonance (data not shown).

In conclusion we hope that our experience related to the use of nanomembrane-based therapeutic apheresis will contribute to increase the effectiveness of the treatment of autoimmune diseases, such as multiple sclerosis.

ACKNOWLEDGEMENTS

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REFERENCES


