Therapeutic apheresis in immunocomplex nephritis: A case report of a successful treatment.

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Abstract

The advantages of the Therapeutic Apheresis (TA) with membrane modules, which became available since the mid-1970s, are a complete separation of the blood cells from the plasma. Autoimmune diseases have an immune pathogenesis and can produce auto antibodies (ab) and Circulating Immune Complexes (CIC), which are the origin of inflammation in various organs. The most patients with these diseases have a poor prognosis without treatment. TA in combination with immunosuppressive drugs has brought an increase in the survival rates over the last 40 years. The origin of autoimmune diseases is still generally unknown. The variety of autoimmune diseases ranges from those diseases in which autoimmunization is solely responsible for the condition (e.g., autoimmune hemolytic anemia) to those in which it possibly has a major influence on the course of the disease (e.g., rheumatoid arthritis), and those in which the autoimmunization results are probably only of diagnostic importance. The auto antibodies (auto-abs) activate different immunological processes which are self-destructive for the organs. These auto antibodies can be directed to all blood cells, too. With a case report of a woman, who was treated with Therapeutic Plasma Exchange (TPE) intermittently since her childhood, the authors show the efficacy of TPE in autoimmune diseases. The patients have had immunocomplex nephritis with a severe nephrotic syndrome which was diagnosed by a renal biopsy in the age of 14 months of the child. In the now more than 30 years old woman acute attacks of immunocomplex nephritis with nephrotic syndrome could be well controlled by TPE without excessive increases in the dosage of immunosuppressive drugs and a significant impairment in renal function.

Keywords: Therapeutic apheresis, Therapeutic plasma exchange, Immunocomplex nephritis, Nephrotic syndrome, ANCA-associated vasculitis.

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Introduction

Since the availability of hollow fiber modules in TPE these are mostly used in nephrology, as these membranes can be used with dialysis equipment. Nephrologists have the best training in the carrying out of detoxification treatments of blood including vascular access, anticoagulation, volume implementation and prescription for solute clearance [1]. The indications for TPE in nephrology expand the clinical practice of these physicians.

There are only few controlled studies available of adequate statistical values to allow definitive conclusions to the therapeutic value of TA. The relative rarity of most diseases under investigation reflects this drawback in part. Many investigators have grouped heterogeneous diseases together and used historical groups as controls to compensate. “The latter design is potentially hazardous, given that earlier diagnosis, recognition of milder cases, and improved general care time may be lost as benefit of plasma exchange” [1].

Immune Complex (IC) is a physiological process and serves to remove toxic material, from bacteria, their components and viruses from the blood. ICs are removed from the blood by the adhesion of the Fc-fragments of the antibodies to the corresponding phagocyte receptors in the liver and spleen. Phagocytosis can even be improved if the ICs activate the complement system (immune clearance). If not all the ICs are removed quickly enough in this way, then they can establish themselves in the intima of the vessels and from there trigger inflammatory lesions through local activation of the complement system [2]. The ICs probably first form in situ; the antigen adheres to the basal membrane and binds circulating antibodies. The IC deposition processes in tissue are not necessarily detectable through serum IC determination and circulating ICs may not indicate organ damage.

Immune complexes are deposited especially in the kidneys, the joints, the lungs and the skin. The ICs deposition in the kidneys is higher because the blood pressure in the glomerular capillaries is four times higher than in other capillaries and because the glomerulus retains immune ICs by a simple filtering effect. ICs may also accumulate in other organ filters [2]. In the regulation of different immune phenomena, circulating immune complexes are involved. The Fc and/or antigen receptors of the T, B, NK cells and macrophages interact with the ICs. The ICs correlate to the primary and secondary immune response [3]. The elimination of the CICs
plays an important therapeutic role. With the eliminating of antibodies by TA it is possible to interrupt the pathological process. The methods of TA such as TPE, double filtration plasma exchange or the different semiselective or selective plasma exchange methods available are published elsewhere and discussed in detail by Bambauer et al. [2,4,5].

The deposition of immune complexes initiates many types of glomerulonephritis which include tissue injury via either engagement of Fc receptors on effector cells or via complement activation [6]. The pathogenic consequences of systemic autoimmune disease are triggered by ICs which is the generation of antibody and subsequent tissue deposition. The modulation of the autoantibody response disrupts pathogenic reactions by preventing the formation of ICs. The uncoupling IC formation from subsequent inflammatory response seems unlikely because of the apparent complexity of the IC-triggered inflammatory cascade [7].

Up to the present the prognosis of patients suffering from immunocomplex nephritis is poor and comparable to that of patients suffering from lupus erythematosus with nephritis [2,8]. The 10-years survival rates are still at or below 40% [9]. Within a couple of years the disease led mostly to a nephrotic syndrome and end stage renal failure with the need of treatment with hemodialysis or kidney transplantation [2]. Comparable to other autoimmune diseases treatment strategies consist in immunosuppressive drugs like corticosteroids alone or together with azathioprine and/or cyclophosphamide or biologics [2,10]. In acute stages of these diseases the drugs can be applied in high doses as pulse therapy. But mostly intensive drug regimens are complicated (infections, cancers, etc.), costly inconvenient, uncomfortable, and potentially toxic [2-4]

Further therapeutic methods consist of the combinations of immunosuppressive treatment with therapeutic apheresis. The presented paper reports the course of a more than 30 years old woman, suffering from an immune complex nephritis since the age of 14 months. Following the diagnosis the girl was treated with conventional therapeutic strategies and intermittent TPE.

Case Report

At the age of 14 months a first renal biopsy was performed. With light microscopy normal glomerular capillaries, normal mesangium and interstitium, but cellular edema and hyaline droplets in the proximal tubules were found. The electron microscopy demonstrated foot process fusion and some endothelial and sub-epithelial deposits suggestive for immunocomplex deposits (The investigation was performed by Prof. Thoenes, Johannes-Gutenberg-University, Mainz, Germany). The diagnosis of immunocomplex nephritis was also confirmed be a re-biopsy two years later. At this time, the immune-histological investigations showed deposits of IgG, IgA, IgM and the complement factors C1q, C3, C4, C5 and C9 at the glomerular basement membrane. Moreover, in the blood there were reduced concentrations of IgG 2.2 g/L (normal range 9-18 g/L, nephelometry) and IgA 0.65 g/L (normal range 1.2-3.6 g/L, nephelometry) together with normal complement factors (nephelometry), a low serum albumin concentration, proteinuria and an elevated blood sedimentation rate.

With the age of 14 months, immediately treatment was started with indometacine up to 100 mg/day. However, after an interval of 1 week due to a lack of efficacy the treatment was changed to prednisolone (2.5 mg/kg BW=50 mg/day) and additional cyclophosphamide (2.5 mg/kg BW=50 mg/day) over a period of 60 days. Although the prednisolone dose was increased up to 80 mg/day and cyclophosphamide was applied continuously, after a short period of improvement an impairment of the nephrotic syndrome was registered during the following year.

With the age of 2 years, the girl was again admitted to hospital with severe peripheral and lung edema. Now high titers of circulating immunoconplex but no ds-DNA-antibodies were found in the blood (Table 1). At this time and after the conservative immunosuppressive therapy had failed, 12 sessions with therapeutic plasma exchange were applied. TPE treatments were carried out using the single-needle technique over a large-bore catheter placed in the superior vena cave after the Seldinger technique [11]. The amount exchanged corresponded to 3% to 5% of the body weight (BW). The substitution solution consisted of a 3% to 5% human albumin electrolyte solution and/or a 5% plasma protein solution and/or fresh frozen plasma. Anticoagulation of the extracorporeal circuit was achieved with heparin (500-2,000 IU). Following the first TPE treatments, the edema disappeared, serum albumin increased and the prednisolone dose could reduce up to 25 mg/day and the application of cyclophosphamide was stopped.

At that time no TPE equipment for children was available in Germany. As a result, due to using the equipment for adults, a lot of technical problems with tubes, membrane separators and blood pumps, but also some side-effects such as blood pressure decrease during the treatments occurred.
Table 1: Laboratory values in the course of a now more than 30 years old woman with ICN diagnosed at the age of 14 months.

<table>
<thead>
<tr>
<th>Laboratory Data / years</th>
<th>2</th>
<th>3</th>
<th>8</th>
<th>10</th>
<th>11</th>
<th>19</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sedimentation rate (Westergreen method: normal 1. h: 3-8 mm, 2. h: 5-18 mm)</td>
<td>145/155</td>
<td>105/135</td>
<td>10-Apr</td>
<td>49/79</td>
<td>8-Apr</td>
<td>50/84</td>
<td>8-Apr</td>
</tr>
<tr>
<td>Total protein (Biuret method: normal: 6.0 - 8.8 g%)</td>
<td>2.85</td>
<td>5.3</td>
<td>5.6</td>
<td>3</td>
<td>6.3</td>
<td>2.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Serum albumin (Biuret method: normal: 54-65%)</td>
<td>---</td>
<td>33.2</td>
<td>66.8</td>
<td>42.4</td>
<td>68.6</td>
<td>34.2</td>
<td>68.6</td>
</tr>
<tr>
<td>Proteinuria (Biuret method: normal: &lt; 20 mg/day)</td>
<td>1</td>
<td>524</td>
<td>0</td>
<td>2</td>
<td>231</td>
<td>15.5</td>
<td>725</td>
</tr>
<tr>
<td>Serum creatinine (Jaffe method: normal: 0.5-1.5 mg/dL)</td>
<td>0.4</td>
<td>0.63</td>
<td>0.36</td>
<td>0.6</td>
<td>0.69</td>
<td>1</td>
<td>0.69</td>
</tr>
<tr>
<td>ds-DNA-antibodies (enzyme immune assay: normal: &lt; 40 IU/mL)</td>
<td>---</td>
<td>---</td>
<td>8</td>
<td>---</td>
<td>3</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Circulating immunocomplex (N-Latex-CIC reagens: normal: &lt; 12 mg/dL)</td>
<td>17.5</td>
<td>---</td>
<td>19.9</td>
<td>12.94</td>
<td>4.5</td>
<td>9.5</td>
<td>5.6</td>
</tr>
<tr>
<td>99m-Tc-DTPA clearance (normal: &gt; 80 mL/min)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>93</td>
<td>95.1</td>
<td>---</td>
<td>90.2</td>
</tr>
<tr>
<td>131-J-Hippuran clearance (normal: &gt; 400 mL/min)</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>508</td>
<td>678</td>
<td>---</td>
<td>587</td>
</tr>
<tr>
<td>Blood pressure (mm/Hg)</td>
<td>115/80</td>
<td>120/85</td>
<td>110/85</td>
<td>120/80</td>
<td>125/80</td>
<td>135/90</td>
<td>115/80</td>
</tr>
</tbody>
</table>

Over a period of 2 years the treatment with TPE was regularly repeated in intervals of 2 to 6 weeks (totally 61 TPE). Following the first ten TPE treatments were carried out using the double-needle technique by peripheral vascular access and later by an arterio-venous shunt. This treatment strategy with TPE led to continuous improvement of nephritic syndrome with proteinuria and serum albumin concentration (Table 1). The application of prednisolone could be stopped after 2 years. From this time up to the age of 10 years only a few TPE treatments were mandatory.

However, the girl at 10 years (growth 1.29 m, weight 24 kg) showed again the symptoms of nephritic syndrome with severe peripheral and lung edema. Treatment with TPE was started again and an improvement of the symptoms of nephrotic syndrome could be observed after 6 TPE treatments. In the following 9 years the patient was in complete remission without any symptoms. No TPE or immunosuppressive therapy was applied.

However, after 9 years of a complete remission, a severe proteinuria, reduced serum albumin (Table 1) and severe edema must be diagnosed. Again TPE, but no immunosuppressive drugs were applied and resulted in a fast improvement of symptoms within two weeks. Following this acute stage there was no impairment by measuring the renal function. At the end of 19 years of the patient the 99m-Tc-DTPA clearance and the 131-J Hippuran clearance were both within the normal range. The laboratory parameters such as serum albumin, blood sedimentation rate, serum creatinine, the titers of C1, ds-DNA-antibodies, C3 and C4 complement factors with the exception of a mild proteinuria of about 1,200 g/day were within the normal range, too. Performing an ultrasound examination there was a documentation of two orthotope kidneys with normal size (right 42x97 mm, left 53x92 mm) and without an alteration of the renal parenchyma. There was only a small cystic structure at the cauda site of the left kidney. The blood pressure was within the normal range.

With 21 years, the woman has a height of 176 cm and a weight of 68 kg.

Discussion

TA therapy can provide an approach in the treatment of crescentic glomerulonephritis by removing nephritogenic factors from the blood, both antiglomerular basement membrane antibodies and C1 [12-14]. However, although the first data of plasmapheresis were published in 1901 [15] and therapeutic apheresis has rapidly developed from an experimental treatment modality to a method used in emergency situations and more and more regularly in the treatment of autoimmune diseases since then, there is still great discussion about its role in the treatment of these diseases. For example, in the treatment of severe systemic lupus erythemathosus, in contrast to the beneficial effects observed for TPE in the other trials [1,3,8,16], a randomised trial performed by Lewis et al. [17] was not able to show an improvement in clinical outcome of the patients compared to those treated with standard regimens alone. But, also patients treated with TPE had a significantly more rapid reduction of serum concentrations of antibodies against ds-DNA and cryoglobulins by Lewis et al. [17].

The most types of glomerulonephritis are followed by deposition of ICs, which induce tissue injury via either engagement of Fc receptors on effector cells or via complement activation [6]. The generation of antibody and subsequent tissue deposition of ICs is thought to trigger the pathogenic consequences of systemic autoimmune disease. Modulation of the auto antibodies response disrupts pathogenesis by preventing the formation of ICs [18].

In view of the devastating pathophysiologic consequences of interaction between circulating ICs and the basement membrane, the authors share the opinions of Lockwood et al. that TPE in combination with immunosuppression should be carried out as quickly as possible [19]. Pusey et al.
recommended TPE for severe cases of immune complex nephritis the cause of Nephrotic Syndrome (NS) of various Glomerulonephritis (GN) such as Focal Sclerosing Glomerulosclerosis (FSGN) [20].

The different forms of glomerulonephritis are treated with immunosuppressive drugs which includes besides corticoids, alkylating agents, and cyclosporine A, or a combination of almost all of these drugs. Other factors must also be considered in addition to an immunological genesis of glomerulonephritis which are suggested by studies with anticoagulants, cyclooxygenase inhibitors, and ACE inhibitors [5]. The first step in improving the overall prognosis for RPGN was the combination of corticoids, immunosuppressive drugs, and TPE in varying combinations. In the last years, RPGN has been treated with a combination of immunosuppressive drugs and IA with good results, too. A generalized benefit of TPE for all patients with RPGN have failed; but subset analysis of all these studies showed TPE to be beneficial for patients presenting with severe disease or dialysis dependency which was reported by Kaplan [1].

The study of Jayne et al. was limited to patients presenting with creatinine levels greater than 5.8 mg/dL [21]. In another study based on a TPE trial, Wngaarden et al. observed that “chronic and acute tubulointerstitial lesions predict the glomerular filtration rate at 12 months; yet it was the use of TPE and the number of normal glomeruli on biopsy that remained positive predictors of dialysis independence in the same time interval” [22]. These results are important because it suggests that unaffected glomeruli determine long-term renal outcome at 1 year. In the second study Wngaarden et al. extended their work in determining the rate of renal recovery [23]. In 69 dialysis patients who were part of the TPE trial, TPE was superior to pulse methylprednisolone with respect to the change of coming of dialysis. The outcome measure depended on the relative number of normal glomeruli (MEPEX study). In this study, Wngaarden et al. showed that “in patients with dialysis-dependent, ANCA-associated vasculitis, the chances of recovery differ depending on the type of adjunctive treatment, the percentage of normal glomeruli and glomerulosclerosis, the extent of tubular atrophy, and the presence of arteriosclerosis. Even with an ominous biopsy at diagnosis in combination with dialysis dependence, the chance of renal recovery exceeds the chance of therapy-related death when the patient is treated with plasma exchange as adjunctive therapy” [23].

Jode et al. reported of TPE in 26 patients with ANCA-Associated Vasculitis (AAV) “which had significant improvement in renal function and similar long-term outcome in both renal and patient’s survival” [24]. Comparable results were found with other authors in the treatment of AAV with TPE [25,26]. After Korsak and Wankowicz, TA “is a first line method applied as an exclusive therapy or with immunosuppressive treatment” [27]. But further studies are necessary.

The cause of nephritic syndrome of different GN such as focal sclerosing glomerulosclerosis, membranoproliferative GN, mesangioproliferative GN etc. is most idiopathic [28,29]. There is evidence pointing to a role of the immune system in pediatric Minimal Change Glomerulonephritis (MCGN). Another hypothesis has shown an association between allergy and MCGN in children. By minor infections and occasionally by reactions to be stings or poisoning relapses in this syndrome are triggered commonly. Abnormalities of both humoral and cellular immunity have been described elsewhere. The induction of remissions by high doses of immunoglobulin G (IgG, 0.4 g/kg BW), corticosteroid, alkylating agents, or cyclosporine A therapy show an indirect evidence for an immune etiology. A direct evidence of immunologically mediated pathogenesis was shown by these observations [30]. Other therapeutic measures for NS are anticoagulants, thrombocyte inhibitors, ACE inhibitors, immunosuppressive drugs, lipid reducers, rituximab, and diet [28,31,32]. In high-risk patients, pre-transplant TA appears to prevent or delay recurrence and TPE is started once recurrence is diagnosed. The number of 5 treatments needed to control proteinuria, surrogate marker of FSGN, is quite variable and can reach 12 and more [28]. The rationale for TPE in ANCA-associated RPGN has the category I with the RG 1A [8,33].

In the case of medication therapy failed or severe progression of the disease, additional TA therapy should be considered, as a continuing treatment given once a week, or every 2 weeks, or once a month. Other renal diseases such as light chain nephropathy, dense deposit diseases or others can be in very severe cases and if the conservative therapy has failed treated with TA, too.

In the present case of a now more than 30 years old woman acute attacks of her immunocomplex nephritis could be well controlled by therapeutic plasma exchange without excessive increases of the dosage of immunosuppressive drugs and a significant impairment in renal function. The application of cyclophosphamide was stopped at the age of 2 years and prednisolone was given only in low doses. These observations and the fact, that additional doses of prednisolone given to treat the first acute attack of nephritic syndrome showed no effect, led to the conclusion, that course of the patient described was mainly affected by TPE.

This long-term benefit with the prevention of hemodialysis or kidney transplantation and other severe complications, together with the normal quality of life justify the high costs of intensive treatment strategies consisting of TPE. The TPE treatment in immunocomplex nephritis may provide an alternative approach by removing of nephritogenic factors such as immunocomplexes from the patients’ blood.

After the guidelines of the American Society for Apheresis (ASFA) “the therapy consists of administration of high-dose corticosteroid and cytotoxic immunosuppressive drug (e.g., cyclophosphamide, azathioprine, or rituximab)”. Other drugs that have been include such as leflounomide, deoxyspergualin, tumor necrosis factor blockers, calcineurin inhibitors, and antibodies against T cells. When performed TA is combined with immunosuppressive therapy [8,28,33]. In the guidelines of the ASFA the ICN has the category III with the recommendation grade 2B. The treated volume must be 1–1.5 total plasma volume, the frequency every other day and the
replacement fluid 5% human albumin-electrolyte solution and/or a 5% plasma protein solution and/or fresh frozen plasma.

Conclusion
The prognosis of patients suffering from immunocomplex nephritis with or without nephrotic syndrome, diagnosed by clinical symptoms, laboratory data such as circulating immune complexes and/or renal biopsy is poor. After a short time the immunocomplex nephritis with or without NS need hemodialysis and/or kidney transplantation. In moderate diseases immunosuppressive drugs such as corticosteroids alone or together with azathioprine, cyclophosphamide or biologic are sufficient. In severe cases or acute stages of the disease many drugs can be applied as pulse therapy. But in severe cases failed to immunosuppression or to avoid severe complications due to the immunosuppressive drugs, TPE in combination with immunosuppression is indicated in an early stage of the disease. A number of 5 TPE or more are needed to control proteinuria or to eliminate CICs. If this therapy regimen is not enough additional TPE is necessary, once a week, or every 2 weeks, or once a month, as shown in the presented cases. The long-term benefit with prevention of hemodialysis or kidney transplantation and other complications justify the high costs of TA. The treated volume must be 1–1.5 total plasma volume, the frequency every other day and the substitution solution a 5% human albumin-electrolyte solution and/or a 5% plasma protein solution and/or fresh frozen plasma.

Conflict of Interest
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References


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