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Changes of the complement system and rheological indicators after therapy with rheohemapheresis

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Abstract

Introduction: In the last 10 years, many studies have been published on the role of the complement system in microcirculation disorders. However, as for the changes of complement components after rheohemapheresis, there is still a lack of detailed data in the literature. Complement changes may play an important role in pathogenesis of some microcirculation disorders, such as age-related macular degeneration and acute hearing loss. The objective of this study was to investigate the effect of rheohemapheresis on the basic complement pathways.

Patients and methods: 32 patients were treated with rheohemapheresis, including 16 patients (10 men and 6 women) for age-related macular degeneration (AMD), mean age 69.7 ± 6.06 years (range 62−87 years) and 16 patients (11 men and 5 women) aged 56.4 ± 11.5 (range 34−73 years) for acute hearing loss.

Results: Rheohemapheresis led to a significant drop of all three complement-activation pathways in both groups of patients. Moreover, complement factor H was also reduced.

Conclusion: The observed reduction in all three basic complement activation pathways after rheohemapheresis could be clinically important. The search continues both to find substances which influence complement systems and to develop more effective new drugs that require less frequent administration and that provide improved intraocular therapy for AMD patients.

Keywords: Complement; Rheology; Rheopheresis; Age-related macular degeneration; Sudden sensorial hearing loss

1. Introduction

Removal of pathogenic substances by extracorporeal elimination is a suitable therapeutic strategy in a number of diseases. Advances in technology have led to improvements in extracorporeal elimination methods from non-selective plasma exchange (complete plasma removal with its subsequent replacement by donor plasma or different substitutes) to more "selective" treatments which attempt a relatively specific removal of pathogenic agents. Rheohemapheresis (or rheopheresis) is a modification of double plasma filtration and its main aim is to improve microcirculation. Mechanistically, individual procedures eliminate

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an exactly defined spectrum of rheologically relevant, high-molecular weight proteins. A single rheopheresis procedure simultaneously eliminates an exactly defined spectrum of rheologically relevant, high-molecular weight plasma proteins (i.e. α2-macroglobulin, fibrinogen, LDL-cholesterol, Lp(a), von Willebrand factor (vWF), IgM, fibronectin and putatively multimeric vitronectin) [1−3]. This results in an immediate pulsed reduction of plasma and whole blood viscosity. These procedures have pleiotropic effects, including favorable modifications of cytokine and adhesive molecule levels, increased production of endothelial NO, improved erythrocyte deformability and reduced aggregability of both erythrocytes and platelets [4−6]. Immediate pulsed reduction of plasma and whole blood viscosity after several procedures may lead to sustained microcirculatory recovery, thus significantly improving the natural course of chronic disease. Rheohemapheresis has been tested in several disorders. These include eye diseases, such as age-related macular degeneration (AMD) (we have performed several successful randomized studies [7−9]), uveitis, uveal effusion syndrome and central vein thrombosis. In nephrology, rheohemapheresis can be employed in FSGS treatment in cases of resistance to standard therapy. It has also been used in some diabetes complications (e.g. retinopathy, diabetic nephropathy, diabetic foot), in coronary artery disease including cardiac X-syndrome and in ear diseases (sudden hearing loss).

In our previous studies, we showed the positive clinical effect of rheohemapheresis in patients with circulation disorders in peripheral vessels, ocular diseases and acute hearing loss. Our observations on the reduction of rheologically important factors by rheohemapheresis were reported earlier [10−12].

In the last 10 years, many studies have been published on the role of the complement in microcirculation disorders. Currently, the theory of inflammation involvement in AMD development is supported by several studies [13−17]. However, as for the changes of complement components after rheohemapheresis in patients with AMD, detailed data are still absent from the literature. We propose that complement changes might play a role in the pathogenesis of other microcirculation disorders, such as acute hearing loss; however, further research is needed to confirm this hypothesis. The objective of this study was to investigate the effect of rheohemapheresis on the basic complement pathways and the association between these pathways and basic rheological factors.

2. Patients and methods

Between the years 2012−2013, 32 patients were treated with rheohemapheresis. Sixteen patients (10 men and 6 women; mean age 69.7 ± 6.06 years, range 62−87 years) had AMD and 16 patients (11 men and 5 women; mean age 56.4 ± 11.5, range 34−73 years) suffered from acute hearing loss. In all patients, basic complement components were examined.

The Institutional Ethics Committee approved the study protocol and the reported investigations were in accordance with the principles of the current version of the Declaration of Helsinki.

2.1. Our modification of rheopheretic treatment

Rheohemapheresis in our modification is an adaptation of double plasmapheresis according to national conditions. Plasma is obtained not by filtration but by centrifugal separators, which, in our circumstances, brings technical and economical benefits. Blood is collected from a peripheral vein. Plasma is obtained by high-speed centrifugation (Cobe-Spectra or Optia blood cell separators, Terumo, Denver, USA) and, in the second grade, is pumped through a high-molecular filter (Evaflux 4A, Kuraray, Osaka, Japan). This filter is made of ethylen-vinyl-alcohol hollow fibers with 0.03 μm sized holes, which captures a sizeable amount of LDL-cholesterol, lipoprotein-a, fibrinogen α2-macroglobulin and immunoglobulins (IgM in particular). The flow of plasma is continual, anticoagulation is ensured with heparin and ACD; the basic amount of processed plasma − one and a half times body volume − is calculated by the blood cell separator computer. The procedures used have been previously described elsewhere [9,10,18]. The patients with AMD underwent 8 rheohemapheretic procedures within 10 weeks while the patients with acute hearing loss underwent 3 procedures within one week. The method of connection is shown in Fig. 1.

Plasma is separated using a blood cell separator (Cobe-Spectra or Optia, Terumo, Denver, USA) and then pumped to the CF 100 monitoring unit (Infomed, Geneva, Switzerland), which controls the plasma flow rate through the Evaflux filter (Kuraray, Osaka, Japan). After crossing the filter, plasma is returned together with the formed elements of the blood back to the patient's bloodstream. In case of increased pressure in the filter capillaries, the filter is automatically rinsed with physiological solution, which is then discarded with the eliminated particles into the waste bag.

2.2. Laboratory methods

Activity of the complement system was analyzed by ELISA technique, using the *Wieslab Complement System Screen* set (Euro-Diagnostics AB, Sweden). This method evaluates the extent of activation in all three pathways of the complement system: classical, alternative and lectin. The classical pathway in the test is activated by aggregated IgM, the alternative pathway by lipopolysaccharide (LPS) and the lectin pathway by mannan-binding lectin. Activation of the complement system in all pathways is measured with the help of quantification of the resulting C5b-9