Review Article

Current Trends in Ophthalmology Plasmapheresis in Ophthalmology

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Abstract

Loss of sight is one of the most severe disabling factors in human. The total number of such people is known to account for millions worldwide. In North America alone more than 1 million are completely blind and about 14 million have some degree of sight loss. There are many different diseases that lead to sight loss such as diabetic retinopathy, senile macular degeneration, various types of autoimmune retinopathy, optic nerves damage and many others. As a rule, they cannot be corrected with glasses, and not always amenable to drug therapy. Often the cause of these diseases is accumulation of various autoantibodies and other metabolites, the molecules large size of which does not allow them to be excreted by the kidneys and the fact of their accumulation indicates impossibility of their removal with help of drug therapy. It makes us resort to such method of their direct removal from the body as plasmapheresis and the aim of this study is to justify its use in ophthalmology.

Keywords: Blindness, Diabetic retinopathy, Optical neuropathy, Autoantibodies, Toxic metabolites, Macular degeneration

Introduction

Many eye diseases progress and inevitably lead to sight loss, which cannot be compensated with glasses. The significant spread of such diseases, which affect millions of people all around the world, shows the problem to be urgent. As a rule, they have an autoimmune nature and are accompanied by accumulation of both autoantibodies and other pathological metabolites, large molecules of which do not allow them to be excreted by the kidneys. They also cannot always be removed or destroyed with help of drug therapy. Their removal is possible only together with the plasma-the liquid part of the blood, in the process of plasmapheresis, which allows treating such diseases more effectively. The main objective of this study is to prove the need to use plasmapheresis not only in treatment but also in prevention of diseases, leading to sight loss.

The main causes of sight loss

Diabetic retinopathy: Diabetic Retinopathy (DR) is
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the main cause of permanent sight loss in the working-age population of the developed countries [1]. In the United States the number of newly blinded patients with DR increases annually by 8,000 people, and in Germany as the result of diabetic retinopathy the incidence of blindness reaches 2.01 per 100,000 of population [2]. According to various findings, in type I diabetes DR develops in 20-48% of patients, while in type II diabetes DR occurs in 7-28% [3-5], and diabetic macular edema appears in 7-15% of patients [6,7].

The final glycation products that accumulate in hyperglycemia play an important role in the DR pathogenesis [8]. On the other hand, elevated levels of apoCIII and apoE lipoproteins are also the risk factors for DR [9]. Presence of hypertension is also important [10]. The factor of hyperglycemia is the predominant risk factor for DR in type I diabetes, while hypertension – in type II diabetes [11]. It is important to increase the level of retinol-bound protein 4 (RBP4) [12], uric acid

[13], and obesity [14]. At the same time, microcirculation and metabolism disorders are closely related, often forming a vicious circle [15]. In DR increase in the levels of inflammatory cytokines, including IL-1 β , IL-6, IL-8, IL-17 and TNF- α , is often observed, which indicates their role in the DR pathogenesis, and also determines its severity and prognosis of mortality [16].

Other complications of diabetes such as nephropathy and lower limb ischemia are often associated with DR [17,18]. The presence of albuminuria is often associated with progression of DR [19]. The risk of deaths and other complications of diabetes increases in DR [20,21].

The retina changes at different times from the onset of diabetes are found in 98.8% (!) of cases [22]. In this case, chorio-vitreous neovascularization of the vitreous body type proliferation is also detected as one of the manifestations of proliferative diabetic retinopathy [23]. In such patients, autoantibodies to phosphatidylethanolamine were found much more frequently than in the control groups [24]. Besides, in these cases the vascular endothelial growth factor (VEGF) in the intraocular fluid increases, which in addition to angiogenesis stimulation contributes to the blood vessels' increased permeability associated with the plasma proteins leakage and formation of extravasal fibrin gel.

There are significant difficulties in the DR treatment. The VEGF role in the DR pathogenesis is considered the key one. Attempts have been made to use anti-VEGF therapy (ranibizumab) [25] and laser photocoagulation of the retina [26]. However, accumulation of toxic end products of proteins glycation, proinflammatory cytokines is the possible indication to apply apheresis therapy. Increased blood viscosity on the background of microcirculatory disorders makes rheopheresis justified, using double filtration methods (cascade plasmapheresis) [27-30].

However, conventional plasmapheresis is justified, too [31,32]. It is believed that such patients are indicated a systematic courses of plasmapheresis 2 times a year, which will delay the DR progression [33]. Plasmapheresis allows to reduce the number of hemorrhages in the retina in 40.5% of patients, in 85% of patients to improve visual acuity with disappearance of "fog" and "flies" before the eyes, in 14% of patients to expand the visual field by 5-7% associated with microcirculation improvement in bulbar conjunctiva and disappearance of "sludge" syndrome, blood flow speed increase and its continuity restoration, per vascular edema reduction, a significant reduction in

levels of cholesterol, triglycerides, and fibrinogen [34,35].

DR mentioned above, leading to irreversible sight loss, is a consequent damage of the retina vessels by secondary toxic metabolites arising during the long-term course of diabetes. The main methods of proliferative diabetic retinopathy treatment are retinal laser photocoagulation and transiliary vitrectomy. However, the frequency of failures remains rather high.

Not only metabolic disorders associated with accumulation of the end toxic products with signs of chronic DIC-syndrome, but also immunologic frustration – decrease in T-cellular immunity along with increase of the CIC level in 81% of patients play its role in DR pathogenesis. In addition, there are also idiopathic autoimmune retinopathies described when progressing degeneration of the retina has occurred in response to influence of antiretinal autoantibodies found in the blood serum of such patients [36].

Therapeutic apheresis gives a chance to remove these pathological products to delay or relieve these vascular lesions [37]. Plasma exchange efficiency is also proved in retinopathies accompanying hyper viscosity syndrome (Waldenström's macroglobulinemia). Thus, not only the IgM level decreases by 46.5% and viscosity of blood – by 44,7%, but also the diameter of the dilated veins decreases by 15.3%, leading to the venous blood-flow increase by 55.2% [38,39].

Idiopathic autoimmune retinopathy: There are reports about idiopathic autoimmune retinopathy (AR) when progressing degeneration of the retina has occurred in response to the effects of anti-retinal autoantibodies that have been found in the blood serum of such patients [40]. AR is often associated with other autoimmune diseases, mainly systemic lupus erythematosus [41-43]. Vascular lesions may also occur in antiphospholipid syndrome [44,45]. There are reports describing paraneoplastic AR associated with melanoma and other forms of cancer [46-48].

Autoantibodies are introduced into the target cells, causing their apoptosis. Photoreceptors that have died during apoptosis also excite other reactions with metabolic products release that stimulates autoimmunization and increase in the blood barrier permeability [49]. In the retina perivascular infiltration of T-lymphocytes is observed [50]. The retina veins oxygen content increases [51]. In the culture of lymphocytes

with addition of recoverin the IFN γ and TNF α content increases [52]. Clinically these patients have bilateral and asymmetric scotomas, photopsias, and field defects trunial with rapidly progressive loss of vision [53].

There are still no generally accepted standards of AR treatment [54]. In addition to the more common long-term courses of immunosuppression [46], introduction of dexamethasone directly into the vitreous body is applied [48]. However, given the autoimmune nature of the pathology, plasmapheresis is pathogenetically justified [55-58].

Apheresis therapy allows the removal of these pathological products to delay or relieve vascular disorders [59].

Anterior ischemic optic neuropathy: It occurs in the result of perfusion decrease in the posterior short ciliary arteries in hypercholesterolemia, increased blood viscosity, hyperglycemia, regional vascular endothelial disorders, and arterial hypertension. Circulatory disorders in the optic disc are the leading cause of reduced sight in individuals over 50 years old [60]. The emerging pericapillary retinal edema contributes to its "folding" [61]. In this case, the ganglion cells thickness of the retinal nerve fibers decreases down to their disappearance [62].

This disease treatment has not been found yet; for neither steroid therapy nor its combination with erythropoietin has produced the desired results [63]. Cascade plasma exchange (up to 600 ml of plasma concentrate) allowed increasing visual acuity from 0.10 ± 0.03 to 0.35 ± 0.05 , to reduce central scotomas, to increase the boundaries of the visual peripheral fields on the background of a two-fold decrease in cholesterol, triglycerides, and fibrinogen of blood plasma [64]. Same results using cascade plasmapheresis achieved by other researchers [29,65].

Sympathetic ophthalmia: It is a rare, bilateral granulomatous inflammation that occurs after a surgical or external injury to some elements of the eye. As you know, formation of antibodies to their own antigens is blocked as long as these antigens do not change their structure as a result of some pathological processes (inflammation, trauma) so that they are no longer perceived as "their" and the mechanisms of autoimmune reactions are started to fight them. That is why in such cases a patient may often develop a lesion of the other eye called sympathetic ophthalmia characterized by

development of granulations consisting of T- and B-lymphocytes, macrophages and giant cells, causing anterior, posterior or panuveitis, which inevitably leads to sight loss [66,67].

Totreatthisconditioninadditiontoimmunosuppressive therapy it is necessary to resort to enucleation of the affected eye to reduce the scale of lesions of the healthy one [68]. However, direct removal of the formed autoantibodies from the body is also indicated by means of plasmapheresis [59,69].

In addition, there are reports about immunization to antigens of own crystalline lens damaged by cataract surgery operations, followed by immune inflammation of the eye-phacoanaphylactic endophthalmitis [70].

Optic nerve neuromyelitis: It is one of the varieties of the nervous system demyelinating diseases and is often combined with multiple sclerosis or opticomyelitis, (Devic disease) [71,72]. In the Central European countries, it occurs in 5 cases per 100 000 of population per year [73]. In pediatric practice it often precedes appearance of acute disseminated encephalomyelitis [74]. To restore the sight, as a rule, aggressive steroid and long-term immunosuppressive therapy is used [75,76]. Nevertheless, plasmapheresis is also used especially in cases of refractory disease [77-80]. In 75% of cases, improvement occurs after a double filtration plasmapheresis [81].

Atypical optic neuritis: In some cases, it occurs due to poisoning by some toxic substances (for example, methanol). It is usually acute condition with progressive sight loss and is insensitive to steroid therapy [82]. In such cases, only emergency and massive apheresis therapy can prevent irreversible sight loss. Hemodialysis or prolonged hemofiltration is usually used, but in some cases plasmapheresis should be performed [83,84]. Plasmapheresis is the second line of treatment for severe optic neuritis, resulting in a significant improvement of visual acuity in more than half of these patients [85].

Uveitis: Autoimmune processes also determine the course of uveitis, which leads to disability in 30% of patients up to blindness (10%) [86]. Uveitis is also accompanied by such a systemic pathology as Behçet's disease [87], as well as juvenile idiopathic arthritis [88] and sarcoidosis [89].

There are different forms of uveitis classified by

localization (anterior, intermediate, posterior, panuveitis), by type of inflammatory process (acute, chronic, recurrent), by etiology (infectious, non-infectious), and histologically (granulomatous and non-granulomatous). In the developed countries anterior idiopathic uveitis is most widespread, while in the developing countries the infectious one (herpes, toxoplasmosis) prevails (30-60%) [90]. Uveitis also occurs as a result of surgical interventions in the eyes (cataract removal, etc.), more often with intraoperative complications [91]. In the elderly uveitis contribute to such age-related risk factors such as immunosuppression, ocular ischemic syndrome, and herpes-virus infection [92]. In children uveitis is more likely to be idiopathic [93,94].

Immunological studies indicate an increase in blood T-active lymphocytes, B-cells and circulating immune complexes, increased secretory IgG in lacrimal fluid. In the latter, you can also find antibodies to the eye tissues -to the retina, lens, cornea and even IgE antibodies [95-98].

Cellular infiltration of the vitreous body develops associated with formation of cyclic membranes, complicated cataract, exudative-hemorrhagic forms of inflammation of the choroid and retina. Animal experiments have also shown the important role of nitric oxide (NO) in the pathogenesis of autoimmune uveoretinitis [99]. Retinochoroidopathy appear to be chronic bilateral form of the posterior autoimmune uveitis. Left untreated it leads to photophobia, night blindness, narrowing of the fields of vision and complete blindness. In some cases patients with uveitis have antibodies of IgG, IgA and IgM type to Chlamydia pneumoniae. Sarcoidosis is also often associated with uveitis, which indicates common autoimmune mechanisms of their pathogenesis [100].

Most often they use long-term steroids and cyclosporine therapy, having such side effects as cataracts, osteoporosis, diabetes and hypertension [101,102]. Conventional immunosuppressive therapy and cytotoxic drugs do not prevent recurrent exacerbations and complex treatment with plasmapheresis provides more stable results [69,103]. Plasmapheresis is used in combination with blood cells ozonation [104]. Plasmapheresis or plasma exchange with replacement of the autologous cryosorbed plasma up to 50% of the circulating plasma volume contribute to a faster resolution of the inflammatory process, transition to remission state, disappearance of adhesions even

without local proteolytic treatment [105]. Such treatment is also indicated to prevent relapses [106]. Courses of plasmapheresis with extracorporeal laser irradiation of the blood are indicated in autoimmune eye diseases even in children [107]. In treatment of acute postoperative uveitis courses of plasmapheresis reduce inflammatory complications rate, reduce the timing and improve the overall results of treatment [108].

Graves' ophthalmopathy: It is an organ-specific autoimmune disease, in which a patient develops infiltration of the orbital tissues by mononuclear cells associated with local release of cytokines, showing the role of activated T-lymphocytes in its pathogenesis [109]. During this active inflammatory phase lymphocytic infiltration and reactive interstitial edema occur in the retrobulbar tissue. Due to the increasing density of the retina vessels the sight loss occurs [110]. Clinical activity and disease severity are classified according to the following indicators: 0 -no signs, no symptoms; 1 - only signs, no symptoms; 2 -involvement of the orbit soft tissues; 3 - proptosis; 4 -the involvement of extra ocular muscle; 5 -corneal involvement; 6 - sight loss [111]. This classification is needed to make an early diagnosis and provide timely treatment [112].

Immunosuppression inhibits this immune inflammation. Effectiveness of immunoglobulins therapy and their massive doses is shown. However, plasmapheresis is also used especially in steroid-resistant cases [113-115]. Use of specific immunoadsorption is also justified [116].

Viral conjunctivitis: Persistent viral conjunctivitis is often the result of weakened immune defense mechanisms. Detection of antibodies to Chlamidia pneumoniae in some of these patients may indicate such a relationship. For immunosuppression usually occurs on the background of some biochemical changes sanitation of the body internal environment and quantum immunostimulation make this disease curable, restoring the broken parts of the immune system.

Keratoconjunctivitis: It often develops on the background of allergies and accompanies atopic dermatitis. In this case the conjunctiva, eyelids, cornea, and lacrimal glands are damaged [117-119]. They are characterized by micro erosions of the epithelium, persistent epithelial defects, severe corneal vascularization and opacities [120]. They can be complicated by cataract, infectious keratitis, blepharitis, and steroid-dependent

glaucoma [121]. Autoimmune “dry” keratoconjunctivitis (xerophthalmia) with Sjögren’s disease may also develop [122,123]. Adenovirus type 8B, 19B, 37B and 54B can promote even epidemic outbreak of keratoconjunctivitis [124]. Steroid therapy is used but, given the autoimmune nature of the disease, plasmapheresis is also performed [59,125].

Ophthalmoplegia: It may have different etiologies. Restrictive, parietic, neurological, and myasthenic conditions may lead to ptosis and decreased mobility of the eye [126,127]. It is possible to develop an orbital myositis of infectious or non-infectious etiology with several extra-ocular muscles lesion [128]. Ophthalmoplegia may accompany multiple sclerosis, Devic’s, Guillain-Barré, Miller-Fisher’s and Bikerstaff’s syndromes, be one of the first symptoms of myasthenia gravis [129-131], and even diabetes [132]. Development of autoimmune damage to the oculomotor muscles can occur. Thus, the concentration of IgG anti-GQ1b antibodies is closely related to acute paresis of the external eye muscles (diplopia) after infections or immunizations. But it could be an isolated paresis of the internal eye muscles called internal ophthalmoplegia, manifested by mydriasis and photophobia. In such cases the underlying disease treatment with plasmapheresis enables to neutralize the ophthalmoplegia manifestations [133,134].

Lattice corneal dystrophy: Lattice corneal dystrophy type IIIA is accompanied by recurrent corneal erosion. This disease is an autosomal type of genetic disease, in which the gene product big-h3 is a secretory protein (68kD keratoepithelin) detectable in the cornea. There are autoantibodies to big-h3, leading to the cornea dystrophy as well as to sub epithelial and intrastromal deposition of amyloid in its stroma [135,136]. In this case there is no specific therapy. However, given the accumulation of amyloid and autoantibodies, plasmapheresis may be useful.

Age-related macular degeneration (AMD): AMD is a common disease affecting the elderly worldwide [137]. At the age of 80 years (73-94) in average AMD occurs in a mild degree in 80 per 1000 people/years, and in the severe degree - in 18 per 1000 people/years [138]. In North America alone about 1 million people are completely blind, more than 7 million have moderate to severe blindness, and about 7 million also have a mild degree of visual impairment [139].

AMD develops due to protein structures deposition

between the choriocapillaries and retinal pigment epithelium, leading to development of central scotoma with significant sight loss. This is accompanied by microcirculation disorders in combination with hypercholesterolemia and hyperfibrinogenemia. They particularly distinguish paraproteinemia maculopathy, associated with pathological accumulation of monoclonal antibodies [140]. Microcirculation disorders disrupt nutrition and oxygen delivery to the retinal pigment epithelial cells. However, there is evidence of the AMD autoimmune nature [141].

There is no effective medication therapy of AMD. More often, intravitreal administration of anti-vascular endothelial growth factor (VEGF) is used [142]. However, aflibercept, bevacizumab, and ranibizumab drug therapy may lead to endophthalmitis and intraocular hypertension development [143,144]. When using ranibizumab, ischemia and necrosis of the distal phalanges of the fingers may develop [145], and bevacizumab on the background of previous myocardial infarction increases the deaths rate in such patients [146].

Prospective multicenter randomized studies showed effectiveness of plasmapheresis with subsequent double plasma filtration up to 8 procedures during 10 weeks. The positive effect persisted after 3 and 12 months and it was considered that there are no other therapeutic alternatives in this pathology except cascade plasmapheresis [28,147-149]. According to the recommendations of ASFA, rheopheresis is the method of choice in the treatment of this pathology [150].

Post-traumatic ophthalmopathy: With help of plasmapheresis a favorable effect is achieved in the course of post-traumatic ophthalmopathy. Along with more rapid resolution of inflammation in the eye the opacities in the vitreous body and hemorrhage on the fundus also resolved, the central visual acuity increased by 20-30%, and the treatment duration of such patients was reduced by 4-5 days [151].

Paraneoplastic optic neuropathy: Plasmapheresis can also be beneficial in paraneoplastic optic neuropathy treatment [152]. Bilateral diffuse melanocytic proliferation of the vascular membrane of the eye is a type of paraneoplastic syndrome. Plasmapheresis prevents the thickening of the eye choroid, which improves the sight [59,153].

Conclusion

The presented findings show that many diseases associated with immune and metabolic disorders, which accumulate large-molecular products involved in the pathogenesis of various eye diseases, can lead to vision loss. At the same time, neither drugs nor surgical interventions are able to completely prevent the progression of such eye lesions. The effectiveness of the direct removal of pathological substances using plasmapheresis is shown. The development of the Russian equipment "Hemofenix" with a single-needle connection to peripheral veins, as well as simple and safe methods of membrane plasmapheresis, allowing such procedures to be carried out even in outpatient settings, including in children, makes it possible to widely introduce such methods in the widest network of medical institutions. This is especially true, given the significant number of people in need of such a treatment method. In addition, it will be possible to carry out such treatment at the very first signs of the disease when irreversible eye damage has not occurred yet.

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Conflict of interest

Authors do not have any conflict of interest regarding the work issues.

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