The Role of Excitotoxicity in the Etiopathogenesis of Central Serous Chorioretinopathy

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Abstract

Purpose: The aim of this study is to investigate the role of excitotoxicity in the etiopathogenesis of central serous chorioretinopathy and evaluate the effectiveness of an anti-excitotoxic supplementation on subretinal fluid resorption.

Patients and methods: A prospective, open-label pilot clinical study was conducted in 52 eyes of 45 patients including 35 men (mean age 52.2 years) and 10 women (mean age 54.6 years) with chronic central serous chorioretinopathy, unilateral in 36 cases and bilateral in 8 cases. For a diagnosis of chronic central serous chorioretinopathy, patients must have had the presence of subretinal fluid for at least 3 months. Patients were treated orally with NOTOX consisting of Mg pidolate, K citrate, Zn gluconate, Se L-methionine, Cu gluconate, Superoxide Dismutase (SOD), vitamin B1, B5, B6, B12, dry root extract of ashwagandha and rhodiola rosea. NOTOX was prescribed once a day and patients were followed at 2, 3 and 6 months. Spectral Domain Optical Coherence Tomography (SD-OCT) is used for diagnosing central serous chorioretinopathy and quantifying subretinal fluid.

Results: After two months of treatment, 23 eyes (44.2%) showed complete reabsorption of subretinal fluid while 29 eyes (55.8%) showed reduction of subretinal fluid. After three months, we had regression of subretinal fluid in 10 more eyes (63.5%) and reduction in 19 eyes (36.5%). After six months, 9 more eyes (80.8%) resolved subretinal fluid completely, the last 10 eyes (19.2%) partially and none got worse.

Conclusion: NOTOX treatment was well tolerated and potentially effective in counteracting retinal excitotoxicity and accumulation of subretinal fluid, contributing to prevention and treatment of central serous chorioretinopathy.

Keywords: Central serous chorioretinopathy; Retinal excitotoxicity; Phototransduction; Phosphodiesterase; Glutamate; Cortisol; Nitric oxide

Introduction

Central Serous Chorioretinopathy (CSC) is an unknown etiopathogenesis ocular disease. It is characterized by decompensation of the Retinal Pigment Epithelium (RPE), which results in a central serous neurosensory retinal detachment and RPE atrophy [1]. CSC is usually unilateral and predominantly affects middle-aged (30 to 50 years) adults and men are affected more frequently than women. It was associated with genetic predisposition [2,3], type A personalities, high stress, pregnancy, obstructive sleep apnea, sleep disturbance, hypercortisolism (endogenous and exogenous) [2] and taking medications as Sildenafil or Tadalafil (5-phosphodiesterase inhibitors) [4], Tamoxifen (selective estrogen receptor modulator) [5], Minoxidil (NO donor) [6], Binimetinib (inhibitor of the mitogen-activated protein kinase enzyme, MEK) [7]. The natural course of CSC is often self-limiting and a spontaneous resolution with complete fluid reabsorption occurs within 2-3 months; however, 30-50% of patients will develop recurrences of the disease, either in the same eye, opposite eye, or both eyes with visual impairment. The most recent hypotheses attribute an important role in the pathogenesis of this disease to the excessive vasodilation and permeability of the choroidal vessels [8]. There have been a number of interventions used in CSC, including non-invasive medical therapies (acetazolamide, finasteride, acetylsalicylic acid, beta-blockers, Ca channel blockers, ketoconazole, melatonin and eplerenone) and invasive therapies (laser treatment, photodynamic therapy, intravitreal injection of anti-vascular endothelial growth factor agents). Excitotoxicity is a condition of increased stimulation of glutamatergic receptors which induces an increase of Glutamate (GLU) into the extracellular space and neuronal toxicity. It is involved in ischemic neuronal pathologies, migraine, epilepsy, neurodegenerative diseases and glaucoma [9]. This is the first study, to my knowledge, that hypothesizes an excitotoxic etiopathogenesis of CSC and proposes a new therapeutic approach with an anti-excitotoxic supplementation. The goal of this anti-excitotoxic therapy is to counteract the psychophysical stress, inappropriate photoreceptor depolarization, restore electrochemical balance in the glutamatergic synapse between photoreceptor and bipolar cell, reabsorb Subretinal Fluid (SRF) and allow the neuroepithelium to be reattached.

Patients and Methods

A prospective, open-label pilot clinical study was conducted in 52 eyes of 45 patients including 35 men (mean age 56.2 years) and 10 women (mean age 56.6 years) with chronic CSC, unilateral in 36 cases and bilateral in 8 cases. For a diagnosis of chronic CSC, patients must have had the presence of SRF for at least 3 months. No patient had previously received invasive therapies. Patients were treated orally with an anti-excitotoxic supplementation (NOTOX) consisting of 300 mg of Mg pidolate, 300 mg of Kcitrate, 10 mg of Zn gluconate, 55 mcg of Se L-methionine, 1 mg of Cu gluconate, 50 mg of superoxide dismutase (SOD), 1,1 mg of vitamin B1, 6 mg of vitamin B5, 1,4 mg of vitamin B6, 2,5 mcg of vitamin B12, 150 mg of dry root extract of ashwagandha and 100 mg of dry root extract of rhodiola rosea. NOTOX was prescribed once a day and patients were followed at 2, 3
and 6 months. Spectral Domain Optical Coherence Tomography (SD-OCT) is used for diagnosing CSC and quantifying SRF.

**Results**

After two months of treatment, 23 eyes (44.2%) showed complete reabsorption of SRF, while 29 eyes (55.8%) showed reduction of SRF (Figure 1).

After three months we had a regression of SRF in 10 more eyes (63.5%) and a reduction in 19 more eyes (36.5%) (Figure 2).

After six months 9 more eyes (80.8%) resolved SRF completely, the last 10 eyes (19.2%) partially and none got worse. Patients also reported an improvement in their psychophysical stress and sleep quality. A 35-year-old man with a kidney transplant for five years was taking 10 mg of prednisone. In 2020 he was diagnosed with a bilateral cataract and chronic CSC. While maintaining steroid therapy, after six months of NOTOX, SRF reabsorbed in both eyes (Figure 3).

In Feb 2019 NOTOX was prescribed to a 47-year-old woman with a chronic central serous neuroepithelium detachment in her left eye diagnosed three years earlier. In April 2019 SRF was completely reabsorbed. Some months later, she interrupted NOTOX on her own initiative. In Dec 2019, after a recurrence, she received an inappropriate intravitreal injection of triamcinolone acetonide elsewhere, which caused an increase in SRF. After two months of NOTOX, she had again the complete reabsorption of SRF. Due to the low compliance, she was advised to continue the treatment.

In Mar 2021 she was diagnosed with Covid-19 and 25 mg of prednisone a day for two weeks was prescribed. In Apr 2021 OCT showed no recurrence (Figure 4).

**Discussion**

GLU is the excitatory neurotransmitter released by photoreceptors and bipolar cells especially at darkness. Phototransduction begins in the outer segment of the photoreceptor where electrotonic potentials that oscillate between -40 mV (at darkness) and -70 mV (at light) are generated and transmitted to the inner segment. Light activates the enzyme 6-phosphodiesterase (6-PDE) which hydrolyses Guanosine-Monophosphate-Cyclic (cGMP). cGMP activates Protein Kinase G (PKG) which phosphorylates serine/threonine and closes Na channels inducing hyperpolarization, reduction of Ca input and GLU release into extracellular space. On the contrary, 6-PDE is inactive at darkness, cGMP increases, numerous Na channels open, depolarization onsets, intracellular Ca increases and much GLU is released. Then, photoreceptors do not generate action potentials but transmit light signals as electrotonic hyperpolarizing pulses rather than depolarizing ones. The most important glutamatergic receptors are ion channels, Alpha-amino-3-hydroxy-5-Methylisoxazole-4-Propionic Acid (AMPA) and N-methyl-D- Aspartate (NMDA), present at the post-synaptic membrane level of ganglion and bipolar off cells. NMDA receptors are activated by an excess of GLU: they are permeable to Na, K and especially to Ca. Their channel is blocked by Mg and modulated by glycine and zinc. Excitotoxicity may result in increased GLU release and intracellular Ca concentration which can alter mitochondrial function and activate proteases (phospholipase A, nitric oxide synthase). These enzymes can synthesize inflammatory mediators (prostaglandins) and free radicals (superoxide anion, NO). Finally, excitotoxicity causes a constant depolarization of the post-synaptic membrane due to a prolonged absence of Mg and Zn ions in NMDA receptors. NO, being a gas, easily spreads through cell membranes and can exercise its activity as a second messenger or increasing the levels of cGMP and intracellular Ca, resulting in massive release of GLU [9] (Figure 6). Among the molecules with antagonist action of NMDA receptor, Mg is the safest and the most manageable one. Mg blocks the opening of the NMDA channel receptor by preventing Ca from entering the cell, reducing the synthesis of NO and GLU [10,11]. Reduced Na/K-ATPase activity associated with magnesium deficiency has been shown to cause defective neurotransmitter transport mechanism, mitochondrial dysfunction, neural degeneration and apoptosis [12]. Zn and Cu affect NMDA receptor excitability and redox status. In the retina and retinal pigment epithelium, Zn interacts with taurine and vitamin A, regulates the light-rhodopsin reaction and modulates synaptic
transmission. Se and SOD have an antioxidant action in the retina [13]. K is essential for the Na/K pump function which regulates the repolarization of the photoreceptor. When the external blood-retinal barrier is damaged, as it happens in CSC, the subretinal fluid can be drained into the vitreous through the aquaporins (AQP4) and inwardly rectifying channels (Kir4) of Müller cells thanks to osmotic and oncotic forces [14,15]. Vitamins B1, B5, B6, B12 are co-enzymes which perform important functions in mitochondrial energy metabolism useful to support proton pumps and modulate steroid receptors [16,17]. Finally, ashwagandha and rhodiola rosea have serotonergic and adaptogenic effects [18]. CSC typically onsets with a unilateral macular detachment of the neurosensory retina caused by defects of the pigment epithelium, sometimes associated with hyperfluorescent areas at dilated choroid vessels. This does not appear compatible with the action of a systemic, vasoactive molecule on the choroidal vessels as some authors speculate [19]. In fact, in this case we would have a diffuse vasodilation and generalized choroidal effusion in both eyes.

Why can CSC also onset after taking Sildenafil (5-PDE inhibitor), Tamoxifen (estrogen receptor antagonist), Binimetinib (inhibitor of the mitogen-activated protein kinase enzyme, MEK) and Minoxidil (NO donor)? The choroid is an erectile tissue analogous to the corpus cavernosum of the penis. The production of NO is caused by nerves and endothelial cells of corpora cavernosa during sexual stimulation. NO induces Guanylate Cyclase (GC) to transform Guanosine Triphosphate (GTP) into cGMP which causes intracellular Ca reduction, vasodilation and erection. 5-PDE hydrolyses cGMP and blocks the cycle. Sildenafil, a 5-PDE inhibitor, allows cGMP to maintain the erection. However, the presence of 5-PDE in the choroidal arteries would not be sufficient to explain vasodilation and onset of unilateral, focal CSC at the posterior pole after taking the drug systemically. 5-PDE inhibitors have ten times less affinity towards 6-PDE [4] which regulates phototransduction in cones and rods. In fact, at the level of the external segment of the photoreceptor, light induces the synthesis of 6-PDE, hyperpolarization and reduced GLU release. At therapeutic dose, in absence of stimuli which increase NO, Sildenafil enhances the thickness of the choroid thanks to the stromal expansion but leaves the caliber of choroidal vessels almost unchanged [20]. Since the presence of NO is fundamental to have erection, where does NO that induces the vascular reaction in the choroid come from? Why does not a diffuse and bilateral choroidal vasodilation occur after taking the drug? Sildenafil can inhibit 6-PDE in the photoreceptor causing increase in cGMP, opening of Na and Ca channels, depolarization and secretion of GLU into the extracellular space. If this phenomenon occurs at light (in condition of hyperpolarization), the inappropriate increase in membrane potential difference will trigger an electrochemical short circuit of the photoreceptor depolarized by Sildenafil. At the level of post-synaptic membrane of the bipolar cell off, the increase in the GLU metabolism induces depolarization and greater input of Ca which, by binding to calmodulin, stimulates Nitric Oxide Synthase (NOS) to produce NO. NO behaves as a second messenger: it enters the photoreceptor, stimulates GC to synthesize cGMP which causes the opening of Na channels, depolarization, Ca input and further release of GLU. The NO → GLU circuit can generate a vicious circle which can self-sustain and excess NO can spread into the choroid. Smooth muscle of the choroidal arteries is innervated by
a perivascular plexus which is formed by fibers of sympathetic and parasympathetic nervous system. The fibers of the parasympathetic system are rich in neurotransmitters with indirect (acetylcholine) and direct (vasoactive intestinal polypeptide and NO) vasodilation action [21]. Choriocapillaris is formed by independent vascular units regulated by the sphincters of the precapillary arterioles and, at the macular level, where choroid is thicker, it has numerous endothelial nitrergic receptors [21]. Blood flow and shear stress exerted by circulating blood are the two main mechanical stimuli which induce the release of NO. The role of NO is much more important in large-caliber arterioles where hydraulic resistance and shear force are greater. In fact, in CSC vasodilation is focal in the choriocapillaris, widespread in the Sattler’s layer and very widespread in the Haller’s one [21]. It has been shown that in patients with CSC there is a vascular endothelium dysfunction which is more sensitive to the vasodilating action of NO [22]. Endothelium dysfunction resulting from stiffening of the arteries and less bioavailability of NO would therefore explain a lower risk for older people to develop the disease [22,23]. The probability of electrochemical breakdown, retinal excitotoxicity and increase of NO will be greater at the posterior pole, due to the miosis, accommodation of the lens and morphology of the macula which promotes hyperpolarization of the photoreceptors most exposed to light. NO interacting with the wall of the arterioles induces synthesis of cGMP and vasodilation which, however, unlike corpora cavernosa of the penis which are completely wrapped in a fibrous tunic, in the choroid it is only contained outside by the sclera. As a result, an excessive increase in hydrostatic pressure exerts its strength on the retina causing exudation and neuroepithelium detachment. Estrogens can attenuate retinal excitotoxicity by inhibiting Ca channels, reducing Ca input into the cell and promoting GLU reuptake by Müller cells [24]. Indeed, in women usually CSC occurs after the age of 40 when the production of estrogens is reduced.

Tamoxifen can therefore promote the excitotoxic process by blocking estrogen receptors. NO released from the so-called "NO donors" drugs (nitrate isosorbide, alkyl nitrates, Minoxidil), can also interfere with phototransduction. 'Poppers maculopathy', caused by inhalation of amyl nitrite, would have an analogy with CSC [25]. In fact, volatile alkyl nitrates release NO which can quickly reach the retina through the eyeballs or tear pathways. High concentration of NO causes an increase in cGMP in outer segment of the foveal cones and, in a state of extreme hyperpolarization, a rapid increase in voltage and current intensity inducing fusion of foveal inner segment/outer segment junction (Joule effect) and blocking of electrotonic transmission to the inner segment (Figure 5).

Binimetinib is an inhibitor of the mitogen-activated protein kinase enzyme (MEK) which was developed to treat various cancers. It is a serine/threonine-specific Protein Kinase (PK) just like PKG which phosphorylates and closes Na channels of the outer segment of photoreceptor during phototransduction. Therefore, this drug might keep depolarization of photoreceptor and trigger the excitotoxic process. Many factors that predispose to this ocular disease involve the alteration of the Hypothalamus-Pituitary-Adrenal (HPA) axis with excessive cortisol production, increase of glutamatergic stimulation and excitotoxicity, a risk also to the nervous system which represents the most vulnerable target for the mood and sleep disorders often present in patients with CSC [26,27]. Furthermore, during the evening the excessive exposure to light activates the intrinsically photosensitive Retinal Ganglion Cells (ipRGC) and through the hypothalamic suprachiasmatic nucleus inhibits the secretion of melatonin contributing to keep high levels of cortisol and GLU. The activation of the Sympathetic-Adrenal Medullary axis is accompanied by the release of catecholamines, while the increased activity of the HPA axis results in release of corticosteroids, especially cortisol.
and aldosterone. When stressor becomes chronic, catecholamines and aldosterone reduce but the level of cortisol remains high compromising the function of HPA axis. Scientific evidence shows the presence of molecules and receptors similar to those of the HPA axis in peripheral organs such as skin, immune system, gastroenteric tract but also in the cells of the retinal pigment epithelium which interact with the external segments of photoreceptors [28]. It has been shown that cells of the pigment epithelium can synthesize cortisol from progesterone (paracrine action) [28]. The action of cortisol on retinal cells may affect the phototransduction and gluttamatergic transmission. In fact, cortisol controls neuronal activity through a slow genomic action, regulating arrestin gene expression in the external segments of photoreceptors [29], or through a rapid non-genomic action, activating in this way specific Glucocorticoid (GR) or Mineralocorticoid (MR) membrane receptors localized at the level of gluttamatergic presynaptic membranes of cones [30], the most widespread photoreceptors at the posterior pole. Furthermore, cones, unlike rods, are less sensitive to light but have a rapid electrical response and do not saturate. Cortisol also binds to non-genomic sites on Gamma-Aminobutyric Acid (GABA) or NMDA receptors and exercises an allosteric modulation. During excessive hormonal stimulation, cortisol can induce rapid effects by binding to MR with high affinity causing Ca to enter the cell and changing the glutamatergic neurotransmission [31]. As a consequence, the inappropriate depolarization of photoreceptor to light causes increase in release of GLU into the extracellular space, excitotoxicity and synthesis of NO which spreads into the choroid (Figure 6). Finally, I also suspect that an analogous mechanism, characterized by small electrochemical interfences repeated for a long time, may contribute to onset of age-related macular degeneration in patients with genetic variants [32].

Conclusion

This is the first study, to my knowledge, which hypothesizes an excitotoxic etiopathogenesis of CSC and proposes a new therapeutic approach with an anti-excitotoxic supplementation. CSC would be the chorioretinal manifestation of a systemic disease in which psychoneuroendocrine alterations, drugs, poor sleep quality and epigenetic factors can interfere with phototransduction and electrotonic potential of photoreceptors (mostly of cones) inducing an electrochemical short circuit, retinal excitotoxicity and synthesis of numerous chemical mediators including NO. NO spreading into the choroid, gives rise to vasodilation, exudation and serous neurosensory retinal detachment. This phenomenon would be more frequent at the posterior pole, the most exposed to hyperpolarizing light. Some researchers have hypothesized that over activation of the MR in chorioidal endothelial cells induces vasodilation and CSC. On the contrary, I suppose that the real effectiveness of eplerenone is due to its binding to MR of cones and to increased potassium and magnesium levels counteraacting excitotoxicity (Figure 6). NOTOX treatment was well tolerated and potentially effective in counteraacting the psychological stress, action of depolarizing molecules, excitotoxicity and accumulation of subretinal fluid, contributing to prevention and treatment of CSC. In addition to its adaptogenic and antioxidant effect, NOTOX would act in a similar way to eplerenone but without side effects. However, in case of prolonged disease or widespread cellular receptors damage, NOTOX may not be effective and therefore CSC will need invasive therapies. Experimental studies and controlled clinical trials are required to confirm this hypothesis and evaluate the effectiveness of this treatment option in the management of CSC.

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Informed consent statement

General consent was obtained in which the patients agree with the research and data with anonymization.

Ethics statement

The study has been evaluated by Ethics Committee of Igea Private Hospital and deemed not to require ethics approval.

References


