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Research Article

Rationale for Neurotrophic Regulation in Conservative Treatment of Keratoconus

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Abstract

Degradation of the corneal stroma is caused by an imbalance of a number of enzymes of the prooxidant and antioxidant systems. An imbalance in the enzymes of the prooxidant and antioxidant systems causes thinning of the stroma and the appearance of stromal scars.

The purpose of our study was to evaluate the neurotrophic regulation of metabolic processes in patients with early stage keratoconus and the possibility of correcting conservative treatment depending on the identified imbalance.

The study used the results of observation of patients with stages I - III of keratoconus (classification by M. Amsler (1961), J. Krumeich (1998). All patients with corneal and corneoscleral rigid gas permeable contact lenses of various models and manufacturers. Duration of observation from 2005 to 2019 year, along with the study of the ophthalmological status of the patients, before starting conservative treatment, cardiointervalography was performed to clarify the vegetative status.

In 97% of cases, autonomic dysfunction was determined in our patients, while in 85% of all those examined, a significant predominance of sympathicotonic neurotrophic regulatory processes was determined. Based on this, we have proposed an effect that allows, at the first stage, to enhance cholinergic neurotrophic regulatory influences and activating aerobic processes in the tissues of the eyeball. At the next stage of treatment for keratoconus, they provide membrane stabilizing (regulation of the synthesis of phospholipids and proteins, stabilization and normalization of the structure of cell membranes), antioxidant (inhibition of the formation of free radicals and lipid peroxidation of cell membranes), and antihypoxic effects.

Analysis of the results of long-term (more than a year) observation of patients with keratoconus receiving conservative treatment aimed at normalizing the neurotrophic effect on regenerative processes in the tissues of the eye showed the possibility of stabilizing the pathological process and revealed disease progression in only three patients from the group with stage II keratoconus, 4% of all patients). All other patients experienced long-term stabilization of the disease. Three patients who had progression of keratoconus from stage II to stage III underwent a corneal collagen cross-linking procedure.

***Keywords**: Keratoconus; Monitoring; Autonomic Reactivity; Neurotrophic Regulation; Oxidative Stress; Conservative Treatment of Keratoconus*

Introduction

Keratoconus in the modern understanding is a multifactorial disease. Complex interactions of genetic and non-genetic factors lead to a disorder of homeostasis at the tissue, organ and organism levels in the form of morphofunctional disorders. The frequency of hereditary forms of the disease testifies in favor of the genetic theory of development. In various populations, hereditary development of keratoconus is observed from 5% to 27.9% [1]. Ophthalmologists are faced with severe cases of pathological manifestations of the shape of the cornea, which are characterized by morphological manifestations in the form of an uneven arrangement of collagen fibers and an increase in interfibrillar spaces [2,3]. Consequently, the main pathological changes in keratoconus are corneal stromal dysplasia in the postnatal period, characterized by defects in the fibrous structures and the underlying substance of the connective tissue. Degradation of the corneal stroma is caused by an imbalance of a number of enzymes of the prooxidant and antioxidant systems [4,5]. Oxidative stress, in turn, activates the adaptation apparatus. Under conditions of stress and hypoxia, the HIF-1 protein penetrates the nucleus, rearranging the cell's genetic apparatus to combat oxidative stress. Activation of genes encoding the synthesis and spatial organization of collagen, structural proteins and protein-carbohydrate complexes occurs [6]. Consequently, an imbalance of enzymes of the pro-oxidant and antioxidant systems is the cause of the development of degradation of the corneal stroma, and as a consequence, the appearance of ruptures of Bowman's membrane, thinning of the stroma, and the appearance of stromal scars.

Purpose of the Study

The purpose of our study was to evaluate the neurotrophic regulation of metabolic processes in patients with early stage keratoconus and the possibility of correcting conservative treatment depending on the identified imbalance.

Materials and Methods

The study used the results of observation of patients with stages I - III of keratoconus (classification by M. Amsler (1961), J. Krumeich (1998) [7,8] 39 people (75 eyes), of which 11 were female, 28 were male. The age of patients at the time of contacting our center was from 16 to 41 years. All patients were corrected with corneal and corneoscleral rigid gas permeable contact lenses of various models and manufacturers. The duration of observation was from 2005 to 2019 inclusive.

At the same time, the follow-up period in 19 patients was 15 years, and 20 patients were at least 10 years.

All patients underwent an ophthalmological examination every 6 to 12 months - visometry, autorefractometry, keratometry, keratotopography, pachymetry, biomicroscopy.

Along with the examination of the ophthalmological status, the patients underwent cardiointervalography before starting conservative treatment. Autonomic homeostasis was assessed using the Mustang-Diagnostic device from the Tekhnika company (Russia) according to the indicators IVT (initial autonomic tone in arbitrary units), IN1 (tension index in arbitrary units in the supine position at rest), IN2 (position standing) and VR (vegetative reactivity) which was calculated according to the ratio IN2/IN1 [9-11].

Results and Discussion

Correction of keratoconus-induced refractive errors with rigid gas permeable contact lenses (GPCs) is also considered by many authors as a mandatory therapeutic measure [11,12]. Based on this, all patients we observed were fitted with individual corneal or corneoscleral gas-permeable contact lenses, which provided maximum vision and ensured a high quality of life.

Conservative treatment was primarily determined by the prescription of pharmacological drugs to improve corneal trophism and stabilize the tear film. Before prescribing drugs that normalize the neurotrophic regulation of metabolic processes, autonomic reactivity

was determined. Considering that autonomic reactivity reflects the direction of the response to external or internal stimulation and obeys Wilder's "initial level" law (1950), we determined heart rate variability to indirectly assess the neurotrophic regulation of the body's homeostasis [13]. According to cardiointervalography data, autonomic dysfunction was determined in 97% of our patients, while in 85% of all examined patients a significant predominance of sympathicotonic neurotrophic regulatory processes was determined. Theoretical and experimental studies we performed earlier [14] allow us to assert that with the predominance of catecholaminergic neurotrophic regulatory mechanisms, most metabolic processes occur with a predominance of anaerobic glycolysis, and accordingly, the manifestations of oxidative stress increase.

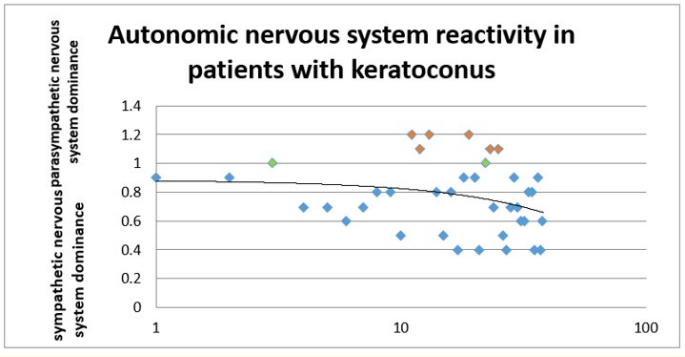

Diagram 1: *Autonomic nervous system reactivity in patients with keratoconus based on the results of cardiointervalography using the Mustang-Diagnostic (Tekhnika, Russia). Autonomic dysfunction was detected in 97% of observed patients with keratoconus, while in 85% of all examined patients a significant predominance of sympathicotonic neurotrophic regulatory processes was determined.*

An increased amount of oxidants leads to the destruction of collagen, fragmentation of collagen fibers, which contributes to disruption of the sphericity of the cornea and the manifestation of clinical symptoms of keratoconus [15,16].

Based on this, we have proposed an effect that allows, at the first stage, to enhance cholinergic neurotrophic regulatory influences and activating aerobic processes in the tissues of the eyeball. For these purposes, we propose to use taurine, a cell osmoregulator, a membrane protector, a regulator of intracellular calcium, which has antioxidant properties, as well as preparations containing dexpanthenol and heparin. From those approved for use in ophthalmological practice, we selected taurine 4%, an aqueous solution of sodium hyaluronate and provitamin B5 - dexpanthenol, sodium heparin 1300 IU for the conservative treatment of keratoconus at the first stage.

At this stage of treatment, we noted the development of slight edema and thickening of the stroma, and looseness of the corneal epithelium. This is due to the fact that with the predominance of trophotropic regulatory mechanisms, the intensity of aerobic glycolysis increases, mitotic activity increases, and protein synthesis increases. These changes in the cornea develop no earlier than two months after the start of treatment.

In order to stop proliferative processes and activate differentiation processes of newly formed proteins, it is necessary to potentiate sympathicotonic (ergotropic) neurotrophic regulatory processes.

The drugs used at this stage of treatment for keratoconus have a membrane-stabilizing (regulation of the synthesis of phospholipids and proteins, stabilization and normalization of the structure of cell membranes), antioxidant (inhibition of the formation of free radicals and lipid peroxidation of cell membranes), and antihypoxic effects. That is, it is necessary to potentiate sympathicotonic (ergotropic) neurotrophic regulatory processes, which is achieved by using methylethylpyridinol 1%, an isotonic 0.1% aqueous solution of sodium hyaluronate, and a lubricant containing vitamin A (250 IU retinol palmitate per 1g). This stage also lasts at least two months.

To assess the dynamics of the pathological process, a complex of ophthalmological research methods was used, but the most informative and revealing were keratometry, keratotopography with calculation of the KISA% index, pachymetry and biomicroscopy.

Visual acuity in the patients we observed remained high throughout the study and did not allow us to reliably assess the dynamics of the development of the pathological process.

When examining patients a year or more after the start of the proposed conservative therapy, we observed some stabilization of the process.

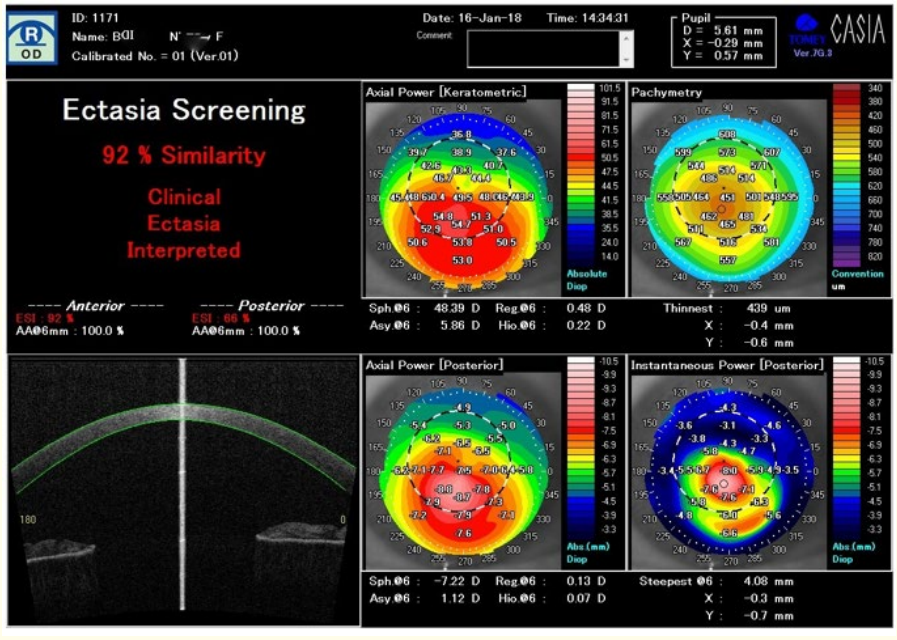

Figure 1: *Keratotopography of patient N. before conservative treatment.*

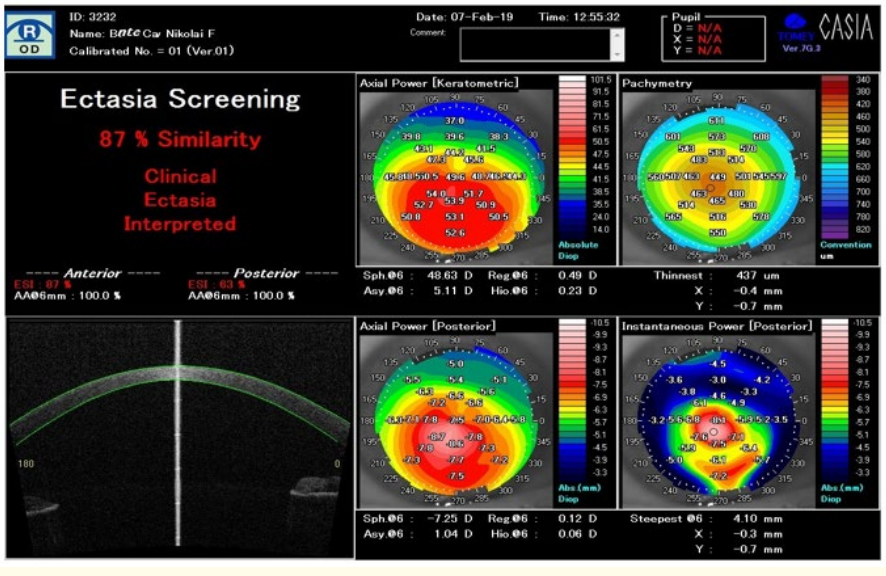

Figure 2: *Keratotopography of patient N. a year after the start of conservative treatment.*

However, when examined one year after the start of treatment, in patients with stage I keratoconus, in 25% of cases, in 20% with stage II and 29% in patients with stage III, a slight increase in diopter power along the steep meridian was observed.

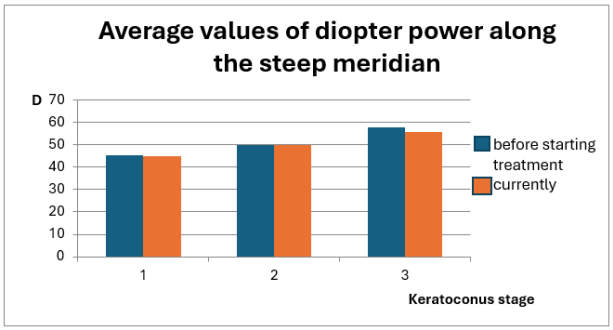

Diagram 2: *Dynamics of changes in the average values of diopter power along the steep meridian in observed patients with keratoconus over the entire observation period.*

Many researchers believe that the integrative indicator KISA% index can more reliably reflect the dynamics of the development of keratotopographic changes in patients with keratoconus [17,18]. A study of the KISA% index revealed a decrease in values in all of our patients, regardless of the stage of development of the disease.

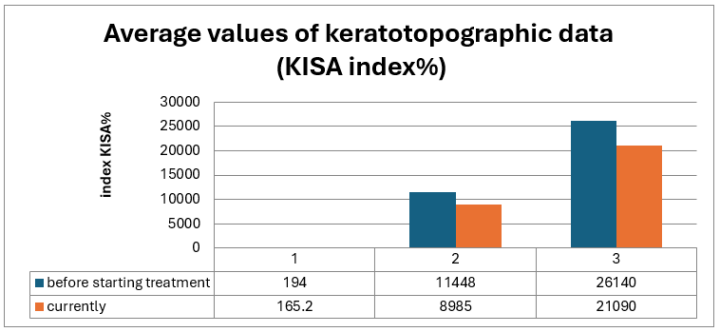

Diagram 3: *Dynamics of changes in average values of keratotopographic data (KISA index%) in observed patients with keratoconus for the entire observation period.*

Analysis of the results of long-term (more than a year) observation of patients with keratoconus receiving conservative treatment aimed at normalizing the neurotrophic effect on regenerative processes in the tissues of the eye showed the possibility of stabilizing the pathological process and revealed disease progression in only three patients from the group with stage II keratoconus, 4% of all patients). All other patients experienced long-term stabilization of the disease. Three patients who had progression of keratoconus from stage II to stage III underwent a corneal collagen cross-linking procedure.

Consequently, the impact on the pathologically altered cornea with pharmacological drugs, taking into account the neurotrophic regulatory effect on the regenerative processes in the eye tissues, leads to stabilization of the pathological process in the cornea.

Conclusion

The combination of therapeutic factors into tonic (trophotropic, anabolic) and phasic (ergotropic, catabolic) regulatory blocks, taking into account their mutual neurodynamic synergism and in accordance with the phase nature of the biorhythmogenesis of reparative processes, provides the possibility of preventing the progression of keratoconus.

The use of a treatment complex that we have developed, including therapeutic treatment and correction with rigid gas-permeable contact lenses, corrects metabolic disorders and stabilizes collagen synthesis, which makes it possible to rehabilitate patients and postpone surgical treatment of patients with keratoconus.

Conflict of Interest

The authors declare that they have no financial interests or conflicts of interest.

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