Nerve growth factor eye drops improve visual acuity and electrofunctional activity in age-related macular degeneration: a case report

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Summary. Age-related macular degeneration (ARMD) is a severe disease affecting visual function in the elderly. Currently available surgical and medical options do not guarantee a significant impact on the outcome of the disease. We describe the effects of nerve growth factor eye drop treatment in a 94 years old female with ARMD, whose visual acuity was progressively worsening in spite of previous surgical and medical treatments. NGF eye drops improved visual acuity and electrofunctional parameters as early as 3 months after initiation of treatment. These results are in line with previous reports on a neuroprotective effect of NGF on retinal cells and on NGF eye drops bioavailability in the retina and optic nerve. No side effects were observed after five years of follow-up, suggesting that topical NGF treatment may be a safe and effective therapy for ARMD.

Key words: macular degeneration, nerve growth factor, visual pathways, retina, eye drops.

INTRODUCTION

A consistent number of studies published in recent years have demonstrated that topical administration of nerve growth factor (NGF) to the eye is a safe therapy able to restore corneal integrity in patients with neurotrophic ulcers [1-3]. The healing properties of NGF have also been reported in cutaneous ulcers caused by diabetes, rheumatoid arthritis and pressure ulcers [4-9]. More recently, studies in animal models of ocular hypertension and glaucoma have shown that retinal cells express NGF receptors and that the degeneration of these cells can be protected by NGF eye drop administration [10, 11]. Based on these data we hypothesized that topical NGF administration to the eye could be a novel therapeutic approach for human macular degeneration.

Age-related macular degeneration (ARMD) is the most common cause of irreversible visual loss in the elderly in the developed countries, and its incidence is constantly increasing [12]. Loss of vision due to ARMD occurs either as a result of choroidal neovascularisation with exudation and haemorrhage (“wet” ARMD) or by slow atrophy of the retinal-pigment epithelium and overlying receptors (“dry” ARMD) [13]. Definitive treatment does not yet exist. About 10% of patients with wet ARMD who present early with distorted vision and an eccentric neovascular lesion can be treated with laser photoacoagulation. However, the recurrence rate is over 60%, with further...
vision being usually lost [14]. Selected patients can also be treated with photodynamic therapy involving low-intensity red laser treatment after intravenous verteporfin infusion, but the functional benefit is usually modest [15]. In the last few years, treatment with repeated intravitreal injections of anti-angiogenic compounds has also been proposed, with substantial success in reducing progression of disease [16, 17]. Nevertheless, several alternative pharmacological interventions are in different phases of clinical development, and researchers are guardedly optimistic that these advances may change the entire approach to ARMD management in the near future.

Based on our long-lasting experience on the healing action of NGF in corneal ulcers, and the evidence that this form of NGF application does not exert side effects or generate circulating NGF antibodies [1], the possible use of topical NGF in ARMD was taken into consideration. The effect of eye NGF treatment was valuated in a 94 years old female patient affected by maculopathy for over three years characterized by progressive worsening of visual acuity and macular degeneration as evidenced by clinical and electrofunctional tests. Moreover, since all available therapies failed to arrest or delay the visual field worsening induced by the maculopathy, informed signed consent was obtained and the patient was treated TID with NGF eye drops. The effects of therapy were followed closely every-other day for the first three weeks and every 3 months thereafter.

The results of this case report are based on the evaluation of visual acuity and electrofunctional parameters during 6 years of NGF treatment.

MATERIALS AND METHODS
A 94 years old female affected by bilateral wet ARMD since 1995 referred to our Department following macular cryotreatment in left eye (in 1996), and laser and photodynamic treatment in right eye (in 2000 and 2001, respectively). Cataract surgery was performed in both eyes (in 2001). Eye examination showed the presence of bilateral macular scar with no evidence of neovascularisation (Figure 1). Fluorescein examination confirmed a central extensive area of retinal atrophy with the absence of choroidal neovascularization. Best corrected visual acuity (BCVA) was 0.05 in right eye and count finger in left eye. J17 was the near visual acuity detectable in the right eye, while it was not detectable in the left eye. At baseline, electrofunctional exams showed a decrease of ERG amplitude (Figure 2).

After all currently available therapies failed to block or delay the visual deficits induced by ARMD progression, the patient signed informed consent to be treated with NGF eye drop on a compassionate basis. Highly purified NGF was prepared following the Bocchini&Angeletti method, as reported in our previous studies. [3, 8, 18] Lyophilized NGF was dissolved in physiological saline solution and one drop (approximately 50 µl) of 200 µg/ml was administrated TID into the conjunctival fornix of the right eye.

RESULTS
The patient was evaluated at baseline and every three months during NGF treatment and the follow-up (6 years) by complete ocular examination including BCVA and electrofunctional exams. No ocular adverse side effects were observed during the treatment and follow-up. Macular morphology was unchanged at the end of follow-up. However, after 3 months of NGF treatment an improvement of ERG
amplitude was observed (Figure 2), followed by an increase of visual acuity in the right eye that reached 0.16 and J7 after 1 year of treatment. No changes were observed in the left eye.

At 1 year of NGF treatment, patient discontinued NGF eye drop for 3 months. Interestingly, the follow-up visit at 3 months of NGF discontinuation showed decreased ERG amplitude, associated with a decreased visual acuity. Thus, patient re-started NGF eye drop treatment and after 3 months of treatment ERG amplitude and visual acuity increased again. At 18 months of NGF treatment both BCVA and ERG value were stable. No morphological changes were observed in the retina of both eyes.

The only side effect recorded during the 6 years of NGF treatment was a weak burning sensation at the time of administration that persisted for the 1st month of treatment.

**DISCUSSION**

Nerve growth factor (NGF) is an endogenous neurotrophin that exerts trophic and differentiative activity on neurons of the central and peripheral nervous systems with protective and/or regenerative effects observed in degenerative diseases or following injury [6, 19-23]. Intraocular administration of NGF in animal models has been shown to inhibit retinal ganglion cell degeneration [24, 25]. Despite the numerous data showing NGF abilities in protecting and recovering retina and optic nerve from injury and/or degeneration, invasive routes of administration, such as intraocular injection, or intraocular insert releasing the growth factors, are not optimal for clinical use. Recently, NGF applied topically to the eye has also been shown to reach the retina, optic nerve and brain [26, 27], indicating that NGF eye drops could be a novel therapy for the treatment of ocular and brain degenerative diseases.

In this study, we report the case of a patient with advanced bilateral ARMD who improved both her BCVA and electrofunctional parameters with TID topical NGF administration in one eye for 5 years, without reporting any side effect except for a mild and transient burning sensation at the site of administration for one month after initiation of treatment.

The efficacy of NGF in improving visual acuity and electrofunctional parameters has been observed in this patient at 3 months after initiation of treatment. This “early” effect of NGF treatment is in line with the NGF action in supporting trophism and functions of central and peripheral neurons *in vitro* as well as *in vivo* [22, 28, 29]. Specifically, several studies have demonstrated a biological activity of NGF in protecting retinal ganglion cells against ischemic, traumatic and hypertensive injuries [24, 25, 30]. This neuroprotective properties of NGF make it a strong candidate for the future treatment of degenerative diseases (such as glaucoma). In fact, it is also noteworthy that in the course of NGF eye drops treatment or during the follow-up, no NGF antibodies were detected in serum, as the murine NGF presents great homology with human NGF and the amount of topically-applied NGF reaching the bloodstream is absent or too low to trigger anti-NGF-antibodies formation [1].

A key question raised by this clinical observation and also by studies on animal models [10, 11, 27, 31], is how NGF, a high-molecular-weight protein, is transported from the ocular surface to the posterior segment of the eye when administered topically as eye drops. The evidence currently available points out to two possible routes: through the cornea, conjunctiva, sclera, choroid, choriocapillaris, and retinal pigment epithelium, or indirectly by traveling through the retrobulbar space to the optic nerve.

Although the clinical observation presented in this report needs to be confirmed on a large scale clinical trial, the good clinical response and the persisting of the improvement during the follow-up stimulate to extend our pilot clinical study. Moreover this study confirms the possibility of using the eye drop NGF for reaching retina, optic nerve and brain in a safe and non-invasive manner, supporting the potential use of topical NGF therapy for ocular and brain degenerative diseases currently considered untreatable.

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References