Investigation of the Association between the Oral and the Gut Microbiome in Glaucoma

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Abstract

Objective: Glaucoma is characterized by a progressive degeneration of retinal ganglion cells (RGC) and their axons leading to painless damage of the visual field and finally blindness. The exact pathophysiology of RGC loss remains unknown. Alterations in the microbiome may be linked to neurodegenerative conditions such as Alzheimer's and Parkinson's diseases, possibly due to associated chronic low-grade inflammation. A recent study linked alterations in the oral microbiome and glaucoma.

Methods: We investigated the microbiome of salivary and fecal samples in patients with normal tension glaucoma (10), ocular hypertension (11) and controls (11) using a case-control design with 16S rDNA sequencing.
Results: For controls, but not the patient groups, salivary and fecal microbiome diversity was correlated in a given patient, suggesting an uncoupled saliva and fecal microbiome in the diseased groups. Such findings suggest that normal tension glaucoma (NTG) and ocular hypertension (OHT) might have similar characteristics. However, ocular hypertension patients seem to be resistant to neurodegenerative disease progression indicating that the uncoupled microbiome might affect characteristics linking ocular hypertension and normal tension glaucoma together. Moreover, we found the salivary microbiome to contain more differential taxa-level abundances of microorganisms suggesting the salivary microbiome might be advantageous to use in future studies investigating novel biomarkers in ophthalmic neurodegenerative diseases.

Conclusion: The finding of an uncoupled microbiome might indicate comparable characteristics among glaucoma patients and ocular hypertension patients.

Introduction:
Androgenic alopecia (AGA) (also known as pattern alopecia) is the most common form a chronic non-scarring hair loss, affecting both men and women [1]. AGA is characterized by progressive hair loss, especially of scalp hair, and has distinctive patterns of loss in women versus men, but in both genders the central scalp is most severely affected [2]. Follicular miniaturization and local high dihydrotestosterone (DHT) activity are considered the main pathological mechanisms involved in AGA [3]. Microinflammation is also a relevant pathogenetic mechanism involved in this clinical condition [4]. Approved therapeutic options are limited to topical minoxidil [5] for both men and women and oral finasteride [6] for men. However, both drugs possess side effects and are effective in less than 50% of treated patients [7]. Autologous Platelet-Rich Plasma (PRP) dermal injection is an additional therapeutic option for the medical treatment of AGA [8]. However, clinical efficacy of this approach in some cases could be disappointing [9]. Positive effects of PRP in AGA seem correlated, at least in part, with a growth factors mimicking action [10]. PRP is rich in growth factors like PDGF (platelet derived growth factor), TGF (transforming growth Factor Beta) and VEGF (Vascular endothelial growth Factor) [11]. A hair scalp lotion containing high-purified, growth factors-like polypeptides (octapeptide 2, acetyl decapeptide 3, oligopeptide 20 and copper tripeptide) with the addition of glycine and taurine (GFM-L) is available. Copper tripeptide has shown to have antioxidant [12], antiinflammatory and blood vessel growth promoting action [13]. Copper tripeptide can increase the activity of FGF (Fibroblast Growth Factor) and VEGF [14]. Interestingly, copper tripeptide decreases the secretion of TGF-β [15] from dermal fibroblasts. TGF-β is involved in inducing catagen phase [16]. Copper tripeptide can also interfere with the activity of 5-αreductase, therefore reducing the production of DHT [17]. Finally, this peptide is also able to stimulate the production of decorin [18]. Decorin, at scalp level, improves the anagen phase [19] and consequently hair growth [20]. The acetyl decapeptide is a synthetic peptide that mimics the action of two growth factors: the keratinocyte growth factor (KGF) and the epidermal growth factor (EGF), which acts on the follicle, promoting the anagen growth phase, through an antiapoptotic effect [21], maintaining the bulge stem cells active [22]. Another component of the growth factor like mixture, octapeptide 2, is able to promote hair growth [23], to reduce apoptosis and to increase keratinocyte proliferation [24]. In this formulation all the 4 oligopeptides are vehiculated in nanosomes of 250 nm in diameter. Published data state that nanosomes with a diameter Published data state that nanosomes with a diameter The peculiar composition of this lotion (mixture of growth factor like peptides and taurine) suggests a potential synergistic effect on hair growth with other therapeutic strategies like PRP treatment. So far, no data regarding the potential synergistic effect of autologous PRP treatment combined with GFM-L are available. We therefore conducted a prospective, randomized, assessorblinded trial to compare the efficacy and tolerability of PRP alone vs. PRP and GFM-L treatment in men and women with AGA.
METHODS
Participants in the study Ten patients with NTG and 11 patients with OHT were compared to 11 age- and gender-matched control subjects who had undergone an eye exam

within 3 month, including visual acuity, slit lamp examination, IOP, funduscopy, visual field testing using Humphrey Field Analyzer (30:2 SITA Fast). The included patients with NTG had characteristic glaucomatous visual field losses and no untreated pressures measured above 16 mmHg. Patients with OHT had untreated IOP above 24 mmHg and no signs of glaucomatous damage. All subjects enrolled in the study were caucasian females between 50 and 96 years of age. Subject were all non-smokers and with no alcohol abuse. They had no previous history of ocular trauma, no disease affecting the retina or the optic nerve, other than glaucomatous characteristics in the patients with NTG patients and increased IOP in patients with OHT. No subjects had significant systemic conditions. Moreover, subjects had no illness related to the gastrointestinal tract and had not used antibiotics three months prior to the collection of faeces and saliva. The use of probiotics amongst the subjects was taken into consideration, but a more extensive registration of diet was not conducted. The characteristics of the participants enrolled are presented in table 1. Table 1: Characteristics of the participants enrolled in the study. *Alcohol within official limits. Clinical data for group CTRL, NTG and OHT Variable CTRL (n=11) NTG (n=10) OHT (n=11) Mean age 67,7 70,3 71,5 Ethnicity (white) 1 1 1 Females 1 1 1 BMI 24,9 22,6 26,5 Smoking 0 0 0 Alcohol* 90,9% 1 1 Pro- or prebiotic intake 18,2% 11,1% 9,1% Patient involvement This research was carried out without involving patients in study design, writing of the manuscript or interpretation of the results. Ophthalmic status Every participant included in the study underwent ophthalmic examination a maximum of three months prior to the analysis of the saliva and faeces. Criteria for the NTG group: an untreated IOP of less than 16 mmHg, an open angle examined by gonioscopy, glaucomatous cupping of the optic nerve head, and characteristic visual field losses examined by Humphrey Field Analyzer on at least one eye. Criteria for the OHT group: Untreated IOP measurements above 24 mmHg,

Keywords: Glaucoma; Microbiome; Ocular hypertension

RESULTS

Microbiomic status of faeces and saliva in patient with NTG, patients with OHT, and healthy age- and gender matched controls To investigate the association between the gut microbiome and the glaucomatous loss of retinal ganglion cells, we collected salivary and fecal samples from 10 NTGs, 11 OHTs, and 11 ageand gender-matched controls. The saliva samples were relatively diverse at class level in all three groups, while the fecal samples were completely dominated by the two classes of Clostridia and Bacteroidia

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