The Journal of Laryngology & Otology

cambridge.org/jlo

Is there any effect of neurotrophin-3 on the pathogenesis of non-allergic nasal polyps?

O Ismi[1], T Kara[2], G Polat[3], O Bobusoglu[3], Y Vayısoglu[1], K Gorur[1] and C Ozcan[1]

Departments of [1]Otorhinolaryngology, [2]Pathology and [3]Biochemistry, Faculty of Medicine, University of Mersin, Turkey

Abstract

Background. Although the role of neurotrophins such as nerve growth factor and brain-derived neurotrophic factor in nasal polyps development has been studied, the contribution of neurotrophin-3 has not been evaluated yet. This study aimed to investigate the possible role of neurotrophin-3 in nasal polyps pathogenesis.

Methods. The study group comprised 70 non-allergic nasal polyps patients and the control group consisted of 53 patients with middle turbinate concha bullosa. Specimens were taken, during surgery, from the ethmoid sinus nasal polyps in the nasal polyps group and from the lateral part of the middle turbinate concha bullosa in the control group. Tissue and serum levels of neurotrophin-3 were assessed by immunohistochemistry and enzyme-linked immunosorbent assay, respectively.

Results. Nasal polyps patients had higher tissue neurotrophin-3 scores ($p < 0.001$). There was no statistically significant difference between groups regarding serum neurotrophin-3 levels ($p = 0.417$). Tissue neurotrophin-3 staining scores in the nasal polyps group had no statistically significant correlation with Lund–Mackay scores ($p = 0.792$).

Conclusion. Neurotrophin-3 may have a local effect in nasal polyps pathogenesis, without joining systemic circulation.

Introduction

Inflammatory nasal polyps are benign masses of the paranasal sinuses and nasal cavity characterised by inflammatory cell infiltration, squamous metaplasia of the surface epithelium, thickening of the basement membrane and oedematous stroma.[1,2] Histologically, they can be divided into four different types: eosinophilic oedematous, chronic inflammatory or fibrotic, seromucinous gland, and atypical stromal.[1] More than 85 per cent of cases demonstrate predominant eosinophilic infiltration.[3]

Nasal polyps affect 1–4 per cent of the population. They cause significant morbidity, with nasal obstruction, anosmia and nasal discharge. Patients with nasal polyps can also have co-morbid diseases such as asthma, acetyl salicylic acid hypersensitivity, cystic fibrosis and sinobronchial syndrome.[2] Although allergy was presumed to be a predisposing factor, recent literature does not support any evidence-based association between allergic rhinitis and nasal polyps development, recurrence or disease severity.[4,5] The underlying pathogenesis of nasal polyps has not been fully elucidated; infections, genetic susceptibility, mucociliary dysfunction and vasomotor imbalance have been hypothesised to be the contributing factors.[6,7] The underlying pathogenesis should be precisely enlightened to pave the way for new therapeutic options.

Some non-immunological factors also aggravate nasal inflammatory reactions, including smells, smoke and environmental pollutants. It is unclear how these trigger factors aggravate the inflammatory response in chronic rhinosinusitis with or without nasal polyps.[3] Neurogenic inflammation is the vicious cycle of neuroimmune reactions that contribute to airway inflammation. Stimulated nasal nociceptive type C fibres are capable of inducing local expression of neuropeptides such as substance P, neurokinin A and calcium gene-related peptide. These neuropeptides in turn cause plasma extravasation, glandular secretion, and activation and differentiation of inflammatory cells, all of which contribute to airway inflammation and nasal hyper-responsiveness.[3,8]

Neurotrophins are a group of nerve growing factors with homologous targets and effects. Nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3 and neurotrophin-4/5 are members of the neurotrophin family in humans. Their primary function is the growth and differentiation of nervous tissue, but they are also able to stimulate the nociceptive fibres to secrete neuropeptides and contribute to neurogenic inflammation of the nasal tissues.[9,10] Nerve growth factor and brain-derived neurotrophic factor expressions have been demonstrated in the nasal mucosa of allergic rhinitis patients.[11] Nerve growth factor has also been shown to be overexpressed in the nasal mucosa of idiopathic rhinitis patients.[12]

There have been two published articles investigating the effect of nerve growth factor and brain-derived neurotrophic factor on nasal polyps pathogenesis in the

Main Article

Dr O Ismi takes responsibility for the integrity of the content of the paper

Cite this article: Ismi O, Kara T, Polat G, Bobusoglu O, Vayısoglu Y, Gorur K, Ozcan C. Is there any effect of neurotrophin-3 on the pathogenesis of non-allergic nasal polyps? *J Laryngol Otol* 2018;**132**:724–728. https://doi.org/10.1017/S0022215118000981

Accepted: 12 February 2018
First published online: 5 July 2018

Key words:
Nasal Polyps; Neurotrophin 3; Inflammation

Author for correspondence:
Dr Onur Ismi,
Mersin Üniversitesi Tıp Fakültesi Hastanesi, Kulak Burun Boğaz AD, Çiftlikköy Kampüsü, Çiftlikköy/Yenişehir, Mersin, Turkey
Fax: +90 3242 380 091
E-mail: dronurismi@gmail.com

English-language literature.[3,9] This study aimed to investigate the possible role of neurotrophin-3 on nasal polyps pathogenesis. As the effect of neurotrophin-3 on allergic rhinitis pathogenesis has been presented before, we studied non-allergic nasal polyps patients to exclude the effect of atopy on our study results.[10]

Materials and methods

Local ethical committee approval was obtained for the current study. The study group comprised 70 patients with non-allergic nasal polyps who underwent functional endoscopic sinus surgery. The control group consisted of 53 patients with bulbous or extensive type middle turbinate concha bullosa, who underwent lateral marsupialisation. All procedures were performed under general anaesthesia, from December 2013 to April 2017, in our tertiary centre otorhinolaryngology department.

The diagnosis of nasal polyps was made according to the European position paper on rhinosinusitis and nasal polyps 2012.[13] Eleven patients in the nasal polyps group had co-morbid asthma according to Global Initiative for Asthma guidelines.[14] The remaining 59 patients were allocated to the nasal polyps without asthma group. The control group patients had no atopy history or rhinitis symptoms except nasal obstruction. The atopy status of the nasal polyps group was assessed using a skin prick test with a standardised allergen prick test panel (Stallergenes, Antony, France) (Table 1) and serum specific immunoglobulin E (IgE) levels. The nasal polyps patients with positive skin prick test results or high specific IgE levels were excluded to eliminate the effect of atopy on the study results. Topical and systemic steroids were discontinued four weeks prior to surgery. Patients were excluded from the study if they had been diagnosed with any of the following: allergic fungal sinusitis, systemic disorders such as rheumatoid arthritis, diabetes mellitus, hypothyroidism or hyperthyroidism, systemic hypertension and neurological disorders including multiple sclerosis, parkinsonism and epilepsy.

The demographic characteristics of the study population are summarised in Table 2. The Lund–Mackay staging system[15] was used to assess the extent of disease in nasal polyps patients.

Immunohistochemistry of tissue specimens

All tissue specimens were collected under general anaesthesia during the surgical procedure. Specimens were taken from the ethmoid sinus nasal polyps in the nasal polyps group and from the lateral part of the middle turbinate concha bullosa in the control group.

The nasal polyps biopsy and concha bullosa mucosa specimens were fixed in 10 per cent formalin solution. Sections of 5 µm thickness were obtained from the formalin-fixed, paraffin embedded tissues of all biopsies, and routine haematoxylin and eosin staining was performed. The sections were immunostained for neurotrophin-3 (dilution 1:200; Santa Cruz, Texas, USA) according to the instructions of the manufacturer, as described by Barcena de Arellano *et al.*[16] For the negative control, specimens were processed in the absence of a primary antibody.

The staining of neurotrophin-3 was observed in the interstitial matrix and the cytoplasm of the inflammatory cells. Briefly, the intensity of immunostaining was analysed. The staining intensity was scored semi-quantitatively in terms of five groups: absent (0), weak (+1), moderate (+2), strong (+3) and very strong (+4), as outlined by Raap *et al.*[11] The pathologist was unaware of the tissue sample group during immunohistochemical analysis. Weak (+1) and very strong (+4) staining levels in the tissue specimens are shown in Figures 1 and 2, respectively.

Enzyme-linked immunosorbent assay

Blood samples from all subjects were collected by venepuncture in plain tubes, and immediately centrifuged at 4000 g for 10 minutes at 4 °C. The serum samples were stored at −20 °C until analysis. Neurotrophin-3 levels were determined in the DSX four-plate, automated enzyme-linked immunosorbent assay processing system (Dynex Technologies, Chantilly, Virginia, USA), using the Human NT-3 ELISA Kit (YH Biosearch Laboratory, Shanghai, China) according

Table 2. Demographic characteristics

Characteristic	Nasal polyps group*	Control group†	*P*-value
Sex (M/F; *n*)	48/22	34/19	0.607
Age (mean ± SD; years)	32.8 ± 8.58	31.6 ± 5.30	0.337
Asthma (*n* (%))	11 (16)	0 (0)	–

*$n = 70$; †$n = 53$. M = males; F = females; SD = standard deviation

Table 1. Allergens in skin prick test panel

House dust mites (*Dermatophagoides farina*, *Dermatophagoides pteronyssinus*)
Grass pollen mix (*Lolium perenne*, *Festuca elatior*, *Phleum pratense*, *Poa pratensis*, *Dactylis glomerata*, *Agrostis (alba) gigantea*, *Anthoxanthum odoratum*)
Weed pollen mix (*Xanthium strumarium*, *Plantago lanceolata*, *Chenopodium album*, *Amaranthus retroflexus*, *Salsola kali*)
Tree pollen mix (*Betula populifolia*, *Alnus serrulata*, *Salix caprea*, *Populus alba*, *Olea europaea*)
Smut mix (*Ustilago maydis*, *Ustilago nuda*, *Ustilago tritici*, *Ustilago avenae*)
Animal epithelia (*Felis catus (domesticus)*, canis sp., *Gallus gallus*, *Anas platyrhynchos*, *Anser anser*)
Fungi (*Alternaria alternata*, *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus nidulans*, *Aspergillus amstelodami*)
Cockroach (*Blattella germanica*)

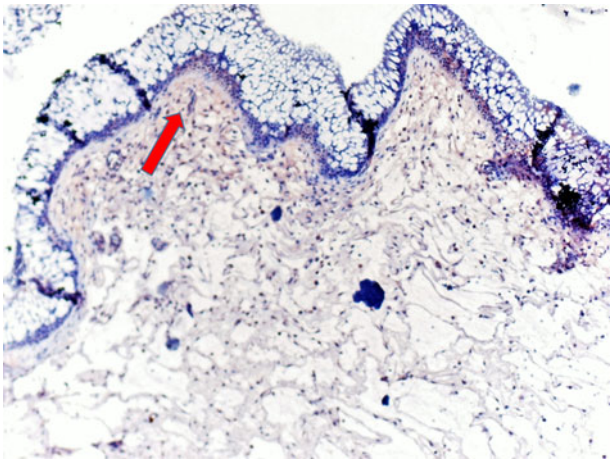

Fig. 1. Weak (+1) staining with neurotrophin-3 in the interstitial matrix (arrow) of a nasal polyps patient without asthma. (Neurotrophin-3; ×100)

https://doi.org/10.1017/S0022215118000981 Published online by Cambridge University Press

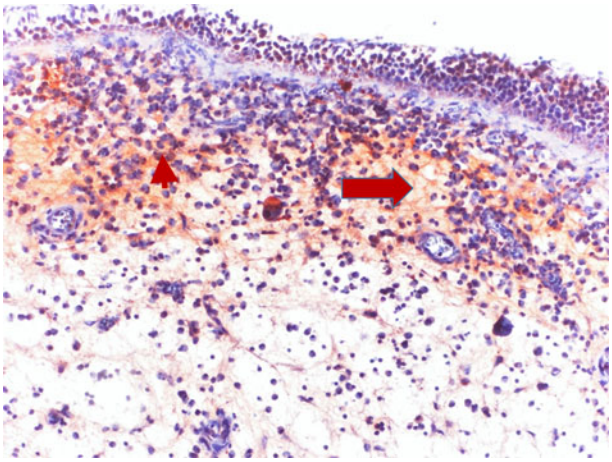

Fig. 2. Very strong staining (+4) with neurotrophin-3 in the interstitial matrix (arrow) and the cytoplasm of eosinophils (arrowhead) in a nasal polyps patient without asthma. (Neurotrophin-3; ×200)

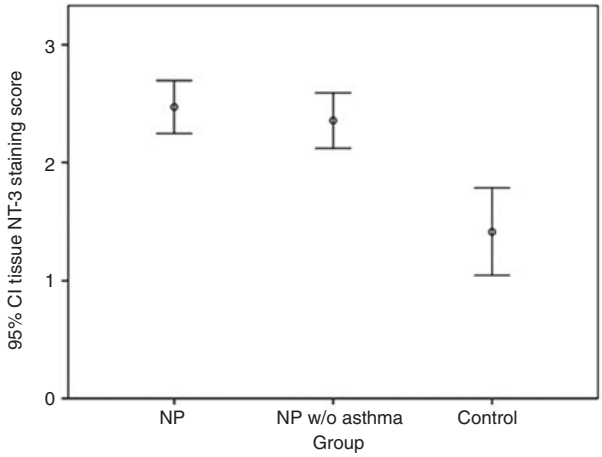

Fig. 3. Comparison of tissue neurotrophin-3 (NT-3) staining scores between groups. CI = confidence interval; NP = nasal polyps; w/o = without

to the manufacturer's instructions. The results are given in units of pg/ml.

Statistical analysis

Statistical analysis was performed using SPSS software, version 23.0 (2015; IBM, Armonk, New York, USA). The chi-square test was used to compare the gender frequencies between groups. The student's *t*-test was used to analyse age differences between groups. Data were controlled for normal distribution with the Shapiro–Wilk test. The Mann–Whitney U test was used to compare serum neurotrophin-3 levels between groups. Tissue neurotrophin-3 staining intensities were also compared using the Mann–Whitney U test as a non-parametric test. Correlation coefficients were used to assess the relationship between tissue staining scores and Lund–Mackay scores in the nasal polyps group. A *p*-value of less than 0.05 was regarded as statistically significant.

Results

There were 48 males in the nasal polyps group and 34 males in the control group. The mean age of the nasal polyps group was 32.9 ± 8.58 years; the mean age of the control group was 31.6 ± 5.3 years. There were no statistically significant differences regarding sex ($p = 0.607$) and age ($p = 0.337$) between the groups (Table 2).

The mean tissue staining scores of the nasal polyps, nasal polyps without asthma, and control groups were 2.47 ± 0.94, 2.35 ± 0.9 and 1.41 ± 1.33, respectively. The nasal polyps patients and nasal polyps without asthma patients had statistically significant higher tissue neurotrophin-3 staining scores compared to the control group patients ($p < 0.001$ for both). A comparison of tissue staining scores between the three groups is demonstrated in Figure 3.

The mean serum neurotrophin-3 levels of the nasal polyps, nasal polyps without asthma, and control groups were 987.9 ± 1414.2 pg/ml, 943.3 ± 1359.5 pg/ml and 850.15 ± 1305.38 pg/ml, respectively. There was no statistically significant difference between the groups regarding serum neurotrophin-3 levels (Table 3).

Regarding Pearson correlation coefficients, there was no statistically significant association between tissue neurotrophin-3 staining scores and Lund–Mackay scores in the nasal polyps group ($p = 0.792$) (Figure 4).

Discussion

In the current study, we found that nasal neurotrophin-3 tissue staining scores were higher in the nasal polyps group compared to the control group, regardless of the presence of asthma, but tissue staining intensity had no correlation with the extent of disease.

Regarding pathogenesis, nasal polyps are benign but complex structures. The underlying aetiology is multifactorial, including host factors (genetics, cystic fibrosis, immotile cilia syndrome, anatomical variations) and environmental factors (infections, trauma and chemical irritants).[2,7,17] Whatever the initial insult, the cascade of events in the paranasal sinuses and nasal cavity mucosa result in chronic ongoing inflammation.[1]

When the inflammatory profile of nasal polyps is investigated, nasal polyps have eosinophil-dominant inflammatory cells in more than 80–85 per cent of cases. In addition to eosinophils, mast cells, basophils and T helper 2 cells are also present in the inflammatory reactions. The cytokine profile of nasal polyps is characterised by type 2 cytokines, including interleukins (ILs) 4, 5 and 13 as the major cytokines. Interleukin 4 is responsible for B cell activation and IgE synthesis, whereas IL-5 stimulates the survival and development of eosinophils. Interleukins 4 and 13 can upregulate vascular adhesion molecule-1 expression and eosinophil chemotaxis. Eosinophils can secrete tumour growth factor β in the inflammatory reactions. Tumour growth factor β increases the secretion of IL-4.[1,18] This vicious cycle enhances the autonomy of eosinophils in nasal polyps pathogenesis.

Neurotrophins are homologous proteins regarding their receptor affinities and physiological assignments. They were originally determined by their important roles in the development and differentiation of the nervous system. The prototype of neurotrophins is nerve growth factor. Other members of the neurotrophin family in humans are brain-derived neurotrophic factor, neurotrophin-3 and neurotrophin-4/5. They accomplish their effects by their high-affinity tyrosine kinase receptors and the low-affinity common $p75^{NTR}$ receptor.[8,19] In addition to their important physiological effects on neuronal tissues, neurotrophins also participate in the

https://doi.org/10.1017/S0022215118000981 Published online by Cambridge University Press

Table 3. Comparison of serum neurotrophin-3 levels between groups

Group	Patients (*n*)	Serum NT-3 level (mean ± SD; pg/ml)	95% CI	*P*-value
Nasal polyps	70	987.9 ± 1414.2	650.7–1325.1	0.417 (*vs* control)
Nasal polyps without asthma	59	943.3 ± 1359.5	589–1297.6	0.465 (*vs* control)
Control	53	850.1 ± 1305.3	490.3–1209.9	

NT-3 = neurotrophin-3; SD = standard deviation; CI = confidence interval

inflammatory reactions of allergic diseases such as allergic rhinitis and asthma.[8,10,20]

The source of neurotrophins in the nasal mucosa is airway epithelial and inflammatory cells, including eosinophils, neutrophils and mast cells.[8,19] Of these, the main inflammatory cells that produce neurotrophins are eosinophils. Noga *et al.*[21] and Kobayashi *et al.*[22] demonstrated that eosinophils can produce, store and release neurotrophins in cases of inflammatory reactions and immunological stimulation. Wu *et al.* reported that 62.2 per cent of activated eosinophils showed nerve growth factor expression, compared to 2 per cent of mast cells in nasal mucosa.[23] Nerve growth factor receptors were found to be present in the submucosal glands and surface epithelium, in addition to nerves, in their study. These findings may demonstrate the autocrine and paracrine immunomodulatory effects of this neurotrophin.

Neurotrophins have multiple mechanisms of action in the cascade reactions of inflammation. They can stimulate the nasal nociceptive type C fibres, and lead to the secretion of neuropeptides such as substance P, calcium gene-related peptide and neurokinin A. These tachykinins in turn contribute to the inflammatory reactions of: mast cell degranulation, increased vascular permeability, mucus secretion, cytokine synthesis and eosinophil chemotaxis.[10] Furthermore, neurotrophins increase the secretion of IL-4 from eosinophils and inhibit their apoptosis.[19]

Neurotrophins have been investigated for their effects on inflammation in nasal polyps development. Jornot *et al.* demonstrated that nasal polyps epithelial cells expressed a higher amount of brain-derived neurotrophic factor compared to turbinate cells, and proinflammatory cytokines increased brain-derived neurotrophic factor expression in cell cultures.[9] The results of Coffey *et al.* were discordant with this study.[3] They found that the mean sinus tissue brain-derived neurotrophic factor concentration was lower in the nasal polyps group compared to the control group, but the nerve growth factor concentration was significantly higher in the nasal polyps group. The serum concentrations of neurotrophins were not investigated in nasal polyps patients in these studies.

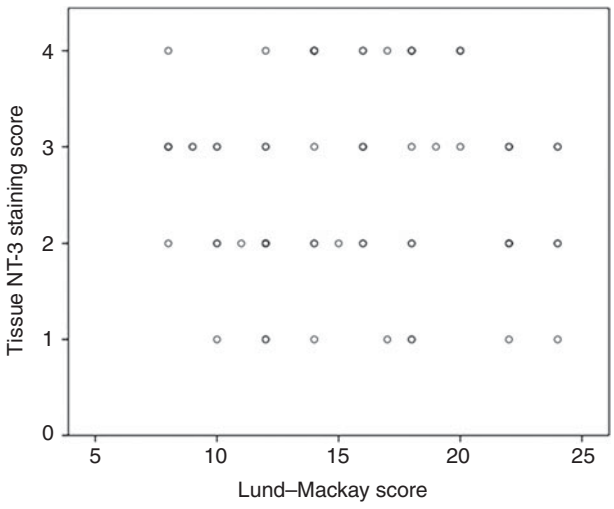

Fig. 4. Association of tissue neurotrophin-3 (NT-3) staining scores and Lund–Mackay scores in the nasal polyps group.

Neurotrophins are regarded as autocrine or paracrine proteins. They act on the surface receptors of the cell from which they are synthesised or from an adjacent cell.[8,20] Our study results demonstrated that neurotrophin-3 may have a local effect in non-allergic nasal polyps pathogenesis, regardless of asthma co-morbidity, without joining the systemic circulation. These proteins are likely to have multiple routes of action in nasal polyps development. Neurotrophins can inhibit apoptosis and elicit chemotaxis of the eosinophils.[10,19] Activated eosinophils represent a major source of new neurotrophin production in the inflammation site, which triggers a repetitive cycle of pathological events and much more neurotrophin production.[20]

The findings of recent literature and of our study indicate that the relationship between neurotrophins and eosinophilic inflammation can be the underlying cause of high levels of neurotrophins in nasal polyps tissue.[3,23] Furthermore, neurotrophins can stimulate the synthesis of tachykinins (substance P, neurokinin A, calcium gene-related peptide). These tachykinins have numerous tasks in the inflammation site, such as leukocyte chemotaxis, increased vascular permeability and cytokine synthesis from cells,[10] all of which are also seen in the inflammatory reactions of nasal polyps development.

- Neurotrophins are neurotrophic factors that have fundamental effects in the nervous system
- Nerve growth factor is the prototype of neurotrophins
- Brain-derived neurotrophic factor, neurotrophin-3 and neurotrophin-4/5 are other members of the neurotrophin family in humans
- These neuropeptides have important roles in allergic inflammation
- Nerve growth factor and brain-derived neurotrophic factor play an active role in nasal polyps pathogenesis
- This study demonstrated that neurotrophin-3 may have a local effect in nasal polyps pathogenesis, without joining systemic circulation

One can expect that if neurotrophins play a role in nasal polyps pathogenesis, substance P, calcium gene-related peptide and neurokinin A should also logically increase in nasal polyps tissue or the nasal secretions of nasal polyps patients with neurotrophins. Recurrent nasal polyps tissue samples expressed large amounts of substance P in the study of Beatrice *et al.*[24] In contrast, Gungor *et al.* reported that the nasal secretion of nasal polyps patients contained a lower amount of these neuropeptides compared to controls.[25] These different results

https://doi.org/10.1017/S0022215118000981 Published online by Cambridge University Press

can be explained by the physiological properties of the tachykinins. These neuropeptides are short-lived mediators that are rapidly degraded, so they have time-limited effects in inflammation.[8] The timing of obtaining the samples can easily affect the study results. In contrast to the abovementioned mediators, neurotrophins are permanently produced in the inflammatory site; hence, they act as long-term modulators during the cascade reactions of inflammation.[8]

A limitation of this study was the lack of identification of the endotypes in nasal polyps patients. Future studies should assess the serum and tissue neurotrophin-3 levels in different inflammatory profile dominant nasal polyps patients.

In conclusion, neurotrophin-3-induced neuronal inflammation may have a local effect in non-allergic nasal polyps pathogenesis. The results of the forthcoming enhanced studies investigating tissue RNA and protein levels may be more supportive for demonstrating the effect of neurotrophin-3 in nasal polyps pathogenesis.

Acknowledgement. This study was funded by Mersin University Academic Research Unit (grant number: 2015-AP2-1341).

Competing interests. None declared

References

1 Pawankar R. Nasal polyposis: an update. *Curr Opin Allergy Clin Immunol* 2003;**3**:1–6
2 Pawankar R, Nonaka M. Inflammatory mechanisms and remodeling in chronic rhinosinusitis and nasal polyps. *Curr Allergy Asthma Rep* 2007;**7**:202–8
3 Coffey CS, Mulligan RM, Schlosser RJ. Mucosal expression of nerve growth factor and brain-derived neurotrophic factor in chronic rhinosinusitis. *Am J Rhinol Allergy* 2009;**23**:571–4
4 Terzakis D, Georgalas C. Polyps, asthma and allergy: what's new. *Curr Opin Otolaryngol Head Neck Surg* 2017;**25**:12–18
5 Li QC, Cheng KJ, Wang F, Zhou SH. Role of atopy in chronic rhinosinusitis with nasal polyps: does an atopic condition affect the severity and recurrence of disease? *J Laryngol Otol* 2016;**130**:640–4
6 Aversa S, Ondolo C, Abbadessa G, Piccione F, Carriero V, Fulcheri A *et al.* Steroid resistance in nasal polyposis: role of glucocorticoid receptor and TGF-1β. *Rhinology* 2012;**50**:427–35
7 Ozcan C, Tamer L, Ates NA, Gorur K. The glutathione-s-transferase gene polymorphisms (Gstt1, Gstm1, and Gstp1) in patients with non-allergic nasal polyposis. *Eur Arch Otorhinolaryngol* 2010;**267**:227–32
8 Nockher WA, Renz H. Neurotrophins and asthma: novel insight into neuroimmune interaction. *J Allergy Clin Immunol* 2006;**117**:67–71
9 Jornot L, Grouzmann E, Lacroix JS, Rochat T. BDNF and DPP-IV in polyps and middle turbinates epithelial cells. *Rhinology* 2007;**45**:129–33
10 Ismi O, Ozcan C, Karabacak T, Polat G, Vayisoglu Y, Gucluturk T *et al.* Local effect of neurotrophin-3 in neuronal inflammation of allergic rhinitis: preliminary report. *Balkan Med J* 2015;**32**:364–70
11 Raap U, Fokkens W, Bruder M, Hoogsteden H, Kapp A, Braunstahl GJ. Modulation of neurotrophin and neurotrophin receptor expression in nasal mucosa after nasal allergen provocation in allergic rhinitis. *Allergy* 2008;**63**:468–75
12 Gelincik A, Aydin F, Ozerman B, Erguven M, Aydın S, Bilir A *et al.* Enhanced nerve growth factor expression by mast cells does not differ significantly between idiopathic and allergic rhinitis. *Ann Allergy Asthma Immunol* 2012;**108**:396–401
13 Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F *et al.* EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012;**50**:1–12
14 Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M *et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;**31**:143–78
15 Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology* 1993;**31**:183–4
16 Barcena de Arellano ML, Wagner MF, Oldeweme J, Arnold J, Ebert A, Schneider A *et al.* Neurotrophin expression is not affected in uteri of women with adenomyosis. *J Mol Neurosci* 2012;**47**:495–504
17 Ozcan C, Zeren H, Talas DU, Kucukoglu M, Gorur K. Antrochoanal polyp: a transmission electron and light microscopic study. *Eur Arch Otorhinolaryngol* 2005;**262**:55–60
18 Dennis SK, Lam K, Luong A. A review of classification schemes for chronic rhinosinusitis with nasal polyposis endotypes. *Laryngoscope Investig Otolaryngol* 2016;**1**:130–4
19 Raap U, Braunstahl GJ. The role of neurotrophins in the pathophysiology of allergic rhinitis. *Curr Opin Allergy Clin Immunol* 2010;**10**:8–13
20 Manti S, Brown P, Perez MK, Piedimonte G. The role of neurotrophins in inflammation and allergy. *Vitam Horm* 2017;**104**:313–41
21 Noga O, Englmann C, Hanf G, Grützkau A, Seybold J, Kunkel G. The production, storage and release of the neurotrophins nerve growth factor, brain-derived neurotrophic factor and neurotrophin-3 by human peripheral eosinophils in allergics and non-allergics. *Clin Exp Allergy* 2003;**33**:649–54
22 Kobayashi H, Gleich GJ, Butterfield JH, Kita H. Human eosinophils produce neurotrophins and secrete nerve growth factor on immunologic stimuli. *Blood* 2002;**99**:2214–20
23 Wu X, Myers AC, Goldstone AC, Togias A, Sanico AM. Localization of nerve growth factor and its receptors in the human nasal mucosa. *J Allergy Clin Immunol* 2006;**118**:428–33
24 Beatrice F, Aluffi P, Bottomicca F, Perlasco L, Sartoris A. Nasal polyps and substance P: a preliminary report [in Italian]. *Acta Otorhinolaryngol Ital* 1994;**14**(suppl 41):35–9
25 Gungor A, Baroody FM, Naclerio RM, White SR, Corey JP. Decreased neuropeptide release may play a role in the pathogenesis of nasal polyps. *Otolaryngol Head Neck Surg* 1999;**121**:585–90

https://doi.org/10.1017/S0022215118000981 Published online by Cambridge University Press