Endotypes of chronic rhinosinusitis with nasal polyps with and without NSAID – intolerance*

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Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a type 2-dominated inflammatory disease of the upper airways. A subgroup of patients with CRSwNP suffer from intolerance to nonsteroidal anti-inflammatory drugs (NSAID) and develop NSAID-exacerbated respiratory disease (NERD). The aim of the study was to compare the cytokine based inflammatory endotype of nasal secretions of CRSwNP patients with and without NSAID intolerance.

Methods: Nasal secretions were collected from twenty-six patients suffering from CRSwNP, thirteen with NERD and thirteen without NSAID intolerance. As control, nasal secretions were collected from fifteen healthy donors. Tryptase and ten human cytokines were analyzed: interleukin (IL)-4, IL-5, IL-6, IL-8, IL-12p70, IL-13, IL-17A, IL-23, IFN-γ, and TNF-α by a cytokine multiple array on a Luminex 200 platform.

Results: Grade of polyposis and frequency of polyp surgery was more severe in NERD- compared to non-NERD patients. IL-6 and IL-5 in CRSwNP was significantly increased compared to healthy participants. IL-5 and IL-13 were significantly increased in subjects suffering from NERD compared to CRSwNP patients without NERD.

Conclusion: We identified IL-13 as a possible specific biomarker in nasal secretions of patients with NERD, which allows us to differentiate between CRSwNP with vs. without NERD. The characterization of inflammatory endotypes in CRSwNP enables the introduction of the best available therapy in the context of precision medicine.

Key words: chronic rhinosinusitis with nasal polyps, asthma, NERD, NSAID, inflammation

Introduction

Chronic rhinosinusitis (CRS) is characterized by inflammation of the nose and paranasal sinuses and affects about 12% of the population [1-3]. It is differentiated into the two major phenotypes: chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP) [2, 4]. CRSwNP affects approximately 1-4% of the general population. According the recent literature in CRSwNP a mixed T-helper (Th)-1/Th2 inflammation can be identified [4, 5]. However, most Caucasians affected by CRSwNP demonstrate an eosinophilic inflammation with mucosal infiltration of type 2 T-cells, innate lymphoid cells (ILCs), eosinophils and mast cells. The cytokine milieu of CRSwNP typically includes interleukin (IL)-4, IL-5-and IL-13, eotaxin-1/2/3 and eosinophilic cationic protein (ECP) [6-8]. An important subtype of CRSwNP patients suffer from non-steroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (NERD) with the clinical symptoms of nasal polyposis and asthma. Approximately 9.7% among patients with nasal polyps, 8.7% among those with chronic sinusitis and 7.1% of asthma patients are suffering from NERD [9, 10]. The pathogenesis of NERD is related to abnormalities of the cyclooxygenase – and lipoxygenase- derived arachidonic acid metabolism [11]. Chronic eosinophilic airway inflammation is more intense and recurren-

ce of nasal polyps after surgery is more frequent in NERD than in NSAID – tolerant CRSwNP patients [10, 12]. In both phenotypes, the histology of polyps shows an eosinophilic inflammation in the tissue but they often present with distinct clinical courses, therefore the underlying inflammatory endotype seems to be different. The aim of this study was to investigate and to compare the inflammatory endotype of CRSwNP patients with NERD and without NSAID intolerance using a non-invasive test to define nasal cytokine patterns.

Materials and methods

Ethics approval and consent to participate

The local ethical Review Board of Zurich approved the study protocol (KEK2017-00810). The study strictly adhered to the principles of good clinical practice and the ethical standards outlined in the declaration of Helsinki [13]. All participants provided written informed consent.

Patients

Fifteen healthy volunteers were recruited from the clinic of otorhinolaryngology for non-CRS related problems. Twenty-six patients suffering from eosinophilic CRSwNP, proven by histology of preceding polyp operations, thirteen meeting the criteria for NERD by a clear medical history of respiratory symptoms 1-2 hours after ingestion of an NSAID, and thirteen CRSwNP patients without NSAID intolerance were recruited from either the department of otorhinolaryngology or clinical immunology after thorough examination by a senior consultant. Complete medical history according asthma was obtained from all participants and every individual underwent clinical examination including rhinoendoscopy. The extent of polyposis was judged according to the Davos scoring system for each side separately.

Collection of nasal secretions

Nasal secretions were collected from all participants in both nostrils separately. Neurosurgical patties (Neuray, Medtronic, Jacksonville, FL, USA) were introduced into the nostrils above the inferior turbinate on both sides and kept in situ for 10 minutes. Patties were then removed and weighed. Immediately after collection two-hundred microliters of diluent (NaCl 0.9%) was added and the patties were centrifuged at 1000 rpm for 5 minutes at room temperature. Secretions were collected, aliquoted and stored at -80°C for analysis.

Cytokine analysis

Cytokines were analysed by a cytokine multiple array on a Luminex 200 platform (Luminex Corporation, Austin, TX, USA) with a high sensitive Milliplex kit (HSTCMAG-28SK-10) customized by Merk Millipore, containing the following ten human cytokines: IL-4, IL-5, IL-6, IL-8, IL-12p70, IL-13, IL-17A, IL-23, IFN-γ, and TNF-α. This array includes cytokines that promote Th cell differentiation or cytokines produced by differentiated Th cell subpopulations. IL-12p70 and IFN-γ are related to Th1 cells, IL-4, IL-5, and IL-13 to Th2 cells, and IL-6, IL-17A and IL-23 to Th17 cells [14]. Monocytes/macrophages and activated T cells are the major producers of TNF-α [15], while IL-8, also called C-X-C Motif Chemokine Ligand (CXCL) 8, is released by a wide variety of immune and non-immune cells to predominantly mobilise neutrophils [16]. Cytokine measurement was always performed with a new aliquot. After thawing, aliquots were not frozen again for further analysis. Aliquots from both nostrils were analyzed and for each cytokine and the tryptase the average was calculated.

Statistical methods

We summarized continuous variables with means and standard deviations (and ranges), and dichotomous variables with percentages. Statistical testing was performed with parametric and non-parametric methods as needed. A p-value < 5% was considered statistically significant. In an exploratory approach, we dichotomized IL-13 mean values at 2.7 pg/ml and IL-5 mean values at 10 pg/ml. This assessment allowed a clustering of subjects into four groups. In two univariate logistic regression models we assessed IL-13 and IL-5 mean values to predict wether NERD was present in CRSwNP patients. We plotted the area under the receiver operating characteristic curve (AUC) of IL-13 values as this parameter was significantly associated with the outcome. From the AUC, we identified the threshold with maximizing specificity at an optimal sensitivity. We calculated sensitivity and specificity along with binomially exact 95% confidence intervals. Statistical analyses were performed using the Stata 16.2 software package (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP).

Results

Clinical characteristics

The analysis was based on 41 consenting participants. Fifteen controls (9 women, 6 men; mean age 34.4 years; SD 16.5; range 21-68); 13 affected by NERD (4 women, 9 men; mean age 47.4 years; SD 13.7; range 31-69) and 13 CRSwNP patients without NSAID intolerance (3 women, 10 men; mean age 54.2 years; SD 15.5; range 28-72). Patients affected by NERD suffered from a higher grade of polyposis (3.1 vs 2.1), suffered more often from asthma (100% vs 31%), and experienced more sinus surgeries (2.2 vs 1.1) compared to the non-NERD patients. Intensity of therapy with topical Glucocorticosteroid (GCS) was comparable, while one patient with NERD was on systemic Prednisone 5mg/d (Table 1).

Comparison of nasal cytokine pattern from healthy controls and patients with CRSwNP with and without NSAID intolerance

The cytokine pattern of nasal secretion was analyzed from

Tabel 1. Characteristics of 26 CRSwNP patients with NERD (13) and without NSAID intolerance (13).

parameter	NERD	no NSAID intolerance
women/men	4 / 9	3 / 10
mean age (years)	47.4 (SD 13.7; range 31-69)	54.2 (SD 15.5; range 28-72)
grade of polyposis (mean)	3.1	2.1
polyp operations (mean)	2.2	1.1
GCS topic	12	13
GCS systemic	1	0
asthma	13 (100%)	4 (31%)

CRSwNP: Chronic rhinosinusitis with nasal polyposis; NERD: NSAID exacerbated respiratory disease; NSAID: non steroidal anti-inflammatory drugs; GCS: Glucocorticosteroids; Dose of systemic GCS: 5mg Prednisone/d; Dose of systemic GCS: 5mg Prednison/d.

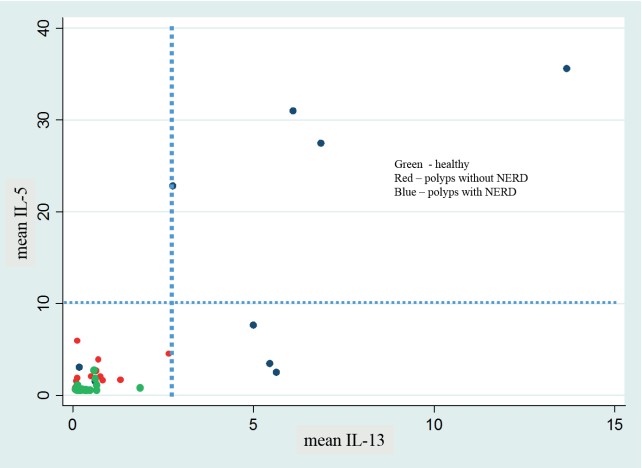

Figure 1. Distribution of subjects within 4 clusters of IL-13 and IL-5. Healthy subjects and all those with absence of NERD are grouped in the lower left quadrant. Most subjects with NERD had IL-13 values ≥ 2.7pg/ml.

fifteen healthy controls and twenty-six patients with CRSwNP of which thirteen were affected from NERD.

Compared to healthy participants, cytokines in nasal secretion of CRSwNP without NERD revealed a significant elevation of IL-6 and IL-5.

In addition NERD patients also showed significantly increased amounts of tryptase and IL-13 when compared to healthy controls.

The difference of the inflammatory endotype between CRSwNP with and without NSAID intolerance was the increased IL-5- and IL-13 values in NERD (Table 2). When setting the IL-13 cut-off value at ≥ 2.7pg/ml, presence of NERD was correctly detected in 10 out of 13 patients (sensitivity: 76.9% (95% CI: 46.2% to 95%)) and correctly detected in all 13 patients without NERD (specifity 100% (95% CI: 75.3% to 100%)). The corresponding AUC was 0.861 (CI: 0.702-1.000) indicating an excellent discrimination.

Figure 1 shows the distribution of subjects within four clusters of IL-13 and IL-5 values. While all healthy subjects and all those presenting with polyps in absence of NERD grouped in the lower left quadrant, subjects with polyps and NERD showed a heterogeneous pattern but predominantly (10/13) had IL-13 values ≥ 2.7pg/ml.

Discussion

In this study we investigated the inflammatory endotype of CRSwNP with and without NSAID intolerance according the cytokine pattern of nasal secretion. We are in need for adequate biomarkers of these patients in order to characterize the different inflammatory endotypes and to establish targeted treatments [17]. The epithelium in CRSwNP is leaky due to malfunctioning tight junctions [18]. Thus we suspect that nasal secretions can be an easily accessible parameter for endotyping this disease. Non-invasive mucus investigations have been done before and cytokine levels in sinus secretions seem to correlate with levels in sinus tissue [19]. There is evidence that the best collection technique for obtaining nasal secretions is passive absorption via capillary action [20, 21].

In line with the current literature we could demonstrate that compared to healthy controls, CRSwNP-patients showed significantly increased amounts of the cytokines IL-6 and IL-5. In peripheral circulation, IL-6 can be released by monocytes, eosinophils, T-cells and B-cells. In the tissue of the respiratory tract it can also be produced by epithelial cells, interstitial fibroblasts and macrophages [22, 23]. IL-5 is a key mediator in eosinophilic inflammation and is associated with increased intensity of nasal polyposis and asthma [4, 24, 25]. CRSwNP in Western white patients most often represent a Th2 dominated inflammation with increased IL-5 and IL-13. The higher the values of these Th2-cytokines, the more severe is the clinical course [5, 8, 26]. NERD patients in our study represent a more intense eosinophilic inflammation and suffer from more severe symptoms compared to subjects with CRSwNP without aspirin sensitivity. This corresponds with the current literature [27, 28]. Baseline values of IL-5 in our NERD patients were significantly higher than in non-NERD patients (Table 2). Tryptase in NERD patients was significantly elevated (Table 2), most probably induced by the impaired PGE2 production which serves as an inhibitor of 5-lipoxygenase, and therefore of mast cell activation. The loss of this inhibition may induce mast cell activation [29, 30]. Interestingly in our NERD population we were able to measure a significantly increased IL-13 compared to subjects with no NSAID induced CRSwNP and to healthy controls (Table 2). IL-13 transmits signals through a shared functional receptor complex (IL-4Rα/IL-13Rα1) and induces asthma

Table 2. Comparison of nasal cytokine pattern from healthy controls and patients with CRSwNP with and without NSAID intolerance.

Variable	#	Mean values pg/ml	SD	#	Mean values pg/ml	SD	p-value
Polyps without NERD vs. polyps with NERD							
Tryptase	11	11.05	17.42	10	20.81	26.56	0.327
IL-33	13	64.57	115.82	13	41.82	64.50	0.542
IFN-γ	13	1.07	1.57	13	1.45	3.38	0.712
IL-4	13	6.59	13.32	13	1.60	1.40	0.192
IL-5	13	1.52	1.52	13	28.17	39.32	**0.022**
IL-6	13	76.27	120.01	13	102.98	63.49	0.485
IL-8	13	396.27	180.75	13	576.54	261.64	0.052
IL-12p70	13	0.36	0.25	13	0.39	0.19	0.739
IL-13	13	0.57	0.74	13	15.02	21.45	**0.023**
IL-17a	13	1.23	0.94	13	1.10	0.89	0.722
IL-23	13	65.50	78.86	13	49.88	37.91	0.526
TNF-α	13	19.44	49.74	13	36.84	79.36	0.509
healthy vs. polyps without NERD							
Tryptase	15	2.98	6.22	11	11.05	17.42	0.109
IL-33	15	36.47	27.53	13	64.57	115.82	0.370
IFN-γ	15	0.64	1.28	13	1.07	1.57	0.428
IL-4	15	1.90	2.21	13	6.59	13.32	0.189
IL-5	15	0.31	0.57	13	1.52	1.52	**0.008**
IL-6	15	8.83	13.29	13	76.27	120.01	**0.040**
IL-8	15	415.46	287.07	13	396.27	180.75	0.837
IL-12p70	15	0.39	0.31	13	0.36	0.25	0.814
IL-13	15	0.40	0.42	13	0.57	0.74	0.460
IL-17a	15	8.07	28.01	13	1.23	0.94	0.388
IL-23	15	72.62	80.29	13	65.50	78.86	0.816
TNF-α	15	3.02	6.93	13	19.44	49.74	0.216
healthy vs. polyps with NERD							
Tryptase	15	2.98	6.22	10	20.81	26.56	**0.019**
IL-33	15	36.47	27.53	13	41.82	64.50	0.772
IFN-γ	15	0.64	1.28	13	1.45	3.38	0.391
IL-4	15	1.90	2.21	13	1.60	1.40	0.686
IL-5	15	0.31	0.57	13	28.17	39.32	**0.011**
IL-6	15	8.83	13.29	13	102.98	63.49	**<0.001**
IL-8	15	415.46	287.07	13	576.54	261.64	0.135
IL-12p70	15	0.39	0.31	13	0.39	0.19	0.969
IL-13	15	0.40	0.42	13	15.02	21.45	**0.014**
IL-17a	15	8.07	28.01	13	1.10	0.89	0.379
IL-23	15	72.62	80.29	13	49.88	37.91	0.359
TNF-α	15	3.02	6.93	13	36.84	79.36	0.111

symptoms by mucus production, smooth muscle alterations and sub-epithelial fibrosis on the airway mucosa independently from IL-4 function [31-33].

Compared to other studies, in NERD patients this characteristic Th2 response with increased IL-5 and IL-13 was only partially detected [4, 5, 8, 27, 34, 35]. We suspect that this heterogeneity of inflammatory endotypes in NERD patients is attributable to the variety of clinical manifestations [36] and differences between assays and

variability in approaches for mucus collection and processing. In CRSwNP refractory to topical GCS, biologicals against IL-5 (mepolizumab) and to the IL-4Rα subunit which inhibits signaling of IL-4 and IL-13 (dupilumab), have expanded the therapeutic possibilities [37-42]. Interestingly dupilumab particularly improved CRSwNP and asthma in the difficult-to-treat subgroup of patient with NERD [43]. These findings let us assume, that dependent on their concentration, IL-5 and IL-13 are main drivers of NERD and are therefore a potential therapeutic target. In our study at a cut off value of 2.7pg/ml, IL-13 allowed differentiating between CRSwNP with vs. without NERD accurately. While this cut-off value requires confirmation in future studies, the study showed that the IL-13 parameter discriminates well between the two groups of CRSwNP.

Although the selected cohort is small, we consider the significant results as valid. A downside of the study is that no provocation tests with NSAID has been performed in diagnosing NERD. However according a recent position paper NERD can be considered in patients with a clear history of suffering from asthma and chronic rhinosinusitis whose symptoms exacerbate after ingestion of aspirin and other COX-1 inhibitors [44].

Conclusion

In our study, we demonstrated that IL-13 is a specific biomarker for patients with NERD, which allows us to differentiate between CRSwNP with vs. without NERD. We therefore suggest that non-invasive cytokine measurement of nasal secretion is a valuable diagnostic assay for endotyping CRSwNP. The characterization of inflammatory endotypes in CRSwNP enables the introduction of the best available therapy in the context of precision medicine [45, 46].

List of abbreviations:

CRS: Chronic rhinosinusitis, CRSsNP: chronic rhinosinusitis without nasal polyps; CRSwNP: Chronic rhinosinusitis with nasal polyposis; CXCL: C-X-C Motif Chemokine Ligand, ECP: eosinophilic cationic protein; GCS: Glucocorticosteroids; IL: interleukin; ILCs: innate lymphoid cells; NSAID: non-steroidal anti-inflammatory drugs NERD: NSAID exacerbated respiratory disease; Th: T helper.

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Authorship contribution

MS, SB, IS, JS, SB, US, KI performed data acquisition and analysis; SB, MS, US analyzed clinical data; AV, LMB, US analyzed cytokine measurements; LMB performed statistical analysis; US and MS designed the research and were the principal writers of the manuscript. All authors reviewed the manuscript and contributed in writing.

Conflict of interest

No competing interests.

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