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Clinical characteristics of acute rhinosinusitis in COVID-19 – a *post-hoc* analysis of a longitudinal study

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ABSTRACT:

Introduction: Acute rhinosinusitis (ARS) is a common and well-defined disorder, primarily of viral aetiology, with rhinovirus and coronavirus accounting for more than 50% of viral ARS. The fight with COVID-19 pandemic resulted in an increased availability of viral testing, which in turn allowed testing for the presence of SARS-CoV-2 in all patients presenting common cold (or ARS) symptoms. The aim of this study was to assess the clinical characteristics of acute rhinosinusitis in patients diagnosed with COVID-19.

Materials and methods: This study is a *post-hoc* analysis. Patients' symptoms were evaluated using a structured questionnaire twice: directly after a positive SARS-CoV-2 result and 7–12 days following the first evaluation. Subjects were asked about the presence of nasal and systemic symptoms as well as headaches.

Results: A total of 130 COVID-19 symptomatic patients were recruited into the study, 58 (45%) patients met EPOS2020 diagnostic criteria for ARS. Of all ARS patients, 72% presented with rhinorrhoea, 69% with pain perceived over paranasal sinuses, 62% with nasal congestion, 52% with cough, 45% with olfactory dysfunction, 38% with fever, 33% with facial pressure, and in 22% pain was exacerbated by sinus palpation.

Conclusions: Half of COVID-19 subjects had ARS. The course of SARS-CoV-2 ARS does not seem to differ significantly from ARS of other aetiologies. Since ARS in the course of COVID-19 seems to meet the definition of ARS proposed by EPOS 2020, we hypothesize that substances validated for ARS treatment, such as intranasal corticosteroids could be effective in SARS-CoV-2 ARS.

KEYWORDS: SARS-CoV-2, sinusitis, upper respiratory tract infection

ABBREVIATIONS:

ABRS – acute bacterial rhinosinusitis
ARS – acute rhinosinusitis
HMPV – metapneumovirus
INCS – intranasal corticosteroids
NSAIDs – non-steroidal anti-inflammatory drugs
RSV – respiratory syncytial virus

INTRODUCTION

Acute rhinosinusitis (ARS) is a common, self-limiting disorder, primarily of viral aetiology (viral rhinosinusitis, or the common cold) [1]. ARS can be induced by a variety of respiratory viruses, such as rhinovirus, respiratory syncytial virus (RSV), influenza virus, coronavirus, parainfluenza virus, adenovirus, and enterovirus [2, 3]. Among these, rhinovirus and coronavirus are the most commonly isolated from adult ARS, accounting for approximately 50% of viral ARS diagnoses [4]. Common cold symptoms are the following (in order of prevalence): nasal discharge, nasal obstruction, cough, headache, and fever [1]. Acute rhinosinusitis in adults is defined as a sudden onset of 2 or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), ± facial pain/pressure, ± reduction or loss of smell for <12 weeks. Acute rhinosinusitis in children is defined as sudden onset of 2 or more of the following symptoms: nasal blockage/obstruction/congestion or discoloured nasal discharge or cough (daytime and night-time). ARS is then divided into the following groups: acute viral rhinosinusitis (or common cold), acute post-viral rhinosinusitis, and acute bacterial rhinosinusitis (ABRS) [1].

The above-mentioned symptoms can also be found in patients infected with SARS-CoV-2. Notably, olfactory dysfunction was highlighted as one of the characteristics of the disease [5–7]. Also, nasal congestion and discharge, cough, and facial pain were identified in SARS-CoV-2 infection [8–10], which is why it is possible to diagnose some COVID-19 patients with ARS. To date several articles on separate sinonasal symptoms and specific rhinologic conditions in COVID-19 have been published [11–15]. However, to the best of our knowledge, no research aiming to identify the

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prevalence of clinically diagnosed ARS in COVID-19 has yet been published. Meanwhile, classifying some SARS-CoV-2 infections as acute rhinosinusitis allows for drawing analogies to non-COVID-19 studies. This, in turn, may help in defining future research assessing prognosis and therapeutic interventions. To estimate how often ARS occurs in symptomatic SARS-CoV-2 infections and what are its features, we planned a *post-hoc* analysis of data obtained during a longitudinal study recently published by our group [16].

MATERIALS AND METHODS

Patients

Data from a bi-center longitudinal study were included in a *post-hoc* analysis. Patients with symptomatic, confirmed SARS-CoV-2 infection were included in the study. Subjects were recruited from primary care or hospital emergency and outpatient departments. Patients were evaluated twice during the disease course (after a positive SARS-CoV-2 test result and 7–12 days following the first evaluation), using a structured questionnaire. Subjects were evaluated for the presence of nasal symptoms (hyposmia/anosmia, nasal discharge, facial pressure), headache, and systemic symptoms (fever, cough, myalgia). Exclusion criteria included chronic sinonasal and neurologic disorders. A detailed description of the study material and methods and its results have been already published and are available in an open-access domain, along with the full study protocol [16]. Criteria proposed by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) (Tab. I.) were used for diagnosis of acute rhinosinusitis [1].

Statistical analysis

The calculations were carried out using the statistical environment R and SPSS software. Qualitative variables were analysed using chi-square tests. In the case of the fourfold contingency tables, continuity correction was used. However, when the conditions for the chi-square test were not met, the Fisher exact test was used with expansion for tables larger than 2x2. Quantitative variables were analysed using parametric tests (student's T-test or ANOVA) or their non-parametric equivalents (Mann-Whitney U test or Kruskal-Wallis test). The selection of tests was made on the basis of variable distribution verified with the Shapiro-Wilk test. In all calculations, the statistical significance level of relationship between variables was assumed to be $P < 0.05$.

RESULTS

A total of 130 COVID-19 symptomatic patients (80 women, 50 men, aged 7–74 years, mean 41.6) were recruited into the study. 59% of subjects were recruited by a primary care physician and 41% were recruited from an outpatient hospital-based practice. 58 (45%) patients meeting EPOS 2020 acute rhinosinusitis criteria (Tab. I.) were assigned to the ARS group. None of the patients developed symptoms indicating acute bacterial rhinosinusitis (ABRS). Group characteristics and reported symptoms collected during consultations are presented in Tab. II. Nasal discharge, nasal congestion, olfactory dysfunction, facial pressure, pain perceived over paranasal sinuses, and cough were associated with ARS. Of all acute rhinosinusitis patients, 42 (72%) presented with rhinorrhoea, 36 (62%) with nasal congestion, 34 (59%) with pain perceived over paranasal sinuses, 19 (33%) with facial pressure, 13 (22%) with pain exacerbated by sinus palpation, 30 (52%) with cough and 22 (38%) with fever. Pain exacerbated by pressure applied over the paranasal sinuses was not found to be associated with ARS. Acute viral rhinosinusitis criteria were met by significantly fewer patients in non-primary care settings ($P = 0.027$). 6 patients with ARS (10%) had symptoms allowing for diagnosis of post-viral ARS at the second consultation while 16 (28%) had smell impairment.

Tab. I. Definition of acute rhinosinusitis (ARS) according to European Position Paper on Rhinosinusitis and Nasal Polyps 2020.

ARS IN ADULTS	ARS IN CHILDREN
sudden onset of 2 or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): · ± facial pain/pressure, · ± reduction or loss of smell for <12 weeks.	sudden onset of two or more of the symptoms: · nasal blockage/obstruction/congestion · or discoloured nasal discharge · or cough (daytime and night-time for < 12 weeks.

Patients presenting with nasal discharge were 16.3 times more likely to meet ARS criteria, and those presenting with nasal congestion were 37.6 times more likely to meet ARS criteria (Tab. III.).

DISCUSSION

To the best of our knowledge, this is the first study assessing the prevalence of acute viral rhinosinusitis in COVID-19. In our study, ARS was present in 58 (44.6%) patients with SARS-CoV-2 infection. A meta-analysis of 148 studies conducted on adult patients found that fever was the most common symptom of COVID-19 and affected 78% of patients. Other frequently reported symptoms included cough (57%), hyposmia (25%), and fatigue (31%). In our study, we obtained similar findings regarding the above symptoms. Fever occurred in 42% of the participants, olfactory disturbances affected 33%, and cough 38%. However, in the meta-analysis, authors observed a rare occurrence of nasal discharge (8%) and nasal congestion (5%), which were frequently reported by patients in our study, with a prevalence of 40% and 30% respectively [17]. Another study, a systematic review, assessed the prevalence of COVID-19 symptoms in children and adolescents under 20 years of age. As in adult patients, the most common symptoms were fever (46%–64%) and cough (32%–56%), while other symptoms such as sore throat, nasal discharge or headache occurred less frequently than in 10–20% of patients [18]. This discrepancy could be explained by the fact that not all of the studies included in the cited reviews gathered data prospectively or using a structured questionnaire. Consequently, these studies were burdened with bias resulting from selective symptom reporting.

Upper respiratory tract infections are often caused by a variety of viruses, including adenoviruses, rhinoviruses, influenza and

Tab. II. Demographic and clinical characteristics of ARS and non-ARS patients.

	ALL PATIENTS N=130	ARS PATIENTS N = 58	NON-ARS PATIENTS N = 72	P-VALUE
Demographic characteristic				
Age (median)	39	39.50	39.00	0.89
Sex (female). n (%)	80 (62)	33 (57)	47 (65)	0.43
Clinical characteristic				
nasal discharge. n (%)	52 (40)	42 (72)	10 (14)	0.001**
nasal congestion. n (%)	39 (30)	36 (62)	3 (4)	0.001**
olfactory dysfunction. n (%)	43 (33)	26 (45)	17 (24)	0.018**
pain perceived over paranasal sinuses. n (%)	55 (42)	34 (59)	21 (29)	0.001**
facial pressure. n (%)	29 (22)	19 (33)	10 (14)	0.018**
facial pressure/pain. n (%)	67 (52)	41 (71)	26 (36)	0.001**
pain exacerbated by pressure applied over the paranasal sinuses. n (%)	25 (19)	13 (22)	12 (17)	0.55
cough. n (%)	50 (38)	30 (52)	20 (28)	0.009**
fever. n (%)	55 (42)	22 (38)	33 (46)	0.47
Patients recruited from primary care	77 (59)	41 (71)	36 (50)	0.027**

parainfluenza viruses, and coronaviruses. The clinical presentation of illnesses caused by mentioned pathogens is similar (Tab. IV.). In a study by Liu et al. evaluating symptoms caused by parainfluenza virus in both adult and children patients, the most prevalent symptoms were cough (80%) and fever (70%), while nasal obstruction, nasal discharge, pharyngeal discomfort, and headache appeared in approximately 1/3 of patients (32%, 37%, 33%, and 25%, respectively) [19]. In a study evaluating the clinical manifestations of influenza virus, patients reported more complaints. Almost every patient presented with a cough (97%) and fever (89%). Other symptoms reported on were sore throat (80%), rhinorrhoea (76%), headache (69%), and nasal congestion (66%) [20]. In contrast, infections caused by rhinovirus are much less likely to cause fever. In a study conducted by Zlateva et al. on adult patients, only 13% had a fever, while other symptoms had similar prevalence as in previously mentioned studies (cough – 99%, nasal discharge– 54%, headache – 35%) [21]. In another study evaluating rhinovirus infections, fever occurred in 15% of patients, while nasal congestion and cough in 40%, and rhinorrhoea in 60% [22]. Another etiologic agent of upper respiratory tract infections is the RSV. RSV particularly affects young children and infants under 2 years of age and causes bronchiolitis. In a study evaluating RSV infection in children under 14 years, the most prevalent symptoms were cough (98%) and fever (71%). Rhinorrhoea occurred in 43% of children, while nasal obstruction in 36% [23]. However, RSV infection may also appear in adults, especially older and immunocompromised. In frail elderly persons, RSV mostly presents with cough (90%–97%), nasal discharge and nasal congestion (67%–92%), sore throat (20%–33%), and fever (20%–56%) [24]. Another study assessed the clinical presentation of infection caused by RSV or metapneumovirus (HMPV) in adult patients. In both groups, the most prevalent was cough – 91% in RSV and 97% in the HMPV group.

Tab. III. Odds ratio (OR) and relative risk (RR) of ARS diagnosis for different symptoms.

	OR 95% CI	RR 95% CI
rhinorrhea	16.3 [6.74. 39.3]	3.12 [2.04. 4.78]
nasal congestion	37.6 [10.6. 134]	2.53 [1.81. 3.52]
olfactory dysfunction	2.63 [1.24. 5.57]	1.38 [1.06. 1.80]
pain perceived over paranasal sinuses	3.93 [1.87. 8.28]	2.12 [1.4. 3.21]
facial pressure	3.02 [1.27. 7.17]	1.28 [1.05. 1.57]
facial pressure	4.27 [2.03. 8.96]	1.96 [1.38. 2.78]

Nasal congestion or discharge were also frequent, with an incidence of 78% in RSV and 73% in HMPV. Fever was reported in 70% in the HMPV group and 59% in the RSV group, while headache – in 66% in RSV and 58% in HMPV [25]. Coronaviruses mostly cause upper respiratory tract infections. In a study evaluating coronavirus infections in children younger than 14 years, the most common symptoms were cough (83%), fever (55.4%), and rhinorrhoea (34%). Sore throat and headache were rarely reported and occurred in 6.6% and 0.8%, respectively [26].

Our study shows a comparable prevalence of symptoms from the upper respiratory tract in COVID-19 as in infections caused by other viruses. However, the aforementioned studies very rarely included pain perceived over paranasal sinuses and facial pressure,

Tab. IV. Clinical presentation of acute upper respiratory tract infections according to different viral aetiologies.

AETIOLOGY	STUDY	COUGH %	FEVER %	NASAL OBSTRUCTION %	NASAL DISCHARGE %	PHARYNGEAL DISCOMFORT OR SORE THROAT %	HEADACHE %
Parainfluenza virus	Liu 2013 (19)	80	70	32	37	33	25
Influenza virus	Yang 2015 (20)	97	89	66	–	80	69
Rhinovirus	Zlateva 2020 (21)	99	13	–	54	–	35
	Gwaltney 1967 (22)	40	15	40	60	–	–
Respiratory syncytial virus (RSV)	Liu 2016 (23)	98	71	36	43	–	–
	Falsey 2000 (24)	90–97	20–56	67–92	67–92	20–33	–
	Widmer 2014 (25)	91	59	78		–	66
Metapneumovirus (HMPV)	Widmer 2014 (25)	97	70	73		–	58
Coronavirus	Zeng 2018 (26)	83	55,4	–	34	6.6	0.8
SARS-CoV-2	**our study**	**38**	**42**	**30**	**40**	**–**	**72**

which were reported quite frequently by our patients (pain perceived over paranasal sinuses – 42%, facial pressure – 22%). Moreover, olfactory dysfunction has not been assessed in the above-cited studies. In our group, 33% of patients reported impairment of olfactory functions. Additionally, in our study, only 38% of patients complained of cough. These results are in the lower range of this symptom frequency in the COVID-19 cohorts [17, 18].

As shown above, COVID-19-related ARS may have a similar clinical presentation to viral ARS caused by other pathogens. This in turn would suggest an analogous prognosis (i.e. occurrence of post-viral ARS, ABRS, persistent olfactory dysfunction). Based on current literature, it is difficult to assess how often viral ARS transforms into a post-viral or bacterial form. Firstly, the distinction between different forms of ARS as proposed by EPOS 2020 is not yet widely used in literature. Secondly, the only available prospective population study evaluating EPOS-defined post--viral ARS (and ABRS) is a study by Hoffmans et al. evaluating the presence of ARS (post-viral or bacterial) using a GA2LEN screening questionnaire sent to a random sample of the Dutch population. The prevalence of ARS was estimated at 18% (post-viral and ABRS) [27]. In our study, post-viral ARS was confirmed in 10% of subjects. Available population-based studies do not allow to compare these results with other cohorts. However, a large analysis of ENT consultations has shown that even 63% of viral ARS cases may develop into post-viral sinusitis [28].

The incidence of ABRS is estimated at 0.5–2% of all viral infections [29]. It is assumed that acute bacterial rhinosinusitis is a complication of (post)viral ARS [30]. Various factors predisposing to acute bacterial rhinosinusitis have been described [30]; some of these factors constituted exclusion criteria in our study: allergic and non-allergic rhinitis, cystic fibrosis, primary ciliary dyskinesia, history of nasal surgery or trauma in the last 12 months. Other factors such as deviated nasal septum, nasal polyps, hypertrophic middle turbinate and tumour did not constitute exclusion criteria per se but patients with such disorders might have been excluded as they presented recurrent or chronic problems with breathing through the nose. This, in conjunction with the small size of our group, could explain why none of the patients developed ABRS.

Smell impairment has been described as a complication of infection with e.g. rhinovirus, parainfluenza [31]. In our study, anosmia or hyposmia was noted by 28% of subjects evaluated at the second consultation. This may indicate that persistent olfactory impairment in COVID-19 is not directly associated with ARS. Future studies should assess whether in ARS caused by other viruses the results are comparable.

45% of patients in our study met the diagnostic criteria for acute viral rhinosinusitis. This in turn could have important implications for clinical decisions in COVID-19 patients. Essentially, ARS is hardly a new disorder and many substances have been confirmed to be effective in its treatment. For example, EPOS 2020 criteria recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, decongestants, antihistamines, intranasal corticosteroids (INCS), herbal medicines, zinc, vitamin C, or saline irrigations [1]. Some of these medications already found their way into COVID-19 treatment guidelines (i.e., NSAIDs, paracetamol) [32]. On the other hand, zinc and ascorbic acid did not reduce symptoms' duration in one study [33], although ARS symptoms were not an endpoint in that trial. Of the above-listed treatment modalities, probably the most promising seem to be INCS. Inhaled budesonide is an effective and recommended COVID-19 treatment in outpatient settings, while dexamethasone has been shown to improve outcomes in hospitalized subjects [32]. Consequently, it seems probable that INCS should improve symptoms of COVID-19-related ARS. In fact, one retrospective study found an association between the use of INCS and reduced COVID-19-related morbidity and mortality [34] although a randomized controlled trial did not show improvement of lower respiratory tract symptoms [35]. Nevertheless, these results indicate a need to assess the efficacy of INCS in COVID-19-related ARS.

In this study, ARS was more prevalent in general practice than in hospital-based care (emergency and outpatient department). This observation may indicate some selection bias that has not been identified by comparison of other confounders (other cohort characteristics did not differ). We hypothesize that patients presenting with SARS-CoV-2 acute rhinosinusitis were more likely to seek help from a primary care physician, although the reason for that remains unclear.

Limitations

There are several limitations to this study. Firstly, this was a clinic-based study, and consequently some groups of patients were not included (e.g., nursing home residents and hospice patients as well as subjects with a very severe disease admitted directly to intensive care units and diagnosed then). Secondly, patients were followed up for up to 13 days after SARS-CoV-2 infection diagnosis, and as progression to severe COVID-19 occurs usually in the second and third week of the disease, some patients that might have required admission to hospital were not reported. As a result, the group of severe COVID-19 cases was too small to allow for an analysis of associations between ARS and hospitalization rate, hypoxemia, or mortality. Thirdly, when it comes to discussing selection bias, we must stress that only patients seeking medical help from participating investigators were included in this study as patients who refrained from medical consultation could not have been evaluated. We hypothesize that this group included asymptomatic or mild cases as well as individuals sceptical to the COVID-19 pandemic and avoiding compulsory isolation. Furthermore, in Poland, people living in the same household as a person diagnosed with a positive SARS-CoV-2 test are obliged to quarantine, which could contribute to the reluctance to testing of individuals presenting mild COVID-19 symptoms. Another limitation of the study is the lack of rhinological assessment, endoscopy, and imaging, though it is important to note, that the EPOS steering group advises on diagnosing ARS on clinical criteria and does not recommend supplementary investigations [1].

CONCLUSION

SARS-CoV-2 causes upper respiratory tract infection and acute rhinosinusitis can be one of its clinical presentations. The course of ARS in COVID-19 shows many similarities to ARS of other aetiologies. This may indicate similarities with regard to prognosis and management. Consequently, we hypothesize that therapeutic methods recommended for ARS treatment could be effective also in ARS related to SARS-CoV-2 infection. However, this proposal should be evaluated by future studies.

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