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Evolution of sinonasal clinical features in children with cystic fibrosis

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INTRODUCTION

The sinonasal mucosa is a respiratory mucosa similar to that of the lower respiratory tract and is therefore subject to similar manifestations in cystic fibrosis (CF). Decreased mucosal secretions, thickening of mucus and impaired mucociliary clearance are responsible for local inflammation and increased risk of bacterial infection.

Chronic rhinosinusitis (CRS) with or without nasal polyps (NP) usually appears during childhood and progressively worsens throughout the disease. Sinonasal symptoms are poorly reported by these children, ranging from 10% to 62% in different studies.^{1,2} This variability may be related to the congenital nature of the disease, making comparison difficult with a rarely healthy baseline.³ Moreover, there is a discrepancy between the observation of clinical or radiological CRS, and a frequent low impact in the various quality of life scales. The Sino-Nasal Outcome Test-16 (SNOT-16) is the most used test in studies. It combines 16 items and allows an overall assessment of the sinonasal and pulmonary quality of life. It is significantly correlated with the severity of lung function.⁴ However, SNOT-16 does not evaluate nasal obstruction, which is one of the most troublesome symptoms in children. More recently, SinoNasal-5 score (SN-5) allows an easier assessment with 5 item groups (sinus infection, nasal obstruction, allergic symptoms, emotional distress, activity limitation).² Thus, in pediatric population, the evaluation of the different sinonasal symptoms separately remains difficult and poorly practiced.⁵

In CF, physical examination frequently observes mucosal inflammation, nasal polyps and medial bulging of the medial wall of the maxillary sinus corresponding to maxillary sinus mucocele-like.⁶ In the literature, CRS in CF affects 74 to 100% of patients, and 10 to 48% of patients have polyps.⁷⁻⁹ To our knowledge, there is no recent study describing sinonasal pathology in CF only in children, especially since the improvement of prognosis of CF in last decades, with better understanding of genetics and pathophysiology, the appearance of new molecules, and management by Cystic Fibrosis Care Centers.^{10,11}

The objective of this study is to describe the evolution of sinonasal symptomatology and physical manifestations in children with cystic fibrosis.

METHODS

This is an observational, descriptive, monocentric study with a retrospective cohort.

SOURCE AND STUDIED POPULATION

The source population concerned all children aged between 4 to 18 years, followed in 2015 in the Pediatric Cystic Fibrosis Care Center of Lyon, France.

The retrospective data were collected by paper medical records analysis from 1997 to 2008 and by electronic medical records from 2008 to 2015.

Access to stored computer data has been approved by an entry in the register of the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés) under number 16-034, and the methods have been approved by the Research ethics committee and by the Committee for Personal Protection (Comité de Protection des Personnes Sud-Est III, Lyon) under number QH 24/2016.

Parents were informed about this study which required access to their child's medical records.

The inclusion criteria were as follows:

- Children aged between 4 to 18 years with a genetic diagnosis of CF
- Followed for their illness only at the Pediatric Cystic Fibrosis Care Center of Lyon, France
- Having had at least two Ear, Nose and Throat (ENT) examinations.

ASSESSMENT OF CYSTIC FIBROSIS

We collected in the Cystic Fibrosis Center database:

- Severity of CFTR genotype: patients were classified either in the "severe genotype" group if both mutations were severe; either in the "mild genotype" group if at least one of the two mutations was mild. (12–16)
- The modality of diagnosis of CF: by routine screening at birth or suggestive symptoms.
- The status of primocolonization or chronic pulmonary infection with *Pseudomonas aeruginosa*.
- Hypersensitivity to airborne allergens.
- The status of pancreatic insufficiency.
- Pulmonary function with the measure of Forced Expiratory Volume in One Second (FEV1 in percent predicted versus age) during spirometry.
- Nutritional status with BMI.

MOMENTS OF ASSESSMENT

The records of all ENT consultations performed for each patient were analyzed. Patients have systematically had an ENT examination at about 4, 7 and 12 years old. The other ENT exams were performed at the request of the patient or the pulmonologist based on functional complaints. Each

examination consisted in questioning the child and the parents, pharyngeal, otoscopic examination and a nasal endoscopy.

We chose to describe the evolution of sinonasal symptoms and the results of physical examinations at three moments:

- T-0: corresponding to the first ENT exam with sinonasal disorder. For patients who have never developed sinonasal disease (who remained asymptomatic and whose physical examination remained normal), the T-0 date corresponded to the first ENT consultation.
- T-max: corresponding to the ENT consultation during which the symptoms were the most severe. For patients who underwent sinus surgery, it was the last pre-operative consultation.
- T-end: corresponding to the last ENT appointment available in the medical records, to estimate the overall effectiveness of medical and surgical management.

ASSESSMENT CRITERIA

We collected the sinonasal symptomatology (nasal obstruction, rhinorrhea, headache or facial pain, hyposmia). These symptoms were evaluated according to the severity of functional impairment: 0 = no symptom, 1 = mild, 2 = moderate, 3 = severe. Indeed, using quality of life scales (for example SNOT-16 or SN-5) is not easy in practice, especially in a pediatric population. In addition, the "MMS classification" (mild, moderate, severe) is statistically validated, and is correlated with visual analogue scale (from 0 to 10) and the impact of sinonasal disorders on quality of life. (20,21)

We also collected the symptoms of snoring and sleep disorders (yes or no).

The sinonasal overall functional impairment (SOFI) was evaluated, taking into account the overall appearance of the discomfort: 0 = no discomfort, 1 = mild, 2 = moderate, 3 = severe.

Then, we collected the ENT physical examination data:

- Nasal polyp (NP) size, with the Lildholdt scale, validated by Johansson (22): 0 = no polyp; 1 = small polyps not reaching the lower edge of the middle turbinate; 2 = polyps extending between the upper and lower edges of the inferior turbinate; 3 = large polyps extending below the lower edge of the inferior turbinate.
- The presence of obstructive lesions: inferior turbinate hypertrophy, bulging of medial wall of the maxillary sinus, septum deviation, adenoid and tonsil hypertrophy. The degree of obstruction was clinically evaluated by the clinician and rated from 0 to 2: 0 = absence; 1 = partially obstructive; 2 = totally obstructive.
- Pus in front of the middle meatus
- Externalized mucocele defined as a periorbital edema or a swelling visible in nasal endoscopy
- Otitis media with effusion

For patients who have never had sinonasal disorder throughout their follow-up, all the items previously described were assessed "0".

STATISTICAL ANALYSIS

The prevalence of all items of data collection was calculated at T-0, T-max and T-end. Comparison between the prevalence of each clinical feature at the three moments was done. We therefore used validated tests to compare paired groups. A Wilcoxon test was used for comparison of symptom severity scores and nasal polyps score (non-normal distribution was verified by Shapiro-Wilk test). For comparison of FEV1, we used the Wilcoxon signed-rank test. For paired binary data (absence or presence), comparisons were made using a Mc Nemar's test. Statistical significance was determined with a p-value less than 0.05.

RESULTS

DESCRIPTION OF STUDY POPULATION

Among the 208 patients followed in the Pediatric Cystic Fibrosis Care Center of Lyon, France, aged from 4 to 18, 173 have had at least two ENT consultations and were included for descriptive analysis. 76.9% of children (n = 133) had chronic sinonasal disorders during their follow-up.

Table 1 evaluates the representativeness of the sample with the source population, comparing criteria related to CF: sex, age at diagnosis, CF diagnostic modality, CFTR genotype, airborne allergy, pancreatic insufficiency and number of lung transplants.

For all these criteria, the study population was statistically comparable to the source population.

Table 2 shows the evolution of pulmonary function, nutritional status and *Pseudomonas aeruginosa* pulmonary infection between T-0, T-max and T-end.

The respiratory function represented by FEV1 decreased progressively and significantly, with an average of 103.0 at T-0; 101.3 at T-max and 93.1 at T-end.

In the opposite way, the occurrence of *Pseudomonas aeruginosa* pulmonary primocolonization increased significantly between each assessment time.

The number of children with chronic *Pseudomonas aeruginosa* lung infection increased slightly between T-0 (12.7%) and T-max (15.6%), and significantly at T-end (22.5%).

The prevalence of children with a BMI <5th percentile increased significantly between T-max (5.2%) and T-end (9.8%) (p = 0.043), and between T-0 (4.0%) and T-end (p = 0.034).

AGES AND DELAY BETWEEN MOMENTS OF EVALUATION

At T-0, the average age of children was 5.4 years old (0.9-16.4). For children who became symptomatic (n = 133), the mean age at the onset of symptoms was similar.

The maximum of their sinonasal disease was reached at an average age of 6.9 years old (0.9-18).

For all children studied, the last ENT appointment found in the medical file (T-end) was on average at the age of 11.3 years (4.5-18).

The total follow-up duration after the first ENT appointment was on average 6.6 years (0.2-13.3).

EVOLUTION OF SINONASAL SYMPTOMATOLOGY

Table 3 indicates the prevalence of the different sinonasal symptoms collected at T-0, T-max and T-end. We can estimate the evolution of each symptom by comparing the severity of these items between each 3 moments.

During the follow-up, the sinonasal overall functional impairment (SOFI), showed a significant worsening from T-0 to T-max ($p=0.0007$) with an increase of the rate of severe forms from 4.6 % to 10.4%. Then, there was a significant improvement of the SOFI from T-max to T-end ($p<0.0001$). In the same way, there was a decrease of severe forms rate (from 10.4% to 2.9%, $p <0.0001$), while the rate of asymptomatic forms increased (from 32.4% to 64.7%, $p<0.0001$). Finally, the SOFI also improved significantly between T-0 and the end of follow up ($p <0.0001$).

The feeling of nasal obstruction evolved in the same direction with a significant worsening between T-0 and T-max ($p = 0.0009$) and then a significant improvement at T-end ($p<0.0001$), reaching better score than at the beginning ($p<0.0001$). At T-end, the prevalence of severe nasal obstruction decreased to 2.9% while the prevalence of children without nasal obstruction increased to 64.2%.

Rhinorrhea stayed fixed between T-0 and T-max ($p = 0.066$), and then improved at T-end ($p <0.0001$). Despite 52 missing data and a low prevalence, headache significantly improved at T-end ($p = 0.01$). Hyposmia was rare too, with 101 missing data and no peculiar evolution.

24.3% of children presented snoring at T-0, 25.4% at T-max and 6.4% at T-end. The improvement at the end of follow-up was significant ($p <0.0001$).

The prevalence of children complaining of sleep disorders was low (1.2% at T-0, 4.0% at T-max, 1.2% at T-end), but the Mc Nemar test found a significant improvement at the end of follow-up ($p = 0.007$).

EVOLUTION OF PHYSICAL EXAMINATION FEATURES

Table 4 shows the prevalence of each ENT physical observation at T-0, T-max and T-end. 27.7% of children have already presented NP at the onset of sinonasal symptoms, reaching a prevalence of 38.7% at T-max, and 29.5% at the end of follow-up. Successive physical examinations showed a significant increase of the NP size (Lildholdt score) at T-max ($p <0.0001$), then a significant improvement at T-end ($p <0.0001$). The advanced forms of NP (Grade 2 or 3) represented 6.4% at T-0, 13.8% at T-max and 6.4% at T-end. There was no significant difference in Lildholdt score between T-0 and T-end.

Regarding inferior turbinate hypertrophy, statistics showed no significant changing between T-0 and T-max ($p = 0.19$). On the other hand, there is a significant decrease at T-end comparing to T-0 ($p < 0.0001$) and to T-max ($p < 0.0001$).

Pus in the middle meatus was significantly more observed at T-max than T-0 ($p = 0.005$), with improvement at T-end ($p = 0.002$).

There was no significant increase in the rate of bulging of the medial wall of the maxillary sinus and of externalized mucocele, conjointly with the worsening of symptomatology. Though, there was an improvement in their prevalence between T-max and T-end (respectively $p = 0.0002$, $p = 0.003$) and between T-0 and T-end (respectively $p = 0.009$, $p = 0.003$).

The prevalence and degree of obstruction by nasal septum deviations significantly increased with time, and the prevalence of obstruction related to adenoids or tonsils hypertrophy decreased significantly between each evaluation moment. Finally, there was a significant decrease in the prevalence of otitis media with effusion at T-end (2.0%) compared with at T-0 (13%, $p < 0.0001$) and at T-max (13%, $p < 0.0001$).

DISCUSSION

In our practice, ENT management of these frail children consisted in closer control of those who developed severe sinonasal symptoms or NP. The medical treatment was started at the onset of symptoms and, according to the severity of CRS, included regular saline nasal irrigation, long-term corticosteroids nasal sprays, sometimes nasal instillations of mucolytics (dornase alfa), and oral treatment of antibiotics and corticosteroids for acute bacterial superinfection. The most severe and medical treatment-resistant cases could benefit from sinus endoscopic surgery (polypectomy, turbinoplasty, sinus drainage).

In our series, the first sinonasal symptoms appeared early at 5.4 years old (only 8.3 months after the first appointment). We then observed a rapid worsening of chronic rhinosinusitis which reached its maximum at the average age of 6.9 years (17.3 months after the onset of symptoms). Thus, it seems necessary to monitor these children closely, as soon as the first sinonasal symptoms appear. With our ENT management, evaluation of sinonasal overall functional impairment showed a significant improvement at the end of ENT follow-up, reaching significantly better scores than at the beginning of management. This peculiar improvement seems to be independent to the worse evolution of pulmonary function, pulmonary chronic infection and undernutrition. This suggests that during childhood, chronic rhinosinusitis remains very sensitive to medical and / or surgical treatment.

Among the functional complaints, nasal obstruction was the predominant symptom. This symptom followed an evolution that was similar to the SOFI, with significantly better scores at the end

of follow-up than at the beginning. Other sinonasal symptoms such as rhinorrhea, headache, snoring and sleep disorders did not show significant worsening between the onset and the worse moment of sinonasal pathology, but we found a significant improvement at the end of follow-up. These improvements are multifactorial. This can be explained by the effectiveness of medical and / or surgical ENT management, but also by a positive effect of growth. Indeed, with age, the relative increase of nasal cavity size, the decrease of adenoids and tonsils size, and their ablation in 15 children, may result in a lower impact of the mucosal pathology on sinonasal discomfort. This can also explain the positive evolution of snoring and sleep disorders.

Rhinorrhea remains a difficult symptom to assess because it is poorly reported in children with cystic fibrosis. The viscosity of the mucus is often responsible for nasal congestion by thickening secretions. In this retrospective study, this symptom probably has been confused with rhinorrhea, although it is not exactly the same symptom.

Few children complained of hyposmia and headache which did not seem to be troublesome symptoms on this pediatric population. In pediatric studies, hyposmia is also a rare symptom, with a prevalence ranging from 12%⁶ to 71%³. This large variability and the gradual increase with age (while the SOFI improves) reflect the difficulty of assessing this symptom in the youngest children. Indeed, these symptoms are very subjective, and can hardly be amenable to parental rater-assessment for the youngest children, which makes it difficult to analyze such symptoms.

In the literature, symptoms evaluation studied one by one, on a pediatric population of cystic fibrosis is rare. In general, studies mostly use global scores such as SNOT-16⁴ or SN-5².

In the large retrospective study of Stern in 1982, with a mixed population of 605 adults and children, symptoms reported were nasal obstruction (62%), rhinorrhea (64%) and mouth breathing (38%).²³

In Brihaye study in 1994 of 84 patients aged 3 months to 34 years, nasal obstruction (60%), cough (60%), and rhinorrhea (52%) were the predominant symptoms, followed by sleep disorders (37%), headache (32%) and hyposmia (12%). This study also reports that nasal obstruction and rhinorrhea were mainly found in children, while headache was the predominant symptom in adolescents and adults.⁶

In a more recent study of 47 children, Chan DK. reports much less frequent complaints: 36% of nasal obstruction, 9% of facial pain, 4% of nasal discharge and 13% of hyposmia.²

In the Nguyen series of 91 children with CRS, but without cystic fibrosis, the same distribution of symptoms was found, with a predominance of nasal obstruction and rhinorrhea.²⁴ It is an additional argument to say that the prevalence of nasal obstruction in CRS is not specific to cystic fibrosis, but to the general pediatric population. Thus, because of the narrowness of nasal cavity in early childhood, the slightest mucosal edema can quickly affect nasal permeability.

In the diagnostic criteria for CRS in children, stated by Fokkens in the “European Position

Paper on Rhinosinusitis and Nasal Polyps 2012”, “cough” is an important symptom for diagnosis.²¹ This is also one of the most frequent symptoms in the Brihaye study, with 60% of complaints.⁶ However, because of the usually dominant pulmonary pathology in cystic fibrosis, the use of “cough” as an evocative symptom of CRS seems unspecific and unsuitable. In children with CF, specific scores for diagnosis and severity assessment of CRS should be created.

Other clinical signs have also been described: voice changes, activity intolerance³, halitosis²⁵, facial deformations with enlargement of nasal bridge⁶, hypertelorism and proptosis.²⁶ These observations were poorly reported in our series and do not seem to be suitable to these children.

With regards to the physical examination, two elements followed a similar evolution to the functional discomfort. Indeed, in these children, we observed mainly NP and lower turbinate hypertrophy.

In the general pediatric population, there is no epidemiological data on the overall incidence of CRS with or without NP, which remains an infrequent disease.²¹ The incidence of NP in CF varies across studies from 10% to 48%^{7-9,23,27}.

In our study, 38.7% have had NP during their follow-up. The rate of NP and of the advanced forms of NP increased until T-max together with the sinonasal symptomatology. At the end of follow-up, NP's rate returned to a state comparable to the initial state ($p = 0.67$); while symptomatology became better at the end. This highlights the relative discrepancy between symptoms and physical observation, and also the chronicity of mucosal inflammation despite medical treatment.

Regarding lower turbinate hypertrophy, more than half of children were concerned and ENT management was efficient by decreasing the rate to one third at the end of follow up. However, this evaluation is quite subjective and may vary depending on the examiner.

The bulging of medial wall of the maxillary sinus, also called "pseudo-mucocele", is linked to a ballooning of maxillary sinuses. This is a well-known anomaly specific to CF. Although this data was not indicated in 14% of files, it concerned in our study more than one quarter of children and improved at the end of management.

The improvement of these obstructive features is multifactorial. It could be the consequence of a good sensitivity to treatments, but also to the increase of the volume of nasal cavities with growth, making these alterations relatively less obstructive.

The aspect of local superinfection by observation of pus has significantly decreased over time, but this is a datum whose evolution could be very variable from one month to month, and there is no valid conclusion to make on that.

Mucoceles followed the same trend, but with a rarer prevalence. However, the description is limited by an amalgam of the term "mucocele", which depending on the practitioners, could sometimes correspond to a true externalized sinus mucocele, or to a "pseudo-turbinate".

We observed a significant increase in the prevalence of septum deviations between each evaluation moment. This anomaly seems to evolve by itself and did not follow the evolution of the CRS. This gradual increase in frequency with age is similar to that observed in general pediatric population.^{28,29} The observation of otitis media with effusion was similar to the general pediatric population and decreased with age.³⁰ Obstructive tonsils and adenoids did not seem to have interfered with the evolution of CRS, with a progressive regressing of obstruction regarding to airway size. In addition, the frequency of these abnormalities was comparable to the general pediatric population.^{31,32}

The strength of this study is the large number of children included, allowing a detailed descriptive study of evolution of sinonasal pathology. This is the largest retrospective cohort over the last 20 years. Moreover, ENT medical records were numerous. Some ENT appointments were performed systematically at 3, 7 and 12 years old, allowing a homogenization of evaluation at these ages. The other ENT evaluations were decided mainly by the pediatric pulmonologists when child sinus condition seemed worrying, but also by the ENTs when sinus monitoring was necessary. On medical records, practitioners systematically described the essential features of sinonasal pathology. Access to computerized data also allowed reliable data collection.

The limits of this study concern primarily the modality of data collection (retrospective cohort). We chose to carry out this study with 3 evaluation points, allowing to have only an approach of sinonasal evolution. Varying delays and rhythm of ENT appointments left up to the practitioners, postponed ENT appointments due to serious pulmonary condition, the lack of functional complaint declared by some children despite a patent CRS, were responsible for heterogeneous follow-up quality according to the children. In fact, younger children at the time of data collection have had a shorter ENT follow-up duration than children reaching the age of 18, and therefore had less time to develop sinonasal pathology. As often happens in retrospective studies, another weakness is the heterogeneity of sinus examination. Actually, had no evaluation protocol, which is responsible for the lack of data available for some items, particularly for very subjective symptoms (headache, hyposmia), and for description of bulging of medial wall of the maxillary sinus. In addition, other observations (such as rhinorrhea, nasal congestion, turbinate hypertrophy obstruction, obstructive adenoids), were left to examiner's subjectivity.

A longitudinal study with a prospective cohort, beginning since the diagnosis of CF up to the age of 18, with more regular and fixed evaluation points, and a reliable homogenized evaluation grid, is a difficult and time-consuming study. However, it would bring a better and more precise appreciation of occurrence of sinonasal features during childhood. In addition, an analysis of the correlation between clinical improvement, CT aspects and / or bacteriological changes could be an interesting complement

to our study. It may be interesting to analyze the risk factors that may lead to severe sinonasal evolution, in order to plan for closer monitoring of children with greater risk.

CONCLUSION

In children with cystic fibrosis, chronic rhinosinusitis begins very early at the age of 5.4 years old, and then rapidly reaches its maximum state at the age of 6.9 years old. It is mainly manifested in sinonasal mucosa inflammation with inferior turbinate hypertrophy, nasal polyps and bulging of medial wall of the maxillary sinus, which are responsible for nasal obstruction and congestion. Concomitant medical, surgical, ENT and pulmonological management seems effective to improve sinonasal condition, and even allows to reach progressively a better state than at early childhood. Multidisciplinary collaboration between ENT and pediatric pulmonologist is thus essential in the care of children with cystic fibrosis.

LIST OF ABBREVIATIONS:

T-0: the time at the onset of chronic rhinosinusitis

T-max: time at the maximum of sinonasal disease

T-end: time à the end of follow-up

CF: Cysticfibrosis

CRS: chronic rhinosinusitis

NP: nasal polyps

SOFI: Sinonasal Overall Functional Impairment

ENT exam: Ear Nose and Throat exam

CT: computer tomography

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Table 1. Representativeness of the source population and of the studied population

		Source population : n=208	Studied population : n=173	p value ^a
Gender	Female	91 (43.8%)	73 (42.2%)	0.76
	Male	117 (56.2%)	100 (57.8%)	
Diagnostic modality	Mean age of diagnosis (year)	1.3 (0-15.9)	1,3 (0-15.9)	0.88 (Mann Whitney) 0.72
	• Newborn screening	94 (45.2%)	75 (43.4%)	
	• On suggestive symptoms:	114 (54.8%)	98 (56.6%)	1
	- Meconium ileus or bowel obstruction	37 (32.5%)	32 (32.7%)	
	- Small for gestation age and congenital malabsorption	43 (32.7%)	36 (36.7%)	
	- Respiratory symptoms	47 (41.2%)	43 (43.9%)	
	- Family history of CF	8 (7.0%)	6 (6.1%)	
	- Other digestive symptoms	12 (10.5%)	9 (9.2%)	
- Congenital absence of the vas deferens	1 (0.5%)	1 (0.6%)		
CFTR genotype	Mild	45 (21.6%)	36 (20.8%)	0.37
	Severe	163 (78.4%)	163 (79.2%)	
Airborne allergy	Yes	23 (11.1%)	22 (12.7%)	0.62
	No	185 (88.9%)	151 (87.3%)	
Pancreatic insufficiency	Yes	186 (89.4%)	156 (90.2%)	0.80
	No	22 (10.6%)	17 (9.8%)	
Lung transplant	Occurence	4 (1.9%)	3 (1.7%)	1
	Mean age (year)	12.9 (8-18)	13.6 (8-18)	

^a **p-value with statistically significant differences highlighted in bold (p<0.05)**

Table 2. Evolution and comparison of respiratory and digestive function, and of *Pseudomonas aeruginosa* pulmonary infection

		At T-0	At T-max	Comparison T-0 VS T-max p-value ^a	At T-end	Comparison T-max VS T-end p-value ^a	Comparison T-0 VS T-end p-value ^a
FEV1 (% predicted versus age)	Mean Minimum Maximum Medians	103.0 51 137 103	101.3 60 145.0 102	p=0.036	93.1 35 137 94	P<0.0001	P<0.0001
<i>Pseudomonas aeruginosa</i> pulmonary infection n=173 N/A=0	Primoinfection	0 1	87 (50.3%) 86 (49.7%)	p<0.0001	48 (27.7%) 125 (72.3%)	p<0.0001	p<0.0001
	Chronic infection	0 1	151 (82.3%) 22 (12.7%)	p=0.074	134 (77.5%) 39 (22.5%)	p=0.0015	p=0.0001
BMI n=173 N/A=0	<5 ^{ème} percentile >5 ^{ème} percentile	7 (4.0%) 166 (96.0%)	9 (5.2%) 164 (94.8%)	p=0.68	17 (9.8%) 156 (90.2%)	p=0.043	p=0.034
^a p-value with statistically significant differences highlighted in bold (p<0.05)							

Table 3. Prevalence of sinonasal symptoms and comparison between T-0, T-max and T-end

			At T-0	At T-max	Comparison T-0 VS T- max p-value ^a	At T-end	Comparison T-max VS T- end p-value ^a	Comparison T-0 VS T-end p-value ^a
SYMPTOMS	Nasal obstruction n=173 N/A=0	0 (none) 1 (mild) 2 (moderate) 3 (severe) Mean score	57 (32.9%) 46 (26.6%) 53 (30.6%) 17 (9.8%) 1.17	54 (31.2%) 33(19.1%) 56(21.4%) 30(17.3%) 1.36	p=0.0009	111 (64.2%) 41 (23.7%) 16 (9.2%) 5 (2.9%) 0.51	p<0.0001	p<0.0001
	Rhinorrhea n=173 N/A=0	0 1 2 3 Mean score	69 (39.9%) 47 (27.2%) 40 (23.1%) 17 (9.8%) 1.03	75 (43.4%) 41 (23.7%) 43 (24.9%) 14 (8.1%) 0.98	p=0.066	112 (64.7%) 46 (26.6%) 15 (8.7%) 0 (0%) 0.44	p<0.0001	p<0.0001
	Headache or nasal pain n=121 N/A=52	0 1 2 3 Mean score	110 (90.9%) 4 (3.3%) 7 (5.8%) 0 (0.0%) 0.15	106 (87.6%) 5 (4.1%) 8 (6.6%) 2 (1.7%) 0.22	p=0.066	113 (93.4%) 6 (5.0%) 2 (1.7%) 0 (0.0%) 0.08	p=0.01	p=0.15
	Hyposmia n=72 N/A=101	0 1 2 3 Mean score	71 (98.6%) 0 (0.0%) 0 (0.0%) 1 (1.4%) 0.04	69 (95.8%) 0 (0.0%) 0 (0.0%) 3 (4.2%) 0.13	p=0.35	68 (94.4%) 1 (1.4%) 1 (1.4%) 2 (2.8%) 0.13	p=1	p=0.18
	Snoring n=173 N/A=0	0 1 Mean score	131 (75.7%) 42 (24.3%) 0.24	129 (74.6%) 44 (25.4%) 0.25	p=0.79	162 (93.6%) 11 (6.4%) 0.06	p<0.0001	p<0.0001
	Sleep disorder n=173 N/A=0	0 1 Mean score	171 (98.8%) 2 (1.2%) 0.01	166 (96.0%) 7 (4.0%) 0.04	p=0.13	171 (98.8%) 2 (1.2%) 0.01	p=0.007	p=1
	Sinonasal overall functional impairment (SOFI) n=173 N/A=0	0 1 2 3 Mean score	57 (32.9%) 49 (28.3%) 59 (34.1%) 8 (4.6%) 1.10	64 (32.4%) 38 (22.0%) 61 (35.3%) 18 (10.4%) 1.24	p=0.007	112 (64.7%) 44 (25.4%) 12 (6.9%) 5 (2.9%) 0.48	p<0.0001	p<0.0001

^a p-value with statistically significant differences highlighted in bold (p<0.05)

Table 4. Prevalence of sinonasal physical examination features and comparison between T-0, T-max and T-end

			At T-0	At T-max	Comparison T-0 VS T-max p-value ^a	At T-end	Comparison T-max VS T-end p-value ^a	Comparison T-0 VS T-end p-value ^a
PHYSICAL EXAMINATION FEATURES	Nasal polyps size (Lildholdt score) n=173 N/A=0	0	125 (72.3%)	106 (61.3%)	p<0.0001	122 (70.5%)	p<0.0001	p=0.52
		1	37 (21.4%)	43 (24.9%)		40 (23.1%)		
		2	11 (6.4%)	14 (8.1%)		8 (4.6%)		
		3	0 (0%)	10 (5.8%)		3 (1.7%)		
		Mean	0.50	0.87		0.54		
	Inferior turbinate hypertrophy n=173 N/A=0	0	83 (48.0%)	79 (45.7%)	p=0.19	115 (66.5%)	p<0.0001	p<0.0001
		1 (partial)	76 (43.9%)	75 (43.4%)		54 (31.2%)		
		2 (total obstruction)	14 (8.1%)	19 (11.0%)		4 (2.3%)		
		Mean	0.60	0.65		0.36		
		Mean	0.22	0.29		0.17		
Pus n=173 N/A=0	0	135 (78.0%)	122 (70.5%)	p=0.005	144 (83.2%)	p=0.002	p=0.13	
	1	38 (22.0%)	51 (29.5%)		29 (16.8%)			
	Mean	0.22	0.29		0.17			
	Mean	0.36	0.45		0.21			
	Mean	0.06	0.08		0.01			
Lateral nasal wall bulging n=148 N/A=25	0	109 (73.6%)	100 (67.6%)	p=0.19	121 (81.8%)	p=0.0002	p=0.009	
	1	24 (16.2%)	29 (19.6%)		23 (15.5%)			
	2	15 (10.1%)	19 (12.8%)		4 (2.7%)			
	Mean	0.36	0.45		0.21			
	Mean	0.06	0.08		0.01			
Externalized mucocele n=173 N/A=0	0	162 (93.6%)	160 (92.5%)	p=0.48	171 (98.8%)	p=0.003	p=0.003	
	1	11 (6.4%)	13 (7.5%)		2 (1.2%)			
	Mean	0.06	0.08		0.01			
	Mean	0.04	0.09		0.15			
	Mean	0.04	0.09		0.15			
Nasal septum deviation n=173 N/A=0	0	166 (96.0%)	149 (86.1%)	p=0.033	159 (91.9%)	p=0.034	p=0.0004	
	1	7 (4.0%)	22 (12.7%)		12 (6.9%)			
	2	0 (0.0%)	2 (1.2%)		2 (1.2%)			
	Mean	0.04	0.09		0.15			
	Mean	0.04	0.09		0.15			
Tonsils hypertrophy n=173 N/A=0	0	158 (91.3%)	167 (96.5%)	p=0.30	156 (90.2%)	p=0.02	p=0.065	
	1	13 (7.5%)	5 (2.9%)		14 (8.1%)			
	2	2 (1.2%)	1 (0.6%)		3 (1.7%)			
	Mean	0.10	0.12		0.04			
	Mean	0.10	0.12		0.04			
Adenoids hypertrophy n=173 N/A=0	0	107 (61.8%)	117 (67.6%)	p=0.027	144 (83.2%)	p<0.0001	p<0.0001	
	1	57 (32.9%)	47 (27.2%)		28 (16.2%)			
	2	9 (5.2%)	9 (5.2%)		1 (0.6%)			
	Mean	0.43	0.38		0.17			
	Mean	0.43	0.38		0.17			
Otitis media with effusion n=173 N/A=0	0	150 (86.7%)	151 (87.3%)	p=0.81	170 (98.3%)	p<0.0001	P<0.0001	
	1	23 (13.3%)	22 (12.7%)		3 (1.7%)			
	Mean	0.13	0.13		0.02			
	Mean	0.13	0.13		0.02			
	Mean	0.13	0.13		0.02			

^a p-value with statistically significant differences highlighted in bold (p<0.05)