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Article *in* The Annals of otology, rhinology, and laryngology · February 2019

DOI: 10.1177/0003489419833714

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Article

Annals of Otology, Rhinology & Laryngology
1–7

DOI: 10.1177/0003489419833714
journals.sagepub.com/home/aor
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Environmental Triggers Associated With Empty Nose Syndrome Symptoms: A Cross-Sectional Study

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Abstract

Objectives: Empty nose syndrome (ENS) is thought to have multiple etiologies, one of which is a postsurgical phenomenon resulting from excessive loss of nasal tissues, particularly the inferior turbinate. Given that the inferior turbinate is instrumental in maintaining nasal homeostasis in different environments, it is believed that ENS symptoms arise only in more arid regions of the world. The aim of this study was to recruit an international population of individuals with ENS to investigate the association of local climate factors on the incidence and severity of ENS-specific symptoms.
Methods: A cross-sectional study was performed of individuals from an international ENS database. ENS status was determined on the basis of a positive ENS questionnaire score (Empty Nose Syndrome 6-Item Questionnaire) and sinus computed tomographic imaging with supporting medical documentation. Participants completed a survey encompassing demographic, geographic, and symptom indicators. Climate variables were collected from global climate databases. Participant location was classified according to the Köppen-Geiger climate system. Pearson correlation analysis was performed using $\alpha = 0.05$ to determine significance.
Results: Fifty-three individuals with ENS were included. Participants were distributed across 5 continents and 15 countries (representing 4 distinct Köppen-Geiger zones). Although local climate factors varied significantly within this cohort, no significant association was found between Empty Nose Syndrome 6-Item Questionnaire symptom severity and these climate factors. However, most study participants reported exacerbation of their ENS symptoms in response to dry air (94%), air conditioning (64%), changes in season and weather (60%), and transitioning between indoors and outdoors (40%). This suggests that everyday local environmental factors may influence the well-being of these patients more than global, climate-level shifts.
Conclusions: ENS symptom severity does not appear to be related to climate or geographic factors. These findings deviate from the traditional dogma that ENS is experienced only in arid regions (or precluded in humid regions) and highlight the importance of recognizing this condition independent of geographic location.

Keywords

empty nose syndrome, sinus surgery, symptom severity, climate

Introduction

Empty nose syndrome (ENS) is often categorized as a subset of secondary atrophic rhinitis.[1] However, the etiology of ENS can be distinguished from other forms of atrophic rhinitis, as it is considered a postsurgical, iatrogenic complication following turbinoplasty and loss of excess nasal turbinate tissue or volume.[2,3] The incidence of this specific condition is largely unknown given that, until recently, validated diagnostic criteria were lacking for ENS, and thus it has been challenging to quantify. The cardinal symptoms of ENS include nasal dryness, a sense of diminished nasal airflow, the nose feeling "too open," a sense of suffocation, nasal crusting, and nasal burning. On the basis of these symptoms, the validated subjective Empty Nose Syndrome 6-Item Questionnaire (ENS6Q) was introduced to better

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segregate true patients with ENS.[4] The ENS6Q, along with the diagnostic in-office cotton test and establishment of radiographic evidence of mucosal change on computed tomographic (CT) imaging, lends support to a physiologic basis for ENS symptoms.[5,6]

The primary function of the nasal turbinates is to warm, filter, and humidify air as it enters the nose[7]; however, turbinates that become inflamed and enlarged can cause prominent symptoms of nasal obstruction that may require procedural treatment. Hypertrophic turbinates that do not respond to medical management may be surgically reduced to improve nasal patency and alleviate symptoms of nasal obstruction.[8] Although the vast majority of these procedures are deemed successful, there is increasing recognition that a small proportion of these cases may develop ENS-type symptoms along a spectrum of severity. ENS symptoms are thought to be potentially related to the altered aerodynamics or receptor expression within the nasal cavity following turbinate surgery.[9] The inferior turbinate is of particular importance in maintaining normal respiratory function when confronted with different environments.[10] When the turbinates are extensively reduced during sinus surgery, there is evidence to suggest that turbinate function could potentially be altered.[11,12] Symptoms of dryness, crusting, and burning may manifest in these cases.[9] Given this possibility, it is thought that similar to atrophic rhinitis, ENS-type symptoms may be more pronounced in arid climates.[13] There is also a hypothesis that ENS has a psychosomatic component, wherein an anxiety disorder (preexisting diagnosis or developing after sinus surgery) may exacerbate the perception of ENS symptoms.[14,15] Finally, there are differences in favored turbinoplasty techniques, with more conservative, mucosal-sparing techniques of turbinate reduction being favored over earlier versions of this procedure.[16,17] Hypothetically, mucosal-sparing techniques should result in minimal disturbance to nasal aerodynamics.

We hypothesized that ENS symptoms would be more severe in arid and/or colder climates because of the potential for impaired buffering capacity of resected inferior turbinates in identified patients with ENS. The aim of this study was to determine if there is an association between climate factors and ENS symptom severity.

Methods

A cross-sectional study was performed of self-identified subjects with ENS registered in an international database hosted by the Stanford Sinus Center. This research received ethics approval from the Stanford University human ethics and research committee. This database was composed of individuals who identified as having ENS but who had not necessarily been formally assessed using the in-office cotton test or the ENS6Q in the past. To be deemed a patient with ENS for this study, candidate subjects had to satisfy the following criteria: positive ENS6Q score (≥11 of 30 possible points) and evidence of inferior turbinate reduction (ITR) on sinus CT images, as well as medical documentation supporting a surgical history of this procedure.[4] In clinical practice, validation of ENS status requires a positive score on the ENS6Q and positive results on a cotton test.[5] However, the ENS6Q has sensitivity of 86.7% and specificity of 96.6% and in combination with objective surgical history (based on CT images and medical documentation) would allow the most accurate diagnosis for self-identified patients with ENS. CT images had to demonstrate clear evidence of ITR upon assessment by 2 investigators to merit inclusion in this study. Candidate subjects were not included if evidence of ITR on CT imaging was not apparent.

The ENS6Q includes 6 questions pertaining to symptoms of nasal dryness, lack of air sensation going through the nasal cavities, suffocation, the nose feeling too open, nasal crusting, and nasal burning.[4] In addition to the ENS6Q, the research survey included questions related to domicile, surgery location (if different), demographics, surgical history, and symptoms. Participants were specifically asked about symptom-exacerbating factors frequently cited by patients with ENS, such as dry air, cold air or air conditioning, allergens, transitioning from indoors to outdoors (and vice versa), and changes in season and weather.

Potential disease-modifying factors related to climate were interrogated from publicly available databases (Table 1). Annual climate averages (dew point, humidity, temperature, precipitation) and altitude data were sourced from the National Climatic Data Center on the basis of 22 to 50 years of accrued data for respective cities. Pollution data were obtained from the World Health Organization Global Urban Ambient Air Pollution Database (on the basis of 2016 data). Pollution is measured in terms of 2 size categories: particulate matter of aerodynamic diameter less than 10 µm (PM-10) and particulate matter of aerodynamic diameter less than 2.5 µm (PM-2.5). Where complete climate data for a patient's specific city were not available, data from a neighboring city up to 15 km away were substituted. This was deemed acceptable as it was well within the 60-km grid cells established by the US Environmental Protection Agency for comparing climate change among regions.

Participants were also categorized by location on the basis of the Köppen-Geiger (K-G) climate classification system, the most widely used climate classification system.[18] Originally designed to study global patterns of vegetation and the impact of climate change, its utility has expanded to public health research.[19] The K-G system consists of 5 main climate groups: A (tropical/megathermal) represents regions where the temperature of the coolest month is 18°C or higher; B (arid and semiarid) represents regions where there is little precipitation; C (temperate/mesothermal) represents regions where the temperature of the warmest month is greater than or equal to 10°C and the temperature of the

Table 1. Local Geographic and Climate Variables Presented as Annual Averages.

Variable	n	Minimum	Maximum	Mean	SD
Temperature, °C	53	−9.6	28.5	12.8	7.3
High temperature, °C	53	−6.2	32.9	18.1	7.0
Low temperature, °C	53	−13.4	24.2	8.2	7.1
Relative humidity, %	52	54.0	83.0	69.6	6.4
Morning humidity, %	39	0.0	91.0	74.9	21.9
Afternoon humidity, %	39	39.0	71.0	56.7	7.3
Dew point, °C	39	−3.0	22.0	7.7	6.3
Annual precipitation, mm	52	98.3	2431.3	903.1	445.9
Annual days of precipitation	39	42.6	364.8	127.0	52.8
PM-10	51	8.0	117.0	22.8	17.7
PM-2.5	51	4.0	63.0	12.8	10.0
Altitude, m	53	0	2131	237.6	454.4

Abbreviations: PM-2.5, particulate matter of aerodynamic diameter less than 2.5 μm; PM-10, particulate matter of aerodynamic diameter less than 10 μm.

coldest month is less than 18°C but greater than −3°C; D (continental/microthermal) represents regions where the temperature of the warmest month is greater than or equal to 10°C and temperature of the coldest month is −3°C or lower; and E (polar and alpine/montane) represents regions where the temperature of the warmest month is less than 10°C. The presence of second and third letters in the K-G classification (eg, Cfa) relates to subgroups denoting the levels of precipitation and heat, respectively.[18]

Statistical Analysis

Descriptive analyses were conducted to evaluate climate variables and symptom severity among this group, along with other key factors. Pearson correlation analysis was performed to assess strength of association between independent climate variables and total ENS6Q symptom score, as well as each of its component symptoms. The nonparametric Kruskal-Wallis test of independent samples was used to assess for strength of correlation between categorical (K-G classification) and linear (ENS6Q and climate) variables. IBM SPSS Statistics version 23 (IBM Corp., Armonk, New York, USA) was used for the analysis, with P values $< .05$ considered to indicate statistical significance.

Results

Ninety-six potential subjects with ENS were screened to participate in this study between December 2016 and March 2017. Of these, 53 individuals with ENS (including 15 women) demonstrated positive ENS6Q scores (mean, 20.57 ± 5.06) and provided sufficient evidence of ITR (on the basis of CT imaging and supporting medical documentation) to be included in the ENS international database. Forty-three candidate participants were excluded because they scored less than 11 on the ENS6Q questionnaire and/or were unable to provide CT and/or documented evidence of turbinoplasty within the data collection period of this study. However, among this excluded cohort (including 11 women), the mean ENS6Q score was still 15.6 ± 6.1.

Table 2. Symptom Severity Among the Study Cohort on the Basis of the ENS6Q.

Variable	n	Minimum	Maximum	Mean	SD
Total ENS6Q score	53	11.00	30.00	20.57	5.06
Symptoms					
Dryness	53	1.00	5.00	4.07	0.91
Airflow	53	0.00	5.00	4.02	1.02
Suffocation	53	0.00	5.00	3.23	1.46
Too open	53	0.00	5.00	3.74	1.57
Crusting	53	0.00	5.00	2.74	1.70
Burning	53	0.00	5.00	2.77	1.82

Abbreviation: ENS6Q, Empty Nose Syndrome 6-Item Questionnaire.

The average age of included participants was 39.8 ± 11.4 years (range, 22-59 years). The reported onset of ENS symptoms typically occurred within 1 year of surgery, and the average duration of symptoms up to the census period was 8.2 ± 7.8 years (range, 0.5-25 years). ENS symptom severity (on the basis of ENS6Q score) was not significantly associated with age, sex, or duration of symptoms. This study cohort (n = 53) was widely distributed across 51 cities, in 15 countries on 5 continents (Figure 1). Climate factors were variable among the 51 locations studied (Table 1). There were no significant associations found between ENS6Q symptom severity (Table 2) and the following climate parameters (annual averages): overall temperature, high temperature, low temperature, relative humidity, morning humidity, evening humidity, dew point, days of precipitation, total precipitation, and pollution indices (PM-10 and PM-2.5) (Table 3). The average annual days of precipitation in a given location were positively correlated with ENS6Q symptom severity; however, this association

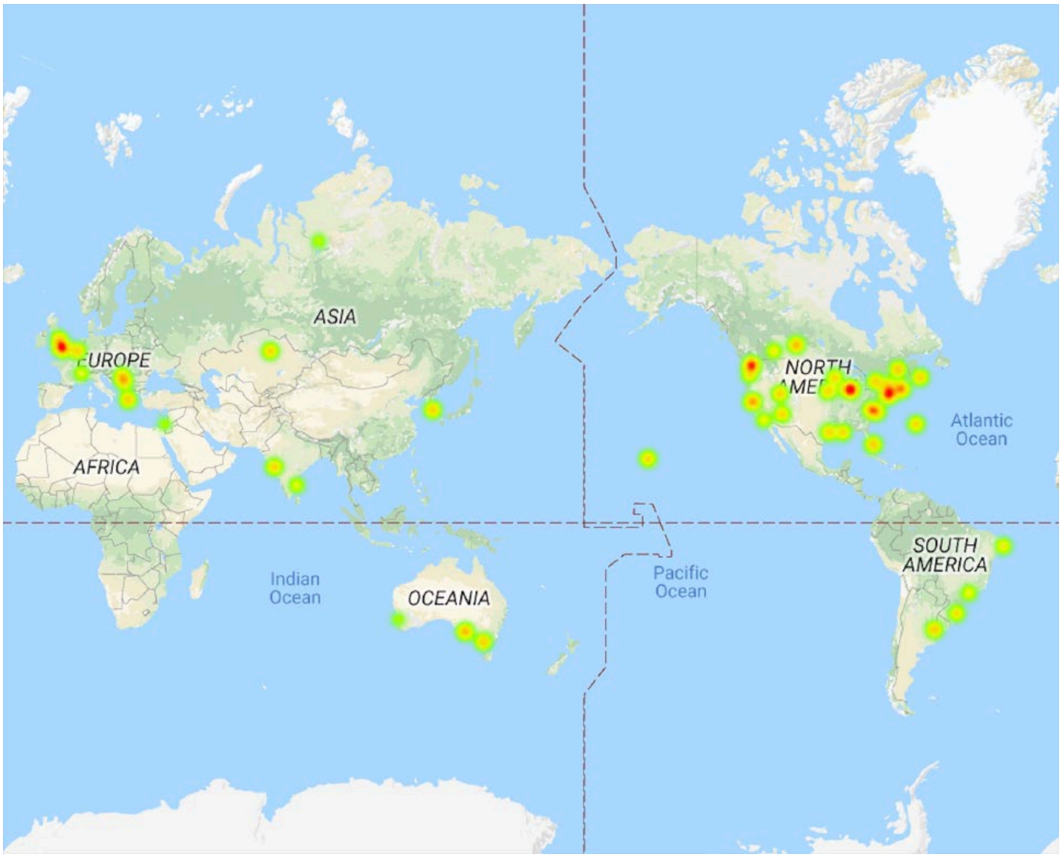

Figure 1. Geographic distribution of participants with empty nose syndrome. The heat map overlay is based on the Empty Nose Syndrome 6-Item Questionnaire (ENS6Q) symptom score. Areas of higher ENS6Q symptom severity are demonstrated by more intense red hues (created with Google Fusion).

Table 3. Correlation of Empty Nose Syndrome 6-Item Questionnaire Score With Climate Variables.

Variable	Pearson Correlation	*P* Value
Dew point	−0.22	.19
Morning humidity	−0.002	.94
Afternoon humidity	0.06	.75
Relative humidity	−0.08	.61
Annual precipitation	0.09	.53
Precipitation days per year	0.27	.07
Average temperature	0.002	.99
High temperature	−0.06	.69
Low temperature	−0.003	.99
PM-10	−0.12	.42
PM-2.5	−0.13	.39
Altitude	−0.16	.25

Abbreviations: PM-2.5, particulate matter of aerodynamic diameter less than 2.5 μm; PM-10, particulate matter of aerodynamic diameter less than 10 μm.

was not statistically significant ($P = .07$; Table 3). This study cohort was also distributed across 4 different K-G climate zones (Table 4). As expected, many of the climate factors studied were significantly different among K-G zones: dew point ($P = .003$), relative humidity ($P = .011$), annual total precipitation ($P = .012$), daily temperature ($P < .001$), daily high temperature ($P < .001$), daily low temperature ($P < .001$), and pollution indices (PM-10 and PM-2.5) ($P = .020$). Despite this variation, the distribution of ENS6Q scores was not significantly different across K-G groups (Figure 2). This was found to be true across all K-G primary categories ($P = .730$) and K-G subgroups ($P = .511$). Notably, many ENS individuals shared that their ENS-specific nasal symptoms became exacerbated in response to dry air (94%), cold air or air conditioning (64%), changes in season and weather (60%), and transitioning between indoors and outdoors (40%).

Fifteen subjects (28.3%) reported undergoing previous office-based procedures for ENS. Forty-six subjects (86.8%)

Table 4. Classification of Study Cohort (n = 53) by the Köppen-Geiger Climate System.

Primary Class	Subcategory	Climate Description	Sample, No. (%)	ENS6Q Score, Mean ± SD
A		Tropical (megathermal)	6 (11.3)	20.0 ± 5.1
	f	Rainforest	1	
	m	Monsoon	1	
	s	Savannah, dry	2	
	w	Savannah, wet	2	
B		Dry (arid and semiarid)	2 (3.8)	17.5 ± 4.9
	Sk	Steppe, cold	2	
C		Temperate (mesothermal)	31 (58.5)	21.5 ± 4.3
	sa	Hot summer, Mediterranean climate	6	
	sb	Warm summer, Mediterranean climate	4	
	wa	Monsoon-influenced humid subtropical climate	1	
	fa	Humid subtropical climate	11	
	fb	Temperate oceanic climate	9	
D		Continental (microthermal)	14 (26.4)	21.4 ± 3.5
	fa	Hot summer, humid continental climate	6	
	fb	Warm summer, humid continental climate	8	
E		Polar and alpine (montane)	0 (0)	-

Abbreviation: ENS6Q, Empty Nose Syndrome 6-Item Questionnaire.

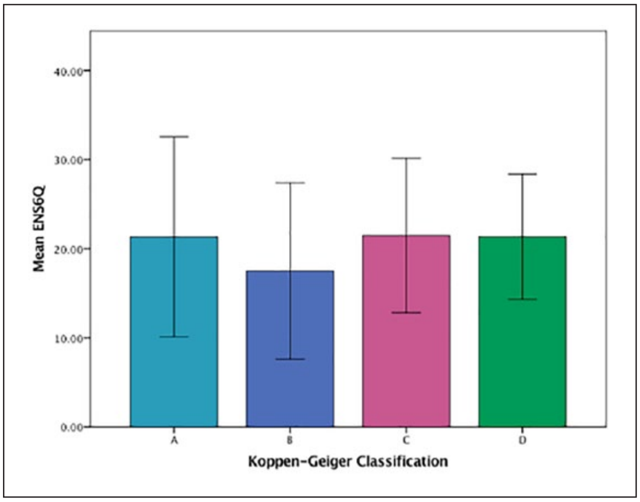

Figure 2. Average Empty Nose Syndrome 6-Item Questionnaire (ENS6Q) score per Köppen-Geiger category. Error bars indicate ±2 SDs.

were currently using recognized topical treatments for ENS, while 7 subjects (13.2%) reported either no current nasal regimen or "other." Among these, saline irrigation was most commonly used (n = 35 [66%]), followed by topical nasal emollients (n = 17 [32%]), topical nasal steroid sprays (n = 11 [20.7%]), and topical nasal decongestants (n = 9 [16.9%]). There was no significant difference in the prevalence of treatment use among K-G categories. Although users of topical decongestants demonstrated lower ENS6Q scores on average than nonusers across all K-G categories, this difference was not statistically significant (*P* = .074).

Discussion

Overview of Results

This study included a relatively large sampling of participants with ENS from around the world compared with other studies regarding this syndrome. These participants resided in a variety of differing climates but were united by a unique cluster of sinonasal symptoms. Figure 1 depicts the global distribution of this study population and includes a heat map overlay demonstrating ENS6Q symptom severity for each participant.

Climate factors such as temperature, humidity, precipitation, and pollution indices varied widely among participant locations (Table 1) and K-G climate zones. The climate factors included in the analysis were well-known exacerbators of both upper and lower respiratory conditions.[20,21] The impact of particulate matter in the atmosphere from urban pollutants on respiratory disease has also been well documented.[22,23] Particulate matter is traditionally subdivided into two size categories, PM-10 and PM-2.5, and each has been studied extensively for its significant impact on upper and lower respiratory tract health outcomes.[24-26] Among this ENS cohort, no significant association was found between ENS6Q symptom severity and any of the included climate factors (Table 3). However, a positive correlation between average annual days of precipitation and

ENS6Q approached statistical significance (Table 3). This was not the case with average annual total precipitation. Subgroup analysis of ENS6Q score between subjects in each K-G classification group also demonstrated no significant difference. Although only 2 subjects resided in "arid" regions (class B), several subjects from classes A and C resided in regions that shared qualities with class B regions in terms of precipitation and average annual temperature. Thus, a comparison between temperate and arid climates was deemed plausible in this study cohort.

Maladaptive Response to Local Environment

Overall, ENS6Q symptom score varied minimally between K-G climate zones (Table 4). Interestingly, these participants reported exacerbations of their symptoms in response to shifts in their local climate such as a change in season, exposure to air conditioning, and transitioning from indoors to outdoors (and vice versa). If these maladaptive response to changes of the environment have been accurately reported, they could potentially be explained by recent literature studying nasal heating and cooling capacities in computational fluid dynamics models of normal sinonasal cavities and those with varying degrees of ITR.[10] In normal healthy models, the nasal cavity was able to warm up or cool down sufficiently in response to extremely cold or hot environments, respectively, to maintain the nasal temperature at approximately 34°C.[10] In models in which there was only a partial reduction of the inferior turbinate, likely more reflective of modern mucosal-sparing techniques of ITR, there were no significant changes in temperature-buffering capacity. Conversely, in models of extensive turbinate reduction, the heating capacity was significantly reduced, yielding nasal cavity temperatures as much as 6.8°C lower than the normal healthy model.[10] As illustrated in a past analysis of CT findings shared by patients with ENS, the ENS nasal passage was demonstrated to develop compensatory mechanisms to attempt to mimic the function of the inferior turbinate.[6] This is accomplished by swelling and autohypertrophy of the remaining nasal tissues, creating pockets of bulk, in the central and posterior nasal septum. Unfortunately, these areas do not appear to have the same erectile nature as the native inferior turbinate, and the compensatory mechanism would ultimately fall short in adapting to abrupt shifts of climate.[6]

Limitations

Although this investigation managed to capture a population that was distributed across a variety of climate types, the reach of this study was limited by the fact that the electronically distributed survey was made available only in English. As a likely result, nearly half of this study cohort resided in North America. This may have also resulted in an overrepresentation of temperate climates (K-G class C) over arid and tropical zones (K-G classes A and B).

The cross-sectional design of this study also meant that only a snapshot of symptom quality could be appreciated. The climatic data obtained were based on annual averages, while data related to patient-specific symptoms may have been more reflective of an acute state. Participants would have also been subject to recall bias when asked to evaluate their responses to acute environmental stressors (air conditioning, transitioning from indoors to outdoors, exposure to allergens, etc). Thus, symptom variation related to acute climate stressors may have been overlooked. To test this new hypothesis, serial ENS6Q assessments between seasons and in response to acute environmental stressors would be required. There are many factors that could potentially influence the development and exacerbation ENS. Any discussion of ENS symptoms would be remiss to omit the significant mental health burden carried by patients with ENS and how that may influence perceptions of sinonasal pain and discomfort on a case-by-case basis.[15] The authors of a recent case study proposed the treatment of ENS as a somatic symptom disorder.[14] The potential interplay among environmental, anatomic, and psychological factors is naturally difficult to discern and was beyond the scope of this survey-based study.

Conclusions

These findings suggest that, contrary to traditional perceptions, ENS may not be defined by geography or climate zones. This study population demonstrates that individuals who meet the symptomatic, historical, and radiographic criteria of ENS can be identified in nearly all parts of the world. Symptom reporting suggests that the morbidities associated with ENS may be more influenced by abrupt shifts in temperature or humidity rather than a single climate type or geographic factor. This deviates from the dogma that ENS is primarily experienced in arid geographic areas and highlights the importance of recognizing this condition by medical and otolaryngology practitioners in all parts of the world.

Authors' Note

These findings were presented as an oral presentation at the annual meeting of the American Rhinologic Society on September 9, 2017, in Chicago.

Acknowledgments

We gratefully acknowledge the contributions of our research coordinator, Kunju Sridhar, in obtaining ethics approval for this project. We would also like to thank the Empty Nose Syndrome International Association for facilitating our recruitment efforts.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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