Post-infectious olfactory dysfunction exhibits a seasonal pattern*

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SUMMARY

Hypothesis: *We investigated whether olfactory dysfunction following infections of the upper respiratory tract (post-URTI) has an incidence matching the seasonality of URTIs.*
Study design: *Retrospective study.*
Methods: *In total, 457 patients (126 male, 331 female) with post-URTI olfactory loss were examined during a 6-year-period (1999-2004). Their records were assessed for age, sex, and time of onset of the disease. The severity of olfactory dysfunction was assessed using the "Sniffin' Sticks" (odour threshold, odour discrimination, and odour identification).*
Results: *Incidence of post-URTI olfactory dysfunction exhibited seasonal fluctuations with deviations from the winter seasonality of URTIs. The overall incidence of the disease differed significantly between months. March (12.7%) and May (12.6%) were the months with the highest incidence of the disease throughout the year. The lowest incidence was observed in September (5.6%). Significant differences were found between these months and months with a high incidence of URTIs.*
Discussion: *The peak incidence of post-URTI olfactory loss in March may be explained by the high incidence of influenza at this time. However, it is unclear why the incidence of the disease presents a second peak in May, when the incidence of respiratory viruses is relatively low. Climate conditions at this time might play a role in the susceptibility of the nasal epithelia towards certain viral infections, e.g. parainfluenza type III.*
Conclusion: *Post-URTI olfactory dysfunction exhibits spring seasonality with peaks in March and May and possible causative factors being influenza and parainfluenza viruses (type III), respectively.*

Key words: anosmia, hyposmia, post-infectious, seasonality

INTRODUCTION

Acute upper respiratory tract viral infections (URTIs) are a major cause of olfactory dysfunction in adults. It is common knowledge that the incidence of URTIs such as common cold and influenza exhibits seasonal fluctuations. Winter seasonality has been reported for a wide range of URTIs caused by over 200 different viruses [1,2]. Whether post-URTI olfactory dysfunction follows the above seasonality is not clear. An answer to this question will be valuable for the counseling of patients. More importantly, it may potentially contribute to the prevention of this disorder, especially when considering that currently no validated treatment is available for this complication of URTIs.

Thus, the present study examined the question whether seasonality of post-infectious olfactory dysfunction exists, analyzing the characteristics of its yearly incidence in comparison to the yearly incidence of certain viruses causing URTIs reported in the literature. In addition it was examined whether local weather conditions would be related to the incidence of this olfactory disorder.

MATERIAL AND METHODS

Patients

This work represents a retrospective study of 457 (126 male, 331 female) patients with olfactory dysfunction following URTI examined at the Smell & Taste Clinic of the ORL Department of the University of Dresden Medical School during a six-year period (1999-2004). The records of these patients were assessed for age, sex, time of onset, and severity of the disease.

Diagnosis was based on the patients' history and clinical examination using both rhinoscopy and nasal endoscopy. All

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patients had a history of olfactory loss following symptoms of common cold. We considered the month when symptoms of the URTI were first present as the month of onset of the olfactory disorder. Those patients were excluded with a positive history of a viral infection but with a delayed onset of olfactory dysfunction 3 weeks or later from the infection.

All patients exhibited patent olfactory clefts in nasal endoscopy. There were no findings suggestive of additional nasal pathology that might have caused olfactory dysfunction.

Olfaction test

The severity of olfactory dysfunction was assessed by means of the "Sniffin' Sticks" test battery (Burghart, Wedel, Germany). Odourants were presented in commercially available felt-tip pens. For odour presentation, the cap was removed by the experimenter, and the pen's tip was placed approximately 2 cm in front of both nostrils for approximately 2 seconds before the pen was capped again. The examination involved tests for phenyl ethyl alcohol odour thresholds, odour discrimination, and identification. The "Sniffin' Sticks" are a well investigated means to assess olfactory function. They have been shown to have a test-retest reliability comparable to other established tests of olfactory function [3].

Odour thresholds were assessed using a single-staircase, triple-forced choice procedure. Three pens were presented in a randomized order, with two containing the solvent and the third the odourant at a certain dilution (a 3-alternative forced choice), starting from the weakest concentration. The task of the blindfolded subject was to identify the odour-containing pen. Reversal of the staircase was triggered when the odour was correctly identified in two successive trials. The next reversal of the staircase followed when subjects failed to correctly identify the odour, etc. Threshold was defined as the mean of the last four out of seven staircase reversal points. In the odour discrimination task, 16 triplets of pens were presented in a randomized order, with two containing the same odourant and the third a different odourant. The blindfolded subjects had to determine which of the three odour-containing pens smelled different. Presentation of triplets was separated by approximately 20 seconds. The interval between presentations of individual pens of a triplet was approximately 3 seconds. The score ranged from 0 to 16. Odour identification was assessed using 16 common odours. Using a multiple choice task identification of individual odourants was performed from a list of 4 descriptors. The interval between odour presentations was again 20 seconds. The score ranged again from 0 to 16. Results of the three subtests were presented as a composite "TDI score" which was the sum of individual scores for threshold, discrimination, and identification measures. Based on a multicentric investigation in more than 1000 patients with olfactory loss, patients with a score below 15 are considered functionally anosmic, with a score between 15 and 31 they are considered hyposmic [3]. The presence of qualitative olfactory disorders (parosmia and phantosmia) was specifically addressed during the interview.

Weather

Local weather conditions were assessed for the same period of time from the climate data archives of Weatheronline Ltd, Cambridge, UK [4]. Specifically, we used the means of maximum temperature, precipitation and relative humidity for every month, in the region of Dresden. Temperature was expressed as degrees Celsius, relative humidity as a percentage, and precipitation in mm. Incidences of influenza and adenoviruses in the region of Dresden were available from the archives of the Robert Koch Institute, Berlin, Germany [5].

Statistics

Results were analyzed using SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics are presented within the body of the text as mean values. A one-way ANOVA was used for the detection of deviations of the overall incidence between months. For comparisons between monthly incidences, t tests for paired samples were employed. The minimum a-level was 0.05.

RESULTS

The male-female ratio of patients was 1:3 with a clear predominance of female patients (71%), which is in agreement with previous work [6,7]. The patients' mean age was 58 years (range 22-89 years) with no sex-related differences (female patients: mean age 58 years, male patients: mean age 57 years).

Analysis of monthly incidence of post-URTI olfactory dysfunction exhibited seasonal fluctuations with significant deviations from the well-known winter seasonality of URTIs. The overall incidence of the disease differed significantly between months ($F [11,48] = 2.06$, $p = 0.043$), occurring mainly during spring (Figure 1). More specifically, March and May were the months with the highest incidence of the disease throughout the year with incidences of 12.7% and 12.6%, respectively. The lowest incidence was found in September (5.6%). Significant differences were found between March and May, and September

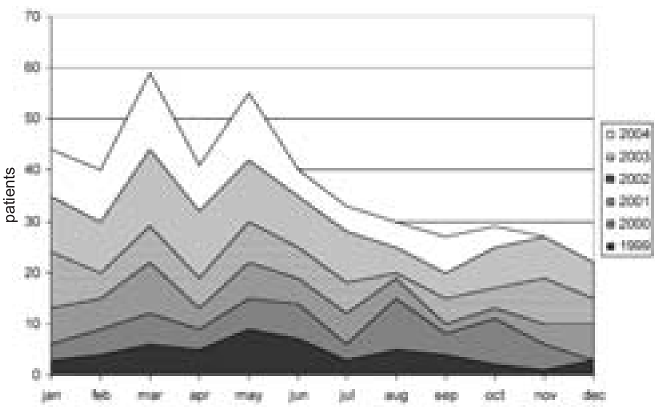

Figure 1. Cumulative monthly incidence of post-URTI olfactory disorders, with peaks of incidence in March and May indicating a repeated pattern of seasonality.

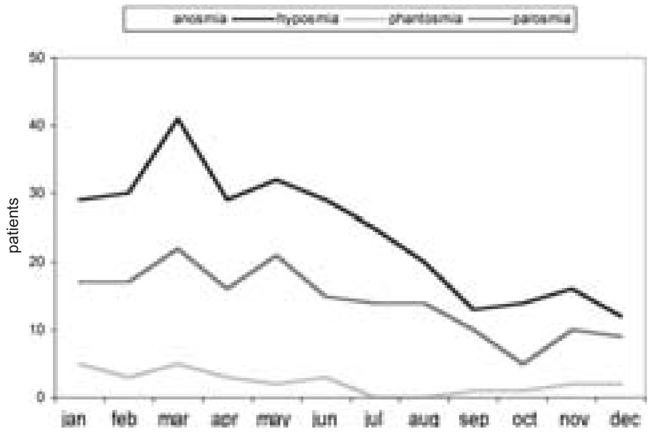

Figure 2. Monthly incidence of post-infectious quantitative (hyposmia, anosmia) and qualitative (parosmia, phantosmia) olfactory disorders.

and December (March–Sep: $p = 0.027$; March–Dec: $p = 0.041$; May–Sep: $p = 0.023$; May–Dec: $p = 0.049$). Tendencies for significant differences ($0.05 < p < 0.10$) were also seen between March and May, and other months such as July, August and October.

The overall incidence of the disease during spring was 34%, which was higher than what was found during winter (25%), fall (18%), and summer (23%). This pattern of seasonality was repeated with only slight differences every year with the vast majority of illness incidence occurring between March and June (43%). Both sexes followed this seasonality with marginal differences between them.

Hyposmia was diagnosed in 290 patients being the most frequent finding in our data (62.9%). Incidence of hyposmia followed the above-mentioned seasonal pattern. However incidence of anosmia (119 patients, 25.8%) exhibited no major changes throughout the year (Figure 2).

A total of 197 patients complained of qualitative olfactory dysfunction. More specifically, 170 patients (36.9%) complained of parosmia and 27 patients mentioned phantosmia (5.9%). Incidence of parosmia followed the above-mentioned seasonality. In contrast, incidence of phantosmia appeared to exhibit no such fluctuations during the year (Figure 2).

DISCUSSION

It is well known that in the more northerly and southerly parts of the hemispheres there is a peak of respiratory illnesses during winter months [1,2,8]. In addition to this "winter seasonality" an early spring peak of illness has frequently been noted [1,2,9]. Although there is an obvious increase of incidence of post-URTI olfactory loss during the winter compared with summer and fall, data from the present investigation exhibit two peaks of high incidence during March and May. Of even higher importance is the fact that these months had always the highest incidence in the year-to-year occurrence of post-infectious olfactory dysfunction.

This pattern of seasonality raises a question about the occurrence of URTI causative agents at this time of the year. The seasonal increase in URTI during the winter months cannot preclude epidemics of URTI during the spring or the summer, but these epidemics have no fixed timing, appearing at various times throughout the year [1]. The regular presence of incidence peaks every year in March and May is an indication that the cause may be found within the families of viruses with a regular high incidence during these months. Although post-URTI olfactory dysfunction is thought to be caused by viral infections, causative viruses have not been identified. This is partly due to the fact that the interval between the initial diagnosis and the onset of URTI symptoms is usually rather long. Patients tend to wait before they visit a doctor and this makes the detection of causative virus difficult.

URTIs may be caused by a variety of viruses, belonging to six main families: rhinoviruses, influenza, coronaviruses, RSV, parainfluenza, and adenoviruses, with the first three causing the vast majority of the disease [1,2,9,10]. The results of our analysis suggest that **influenza viruses** could be the cause of post-infectious olfactory disorder during March, as their prevalence in the region of Dresden is relatively high (32.05 pt /100.000 population) [5]. Epidemics of influenza can be noted at any time during a year. However for the region of Dresden incidence of influenza seems to have a permanent outbreak every March (Figure 3). In addition, the incidence of post-URTI olfactory dysfunction followed the fluctuations of influenza incidence for the period between 2001 and 2003. More specifically, the incidence of influenza exhibited a slight decrease from 2001 to 2002, and it reached a significant peak in March of 2003, a trend reflected also in our data (2001: 10 patients, 2002: 7 patients, 2003: 18 patients). As influenza establishes one of the major causes of URTI and may produce central-nervous symptoms, we conclude that this family of viruses must be considered as one of the causative agents of olfactory dysfunction.

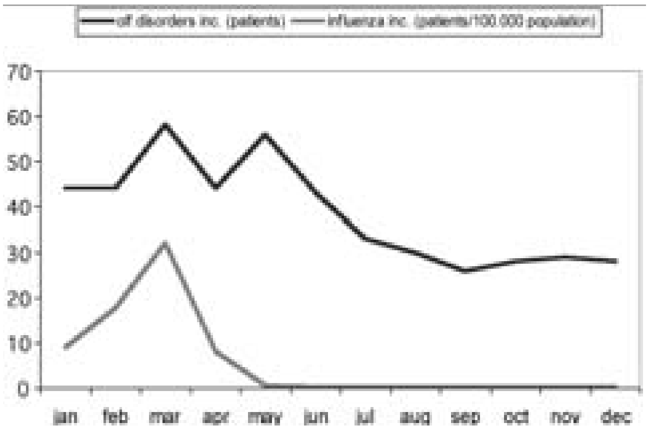

Figure 3. Incidence of post-infectious olfactory disorders in comparison with influenza incidence in Dresden area from the Robert Koch Institute.

We did not consider **coronaviruses** as one of the possible causes of post-infectious smell dysfunction. Their incidence is reported only in a limited number of studies, and the peak season of coronaviruses is mainly in midwinter [9,10]. **RSV** transmission typically occurs in midwinter. Other authors described a cycle with a major outbreak in midwinter in one year and a smaller outbreak 15 months later in late winter/early spring [9]. Both of the above seasonal patterns are not congruent to our results on the incidence of post-URTI olfactory loss. We also excluded **adenoviruses** from our suggestions as their prevalence does not present significant fluctuations throughout the year and relatively low percentage of incidence [5].

The peak of the incidence of post-infectious olfactory loss in May cannot be explained with one of the major causes of URTI (influenza, coronaviruses, and RSV) because their incidence does not peak in spring. This is different for the family of rhinoviruses, which exhibits a relatively high incidence at this time, however, rhinoviruses exhibit their highest prevalence in September and October where the incidence of post-URTI olfactory loss is low [9-11]. On the other hand, this family of viruses includes over 100 serotypes, and one can speculate that certain serotypes may cause this outbreak of olfactory disease in May. However, the lack of evidence in the literature about the neurotropic behaviour of rhinoviruses also does not support the idea that rhinoviruses can be considered as the cause of the above-mentioned peak of smell dysfunction [2,10,11].

Parainfluenza viruses display a specific seasonal pattern dependent on type. Type 1 and type 2 peak in mid-fall and mid-winter, respectively. However, type 3 is reported to increase in late spring with a peak in May [1,7,10]. Therefore parainfluenza virus type 3 may be responsible for the peak of olfactory dysfunction in May.

In all of the present observations, climatic variation must be taken into account. Although certain patterns are observed in most of the northerly countries, variations can occur between localities with different climates. Laboratory studies showed that airborne viruses stay in the air for a longer period of time during conditions of low humidity. Therefore, transmission to other individuals appears to be easier [2]. Other studies showed that outbreaks of viral infections occur in the rainy season [12,13]. Based on these observations it seems that climatic conditions mainly affect viruses with transmission by aerosol spread, and not those transmitted by direct contact, as rhinoviruses and RSV. In our data peak season, March was related to a relatively low humidity of 78% combined with a low mean maximum temperature (8^{o}C) (Figure 4A). The combination of low humidity and low temperature has been proposed in several studies as a factor improving influenza transmission, a fact in agreement with our proposal for the peak season in this month [2,8].

Climatic conditions in May present a combination of the lowest relative humidity throughout the year (68%) with a relatively high mean maximum temperature (18^{o}C) (Figure 4A). Considering that low temperature is correlated in many studies with high influenza incidence [2,8,14], the difference in mean maximum temperature (10^{o}C) between March and May may be also an indication that two different viral agents are the causes of the two peak seasons. Precipitation does not seem to be a significant factor for viral transmission in the area of Dresden compared to other climatic parameters (Figure 4B). In the Dresden area precipitation has significant differences between years from heavy rainfall to dryness. However post-infectious olfactory dysfunction presents certain seasonality every year. This is not in agreement with studies suggesting that rainfall can positively affect the incidence of influenza, but these studies examined influenza transmission in tropic cli-

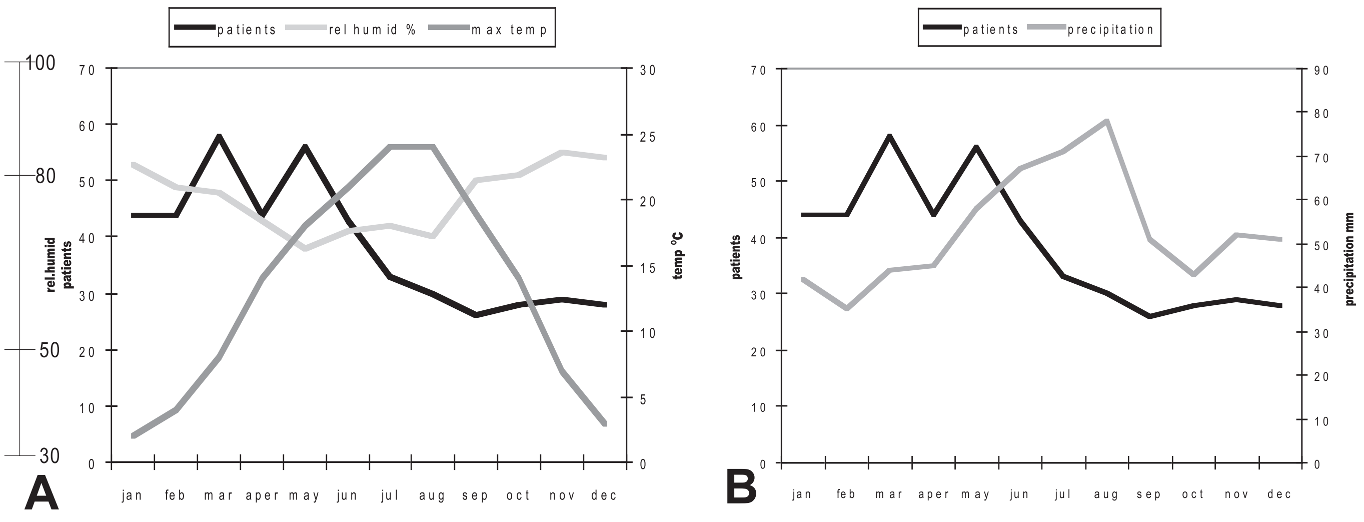

Figure 4. (a) Incidence of post-infectious olfactory disorders and precipitation in Dresden. (b) Relative humidity and mean maximum temperature for the same area and relation

mates [12,13].

Risk factors for viral–induced smell dysfunction remain unclear. However, the vast majority of our patients were above the age of 50, suggesting the potential importance of cumulative insult and the possibly reduced regeneration capabilities of the olfactory neuroepithelium in advanced age [6,15]. Moreover, the incidence of post-infectious smell dysfunction in our data follows a certain pattern of seasonality, especially in patients of middle and older age, indicating an increased risk for these patients towards specific viruses. The female predominance among patients especially in post-menopause ages is in agreement with other studies suggesting that olfaction seems to be at risk after menopause [6,9]. However, an effect of estrogens in post-menopausal women suffering from olfactory disturbance has not been shown [16].

Problems in isolation of viruses in the acute phase of an URTI and the lack of clear differences between symptoms caused by URTI viruses make the role of weather conditions in viral incidence an interesting field for investigation. Further studies are needed to clarify the seasonality of certain respiratory viruses in correlation with different climatic conditions. Development of self-administered common cold olfactory screening tests for early diagnosis of the olfactory disorder could be helpful for viral isolation during the acute phase.

CONCLUSION

Post-URTI olfactory dysfunction exhibits spring seasonality with two peaks in March and May, with possible causative factors being influenza viruses and parainfluenza viruses (type III), respectively. As currently no validated treatment is available for this complication of URTIs this kind of information will be valuable for the counseling of patients. The role of climatic conditions in post-URTI olfactory disorders incidence is a field where further investigations are needed.

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