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Evaluation of Chronotypes Among Patients of Allergic Rhinitis and its Association with Disease Symptomatology

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ABSTRACT

Allergic Rhinitis is a clinical hypersensitivity of nasal mucosa to the foreign substances mediated by IgE antibodies. It is characterised by sneezing, nasal itching, rhinorrhoea, nasal obstruction. Non-nasal symptoms include ocular itching, ocular redness, throat itching, cough. Other conditions associated with it are asthma, atopic dermatitis and nasal polyp. Studies have shown that the occurrence of Allergic Rhinitis has been on the rise in India in recent years. Manifestations and severity of allergic rhinitis symptoms exhibit prominent 24 hour variations. In most persons they are worse overnight or in early morning. Study of chronobiology of allergic rhinitis began five decades ago. Recent studies have proved that internal timekeeping system, called the circadian clock plays a key role in temporal regulation of allergic reactions. Chronotype is defined as personal preference of sleep and activity timing. Three major variations of chronotypes exist among human beings, those who prefer to wake up early in morning and sleep early at night(Morning types or "larks"), those who prefer to sleep late at night and wake up late at morning(Evening types or "owls") and those who remain in between (Intermediate type).On the backdrop of the evidences of chronotype and allergic rhinitis, we have chosen to pursue the study on this topic to control allergic rhinitis and also so that our understanding about chronotype association of allergic rhinitis and its managements are enriched with prevention of further complications of allergic rhinitis.

INTRODUCTION

Allergic rhinitis is a medical condition characterized by an exaggerated sensitivity of the nasal lining to external substances, which is facilitated by IgE antibodies.

According to a survey conducted by the All India Co-ordinated Project on Aeroallergens and human health in New Delhi in 2000, the prevalence of Allergic Rhinitis in India is estimated to be between 20% and 30%. India experiences an annual incidence of around 10 million cases. Research has indicated that the occurrence of Allergic Rhinitis has been on the rise in India recently. The condition is marked by repeated sneezing, nasal itching, rhinorrhea and nasal obstruction. Non-nasal symptoms may encompass visual symptoms such as eye discomfort and redness, as well as respiratory symptoms including throat itching and coughing. Several other illnesses are linked to Allergic Rhinitis including Asthma, Atopic dermatitis and Nasal Polyps.

Asthma is more likely to develop in individuals with Allergic Rhinitis. A significant proportion of individuals with allergic rhinitis display indications of bronchial hyperactivity, with around 30% at risk of developing asthma in the future. Approximately 70-80% of Indian patients experience the simultaneous presence of allergic rhinitis and asthma[1,2]. Allergic rhinitis has a negative impact on the health-related quality of life among patients in India. Relevant aeroallergens often found in India that contribute to allergic rhinitis and asthma include house dust mite, cockroach, pollen and mold spores[1]. The diagnosis and treatment of Allergic Rhinitis should follow ARIA(Allergic Rhinitis and its Impact on Asthma) guidelines. The points for the ARIA guidelines are as follows: Allergic rhinitis is subdivided by symptom duration and severity of allergic rhinitis.

Stepwise therapeutic approach is needed depending on the ARIA classification. Patients with persistent allergic rhinitis should be evaluated for asthma. Disease severity was classified as "mild" and "moderate" considering its influence on work/school performance, daily activities, sleep, troublesome symptoms.

Illustration adapted from Scott-Brown's Otorhinolaryngology Head and Neck Surgery, Eighth Edition Diagnosis of Allergic Rhinitis is based on history and clinical examination. Then diagnosis is confirmed by Skin prick test (SPT) and specific IgE (sIgE) measurements.

Chronotypes are attributed to differences in circadian clock. Chronotype refers to an individual's preference for the timing of sleep, awakeness and activity. It is a well-defined psycho-behavioral trait systematized with physiological and psychological measures. There are three primary types of chronotypes observed in humans: Morning types, also known as "larks," who like to wake up early in morning and sleep early at night; Evening types, often known as "owls," who prefer to sleep late at night and wake up late in the morning; and intermediate types, who fall somewhere in between[3]. Chronotype is a significant internal indicator that regulates biological activities based on the body's circadian rhythm[4]. The circadian rhythm is an endogenously driven cyclical process that monitors most of the physiological processes like sleep-wakefulness. It has been shown by recent studies that the circadian clock underlies the circadian pathophysiology of allergic diseases.

A growing body of research indicates that individuals with different chronotypes, such as those who engage in more night time activities are vulnerable to circadian misalignments. Also people with night time activities are prone to develop cardiac, metabolic and psychiatric illnesses[5-7].

Therefore, chronotyping might be useful in better evaluation of the relation between circadian rhythm, physical and mental performance and disease.

There is plethora of evidences which have thrown light on the chronotype of allergic rhinitis and its influential role on the symptomatology of allergic rhinitis.

Aims and objectives

Aims: The main aim of our study is to evaluate the chronobiology of allergic rhinitis and its impact on disease severity.

The secondary objectives of our study are to determine the association between the various chronotypes and symptoms of allergic rhinitis.

MATERIALS AND METHODS

Place of Study: Department of Otorhinolaryngology and Allergy Immunology of Apollo Multispeciality Hospitals, Kolkata, India.

Study Population: People coming with Allergic rhinitis in the OPD of Otorhinolaryngology and Allergy Immunology in Apollo Multispeciality Hospitals, Kolkata, India.

Sampling Technique: Convenience Sampling.

Study Period: December 2020-May 2021.

Sample Size: One hundred and ten.

Study Design: Cross-sectional Observational Study.

Sampling Procedure: People attending the opd of Otorhinolaryngology and Allergy Immunology in Apollo Multispeciality Hospitals, Kolkata, India with allergic

rhinitis were considered for recruitment in the study after due consideration of inclusion and exclusion criteria. After approval of institutional ethical committee, informed and signed consents were taken from 110 patients.

Inclusion Criteria:

- Patients of age group of 18-60 years
- Patients with symptoms of allergic rhinitis for minimum 2 years period
- Patients with hypersensitivity to any particular aeroallergen
- Patients willing to participate in the study by informed signed consent

Exclusion Criteria:

- Patients with mass/malignancy.
- Patients with deviated nasal septum.
- Patients refusing to participate in study
- Allergic rhinitis in severe immunocompromised state

Statistical Analysis: Descriptive statistics would be used to describe data set and difference in mean between comparable groups would be Chi-square test. For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. One-way analysis of variance (one-way ANOVA) was a technique used to compare means of three or more samples for numerical data (using the F distribution). A chi-squared test (χ^2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

Explicit expressions that can be used to carry out various t-tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a t-distribution under the null hypothesis is given. Also, the appropriate degrees of freedom are given in each case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test.

Once a t value is determined, a p-value can be found using a table of values from Student's t-distribution. If the calculated p-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis.

P-value $\leq$0.05 was considered for statistically significant.

RESULTS AND DISCUSSION

In Morning Type, 5 (14.7%) patients were $\leq$30 years old, 13 (38.2%) patients were 31-40 years old and 16 (47.1%) patients were 41-50 years old. In Intermediate Type, 7 (19.4%) patients were $\leq$30 years old, 9 (25.0%) patients were 31-40 years old, 19 (52.8%) patients were 41-50 years old and 1 (2.8%) patient were >50 years old. In Evening Type, 4 (10.0%) patients were $\leq$30 years old, 18 (45.0%) patients were 31-40 years old, 17 (42.7%) patients were 41-50 years old and 1 (2.5%) patient were >50 years old. Association between Age in Chronotype group was not statistically significant (p = 0.5933) (Table 1).

In Intermediate Type, 35 (97.2%) patients had sneezing. In Evening Type, 39 (97.5%) patients had sneezing. Association of Sneezing vs. chronotype groups was statistically significant (p<0.0001). In intermediate chronotype, 4 (11.1%) patients had itching. In evening chronotype, 9 (22.5%) patients had itching. Association of itching vs. chronotype group was statistically significant (p = 0.0114). In intermediate chronotype, 5 (13.9%) patients had rhinorrhoea. In evening chronotype, 28 (70.0%) patients had rhinorrhoea. Association of rhinorrhoea vs. group was statistically significant (p<0.0001). In morning chronotype, 1 (2.9%) patient had asthma. In intermediate chronotype, 18 (50.0%) patients had asthma. In evening Type, 31 (77.5%) patients had asthma. Association of asthma vs. group was statistically significant (p<0.0001). In intermediate chronotype, 3 (8.3%) patients had nasal obstruction. In evening chronotype, 12 (30.0%) patients had nasal obstruction. Association of nasal obstruction vs. chronotype groups was statistically significant (p = 0.0005). In intermediate chronotype, 3 (8.3%) patients had nasal polyp. In evening chronotype, 11

Table 1: Association between ages in Chronotype group

Age in group (years)	Morning Type	Intermediate Type	Evening Type	Total	p-value	Chi-square value
≤30	5	7	4	16	0.5933	4.6210
Row (%)	31.3	43.8	25	100		
Col (%)	14.7	19.4	10	14.5		
31-40	13	9	18	40		
Row (%)	32.5	22.5	45	100		
Col (%)	38.2	25	45	36.4		
41-50	16	19	17	52		
Row (%)	30.8	36.5	32.7	100		
Col (%)	47.1	52.8	42.5	47.3		
>50	0	1	1	2		
Row (%)	0	50	50	100		
Col (%)	0	2.8	2.5	1.8		
Total	34	36	40	110		
Row (%)	30.9	32.7	36.4	100		
Col (%)	100	100	100	100		

Table 2: Comparison between All features of allergic rhinitis and Chronotype Group

Group	All features of allergic rhinitis	Morning type	Intermediate type	Evening type	Total	p-value	Chi-square value
Sneezing	No	34	1	1	36	<0.0001	101.1556
	Row (%)	94.4	2.8	2.8	100		
	Col (%)	100	2.8	2.5	32.7		
	Yes	0	35	39	74		
	Row (%)	0	47.3	52.7	100		
	Col (%)	0	97.2	97.5	67.3		
	Total	34	36	40	110		
	Row (%)	30.9	32.7	36.4	100		
	Col (%)	100	100	100	100		
Itching	No	34	32	31	97	8.9534	0.0113
	Row (%)	35.1	33	32	100		
	Col (%)	100	88.9	77.5	88.2		
	Yes	0	4	9	13		
	Row (%)	0	30.8	69.2	100		
	Col (%)	0	11.1	22.5	11.8		
	Total	34	36	40	110		
	Row (%)	30.9	32.7	36.4	100		
	Col (%)	100	100	100	100		
Rhinorrhoea	No	34	31	12	77	<0.0001	49.4973
	Row (%)	44.2	40.3	15.6	100		
	Col (%)	100	86.1	30	70		
	Yes	0	5	28	33		
	Row (%)	0	15.2	84.8	100		
	Col (%)	0	13.9	70	30		
	Total	34	36	40	110		
	Row (%)	30.9	32.7	36.4	100		
	Col (%)	100	100	100	100		
Asthma	Yes	1	18	31	50	<0.0001	41.6527
	Row (%)	2	36	62	100		
	Col (%)	2.9	50	77.5	45.5		
	No	33	18	9	60		
	Row (%)	55	30	15	100		
	Col (%)	97.1	50	22.5	54.5		
	Total	34	36	40	110		
	Row (%)	30.9	32.7	36.4	100		
	Col (%)	100	100	100	100		
Nasal Obstruction	No	34	33	28	95	0.0004	15.3228
	Row (%)	35.8	34.7	29.5	100		
	Col (%)	100	91.7	70	86.4		
	Yes	0	3	12	15		
	Row (%)	0	20	80	100		
	Col (%)	0	8.3	30	13.6		
	Total	34	36	40	110		
	Row (%)	30.9	32.7	36.4	100		
	Col (%)	100	100	100	100		
Skin Rash	No	33	34	19	86	<0.0001	34.7591
	Row (%)	38.4	39.5	22.1	100		
	Col (%)	97.1	94.4	47.5	78.2		
	Yes	1	2	21	24		
	Row (%)	4.2	8.3	87.5	100		
	Col (%)	2.9	5.6	52.5	21.8		
	Total	34	36	40	110		
	Row (%)	30.9	32.7	36.4	100		
	Col (%)	100	100	100	100		
Nasal Polyp	Yes	0	3	11	14	0.0012	13.4430
	Row (%)	0	30	70	100		
	Column (%)	0	8.3	27.5	12.7		
	No	34	33	29	96		
	Row (%)	35.4	34.4	30.2	100		
	Column (%)	100	91.7	72.5	87.3		
	Total	34	36	40	110		
	Row (%)	30.9	32.7	36.4	100		
	Col (%)	100	100	100	100		

(27.5%) patients had nasal polyp. Association of Nasal Polyp vs. group was statistically significant (p = 0.0048). In morning chronotype, 1 (2.9%) patients had skin rash. In intermediate chronotype, 2 (5.6%) patients had skin rash. In evening chronotype, 21 (52.5%) patients had skin rash. Association of skin rash vs. group was statistically significant (p<0.0001) (Table 2).

In morning chronotype no patients complained of sleep disturbance due to social media. In intermediate chronotype, 25 (69.4%) patients had sleep disturbance due to social media. In evening chronotype, 38 (95.0%) patients had sleep disturbance due to social media. Association of sleep disturbance due to social media vs chronotype groups was statistically significant (p<0.0001) (Table 3).

Mecacci *et al*.[8] found significant correlations between circadian typology scores and data relative to personality, psychosomatic disorders and stress-prone behaviour were analyzed. Evening types reported

Table 3: Comparison between Sleep disturbance due to social media and Chronotype Group

Sleep disturbance due to social media	Morning Type	Intermediate Type	Evening Type	Total
No	34	11	2	47
Row (%)	72.3	23.4	4.3	100
Col (%)	100	30.6	5	42.7
Yes	0	25	38	63
Row (%)	0	39.7	60.3	100
Col (%)	0	69.4	95	57.3
Total	34	36	40	110
Row (%)	30.9	32.7	36.4	100
Col (%)	100	100	100	100

Chi-square value: 71.0197; p-value: <0.0001

psychological and psychosomatic disturbances more frequently and intensively than morning types and showed more problems in coping with environmental and social demands.

In our study rate of sneezing was higher in evening chronotype group [39(97.5%)] compared to the intermediate chronotype group [35(97.2%)] and it was statistically significant (p<0.0001).

We also found that rate of itching problem was higher in evening chronotype patients' group [9(22.5%)] compared to intermediate chronotype group [4(11.1%)] which was statistically significant (p = 0.0114).

In intermediate chronotype, 5 (13.9%) patients had rhinorrhoea. In evening chronotype, 28 (70.0%) patients had rhinorrhoea. Association of rhinorrhoea vs group was statistically significant (p<0.0001).

In our study we found that 31 (77.5%) evening chronoype patients had asthma whereas on the other hand 18 (50.0%) intermediate chronotype patients had asthma and only 1 (2.9%) morning chronotype patients had asthma. This was statistically significant (p<0.0001).

Torsvall *et al*.[9] in their study found that the morning active individuals had fewer sleep complaints than the evening active individuals. The correlation was high (r-0.79, p-value less than 0.001) for the index between the two administrations with a 1-a interval in between. Those who had changed from shift work to day work tended to report a more pronounced morning active disposition. However the interindividual consistency was still pronounced.

In our study more evening type patients 38 (95.0%)] had sleep disturbance due to social media compared to intermediate chronotype patients [25(69.4%)] which was statistically significant (p<0.0001).

Merikanto *et al*.[10] showed that earlier studies have found associations of chronotypes with a range of health-related factors. In the light of these findings, the behavioral trait of eveningness in particular associates with determinants that might have a negative impact on health. In this study, based on a random sample of population aged 25-74 years living in five large geographical areas in Finland (N = 6089), it was tested whether the evening chronotypes have the increased odds for respiratory symptoms and diseases. As a result, after controlling for socio-demographic and lifestyle factors, it was observed that evening-types had wheezy breathing without respiratory infection, with diagnosed or treated bronchial asthma, who woke up due to shortness of breath, who woke up due to difficulty in breathing, wheezy breathing with dyspnea, wheezy breathing as such and medication for asthma more often than morning-types (odds ratios (ORs) of 1.5-1.9) and intermediate-types (ORs of 1.3-1.6). In addition, evening-types had current medication for asthma and awoken in coughing more often (OR = 1.5 and OR = 1.4, respectively) than morning-types. Evening-types did have a diagnosed or treatedchronic bronchitis more frequently than others. Our results suggest that the behavioral trait of eveningness associates had the increased odds for the bronchial asthma and nocturnal asthma in particular.

In our study it was found that in morning chronotype, 1 (2.9%) patient had asthma. In intermediate chronotype, 18 (50.0%) patients had asthma. In evening Type, 31 (77.5%) patients had asthma. Association of asthma vs. group was statistically significant (p<0.0001).

Honma *et al*.[11] evaluated sleep quality and circadian rhythms in allergic rhinitis patients and investigated its relationship to the symptom severity. A total of 19 allergic rhinitis patients and 17 healthy controls were recruited. Symptom severity was assessed by questionnaires and nasal mucus cytokine levels using the Bead-based multiplex immunoassay, subjective sleep quality by the Pittsburgh Sleep Quality Index, diurnal somnolence by the Epworth Sleepiness Scale and chronotype, a phenotype of circadian rhythms by the Munich Chronotype Questionnaire. Objective sleep quality was assessed by 2-week actigraphy. Melatonin and cortisol rhythms were analyzed using urine radioimmunoassay and the cosinor fitting. Poor sleep quality was observed in patient group from the Pittsburgh Sleep Quality Index (6.6±0.6) with 68% reporting poor sleep. No significant group differences were observed in daytime sleepiness vs. chronotype. Nasal mucus IL-17 level was higher in allergic rhinitis patients with significantly prolonged sleep latency. IL-6 level showed negative correlation to sleep duration. Urinary aMT6S, a melatonin metabolite and cortisol levels were higher in patients without any differences in the daily rhythms. Prolonged sleep latency associated with allergic rhinitis had a significant impact on patients' sleep quality. Increased aMT6S in patients suggests that melatonin, having antioxidative and immunomodulatory effects, may play an important role in the pathogenesis of Allergic Rhinitis.

Limitations-Our study had small sample size and we had to do time-bound study. Our study yielded

encouraging results, which opens up other areas of research on chronobiology and allergic rhinitis.

CONCLUSION

Our findings indicate that sneezing and itching were more prevalent in patients of Evening chronotypes, compared to those of Intermediate and Morning types. These differences were statistically significant. Rhinorrhoea and Asthma had a considerably higher prevalence among patients classified as Evening type, as compared to those classified as Intermediate Type and Morning Type. Nasal obstruction, nasal polyp and skin rash were shown to be more prevalent in patients of Evening chronotypes, as opposed to those of the Intermediate and Morning types. These differences were statistically significant. A significantly greater percentage of Evening Type patients experienced sleep disturbances as a result of social media usage. There is emerging evidence regarding an increasing incidence of allergic diseases in India. Also, treatment of allergic rhinitis is not up to the standard in a significant proportion of cases due to multiple factors relating to unaffordability to buy medications, low national gross domestic product (GDP), religious beliefs and stigma regarding chronic ailment, lack of education, lack of allergy specialists and lack of access to allergen-specific immunotherapy for allergic rhinitis. By addressing these multiple environmental and social factors and by modifying our lifestyles it is possible to control Allergic Rhinitis to a great extent.

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