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ORIGINAL PAPER/*PRACA ORYGINALNA*

Autonomic nervous system dysfunction and the effect of vitamin D level in vasomotor rhinitis patients

Dysfunkcja autonomicznego układu nerwowego i wpływ stężenia witaminy D u chorych na naczynioruchowy nieżyt nosa

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ABSTRACT

Introduction: Considering the role of the autonomic nervous system in thermoregulation, studies showing that it plays an important role in the pathophysiology of vasomotor rhinitis triggered by temperature change have been known for a long time.

Aim: The present study was to evaluate patients with vasomotor rhinitis who have no organic causes for symptoms of thermodysregulation such as chills, hot flashes/sweating, and to determine the effect of regulator hormone vitamin D on symptoms of rhinitis and thermoregulation.

Material and methods: Between January and December 2019, a total of 183 patients were diagnosed with non-allergic persistent rhinitis. Smoking history and drugs used were questioned. Allergy tests were performed with either a skin prick test or specific IgE measurement. Patients were evaluated for endocrinological diseases, anemia and vitamin D levels. Presence of nasal polyposis was evaluated with anterior rhinoscopy. Currently there is no validated test method that can show autonomic dysfunction. We prepared a questionnaire consisting of 24 questions that evaluates thermodysregulation and used it in this survey.

Results: 130 patients were diagnosed as vasomotor rhinitis. The distribution of patients by gender was 26 men and 104 women. All patients had persistent moderate to severe rhinitis. A total of 81 (62%) patients had cold intolerance and 49 (38%) had heat intolerance. Of the patients with cold intolerance, 76 stated that their complaints have increased upon a sudden decrease in external environmental temperature. All patients with heat intolerance were complaining of excessive sweating. With regular sports activities, 24 patients reported decreased rhinitis symptoms. Of the patients with vasomotor rhinitis, symptoms of rhinitis decreased in 42 (32%) due to sunbathing. A total of 69 (53%) patients received vitamin D replacement therapy. All of these patients stated that their complaints decreased after vitamin D replacement.

Conclusions: We showed that the coexistence of vasomotor rhinitis and thermoregulation disorder is common. We think that thermoregulation disorder may be due to autonomic nervous system dysfunction and may share common mechanisms with vasomotor rhinitis.

KEY WORDS

autonomic nervous system dysfunction, vasomotor rhinitis, vitamin D level, rhinitis.

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INTRODUCTION

The autonomic nervous system helps us adapt to the external environment by regulating the functioning of the internal organs and plays an important role in homeostasis. It consists of two parts that work opposite each other. The sympathetic nervous system is known as run or fight, and the parasympathetic nervous system is known as rest and digest [1]. Presently, it is thought that many diseases whose etiology is not clearly clarified are related to autonomic nervous system abnormality. Considering the role of the autonomic nervous system in thermoregulation, studies showing that it plays an important role in the pathophysiology of vasomotor rhinitis triggered by temperature change have been known for a long time. Firstly, Hill and Muecke showed that temperature changes on the cutaneous surface trigger ischemia rather than vasodilation in the nose and throat. The diagnosis of vasomotor rhinitis was made at the beginning of the 20th century; the blind folded patient immersing his finger in a glass filled with ice water and then is triggered by sneezing, rhinitis symptoms [2].

AIM

The current study aims to evaluate patients with vasomotor rhinitis who have no organic causes for thermodysregulation such as chills, hot flashes/sweating complaints and to determine the relationship between the level of vitamin D which is a regulator hormone and thermoregulation.

MATERIAL AND METHODS

We evaluated 561 patients with rhinitis complaints between January and December 2019 in Hacettepe University Immunology and Allergy Outpatient Clinic. 183 patients were diagnosed with non-allergic persistent rhinitis. Smoking history in the last 6 months and drugs used (ACE inhibitor, α-blocker, β-blocker, oral contraceptive, etc.) were questioned. Skin and serum allergy tests were performed. Patients were examined for endocrinological diseases such as hypothyroidism and hyperthyroidism. Anatomical disorders in the nose and nasal polyp were checked by anterior rhinoscopy.

130 patients were diagnosed as vasomotor rhinitis due to their complaints that continued throughout the year and when patients were exposed to the allergen which they were sensitive to, there was no increase in complaints. There is no valid test that can show autonomic dysfunction so thermoregulation of patients was evaluated with a questionnaire consisting of 24 questions. Patients were examined to rule out organic causes that may cause thermoregulation disorder and to determine vitamin D level. < 10 µg/l 25-OH Vitamin D is seriously deficient, 10–24 µg/l 25-OH Vitamin D is moderately deficient, and 25-80 µg/l 25-OH Vitamin D is considered optimum. The diagnosis of anemia was made according to the definition of the World Health Organization and was considered as anemia below hemoglobin (Hb) 13 g/dl in male patients and 12 g/dl in female patients. Free T4 and TSH (thyroid stimulating hormone) were measured for patients to evaluate thyroid functions. The reference range for TSH was 0.38–5.33 IU/ml and for free T4, the reference range was 7.86–14.41 pmol/l. High thyroid hormones with low TSH were considered as hyperthyroidism, and low serum sT4 levels with high TSH were considered as primary hypothyroidism. When serum sT4 level was normal and TSH level was high it was defined as subclinical hypothyroidism.

Body mass index (BMI) was calculated by dividing body mass (kg) by the square of its height in meters. According to the BMI range, it was defined as < 20 weak, 20–24.9 kg/m^2 normal, 25–29.9 kg/m^2 light fat, 30–34.9 kg/m^2 fat, 35–44.9 kg/m^2 important for health, 45–49.9 kg/m^2 overweight and > 50 morbid obese.

This study was approved by the institutional review board, College of Medicine Research Center, Hacettepe University (reference number GO/19/205). All patient data were confidential and used for research purposes only, and all the patients were coded with a serial number without mentioning their names; and informed consent was obtained from the patients. This study was conducted in accordance with the Declaration of Helsinki.

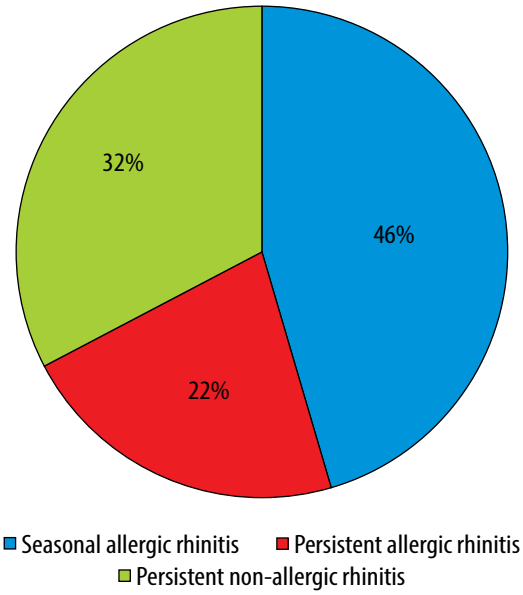

FIGURE 1. Distribution of rhinitis patients admitted to the outpatient clinic in January-December 2019

RESULTS

During 1 year, 561 patients showed rhinitis symptoms. Of these patients, 183 were diagnosed as persistent non-allergic rhinitis, 122 patients were persistent allergic rhinitis, and 256 patients were seasonal allergic rhinitis (Figure 1). Allergy tests were performed with perineal allergens in patients with allergic rhinitis. Dermatophagoides pteronyssinus sensitivity in 97 patients, cat sensitivity in 27 patients, Blattella germanica sensitivity in 7 patients, dog sensitivity in 5 patients, aspergillus sensitivity in 3 patients, alternaria alternata sensitivity in 3 patients, cladosporium sensitivity in 1 patient were determined in with persistent rhinitis. 53 of 183 persistent non-allergic patients were diagnosed with other non-allergic rhinitis such as occupational rhinitis and drug-induced rhinitis. 130 patients were included in the study.

The distribution of patients by gender was 26 men and 104 women, and the mean age of the patients was 34.86 ±12.43. The average age of male patients was 32.96 (18–65), and the average age of female patients was 35.34 ±12.45 years (19–65). The average BMI of male patients was 24.61 ±12.37 (18.7–30.4), and the average BMI of female patients was 24.15 (17–40.2). 44 (4 male, 44 female) patients were followed up with the diagnosis of asthma and the duration of the disease was on average 8.09 ±8.42 years (1–30 years).

All patients had persistent moderate to severe rhinitis with an average disease duration of 10.11 ±9.42 (1–45) years. The duration of the disease was 9.99 ±9.61 years (1–45) on average in female patients and 10.57 ±8.89 years (1–40) in male patients.

Eight patients had a history of upper airway surgery, and 5 of these patients had increased complaints after rhinoplasty surgery.

Microcytic anemia was present in 4 of 130 patients and the average hemoglobin (Hb) value was determined as 13.41 ±1.9 g/dl. The mean Hb value was 15.22 g/dl (12.8–17.4) in male patients and 12.99 (8.6–16.1) g/dl in female patients.

Hypothyroidism was detected in 3 patients and diabetes was detected in 2 patients. All of the patients with anemia were women and 3 of them had paradoxically heat intolerance and 1 patient has cold intolerance as expected. The mean value of vitamin D was 17.56 ±15.59 µg/l (5–73.5) in male patients, and 14.82 ±9.59 µg/l (5.25–49) in female patients.

Vitamin D levels of 40 patients were found to be seriously deficient. 36 of these patients were female and 4 were male. Vitamin D levels of 52 patients were found to be moderately deficient. 41 of these patients were women and 11 were men. Vitamin D level of 18 patients was determined at the optimum level. 16 of these patients were women and 2 were men. Vitamin D levels of 11 patients were measured in the outer center and were found to be low. Six of these patients were women and five were men. Nine patients did not want to have their vitamin D values measured.

Three patients had menstrual irregularities, 4 patients were in menopause. Three patients undergoing menopause had cold intolerance and 1 patient had heat intolerance (Table 1).

Skin prick testing was performed to demonstrate atopy determination and allergen sensitivity in patients. The Phadiatop test was studied as a screening test in 7 patients that might affect DPT results such as drug use. Phadiatop is a commercially available qualitative serological test employed for screening of allergic sensitization in patients with suspected allergic diseases. Allergen sensitivity was detected in the SPT of 20 patients. Nine patients had pollen sensitivity, 5 patients had dermatophagoides pteronyssinus sensitivity, 3 patients had pollen and dermatophagoides pteronyssinus sensitivity, 2 patients had pollen and cat sensitivity, 1 patient had dermatophagoides pteronyssinus and cat sensitivity. Phadiatop was measured to class 0 (< 0.35 kU/l) in 3 of 7 patients, class 1 (0.35–0.70 kU/l) in 1 patient, class 2 (0.70–3.5 kU/l) in 2 patients, and class 3 (3.5–17.5 kU/l) in 1 patient. Patients were diagnosed as vasomotor rhinitis when their complaints were not increased after allergen exposure with anamnesis evaluated.

81 of 130 patients had cold intolerance and 49 had heat intolerance. 80 patients with cold intolerance stated that they suffer from a runny nose or congestion when they get out of bed in the morning. The patients stated

TABLE 1. Demographic characteristics of patients, patients' laboratory results

Parameter	Male	Female	Total
N	26	104	130
Average age	32.96 (18–65)	35.34 (19–65)	
BMI	24.61 (18.7–30.4)	24.15 (17–40.2)	
Asthma (disease duration 8.09 years (1–30))	4	40	44
Rhinitis disease duration	9.99 years (1–45)	10.57 years (1–40)	
Average HB value	15.22 (12.8–17.4) gr/dl	12.99 (8.6–16.1) gr/dl	
Average vitamin D value	17.56 (5–73.5) µg/l	14.82 (5.25–49) µg/l	
Vitamin D level seriously deficient ($n = 40$)	4	36	40
Vitamin D level moderately deficient ($n = 52$)	11	41	52
Vitamin D level is optimum ($n = 18$)	2	16	18
Cold intolerance	13	68	81
Heat intolerance	13	36	49

that they had experienced rhinitis symptoms when they woke up on average on 21.62 days (5–30) per month. 76 patients with cold intolerance stated that their complaints increased in environments that caused heat changes such as air-conditioned environment, long waiting in front of the refrigerator or exposure to wind. When these complaints were examined, 62 patients had sneezing, 45 patients had cough, and 63 patients had an increased complaint of excessive chills. Sneeze was the most common complaint.

78 of 81 patients complained of excessive chill in their lower or upper extremities. 60 of these patients stated that they could not sleep without wearing socks at night because their feet were very cold. 49 patients stated that they were wearing underwear or thermal tights. 45 patients stated that they were wearing underwear or thermal tights during the cold season and 4 patients during the year. In the cold seasons, patients stated that they wore underwear or thermal tights on average on 22.3 days/month. 80 patients with cold intolerance stated that they were wearing warm clothes more often than other people. Patients with cold intolerance stated that the frequency of shower was 3.7 days per week. 66 patients stated that they took a shower with extremely hot water and 15 patients with warm water. 60 patients stated that the symptoms of rhinitis increased after cold food consumption, especially their sneezing complaints.

Of the 49 patients with heat intolerance, 13 were men and 36 were women, and the patients complained of rash for an average of 13.65 (2–60) years. All of these patients had complaints of excessive sweating. 28 patients complained of excessive sweating in the head and neck, 19 patients in lower and upper extremities, 31 patients in the trunk and back, and 19 patients palms and soles of feet. 47 patients stated that they experienced rhinitis symptoms when they woke up on average on 21.94 days (6–30) per month. The complaints of 12 patients continue throughout the year, and 37 patients complain of seasonally altered symptoms. It was found out that the complaints of 16 patients increased in the spring season, 7 patients complained of increasing in the summer season, 8 patients complained of increasing in the winter season and 3 patients complained of increasing in both spring and autumn seasons. 35 patients stated that they woke on average on 12.28 days a month due to night sweating complaints. 23 patients stated that they had to wake up due to night sweats and have to change underwear for an average of 10 days a month. 48 patients with heat intolerance stated that triggered nasal complaints by remaining in a warm environment or sun exposure. 31 patients expressed an increase in their rhinitis symptoms after the consumption of hot food. Patients with heat intolerance stated that they had a bath on 3.97 days per week. 41 patients stated that they took a shower with warm water, 5 patients with cold water and 3 patients with hot water. 36 patients stated that their rhinitis symptoms increased with effort.

While the lifestyle of all patients was questioned, 24 patients stated that they were regularly doing sports and their symptoms of rhinitis were decreased. Patients who could not exercise regularly also stated that they have noticed there was a decrease in symptoms of rhinitis when they were exercising from time to time. 24 patients of regular exercisers included 20 females and 4 males; (with 12 and 8 female patients with cold and heat intolerance respectively and with 1 and 3 male patients with cold and heat intolerance respectively).

42 patients stated that they benefited from the sunshine and rhinitis symptoms eased especially when

the sun exposure time increased. 9 patients were male and 7 of them had cold intolerance and 2 had heat intolerance. And also 33 were female; 7 of them had heat intolerance and rest of 26 had cold intolerance.

Nine patients had a history of systemic steroid use for rhinitis symptoms. All of these patients were women and 3 had heat intolerance, while 6 had cold intolerance. 8 of 9 patients stated that they benefited from systemic steroid use.

69 patients received vitamin D replacement therapy. 62 of these patients were female and 7 patients were male. For females, 41 of them had cold intolerance and 21 of them had heat intolerance. For males, heat intolerance was detected in 4 of them and cold intolerance in 3 of them.

All of these patients stated that their complaints decreased after vitamin D replacement therapy. It was found that 90 of 130 patients had a thermoregulation disorder in some of their family members. 44 patients were followed up for asthma and 37 patients were receiving regular medical treatment. For these 37 patients, 27 were receiving inhaled corticosteroids (ICS) and 10 were receiving ICS + long-acting β-agonists (LABA) (Table 2).

DISCUSSION

The prevalence of allergic and non-allergic rhinitis varies geographically and is 10–40% [3]. When rhinitis patients are evaluated, the rate of persistent non-allergic rhinitis patients is 17–52% [4]. There are no special symptoms and signs that discriminate vasomotor rhinitis and allergic rhinitis patients. Therefore, it is necessary to analyze the factors that trigger the patient's complaints. In allergic rhinitis; type 1 hypersensitivity reaction develops with exposure to the allergen although vasomotor rhinitis is mainly triggered by physical factors such as cold exposure, sudden heat change, fatigue, and wet skin [5]. All patients participating in our study had rhinitis complaints triggered by cold exposure, sudden temperature change and bathing. Although there are studies showing that autonomic nervous system dysfunction causes lower respiratory diseases but its effect on upper airway diseases has not been clearly explained. In some chronic diseases, including cardiovascular diseases, chronic rhinosinusitis frequently accompanies the main disease. This is thought to be secondary to autonomic nervous system dysfunction [6, 7]. Nose plays an important role in heating, humidification and cleaning of inspired air, and it is rich in autonomic innervation. Vascular structures in the nasal mucosa are constricted through α2 receptors, and dilated with β2 receptors. Alpha receptors are more dominant in the nasal vascular structures than beta receptors [8, 9]. Sympathetic activity plays a key role of vasoconstriction in nasal mucosa. The vascular structures in the nasal mucosa constrict with activation in the sympathetic nervous system, the vascular structures become dilated by inhibition of the sympathetic nervous system. In the nose, parasympathetic nervous system stimulation causes vasodilation through M1 and M3 muscarinic receptors [10]. Vasomotor rhinitis develops due to parasympathetic system hyperfunction or impaired sympathetic/parasympathetic system balance. With the activation of the cholinergic system; rich lysozyme, Ig A and glycoprotein is secreted and this causes nasal congestion, a runny nose, and triggers facial pain. In the sneeze reflex; the afferent arm of the autonomic nervous system, H1 receptors and the trigeminal nerve play a role, the first stage of sneezing occurs with increased secretion as a result of parasympathetic activation [11]. Core temperature in the central nervous system is constant (37 ±0.5°) but skin temperature varies according to the outdoor temperature [12]. The number of receptors sensing the temperature in the central nervous system is higher than the number of receptors sensing the cold. Peripheral thermoreceptors are located on the skin and gastrointestinal system. Vasodilation and sweating cause heat loss on the skin although increase in the metabolic rate and tremor increase heat, vasoconstriction prevents heat loss. Cold-sensitive receptors are located in the epidermis, heat-sensitive receptors are located in the dermis. Unlike the central nervous system, the number of receptors sensitive for cold in the skin is higher than the number of receptors sensitive for heat [13]. In the cold environment, sympathetic nervous system is activated and epinephrine binds to alpha receptors and leads to vasoconstriction. In the heat environment, sympathetic activity suppresses and blood flow in the skin increases [14].

Sweating occurs due to the increase in core temperature and causes heat loss through evaporation. When the environmental temperature decreases, it may not be enough to reduce the heat loss through the skin. In this case, heat production occurs due to an increase in the metabolic rate. This happens in two ways: with tremor,

TABLE 2. The patients' lifestyles and treatments

Variable	Total	Benefit rate
Regular sports	24	24 (100%)
Sunbathing	42	42 (100%)
Vitamin D replacement	69	69 (100%)
Systemic steroid	9	8 (89%)
Nasal steroid	127	
Antihistamines	127	
Leukotriene antagonist	63	

firstly carbohydrates are consumed and involuntarily muscle contraction occurs with lipid oxidation. The second way is through heat production in brown adipose tissue. Sneezing is one of the evolutionary protective reflex aimed at increasing body temperature by triggering especially in the cold environment such as cough. When organic causes are excluded, it is thought that autonomic nervous system dysfunction is the cause of heat imbalance in patients with complaints of cold or hot flashes/sweating. The existing pathophysiological pathway is common with vasomotor rhinitis. The current study shows that all patients diagnosed with vasomotor rhinitis have a defect in thermoregulation and also we have seen that most of these patients have thermoregulation disorder in their family.

There is no specific test that can detect autonomic nervous system dysfunction. Also, in patients with autonomic nervous system dysfunction, every organ or system may not be affected equally. It is not a coincidence that the triggering factor is a sudden heat change, especially in people with vasomotor rhinitis and thermoregulation disorders. There are some tests such as thermoregulatory sweat test, sudomotor function test, which show heat regulation disorder [15]. Sympathetic nervous system activation differs by gender. The capacity of women to inhibit the sympathetic nervous system is greater than in men. This is caused by hormones, especially estrogen. Therefore, sex hormones protect women against idiopathic hypertension. The reason why the majority of patients with vasomotor rhinitis are females is the ability to be suppressed by the activation of the sympathetic nervous system. In the current study, the majority of patients were women [16].

Vitamin D, defined as a regulatory hormone, is known to be associated with autonomic nervous system dysfunction. Vitamin D deficiency has been demonstrated in patients with cardiac autonomic suppression, orthostatic hypotension, and orthostatic tachycardia syndrome [17]. Vitamin D deficiency was noteworthy in our patients. Only 18 patients had optimum vitamin D levels. 69 patients stated improved thermoregulation and rhinitis complaints after replacement of vitamin D. The patients stated that as the duration of sunbathing increased, complaints of rhinitis decreased.

Upright posture, exercise and transition to temperature changes increase the heart rate. Increased heart rate indicates that the sympathetic nervous system is active [18–20]. In the current study, we observed that rhinitis symptoms regressed and thermoregulation improved with regular exercise in 24 patients. Although the role of histamine secreted from mast cells in allergic rhinitis is well known, histamine causes vasodilation by inhibiting norepinephrine secretion. Antihistamine therapy is useful in controlling rhinitis symptoms [21]. The current study shows that antihistamine therapy was effective in controlling patients' symptoms. Although there is no study that shows the effectiveness of leukotriene antagonists in the treatment of vasomotor rhinitis, it was prescribed for controlling symptoms in patients.

Endogenous glucocorticoids cross the blood-brain barrier and reach the nervous system. There are 2 types of receptors in the nervous system. The sympathetic system is activated by the stimulation of mineralocorticoid receptors (MR) but the sympathetic nervous system stimulation and cardiovascular effects of glucocorticoid receptors are not well known. In the current study, 88% of patients stated that they had previously used systemic steroids and had improved rhinitis symptoms and improved thermoregulation. Therefore, for patients with severe persistent rhinitis, treatment should be started with a systemic steroid and continued with nasal steroids.

CONCLUSIONS

As a result, the coexistence of vasomotor rhinitis and thermoregulation disorder is common. We think that thermoregulation disorder may be due to autonomic nerve dysfunction after the organic causes are excluded. Changes in lifestyle such as sunbathing, sports, weight control and vitamin D replacement treatment have a regulatory effect on the autonomic nervous system. It may be beneficial to start a systemic steroid especially if the patient's complaints cannot be controlled with nasal steroids, antihistamine and leukotriene antagonists, in case of intense temperature changes in the external environment. Excessive heat or cold food consumption may trigger complaints of patients with vasomotor rhinitis and this should not be confused with gustatory rhinitis. Even if atopy is detected in patients followed by chronic rhinosinusitis, the association of autonomic nerve dysfunction and vasomotor rhinitis should not be forgotten.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX 1. ASSESSMENT OF COLD INTOLERANCE

1. Do you feel cold more than normal for your age?
Yes ☐ No ☐

2. When you wake up in the morning, do you have a runny nose, nasal congestion, sneezing?
Yes ☐ No ☐

3. Do you have a runny nose or nasal congestion that when you are exposed to the air-conditioned environment, wind and cold?
Yes ☐ No ☐

4. Are your hands and feet colder than these of your peers?
Yes ☐ No ☐

5. Do you wear socks at night as your feet are cold?
Yes ☐ No ☐

6. Do you wear thermal or warm underwear as you feel are colder than your peers?
Yes ☐ No ☐

7. Do you wear warmer body temperature regulation clothes because you are cold compared to your peers?
Yes ☐ No ☐

8. Do you bath with very hot water?
Yes ☐ No ☐

9. Do you have complaints such as nasal congestion, sneezing and coughing after eating cold food or cold drinks?
Yes ☐ No ☐

10. Do you like going to a Turkish bath or hot bath to warm your body?
Yes ☐ No ☐

APPENDIX 2. QUESTIONNAIRE 2

1. Do you have more complaints such as sweating or hot flashes than your peers?
Yes ☐ No ☐

2. Do you have complaints such as a runny nose, nasal congestion, sneezing or coughing due to sweating or hot flashes at night or when you sleeping ?
Yes ☐ No ☐

3. Do you have complaints such as a runny nose, nasal congestion, sneezing or coughing when you move from a cold environment to a warm environment or very hot weather?
Yes ☐ No ☐

4. Do your hands and feet sweat more than your peers' hands?
Yes ☐ No ☐

5. Do you wake up at sleeping because you sweat?
Yes ☐ No ☐

6. Do you wear light clothes because you sweat more than your peers?
Yes ☐ No ☐

7. Does sunbathing increase your sweating and hot flashes?
Yes ☐ No ☐

8. Do you frequently take a bath with cold water or go into a cold pool?
Yes ☐ No ☐

9. Do you have complaints such as a runny nose, nasal congestion, sneezing or coughing after consuming hot drinks or food?
Yes ☐ No ☐

10. Do you often use the air conditioner to cool off?
Yes ☐ No ☐