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Hot and Cold Natures and Some Parameters of Neuroendocrine and Immune Systems in Traditional Iranian Medicine: A Preliminary Study

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ABSTRACT

Aim: The purpose of this study was to assess differences in persons of a Hot or Cold nature (according to traditional Iranian medicine), in terms of changes in their neuroendocrine and immune systems.

Materials and methods: Thirty-seven (37) male volunteers (20–40 years old) were divided into two groups, by whether they had a Hot or Cold nature. In addition, the Warmth/Coldness ratio of all the volunteers was assessed. Plasma concentrations of epinephrine, norepinephrine and cortisol, and also the concentrations of interferon (IFN)-γ and interleukin (IL)-4 produced by peripheral blood mononuclear cells stimulated by mitogen were measured.

Results: The results showed that norepinephrine/epinephrine and norepinephrine/cortisol ratios were significantly higher, and that there was a borderline significantly increased IL-4/IFN-γ ratio in the Hot nature group compared with those in the Cold nature group. In addition, there was a significant linear positive correlation between the norepinephrine/epinephrine and Warmth/Coldness ratios and a significant nonlinear association between the IL-4/IFN-γ and Warmth/Coldness ratios.

Conclusions: It can be deduced that the persons of a Hot nature had more sympathetic nervous system activity, less adrenal sympathetic, adrenal corticosteroid, and parasympathetic nervous system activities and more deviation of the immune system toward T-helper (Th)2 responses than the persons of a Cold nature. Moreover, the activity of the sympathetic nervous system was increased and adrenal sympathetic was decreased with an increasing Warmth/Coldness ratio. Furthermore, when the person's nature veered toward extreme Warmth or extreme Coldness, the deviation of the immune system toward Th2-like responses was greater, but this increased deviation was much more marked when veering toward extreme Warmth than toward extreme Coldness.

INTRODUCTION

For the past 30 years, in order to implement the slogan "Health for Everybody up to 2000," the World Health Organization has considered the development of traditional medicine.[1] In countries where the dominant health care system is based on allopathic medicine, or where traditional medicine has not been incorporated into the national health care system, traditional medicine is often termed complementary, alternative, or nonconventional medicine.[1–3] The

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traditional medicine practiced in Iran is termed Traditional Iranian medicine (TIM), the roots of which go back over 2000 years.[2,3] However, although the usefulness of TIM, and the fact that it is associated with very few side-effects, has been demonstrated, we know little about its mechanisms, and despite the progression of various sciences, the therapeutic methods of TIM, like other traditional medicines, are based on experiences and texts belonging to a very far distant past.

Cold and Hot natures (*Midzaj*) have been believed to exist in TIM and also in many other traditional medical theories, including Unani (Greek), Arabic, Roman, Indian, European, and Chinese traditional medicines.[4–9]

The elaboration of the theory of Hot and Cold natures finds its origin in ancient Greece, by Hippocrates (Greek physician, 460–375 BC) and Galen (199–129 BC).[6,9,10] By the fifth century AD, the center of classical learning shifted to the East. The most important piece of work, carried out in the East, was the book *Canon of Medicine* (*Qanun dar Tib*), written by Avicenna (Persian physician, 973–1037 AD). The book was an excellent collection and classification of all the ancient beliefs that still survived, mixed with the medical theories of the time and Avicenna's own experiences as a physician.[9,10]

The most important rule of all the ancient theories was the maintenance of the balance between the fundamental body elements, among which Warmth and Coldness played an absolutely essential role. In the humoral theory, in which people are categorized regarding their dominant body fluid, the people with a dominant Hot humor (sanguine temperament that is Hot and Moist and choleric temperament that is Hot and Dry) were considered to have a Hot nature, and the people with a dominant Cold humor (melancholic temperament that is Cold and Dry and Phlegmatic temperament that is Cold and Moist) were considered to have a cold nature.[4–9] This categorization is performed regardless of whether a person is healthy or sick, infant or advanced in years, and takes account of a unique combination of all his/her inherited and concrete traits and concrete conditions of his/her living and activities.[11] Some characteristics of the abovementioned temperaments are as follows[12]:

- *Sanguine Temperament*—This temperament is typified by a fair and ruddy complexion, full muscular development, large full veins, and a strong pulse. These are confident and positive people who are rarely anxious. They are very prone to involve themselves with physical excesses and, as a result, these people often suffer from injuries and their sequelae. This type of temperment has also been called the "muscular" temperament.
- *Phlegmatic Temperament*—Persons with this temperment have a fair complexion, light hair, general softness and laxity of tissues, and pulses that are soft and wide. Because of the excessive metabolic activity of the immune system, heat tends to be drawn inward and the exterior is cold; hence people of this type tend to feel the cold acutely. The Phlegmatic type of patient is slow and sluggish, apathetic, and not readily excited, and easily becomes flabby and overweight. This type of temperment has also been called the "lymphatic" temperament.
- *Choleric Temperament*—This temperment is characterized by a slim build and by much nervous activity. These are passionate people, quick to become excited or angry and just as quick to forget their excitement. They live on their nerves and, because of this, they are susceptible to brain and nervous disorders. Their pulses tend to be sharp and quick. Their skin appears yellowish, and this temperament occurs often in those with brown hair. This type of temperament has also been referred to as the "nervous" temperament.
- *Melancholic Temperament*—The person usually has a darkish complexion and appears emaciated. The patient's tissues are hard and dry and the pulse is narrow and thready. Patients with this temperament are prone to frequent spells of pessimism, a gloomy state of mind with much depression and moroseness.

When attempting to determine a person's temperament, it is observed that manifestation of intermediate forms or combinations of two or more temperaments are the rule rather than the exception. Therefore, most people are under influence of both the Hot and the Cold elements.[12] So in addition to categorization of people to the Hot and the Cold natures, it is possible to evaluate the severity of each nature in a person. The relative severity of Warmth to Coldness can be shown as Warmth/Coldness ratio. In a person with a very Hot nature, the severity of the Warmth element is high and that of Coldness element is low. Therefore, in such a person, the Warmth/Coldness ratio is high. In a person with a very Cold nature, the severity of the Warmth element is low and that of the Coldness element is high. Therefore, in such a person the Warmth/Coldness ratio is low.

The brain and the immune system are the two major adaptive systems of the body. The last 2 to 3 decades provided strong evidence that the central nervous system (CNS) receives messages from the immune system and *vice versa* messages from the brain modulate immune functions. Thus, the brain and the immune system are involved in functionally relevant *cross-talk*, whose main function is to maintain homeostasis.[13]

Two pathways link the brain and the immune system: the autonomic nervous system (ANS), and the pituitary–adrenal axis.[13] However, the adrenal medulla is often activated and secretes catecholamines in association with the peripheral sympathetic nervous system, but under certain circumstances (e.g., during hypoglycemia), the adrenal medulla is probably activated selectively, with less involvement of the peripheral sympathetic nervous system.[14] Furthermore, although there is considerable overlap between the actions of epinephrine and norepinephrine, there are also some differ-

ences, since epinephrine tends to react more strongly with β-adrenoreceptors, and norepinephrine with α-adrenoreceptors. There are, therefore, some differences between the peripheral sympathetic nervous system and adrenal medulla in affecting homeostasis.[14] The plasma concentrations of epinephrine, norepinephrine, and cortisol can be suitable parameters for the assessment of the activity of the sympathetic nervous system and adrenal glands. Therefore, the calculation of the norepinephrine/cortisol ratio is used for assessing the balance between peripheral sympathetic and adrenal corticosteroid activities. The norepinephrine/epinephrine ratio is a good marker for the assessment of the balance between peripheral sympathetic nervous system and adrenal sympathetic activity.[15–18]

Immune responses are divided into two groups: T-helper (Th)1 and Th2. Th1 responses accelerate cellular immunity and Th2 responses increase humoral immunity and also allergic reactions. These two types of immune responses inhibit each other[19] and on the other hand, influence CNS.[13] Since production of interleukin (IL)-4 is a marker of Th2 immune responses and interferon (IFN)-γ is the main cytokine produced in Th1 immune response, the ratio of the production of IL-4 to IFN-γ by peripheral blood mononuclear cells (PBMCs) is used to assess the deviation of immune responses toward Th2/Th1.[20]

Because of differing effects of the abovementioned systems on the homeostasis of the body,[21] it is postulated that the activity of the abovementioned systems may be different in persons of a Hot and Cold nature. The purpose of this study was to assess the differences between such individuals (according to TIM) in terms of the abovementioned systems.

MATERIALS AND METHODS

This work was carried out in accordance with the research committee of the Immunology, Asthma and Allergy Research Institute affiliated with Tehran University of Medical Sciences, and with the ethical standards set out in the Helsinki Declaration of 1975.

Selection of subjects

The subjects were chosen from healthy 20–40 year-old male volunteers, and their temperaments and natures were determined according to TIM, using a standard questionnaire, which is presented in Appendix A. The persons with a dominant Hot humor (sanguine and choleric temperaments) were considered to have a Hot nature, and the persons with a dominant Cold humor (melancholic and phlegmatic temperaments) were considered to have a Cold nature. The Warmth/Coldness ratio was calculated for all volunteers based on the results obtained by the questionnaire. Sampling of all the volunteers was performed from October 23, 2005 to December 22, 2005, between 3 PM and 5 PM. The volunteers were forbidden to consume any excessively Hot or Cold nature foods, or any kind of drug, in the 24 hours before sampling. According to the questionnaire, none of the participants had any kind of disease at the time of sampling, or any history of a chronic medical problem. In addition, to confirm the health of volunteers, part of the blood sample taken from the participants was used to carry out the following tests: blood cell count and differentiation, blood urea nitrogen, serum creatinine, triglyceride, cholesterol and uric acid, fasting blood sugar, and erythrocyte sedimentation rate. If any of the abovementioned parameters pertaining to a volunteer was abnormal, that volunteer was excluded from the study. Ultimately, 37 volunteers were chosen for the study and were allocated to one of two groups: Hot nature (22 persons) and Cold nature (15 persons).

Sampling

Volunteers rested for 1 hour before sampling. Ten (10) mL of heparinized blood was obtained and divided into two parts: one part for the hormonal assay and the other for the cytokine assay.

Hormone assay

The blood sample was immediately centrifuged at 4000 rpm at 4°C, and their plasma was separated and kept frozen at −70°C for the hormonal assay.

The concentrations of plasma epinephrine, norepinephrine, and cortisol (ng/mL) were determined using enzyme-linked immunosorbent assay (ELISA) kits. The ELISA kits used for the epinephrine and norepinephrine assay were purchased from IBL (Hamburg, Germany) and those for the cortisol assay from DBC (Ontario, Canada).

Isolation of the PBMCs

PBMCs were separated using a Ficoll-Hypaque density gradient (Sigma, St. Louis, MO), counted in a Neubauer hemocytometer (Precicolor, HBG, Germany), and their viability was assessed by Trypan (Sigma) blue dye exclusion.

Table 1. Means of Norepinephrine/Epinephrine, Norepinephrine/Cortisol, and IL-4/IFN-γ Ratios in Hot Nature and Cold Nature Groups

Mean	*Group*	*Ratio*
8.3314 ± 5.40834	Hot nature	Norepinephrine/epinephrine
3.5447 ± 3.10862	Cold nature	
5.8829 ± 5.189381	Hot nature	Norepinephrine/cortisol
2.9140 ± 1.56302	Cold nature	
1.8033 ± 1.54857	Hot nature	IL-4/IFN-γ
0.9047 ± 0.56534	Cold nature	

IL-4, interleukin-4; IFN-γ, interferon-γ.

Cell culture

PBMCs isolated from the whole blood samples were washed twice in RPMI 1640 and resuspended in the culture medium (RPMI 1640, fetal bovine serum 10%, HEPES 10 mmol/L, L-glutamine 2 mmol/L, gentamicin 50 μg/mL, penicillin 100 U/mL, streptomycin 100 μg/mL, and amphotericin B 0.25 μg) at a concentration of 10^6/mL. Two hundred (200) μL of the cell suspension was then added to the wells of a 96-well tissue culture plate, and 5 μg of mitogen (phytohemagglutinin, Sigma) was added to the wells. The plates were incubated for 72 hours (37°C, 5% CO_2, and 100% humidity). The cell culture supernatants were then harvested and kept frozen at −70°C for the cytokine assay.

Cytokine assay

The cell culture supernatants were analyzed for IL-4 and IFN-γ by ELISA techniques using commercially available kits (R & D Systems, Minneapolis, MN)

Data analysis

Norepinephrine/epinephrine, norepinephrine/cortisol, and IL-4/IFN-γ ratios for the Hot and Cold nature groups were compared using the nonparametric Mann-Whitney test.

The existence of a significant correlation between the abovementioned ratios and the Warmth/Coldness ratio was assessed using the nonparametric Spearman correlation test.

RESULTS

The means of norepinephrine/epinephrine, norepinephrine/cortisol, and IL-4/IFN-γ ratios in the Hot and Cold nature groups are shown in Table 1.

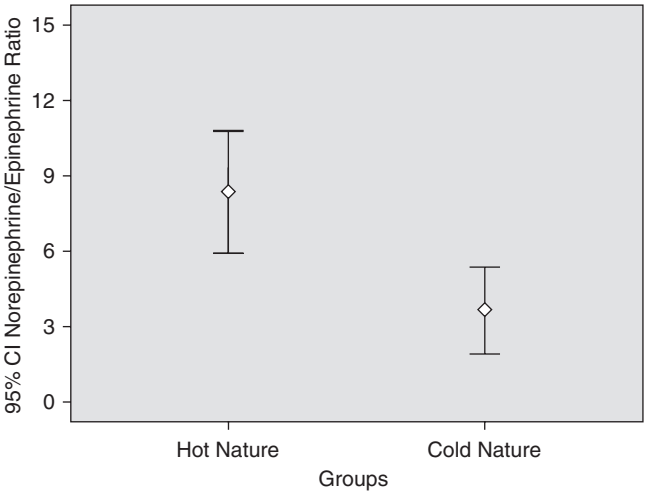

FIG. 1. Ninety-five percent (95%) confidence interval for the mean norepinephrine/epinephrine ratio in Hot and Cold nature groups. The mean norepinephrine/epinephrine ratio in the Hot nature group is significantly greater that in the Cold nature group (Mann-Whitney test; $p = 0.006$).

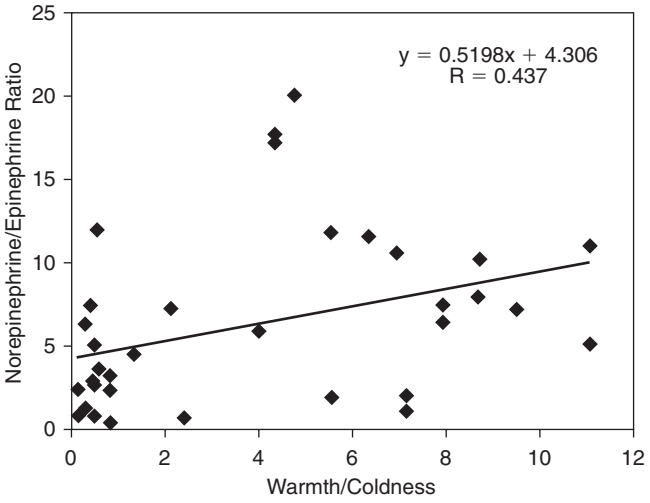

FIG. 2. The correlation between norepinephrine/epinephrine and Warmth/Coldness ratios. There is a significant positive correlation between norepinephrine/epinephrine and Warmth/Coldness ratios. The norepinephrine/epinephrine ratio is increased significantly, while the Warmth/Coldness ratio is increased (nonparametric Spearman correlation test; $p = 0.008$).

The mean norepinephrine/epinephrine ratio in the Hot nature group was significantly higher than that in the Cold nature group ($p = 0.006$; Fig. 1). Furthermore, there was a significant positive correlation ($r = 0.437$) between the norepinephrine/epinephrine ratio and the Warmth/Coldness ratio of participants ($p = 0.008$; Fig. 2). This means that as the Warmth/Coldness ratio increases, the norepinephrine/epinephrine ratio also significantly increases.

The mean norepinephrine/cortisol ratio in the Hot nature group was significantly higher than that in the Cold nature group ($p = 0.007$; Fig. 3). In addition, there was not a significant correlation ($r = 0.275$) between the norepinephrine/cortisol ratio and the Warmth/Coldness ratio ($p = 0.1$; Fig. 4).

The mean IL-4/IFN-γ ratio in the Hot nature group was higher than that in the Cold nature group. The difference between the two groups was of borderline significance ($p = 0.08$; Fig. 5). Furthermore, there was a significant correlation ($r = 0.387$) between the IL-4/IFN-γ ratio and the Warmth/Coldness ratio of the participants ($p = 0.022$). The correlation between the IL-4/IFN-γ ratio and the Warmth/Coldness ratio of the participants had a nonlinear association and, as shown in Figure 6, as the Warmth/Coldness ratio increased, at first the IL-4/IFN-γ ratio decreased slightly and then, after a cut point, increased sharply.

DISCUSSION

Because it seems that the imbalance between the temperates results mainly in derangement of the homeostasis,

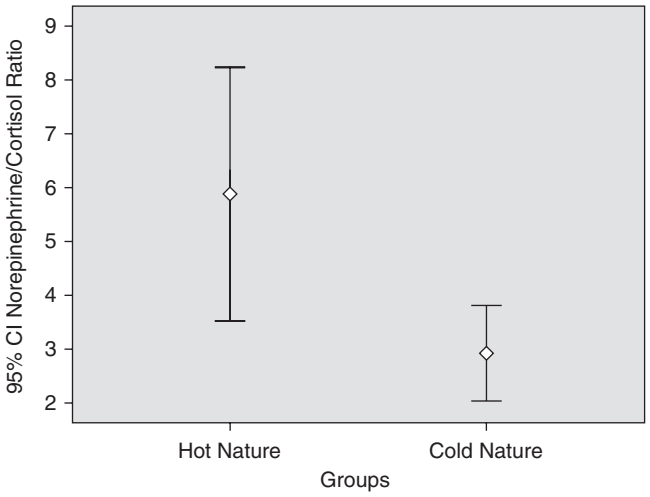

FIG. 3. Ninety-five percent (95%) confidence interval for the mean norepinephrine/cortisol ratios in Hot and Cold nature groups. The mean norepinephrine/cortisol ratio in the Hot nature group is significantly higher that in the Cold nature group (Mann-Whitney test; $p = 0.007$).

and on the other hand, as mentioned above, the cross-talk between the brain and the immune system is critical in maintaining the homeostasis, we tried to evaluate the differences of Hot and Cold nature persons in three main pathways by which brain and immune system cross-talk: the ANS, the adrenal glands, and shifting of the immune system toward a Th1/Th2 pattern.

As mentioned in the Introduction, in response to stresses, three main systems are activated in the body: the sympathetic nervous system, parasympathetic nervous system, and the pituitary–adrenal axis.[21,22] These systems also show a low level of activity in the absence of any stressors.[14] The purpose of the current study was to examine this hypothesis that the host factor (here, the warmth or coldness of one's nature) can determine the relative basic activity of the abovementioned systems. The comparison of the norepinephrine/epinephrine and norepinephrine/cortisol ratios between the Hot and Cold nature groups showed that Hot nature participants had significantly higher peripheral sympathetic activity but lower adrenal sympathetic and corticosteroid activity compared with the Cold nature participants. However, as the Warmth/Coldness of the nature increased, the ratio of peripheral sympathetic activity to adrenal sympathetic activity increased. It can therefore be concluded that increasing the Warmth of a person's nature is accompanied by an increase in their peripheral sympathetic activity and/or decrease in their adrenal sympathetic activity, whereas increasing the Coldness of a person's nature is accompanied by an increase in their adrenal sympathetic activity and/or a decrease in their peripheral sympathetic activity.

Since the pituitary–adrenocortical response is connected to the activity of the parasympathetic nervous system,[18,22] the ratio of blood norepinephrine to cortisol levels at rest has been suggested as providing an estimate of the balance between peripheral sympathetic and parasympathetic nervous system activities.[18,22] Therefore, it can be concluded from the abovementioned results that the Cold nature participants had higher parasympathetic activity in comparison with the Hot nature participants. These conclusions are in agreement with the complications relating to Hot or Cold nature dominance. For example, hypertension is a condition associated with a Hot nature, and so has a higher prevalence in persons of a Hot nature[23]; this can be attributed to the relatively lower parasympathetic (vagal) activity over a long period. By contrast, the hypotension associated with persons of a Cold nature may be due to the relatively higher parasympathetic activity, because it is well known that parasympathetic activity can reduce blood pressure, resulting in hypotension.[24,25] The rapid and deep pulse of Hot nature persons versus the slow pulse of Cold nature persons[4] can be attributed to the higher peripheral sympathetic nervous system and lower parasympathetic nervous system activities of Hot compared with Cold nature people, because the activity of the sympathetic and parasympathetic nervous systems causes the pulse rate to increase and decrease, respectively.[14] The finding that the ratio of peripheral sympathetic activity to corticosteroid activity did not increase with increasing Warmth/Coldness of nature showed that the activity of the parasympathetic nervous system did not increase with increasing Coldness of nature. This may be due to the influence of factors other than the severity of Warmth and Coldness of nature on parasympathetic activity.

The findings of high adrenal sympathetic and corticosteroid activities in Cold nature persons are in agreement with the findings of studies showing a close link between the adrenocortical corticosteroid and adrenomedullary sympa-

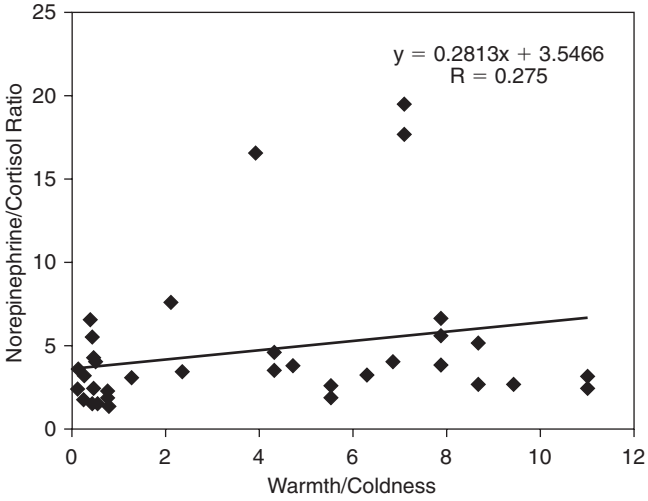

FIG. 4. The correlation between norepinephrine/cortisol and Warmth/Coldness ratios. There is not a significant positive correlation between norepinephrine/cortisol and Warmth/Coldness ratios (nonparametric Spearman correlation test; $p = 0.1$).

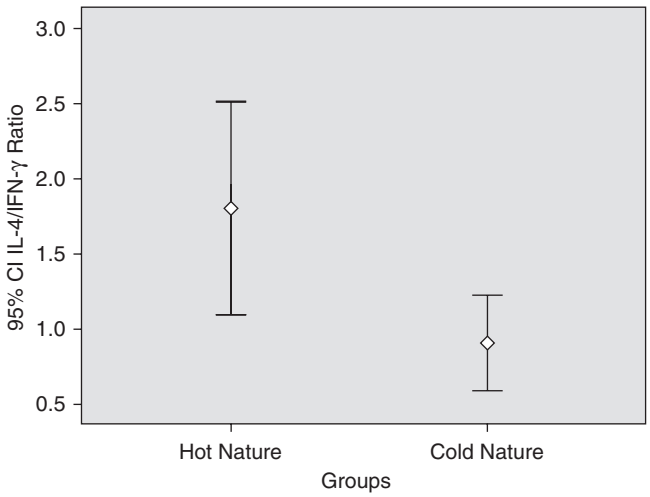

FIG. 5. Ninety-five percent (95%) confidence interval for the mean interelukin-4/interferon-γ (IL-4/IFN-γ) ratios in Hot and Cold nature groups. The mean IL-4/IFN-γ ratio in the Hot nature group is higher that in the Cold nature group (Mann-Whitney test, $p = 0.08$).

thetic responses during stress.[26,27] For example, it has been shown that public speaking markedly increased plasma levels and urinary excretion of cortisol and epinephrine, with only small changes in norepinephrine level.[28] Also, in humans playing a video game, the responses of adrenocorticotropin hormone levels have been correlated positively with the responses of epinephrine, but not norepinephrine.[27] Passive avoidance elicited large plasma epinephrine and corticosterone responses, but small plasma norepinephrine responses.[29] The close link between the adrenocortical corticosteroid and adrenomedullary sympathetic activities can be attributed to the stimulatory effects of adrenomedullary catecholamines on the secretion of adrenocortical corticosteroids, and *vice versa*.[26]

The study of IL-4/IFN-γ ratios showed that the tendency of the Hot nature participants was to deviate toward Th2-like immune responses to a greater extent than that of the Cold nature participants. However, as shown in Figure 6, when the nature veered toward extreme Warmth or extreme Coldness, the deviation of the immune system toward Th2-like responses would increase, but this increase was much greater when veering toward extreme Warmth than toward extreme Coldness. These findings are in agreement with the results indicating more peripheral sympathetic nervous system activity in the Hot nature participants, because stimulation of the peripheral sympathetic nervous system deviates immune responses toward Th2-like responses.[13] Although glucocorticoids and epinephrine secreted by the adrenal glands resemble the sympathetic nervous system in shifting the immune system toward Th2-like responses, and this could be the cause of the slight deviation of the immune system toward Th2-like immune responses when the nature veered toward extreme Coldness, because of the innervation of most tissues (including lymphatic organs) by the sympathetic nervous system,[13,30] it seems that the peripheral sympathetic nervous system is more potent than the adrenal glands in shifting the immune system toward Th2-like responses. Therefore, veering toward an extreme Hot nature caused a greater deviation toward Th2-like immune responses than did veering toward an extreme Cold nature. The association between increasing Warmth of nature and deviation of the immune responses toward Th2-like responses is in agreement with the view of Avicenna, that the smelling of a Hot nature substance such as saffron can result in rhinorrhea,[31] because it seems that Avicenna was describing a type of allergy,[31] and it is now clearly established that there is deviation of immune responses toward Th2 in allergy.[19] Therefore, it is possible that the smelling of a Hot nature substance can result in allergic reaction by shifting the immune responses toward a Th2-like response.

The findings of the current research may confirm the importance of host factors in determining the type of response to stresses. Different individuals may respond differently to a homeostasis-disturbing agent, and may have a different balance of sympathetic, parasympathetic, and adrenal activities, as well different deviations of the immune system. This concept can be one of the causes (in addition to others) of differing susceptibilities to specific diseases between different people. Hypertension might be a good example of this. A considerable amount of circumstantial evidence supports a role for salt in the genesis of hypertension by increasing sodium levels in the body.[24] To induce hypertension, some of that excess sodium must be retained by the kidneys. Such retention could arise in a number of ways, including the increased secretion of renin, resulting in an increase in the renal retention of sodium and water.[24] Since

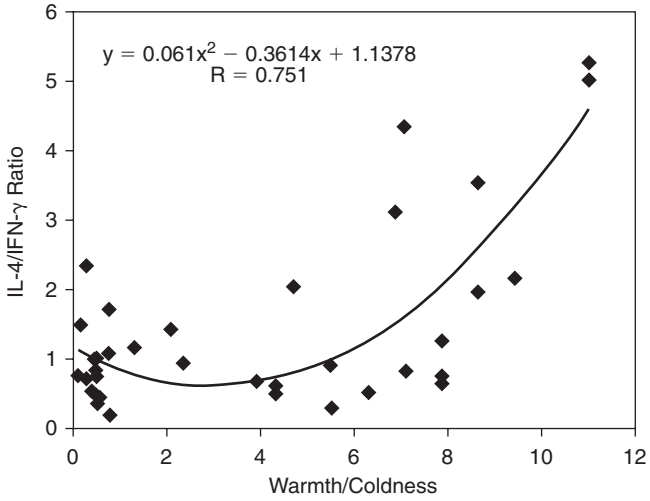

FIG. 6. The correlation between interleukin-4/interferon-r (IL-4/IFN-γ) and Warmth/Coldness ratios. There is a nonlinear association between IL-4/IFN-γ and Warmth/Coldness ratios (nonparametric Spearman correlation test; $p = 0.022$).

the sympathetic nervous system can stimulate renin release, a Hot nature person, because of increased activity of the peripheral sympathetic nervous system, will have a greater susceptibility to hypertension due to high salt intake.[24] Because high parasympathetic nervous system activity has an inhibitory effect on the development of hypertension,[25] despite there being higher adrenal sympathetic activity in Cold nature persons as compared with Hot nature persons, Cold nature persons may have a lower risk than Hot nature persons to develop hypertension due to a high-salt diet.

The nature of a person can also be important in connection with allergy. It seems that an allergen can induce allergic reaction in Hot nature persons with a higher probability than in cold nature persons, because the former have a greater tendency to Th2-like responses compared with the latter, and, as mentioned above, Th2-like responses to an allergen are necessary for the development of an allergic reaction to the allergen.[19]

The consequences of a person's exposure to acute or chronic stresses may be influenced by the nature of the person. For example, an extreme Cold nature person may faint in response to fright stimuli with a higher probability than an extreme Hot nature person, because the former have a greater parasympathetic nervous system activity compared with the latter.

Increasing evidence indicates that immune responses during infancy and early childhood are dominated by Th2 cytokines, but the shifting toward Th2 pattern decreases with age.[32–35] According our results, this is in agreement with TIM's belief that the nature is dominated by Warmth at birth but its Warmth decreases with age.[4] Also, our results are in concordance with TIM practitioners' view that multiple sclerosis (MS), which is a Th1-mediated autoimmune disease, is more prevalent in Cold nature persons than in Hot nature persons.

Confirmation of the importance of the Warmth or Coldness of foods, advocated by many traditional medical theories, may be one of the other conclusions of the present study. If, as the results of this study indicate, the intensity of Warmth or Coldness of nature has different effects on homeostasis, it is highly possible that Hot or Cold nature substances have such an effect as well, because Hot nature substances accelerate Warmth of nature, and Cold nature substances accelerate Coldness of nature in people. Therefore, paying due attention to the nature of the diet of patients may be important for the treatment of their diseases and to prevent their acceleration. In addition, such an observance of the diet of healthy persons dominated by Cold or Hot nature may be useful for maintaining homeostasis and preventing many diseases. For example, according to the results of this study, in a person suffering from an autoimmune disease with a deviation toward Th1 immune responses, consumption of Hot nature foods may be useful because they can accelerate warmth of nature and deviation toward Th2 immune responses. This would mean less deviation toward Th1 immune responses and may lead to a reduction in disease severity. This is in agreement with TIM practitioners' view that consumption of Hot nature foods is useful for MS patients, while consumption of Cold nature foods aggravates their disease.[36]

Although the questionnaire used in this study for categorization of the participants to Hot and Cold nature groups was in accordance with TIM, since the characteristics of Hot and Cold natures in TIM are very similar to those in many other traditional medical theories, the results of this study may be extended to Cold and Warm nature persons according to the other traditional medical theories (e.g., Arabic, Unani [Greek], and Chinese theories).

In brief, the results of the current study indicated that Hot nature persons (according to TIM) have a more active sympathetic nervous system; less active parasympathetic nervous system (vagus nerve), adrenal corticosteroid, and adrenal sympathetic activities; and also a higher rate of deviation of the immune system toward Th2 responses in comparison with Cold nature persons. In other words, it seems that Hot nature participants had a more active peripheral sympathetic nervous system and a less active adrenal system in comparison with Cold nature participants. In addition, the activity of the sympathetic nervous system increased and adrenal sympathetic activity decreased with increasing Warmth/Coldness ratio. Furthermore, when a person's nature veered toward extreme Warmth or Coldness, the deviation of the immune system toward Th2-like responses increased, but this increase was much greater when veering toward extreme Warmth than extreme Coldness.

CONCLUSIONS

This research was a preliminary study and the first of its kind to be carried out; therefore, more research is needed to reach absolute conclusions about the relationships between Hot and Cold natures and the parameters studied here, and also other possible mechanisms. The parameters studied here were chosen because, as mentioned above, autonomic nervous and immune systems are critical in maintaining the homeostasis; therefore, we suggest that the other factors affecting the homeostasis (e.g., basal metabolic rate, sex hormones, blood circulation parameters, thyroid hormones, etc.) be considered in the studies on traditional medicines.

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Appendix: The Questionnaire Used to Determine Natures and Temperaments of the Participants

				Choleric	*Sanguine*	*Phlegmatic*	*Melancholic*				*Choleric*	*Sanguine*	*Phlegmatic*	*Melancholic*
Appearance	Body	1	Corpulent			○		Characteristics and behavior						
		2	Muscular		○									
		3	Thin	○					27	High arousal	○			
		4	Bony				○		28	Low arousal			○	
	Face	5	Fresh		○	○			29	Sensitive	○			○
		6	Pallid				○		30	Insensitive			○	
		7	Rosy		○				31	Extroverted		○		
		8	Brunet				○		32	Introverted				○
		9	Whitish			○			33	Sociable		○		
		10	Sallow	○					34	Unsociable				○
		11	Gray spots on sclera				○		35	Rapid rate of speech	○			
		12	Yellow spots on sclera	○					36	Slow rate of speech		○	○	
	Hair	13	Straight			○			37	Flexible				○
		14	Waved		○				38	Inflexible		○		
		15	Curly	□			○		39	Resolute	○			
		16	Blond		○	○			40	Steadfast		○		
		17	Dark	○			○		41	Optimistic		○		
		18	Turned gray			○	□		42	Pessimistic				○
		19	Not turned gray	○	○				43	Depressed				○
		20	Dense	□	○				44	Disappointed				○
		21	Sparse			○	○		45	Timorous				○
		22	Partly bald		○		○		46	Anxious				○
		23	Rapid growth		○	○			47	Hasty	○			
		24	Slow growth	□			○							
	Skin	25	Soft		○	○								
		26	Dry	○			○							
Physical ability		48	Active		○			Thirst	73	Low			○	○
		49	Passive			○			74	High	□	○		
		50	Quick	○				Appetite	75	Low	○			
		51	Slow				○		76	Normal		○		
		52	Sluggish			○			77	High			○	
		53	Strong		○				78	Desire to have snacks				○
		54	Weak			○			79	False appetite				○
Mental ability		55	Quick-witted	○				Dominant signs and symptoms	80	Malaise		○		
		56	Slow-witted		○	○			81	Muscle spasm				○
		57	Weak acquisition		○	○			82	Joints pain		○		
		58	Weak memory			○			83	Rash		○		
		59	Neglectful		○	○			84	Shedding of the hair		○		
		60	Pensive				○		85	Heavy growth of the hair				○
									86	Profuse perspiration	○	□		
									87	Profuse secretion of saliva			○	

APPENDIX: THE QUESTIONNAIRE USED TO DETERMINE NATURES AND TEMPERAMENTS OF THE PARTICIPANTS (CONT'D)

				Choleric	*Sanguine*	*Phlegmatic*	*Melancholic*				*Choleric*	*Sanguine*	*Phlegmatic*	*Melancholic*
Sleep		61	Heavy		○	□			88	Dryness of the mouth	○			
		62	Light				○		89	Cracking and/or scaling of the lips	○			○
		63	Gratifying		○				90	Coarseness of the tongue	○			
		64	Not beneficial			○			91	Redness of the tongue		○		
		65	Lots of sleep		○	○			92	Bitter taste in the mouth	○			
		66	Drowsy		○				93	Sweet taste in the mouth		○		
		67	Lots of yawns		○				94	Dryness of the nose	○			
		68	Desire to take siesta		○				95	Epistaxis	○	□		○
		69	Difficulty in getting to sleep	○					96	Weak digestion			○	
		70	Insomnia	○			○		97	Dyspepsia			○	
		71	Uncomfortable				○		98	Suffering from acidity			○	
		72	Nightmare	○			○		99	Heartburn				○
									100	Constipation	○			○

	Hot nature	*Cold nature*
1 Feeling Cold *more than normal* in a cold condition		○
2 Feeling Hot *more than normal* in a hot condition	○	
3 Can't stand a Cold condition		○
4 Can't stand a Hot condition	○	
5 Getting cool easily in a Hot condition		○
6 Getting warm easily in a Cold condition	○	
7 Cold fingertips *in a normal condition*		○
8 Warm fingertips *in a normal condition*	○	
9 Preferring hot drinks		○
10 Preferring cold drinks	○	
11 Can't stand hunger		○
12 Can't easily stand hunger	○	
13 Suffering from lack of energy		○
14 Having sufficient energy	○	
15 Having poor health		○
16 Healthy and strong	○	
17 Catching cold repeatedly		○
18 Suffering from eye and head aches	○	
19 A sudden hot feeling *in a normal condition*	○	
20 Blood hypertension	○	
21 Blood hypotension		○
22 Having problems after consuming Hot nature foods	○	
23 Having problems after consuming Cold nature foods		○

○, Positive; □, severe.