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Association between atopy and allergic contact dermatitis in Dr. Sardjito General Hospital Yogyakarta

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ABSTRACT

Association between atopy and development of allergic contact dermatitis (ACD) remains controversial. T cell disfunctions in a patient with atopy complicate the process of nickel sensitization. On the other, the decrease of the skin barrier function and overexpression of Langerhans cells in the patient facilitate the sensitization. This study aimed to evaluate the association between atopy and incidence of nickel ACD. A case-control study was carried out in Allergic and Immunology Sub Department of Dermato-Venereology Policlinic, Dr. Sardjito General Hospital, Yogyakarta, involving 54 nickel ACD patients as case group and 74 healthy subjects as control group. All subjects underwent prick test allergens i.e. house dust, dust mite, cockroach, mixed fungi, nuts and egg white. The skin reaction was considered as a positive result if a wheal diameter of at least 3 mm larger than the negative control or a minimum of half of the positive control. The relationship between atopy and the nickel ACD incidence was analyzed using Chi-Square test with confidence interval (CI) of 95%. A significant association between atopy and the nickel ACD incidence was observed in this study. Subjects with atopy to 1 allergen had risk of nickel ACD 3.74 higher than subjects without atopy (odds ratio/ OR = 3.74; 95%CI = 1.64-8.53). Furtheremore, subjects with atopy to 2 allergens had risk of nickel ACD 3.74 higher than subjects without atopy (OR = 2.08; 95%CI = 1.01-4.29). In conclusion, atopy is a risk factor of nickel ACD.

ABSTRAK

Hubungan antara atopi dan munculnya dermatitis kontak alergi (DKA) masih kontroversial. Pada penderita atopi terjadi gangguan fungsi sel T yang menghambat proses sensitisasi nikel. Di sisi lain, fungsi sawar kulit penderita atopi menurun dan terjadi ekspresi berlebih sel Langerhans yang mempermudah sensitisasi. Penelitian ini bertujuan untuk mengkaji hubungan antara atopi dan kejadian DKA nikel. Penelitian menggunakan rancangan kasus kontrol dilakukan di Divisi Alergi dan Imunologi, Poliklinik Kulit dan Kelamin, Rumah Sakit Umum Dr. Sardjito Yogyakarta yang melibatkan 54 pasien DKA nikel positif sebagai kelompok kasus dan 74 sukarelawan sehat sebagai kelompok kontrol. Semua subjek menjalai tes tusuk dengan beberap alergen yaitu debu rumah, tungau debu, kecoa, *mixed* fungi, kacang tanah dan putih telur. Hasil tes dikatakan positif bila diameter reaksi kulit e" 3 mm dari kontrol negatif atau separo dari kontrol positif. Hubungan antara atopi dengan kejadian DKA nikel dianalisis menggunakan uji Chi-Square dengan taraf kepercayaan 95%. Hubungan nyata antara atopi dengan kejadian DKA nikel ditemukan dalam penelitian ini. Subjek dengan atopi terhadap 1 alergen mempunyai risiko DKA nikel 3,74 lebih tinggi dibandingkan dengan subjek tanpa atopi (OR = 3,74; 95%CI = 1,64-8,53). Selanjutnya subjek dengan atopi terhadap 2 alergen mempunyai risiko DKA nikel 2,08 lebih tinggi dibandingkan dengan subjek tanpa atopi (OR = 2,08; 95%CI = 1,01-4,29). Dapat disimpulkan bahwa atopi merupakan faktor risiko DKA nikel.

Keywords: atopy - allergic contact dermatitis - nickel allergy - prick test - allergen

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INTRODUCTION

Allergic contact dermatitis (ACD) is type IV hypersensitive reaction, mediated by cellular response caused by contact with spesific allergen to sensitized individuals. Allergic contact dermatitis frequently occurs in daily life and can influence patient's quality of life.[1-4] Prevalence of ACD is about 12.5-40.6% in general population and 4-10% based on patient visit data in dermatology clinic in Thailand and Saudi Arabia.[2-4] In Dermatology-Venereology Policlinic of Dr. Sarjito General Hospital, Yogyakarta in 2010, 5.3% patients of ACD case out of the whole patient visits were diagnozed.

Nickel ACD is the most frequent ACD that occurs in about 10-20% out of the all patients who underwent patch test. The high incidence of nickel ACD is caused by many equipments used in daily life that contain nickel.[4,5] Diagnosis of nickel ACD is easy to be performed due to its specific clinical manifestation. However, patch test is gold standard method to diagnose the sensitivity existence to an allergen substance in ACD.[6]

Atopy is a kind of hypersensitive reaction to an environment allergen that associated with multiple abnormalities including Langerhans cell over-expression, immunoglobulin E (IgE) dysregulation through Th2 immune response, eosinophyl overactivities and genetic predisposition.[7]

A strong predisposition toward atopy has been reported and studies to map susceptibility genes for atopy have been performed by investigators. One of gene i.e. filaggrin has become the gene with the most widely associated to atopic eczema. Filaggrin null mutations cause defective skinbarrier functions lead to ease the penetration of environment allergens, increase trans-epidermal water loss (TEWL) and decrease skin hydration that stimulate skin inflammation reactions by increasing cytokin proinflamation production.[8,9] Other gen that involved on the pathophysiology of atopic diseases is a gene that encodes fragment crystallizable epsilon receptor I (Fc[RI). The Fc[RI is a protein found on the surface of cells that binds to a part of IgE known as the Fc (Fragment, crystallizable) region. In atopic diseases, a strong upregulation of Fc[RI on effector cells of anaphylaxis such as mast cells and basophils is observed. Ligation of the high-affinity Fc[RI on the effector cells can induce cell activation and immediate release of inflammatory mediator.[10]

The prevalence of atopy in Western countries is about 20-45% and it becomes the main cause of chronic diseases among children.[11] A person with atopy typically presents with one or more of the following symptoms such as allergic asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatitis.[7] Exposure to possible exacerbating factors of environment such as aeroallergen, irritating chemical and foods can be examined by skin Prick test or IgE specific antigen-antibody test.[12]

This study was conducted to verify the association between atopy and ACD occurrence among patients visiting Dr. Sardjito General Hospital, Yogyakarta, Indonesia.

MATERIALS AND METHODS

Subjects

This was a case control study conducted in Allergic and Immunology Sub Department of Dermato-Venereology Policlinic, Dr. Sardjito General Hospital, Yogyakarta. The study was started on September 2011 until the numbers of samples obtained. The case group was all nickel ACD patients with positive nickel result in patch test, while the control group was healthy individuals without dermatitis lesions. All subjects would undergo a prick test of house

dust, dust mite, cockroach, mixed fungi, peanuts and white egg allergen.

All subjects were asked to sign an informed consent. The subject would be excluded from the study in the condition of 1) consume systemic antihistamine within 5 days before the research, except ketotifen (15 days); 2) consume systemic corticosteroid more than 20mg/day within 2 weeks before study; 3) topical corticosteroid application on the test spot during 2 weeks before study; 4) consume systemic immuno-modulator agents within the last 4 weeks before study.

The protocol of study has been approved by the Medical and Health Research Ethic Committee, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta.

Protocol of study

Subject who met the inclusion and exclusion criteria was given an explanation concerning the background, objectives, and benefit of the study. Subjects who were willing to be involved in the study, an informed consent was given to be signed. Subjects then underwent anamnesis and clinical examination to obtain the characteristics of subjects, history of illness, ect. Dermatology picture were taken and used as base line data of the skin conditions before patch test.

The patch test was performed for subjects suspected of suffering from nickel ACD. Left upper arm skin was cleaned with 0.9% NaCl solution and dried with a tissue. A □-chamber containing 20 µL Trolab® 5% nickel sulphate allergen was applied onto the skin of upper left arm and fixed with an adhesice tape (HipaFix®). Subjects were then asked to back home with an instruction form. The subsequent assessment of skin reaction using a magnifying lamp was performed by Dermatologist from Allergic and Immunology Sub Department of Dermato-Venereology Policlinic, Dr. Sardjito General Hospital after 2, 3 and 4 days. The skin reaction was measured based on the International Contact Dermatitis Research Group (ICDRG) scoring system. Dermatology picture were taken again and used as data of the skin conditions after the patch test. Results of the patch test were then informed to the subjects.

All subjects in both group then underwent a prick test. The forearm skin of the subject was cleaned with 0.9% NaCl solution and dried with a tissue. Skin prick solution of the appropriate allergen (0.1 mL house dust, dust mite, cockroach, mixed fungi, white egg and peanuts solution) was pricked smoothly using a 23 g syringe needle in several sites with each site should be a minimum of 2 cm apart. The skin reaction was measured in diameter 15-20 minutes after the skin prick. The skin reaction was considered as a positive result if a wheal diameter of at least 3 mm larger than the negative control or a minimum of half of the positive control. All measurements were recorded and informed to the subjects.

Statistical analysis

Data analysis was conducted using non parametric Chi-Square test to evaluate the hypothesis dealing with the association between atopy and nickel ACD incidence. If the Chi-Square test requirement was not fulfilled, Fisher test would be used. Sum of risk factor was calculated using odds ratio (OR) with confidence interval of 95%.

RESULTS

One hundred and twenty eigh subjects that consisted of 54 subjects of nickel ACD as case group and 74 healthy subjects as control group were involved in this study. Subject characteristics are presented in TABLE 1. The subjects

consisted of 86 female (67.2%) and 42 male (32.8%). The nickel ACD group consisted of 38 female (29.7%) and 16 male (12.5%), while the control group consisted of 48 female (37.5%) and 26 male (20.3%). In this study, the incidence of nickel ACD was higher on female than male subjects. The mean of age of subjects in the nickel ACD group was 30.69± 9.447 years, while in the control group was 30.23 ± 9.632 years.

TABLE 1. Main characteristic of subjects in both group

Characteristics	Nickel ACD group	Control group	p
Sex (n or %)			
• Female	38 (29.7)	48 (37.5)	0.512
• Male	16 (12.5)	26 (20.3)	
Age (mean ± SD year)	30.69 ± 9.447	30.23 ± 9.632	0.644

Positive prick test result to allergens of house dust, dust mite, cockroach, mixed fungi, white egg and peanuts is presented in TABLE 2. In this study, the most positive results of allergen prick test were dust mite (38.2%) and cockroach (28.1%). The dust mite positive result occuring on the nickel ACD group (29 or 22.7% of subjects) was significantly hinger ($p<0.05$) than on the control group (21 or 16.4 subjects).

TABLE 2. Comparison of prick test result in the nickel ACD group and the control groups

Allergens	Prick test result				p
	Positive		Negative		
	Nickel ACD n (%)	Control n (%)	Nickel ACD n (%)	Control n (%)	
House dust	12 (9.4)	22 (17.2)	42 (32.8)	52 (40.6)	0.342
Dust mite	29 (22.7)	21 (16.4)	25 (19.5)	53 (41.4)	0.004
Cockroach	19 (14.8)	17 (13.3)	35 (27.3)	57 (44.5)	0.129
Mixe fungi	16 (12.5)	12 (9.4)	38 (29.7)	62 (48.4)	0.070
White egg	0	1 (0.8)	54 (42.2)	73 (57.0)	0.391
Penuts	12 (9.4)	6 (4.7)	42 (32.8)	68 (53.1)	0.023

The frequency of positive reaction on prick test to allergens in this study is presented in TABLE 3. The TABLE 3 shows that 10 (7.8%) subjects of the nickel ACD group and 34 (26.6%) subjects of the control group gave negative result on prick test. Positive result on prick test to one allergen was obtained on 17 (13.3%) subjects of the nickel ACD group and 16 (12.56%) of the control group, while positive result to two allergens or more was obtained on 27 (21.1%) subjects of the nickel ACD group and 24 (18.7%) subjects of the control group.

TABLE 3. Frequency of positive reaction on prick test to allergens between the nickel ACD and the control groups

Number of positive reaction to allergens	Nickel ACD (%)	Control (%)	Total (%)
0	10 (7.8)	34 (26.6)	44 (34.4)
1	17 (13.3)	16 (12.5)	33 (25.8)
2	13 (10.2)	14 (10.9)	27 (21.1)
3	11 (8.6)	6 (4.7)	17 (13.3)
4	3 (2.3)	3 (2.3)	6 (4.7)
5	0	1 (0.8)	1 (0.8)

The frequency of atopy based on positive result of prick test to one allergen or more in the nickel ACD group and the control group is presented on TABLE 4. This study found that in the nickel ACD, atopy was found on 44 (34.4%) subjects and non atopy was found on 10 (7.8%) subjects, whereas in the control group, atopy was found on 40 (31.3%) subjects and non atopy was found on 34 (26.6%) subjects. Statistical analysis showed that subjects with atopy had risk of nickel ACD 3.74 higher than subjects without atopy (OR=3.74; 95%CI = 1.64-8.53).

TABLE 4. Frequency of atopy based on positive result of prick test to 1 allergen in nickel ACD and control groups

Characteristics	Nickel ACD Group (%)	Control Group (%)	Total (%)	OR	95%CI
Atopy	44 (34.4)	40 (31.3)	84 (6.6)	3.74	1.639-8.533
Non atopy	10 (7.8)	34 (26.6)	44 (34.4)		
Total	54 (42.2)	74 (57.8)	128 (100)		

The incidence of atopy based on positive result on patch test to two or more allergens is shown in TABLE 5. The TABLE 5 shows that atopy was found on 31 (24.2%) subjects and non atopy was found on 31 (24.2%) subjects in the nickel ACD group, while in the control group, atopy was found on 21 (16.4%) subjects, and non atopy was found on 45 (35.2%) subjects. This study showed that atopy is still the risk factor of nickel ACD. Subjects with atopy had risk of nickel ACD 2.08 higher than subjects without atopy (OR=2.08; 95%CI = 1.01-4.29). Additionally, statistical analysis using Chi-square showed a significant relationship between atopy and nickel ACD incidences.

TABLE 5. Incidence of atopy based on positive result of prick test to two or more allergens in the nickel ACD and control groups

Characteristics	Nickel ACD (%)	Control (%)	Total (%)	OR	95%CI
Atopy	27 (21.1)	24 (18.7)	51 (39.8)	2.08	1.012-4.289
Non atopy	27 (21.1)	50 (39.1)	77 (60.2)		
Total	54 (42.2)	74 (57.8)	128 (100)		

DISCUSSION

This study found that the incidence of nickel ACD was higher on female than male subjects. Study in Norway conducted by Dotterud and Sivertsen[13] also reported that incidence of nickel ACD appeared more higher on female (31.1%) than on male (5.0%). Another study conducted in Denmark in 1992-2009 also reported that incidence of nickel ACD was higher on female (21.7%) than on male (5.2%).[14] Moreover, this restrospective study reported that the higher incidence of nickel ACD was found on the age more than 25 years (34.9%) compared to on the age less than 25 years (22.1%).[14] The higher incidence of nickel ACD on female and on older people due to they tend to have more intense contact to equipments containing nickel such as jewelries and house-wares. While males tend to have sensitivity on nickel resulted from equipments in their working places.[15,16]

This study found that the most positive results of allergen prick test were dust mite (38.2%) and cockroach (28.1%). This result is similar to that which has been found in other studies conducted in other countries. A study conducted in China also reported that the most common sensitizing aeroallergens are dust mite (30.6%) and cockroach (25.2%).[17] Another study conducted in Uganda reported that the sensitization to house dust mite allergens (27.7%) and cockroach (15.8%) is the most common in the environment.[18] The high sensitivity to dust mite and cockroach allergens may be caused theses two allergens are easily found anywhere, particularly in houses and habitations.[17,18]

This study also showed that atopy is still the risk factor of nickel ACD. Subjects with atopy had risk of nickel ACD 2.08 higher than subjects non atopy. This result is similar to that which has been reported in other studies. A study conducted by Thyssen *et al.*[19] also reported that subject with atopy had risk of nickel ACD 1.5 higher in comparison to subject non atopy. Moreover, it was reported that the rate of atopy in patients with nickel ACD showed an increase from 23% in 1982 to 33% in 1997. Nickel is thought to be a contributory factor in causing occupational dermatitis.[20]

The higher prevalence of nickel ACD on subjects with atopy could be caused by the increase of absorption and penetration of nickel allergens due to the decrease of skin barrier function in subject with atopy. It leads the catching of hapten-protein complex by Langer-hans cells easier. The decrease of the skin barrier function is caused by the down regulation of filaggrin and loricrin, as well as numbers of ceramide, the increase of endogen proteolitic enzyme prodction and the higher loss of trans-epidermal water.[21,22] Filaggrin is crucial for the maintenance of the skin barrier function. Loss-of-function mutations within the filaggrin gene are associated with skin barrier diseases. In addition, filaggrin deficiency may also represent

a risk factor for contact sensitization to allergens especially nickel allergen.[21] Tanaka *et al.*[23] reported that subject with atopy had disfunction of skin barrier characterized by lower skin surface hydration levels that caused allergen agents or irritants easier crossed the skin barrier. It was also reported that approximately 77% subjects with atopy had positive patch test result indicating that atopy has an impotant role in the incidence of contact hypesensitivity.[24]

Other factors that have an impotant role in the etiology of atopy is cytokines pro-inflammatory such as like TNF↦ and IL-1 and keratinocyte cytokines such as IL-6, IL-8, IL-10, GM-CSF and TGF↦ produced on a skin barrier disfunction. The increase of TNF↦ and IL-1 production leads to upregulation of MCH class I and II, but downregulation of E-cadherin that binds to Langerhans cells in epidermis. It stimulates migration of the Langerhans cells from epidermis to lymph nodes tissue and induces an antigen presentation to specific T cell. This process causes an excessive Langerhans cells response to allergens and increases an incidence of sensitization.[25]

CONCLUSION

In conclusion, atopy is a risk factor of nickel ACD.

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