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Is the Hygiene (Microbial) Hypothesis Related to Maternal Contamination Obsessions and Washing Compulsions?

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Abstract

Background: Atopic dermatitis (AD) is a common skin condition and is a member of the atopic disease group along with allergic rhinoconjunctivitis and asthma. The pathogenesis are not fully understood. In hygiene hypothesis is that environmental factors are thought to play a crucial role in the etiology together with westernization phenomenon. Thus their parents, especially their mothers, create the major environmental factors for Atopic Children. Therefore, an understanding of maternal characteristics is critical for determining the environmental factors of atopic children.

Material and Methods: This study used a comparative design to evaluate differences in obsessive-compulsive variables and parenting attitudes between mothers of children with atopic dermatitis (atopic dermatitis group) and mothers of children who did not have atopic dermatitits (non atopic-control group). We evaluated 50 mothers in the atopic dermatitis group and 50 mothers in the nonatopic dermatitis group. Demographic characteristics were retrieved. The mothers completed questionnaires including the obsessive-compulsive questionnaire form (Padua Inventory) and family attitude scale (Parental Attitude Research Instrument; PARI)

Results: In the disease group, 80% of children had a history of atopy in one first-degree family member, while 20% of children in the control group did. The total score of the contamination subscale of the Padua Inventory was 40 ± 19.64 in the disease group and 35 ± 15.90 in the control group. The result was statistically higher in the disease group (p=0.012) maternal overprotection was 39.56 ± 8.8 in the disease group and 37.61 ± 7.2 in the control group (p=0.2). The total score of this subscale did not show a statistically significant difference between groups. In addition, democratic attitude (24.96 ± 3.5 disease and 24.59 ± 3.8 control; p=0.5), rejecting attitude (25.23 ± 6.61 disease and 28.20 ± 6.1 control; p=0.2), misunderstanding attitude (12.21 ± 3.90 disease and 14.02 ± 3.30 control; p=0.3), and authoritarian attitude (32.35 ± 7.5 disease and 34.37 ± 7.17 control; p=0.1) were not statistically different.

Conclusion: This was the first study investigating the parental and environmental factors using the Padua Inventory and PARI instruments. Having a parental history of allergic diseases and having a mother with contamination obsession-compulsion are the main predictors for the child's AD.

Introduction

Atopic dermatitis (AD) is a common skin condition, often manifesting in early infancy, that affects 25% of young children [1]. It is a member of the atopic disease group along with allergic rhinoconjunctivitis and asthma. These

diseases are defined by increased production of allergen-specific immunoglobulin E antibodies [**2**]. The pathogenesis, natural course, and mechanism, however, are not fully understood [**3**]. It has been hypothesized that environmental factors during early infancy can affect immune system development. Gender, socio-economic status, family size, infant feeding, environmental pollutants, and genetic factors appear to be important in the pathogenesis of atopic dermatitis [**4**]. Atopic diseases in children are widespread in western societies [**3**]. In 1989, Strachan hypothesized that reduced exposure to infectious agents during the development of the immune system because of the phenomenon of Westernization may result in the expression of atopic diseases. He claimed that early infections during the childhood period could be beneficial and may lead to protection against atopic diseases [**5**]. The proposed mechanism was in the roles of T cells. The subtypes of T helper cells (Th1 and Th2) are the main components of the immune system that first recognize foreign antigens and secrete cyt okines. The mature immune system has a Th1/Th2 balance, and, if this balance fails despite the absence of infectious exposure, atopic disease and asthma increase [**6**]. The summary of the hygiene hypothesis is that environmental factors are thought to play a crucial role in the etiology together with westernization phenomenon [**7**]. It was proposed that changes in personal hygiene, improvements in household amenities, and declining family sizes after the industrial revolution are accompanied by increases in the prevelance of atopic diseases [**5,8**]. Atopic dermatitis affects young children; thus their parents, especially their mothers, create the major environmental factors for them. Therefore, an understanding of maternal characteristics is critical for determining the environmental factors of atopic children.

This study compared the obsessive compulsive symptoms of mothers who have children with atopic dermatitis with those of mothers of children without atopic dermatitis (contamination obsessions-washing compulsions, obsessional thoughts, obsessional impulses, checking-control compulsions, dressing-grooming compulsions) and child-rearing attitudes (maternal over-protection, democratic attitude, rejecting, misunderstanding, authoritarian attitude) using PARI (Parental Attitude Research Instrument)[**9**]. and Padua In-ventories [**10**].

Methods

This study used a comparative design to evaluate differences in obsessive-compulsive variables and parenting attitudes between mothers of children with atopic dermatitis (atopic dermatitis group) and mothers of children who did not have atopic dermatitits (non atopic-control group). The patient selection was children aged between 6 months and 4 years in whom atopic dermatitis was diagnosed for the first time in our clinics.

We evaluated 50 mothers in the atopic dermatitis group and 50 mothers in the nonatopic dermatitis group. The groups were recruited from the dermatology clinic at Samsun State Hospital, and the mothers gave written informed consent in order to participate. The study was approved by the Ethical Committee of Samsun Education and Research Hospital.

Selection criteria were that the children must have been diagnosed with AD according to Hanifin and Rajka's criteria (sensitivity 96%, specificity 93.75%) [**11**] and not currently be enrolled in any other AD care programs; children were excluded from the study if they had other chronic diseases, skin diseases other than AD, or any other medically severe condition. The control group was selected from among mothers of healthy children of about the same age who were admitted to the pediatric clinic for routine well-child appointments.

Demographic characteristics were retrieved. The mothers completed questionnaires including the obsessive-compulsive questionnaire form (Padua Inventory) and family attitude scale (Parental Attitude Research Instrument; PARI)

Measurements

Demographic characteristics: Demographic data were the mother's age, occupation, education (years), family income, history of atopy in first-degree relatives, and the questions of 'Do you feel self-sufficient in child rearing?' and 'Have you spent enough time with the m?

Padua Inventory-Washington State University Revision (PI-WSUR)

This is a 41-item inventory that assesses obsessive–compulsive symptoms. It is a revised version of the Padua Inventory (Saravio, 1988) [**12**]. Items are scored on a five-point scale between 0=not at all and 4=very much. The inventory consists of five subscales. The total score of the subscales are calculated with the sum of the given scores on each question.

1. Contamination obsessions and washing compulsions subscale: For instance 'I wash my hands for a long time'. There are 10 questions about this topic.

2. Dressing/grooming compulsions: For instance 'I follow a specific sequence of steps when I am getting dressed and taking a bath'. There are 8 questions in this group.

3. Checking compulsions subscale: For instance 'I need to control the things that I do in my daily life more often '. There are 8 questions in this subscale.

4. Obsessional thoughts about harm to self/others subscale: For instance 'Sometimes I think unwanted and harmful thoughts, and I can't get over it'. There are 10 questions in this subscale.

5. Obsessional Impulses to harm self/others subscale. For instance 'I get excited when I see weapons or sharp materials and unwanted impulses arise'. This subscale consists of 7 questions [**13**].

The PI-WSUR has been translated to Turkish. A previous study has shown that the Turkish translation has good discriminate and convergent validity [**14**].

PARI (Parental Child Rearing Attitudes)

PARI were assessed with the Amsterdam version of the A-PARI. We evaluated the mother's attitude toward her child(ren). This study investigates the association between parental child-rearing attitudes and atopic dermatitis. The attitude was based on five subscales. The total score of subscales are calculated with the sum of the given scores in each question.

1. Maternal overprotection; for instance, 'I believe a child should follow what parents want to do'. There are 16 questions in this section.

2. Democratic attitudes; for instance, 'I try to let my child do what he/she has to do by him/herself.' There are 9 questions about this topic.

3. Rejecting; for instance, 'I tend to ignore what my child wants.' There are 13 questions about rejecting.

4. Misunderstanding between couples; for instance, 'If the father doesn't do his mission at home, it is the reason that the mother cannot take care of her child.' There were 6 other questions in this section.

5. Authoritarian; for instance, 'An authoritarian is needed to become a happy and good person in the future.' It consists of 16 questions.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 15.0 (SPSS, Inc, Chicago, IL, USA). Data were expressed as means ± standard deviation. Pearson's chi-square test was used to compare the categorical variables. Student's t-

test and Mann–Whitney U-test were used to compare values from patients and healthy controls. Statistical evaluation was done question-by-question, and the given answers of related subscales

were summed to obtain the total scores. These total scores of the subscales were compared between the groups. The level of statistical significance was set at $p < 0.05$.

Results

Fifty mothers of children with atopic dermatitis and 50 mothers of healthy children were enrolled in our prospective analysis. The age of the children was between 6 months and 4 years. In the disease group, 80% of children had a history of atopy in one first-degree family member, while 20% of children in the control group did. The mean age of the mothers in the two groups was similar, and the average age range was 31-35 years. Education (years) was analyzed, and the control group had a longer education period when compared to the disease group. According to this result, the number of people who had a job and were studying elsewhere was higher in the control group. The family income was statistically higher in the control group than in the disease group.

The questions 'Do you feel self sufficient in child rearing'and 'Have you spent enough time with them' were negatively higher in the control group than in the disease group. The control group attributed this result to working (33.7%) and having no time (25.3%). The disease group revealed that they spend time with their children and they take care of them much more than the control group ($p<0.05$).

Padua Inventory

The total score of the contamination subscale of the Padua Inventory was 40 ± 19.64 in the disease group and 35 ± 15.90 in the control group. The result was statistically higher in the disease group ($p=0.012$)

The total score of dressing/grooming was 5.04 ± 4.53 in the disease group and 5.10 ± 4.98 in the control group (p=0.05). Checking compulsions score was 28 ± 11.60 in the disease group and 29 ± 10.10 in the control group; the difference was not statistically significant (p=0.573)

Obsessional thoughts score was 13.34 ± 9.52 in the disease group and 11.46 ± 8.39 in control group (p= 0.4). The final subscale—obsessional impulses—score was 5.20 ± 5.75 in the disease group and 3.76 ± 4.79 in the control group (p=0.4). Other than the contamination obsessions-compulsions subscale, the other four subscales were not statistically different, and no associations were found between the groups. The results are summarized in (**Table 1**).

PARI

In Parental Attitude Research Instrument, statistical analysis was performed question-by- question between groups. All of the questions did not show a statistically significant difference except the question "If fathers just become less selfish, then they do their duty concerning child- rearing". When we compare the question with the control group, control group was related with the significantly higher answers of 3=much and 4=very much (p<0.004) However, the disease group answered 'not at all' much more than the control group. Seven mothers did not answer this question in the control group.

The total scores of subscales were as follows: maternal overprotection was 39.56 ± 8.8 in the disease group and 37.61 ± 7.2 in the control group (p=0.2). The total score of this subscale did not show a statistically significant difference between groups. In addition, democratic attitude (24.96 ± 3.5 disease and 24.59 ± 3.8 control; p=0.5), rejecting attitude (25.23 ± 6.61 disease and 28.20 ± 6.1 control; p=0.2), misunderstanding attitude (12.21 ± 3.90 disease and 14.02 ± 3.30 control; p=0.3), and authoritarian attitude (32.35 ± 7.5 disease and 34.37 ± 7.17 control; p=0.1) were not statistically different (**Table 2**).

Discussion

Having a parental history of allergic diseases and having a mother with contamination obsession-compulsion are the main predictors for the child's AD according to our study. Environmental factors acting in utero or in early infancy play an important role in the immune status of children. Maternal factors have a large role in the environmental factors of unborn-newborn babies, early infants, and children before age 4. This is the first study in which the Padua Inventory used for evaluating obsessional and compulsional behaviors of mothers, which could be a factor related to the hygiene hypothesis.

The contamination obsessions and washing compulsions subscale was statistically higher in mothers of the AD group (p=0.012). In 1989, David Strachan first introduced the hygiene hypothesis. The summary of hygiene hypothesis suggests that altered microbial exposure during childhood is associated with allergic sensitization. "Western" lifestyles are therefore responsible for allergic diseases.5 From this point of view, we decided to investigate the daily obsessions of the mothers of children who have atopic dermatitis—compulsions in contamination and washing, dressing/grooming compulsions, checking comp ulsions, obsessional thoughts, and lastly ob-

Table 1. Summary of Padua Invantory with Subscales

Padua Subscales	Disease Group (mean ± SD)	Control Group (mean ± SD)	P
Contamination obsessions and washing compulsions	19,64 ± 9,51	15,90 ± 7,70	0.012 *
Dressing/grooming compulsions	5,04 ± 4,53	5,10 ± 4,98	0.05
Checking compulsions	11,60 ± 7,18	10.10 ± 7.12	0.5
Obsessional thoughts about harm to self / others	13,34 ± 9.52	11,46 ± 8,39	0.4
Obessional Impulses to harm self / other	5,20 ± 5,75	3,76 ± 4,79	0.4

Table 2. Summary of PARI Instrument with Subscales

PARI Subscales	Disease Group (mean ± SD)	Control Group (mean ± SD)	p
Maternal overprotection	39,56 ± 8,82	37,61 ± 7,27	0,2
Democratic attitudes	24,96 ± 3,57	24,59 ± 3,84	0,5
Rejecting	25,23 ± 6,61	28,20 ± 6,15	0,2
Misunderstanding between couples	12,21 ± 3,90	14,02 ± 3,30	0,3
Authoritarian	32,35 ± 7,50	34,37 ± 7,17	0,1

sessional impulses. We were not suprised that contamination obsessions and washing compulsions scores were 19.64 ± 9.5 in the disease group, statistically higher when compared with the control group (15.90 ± 7.70) (p=0.012). The other obsessional and compulsional thoughts and impulses were not statistically different between the groups. These findings could be a secondary result for mothers when their children were diagnosed with atopic dermatitis; to exclude this, we selected the children of mothers who were diagnosed with atopic dermatitis for the first time in our clinic.

The hygiene hypothesis proposes that, despite the lack of infection, activation of antigen presenting cells of CD4+ T cells occurs, and T cells are polarized toward Th2 cells that secrete IL-4, IL-5 and IL-13 cytokines and stimulate B cells. B cell stimulation results in production of IgE antibody, increasing mast cell and eosinophil counts [**15**]. How it acts is not fully understood.

The literature on hygiene hypothesis-related atopic dermatitis is inconclusive. Karadağ et al. researched the environmental determinants of atopic eczema with collection of the house dust of children of farmers and their atopy status. Endotoxin, 1-3-glucans, and fungal extracellular polysaccharides (EPS) were measured. Levels of ·-1-3-glucans in mattress dust were inversely related with the atopic dermatitis phenotype associated with asthma and wheezing, and they found that exposure to β-1-3-glucans and endotoxin were found to be protective for the respective asthma-associated atopic eczema [**16**]. Our study supports this association, and hypothesized that having a mother with contamination obsession is equal to decreased EPS and ·-1-3-glucans levels in house dust. However, we could not measure these levels. Zutavern et al. evaluated factors including day care attendance and number of older siblings (which are related to the hygiene hypothesis), and they were not associated with a decreased risk of AD [**17**]. There are considerable arguments in favor of and against this hypo thesis [**18**].

Bloomfield et al. revealed that the increase in allergic disorders does not correlate with the decrease in infection with pathogenic organisms, nor can it be explained by changes in domestic hygiene [**19**]. According to this study, more fundamental changes in lifestyle have led to decreased exposure to certain microbial or other species, such as helminths, that are important for the development of immunoregulatory mechanisms. They suggested renaming the hypothesis, i.e., as the 'microbial exposure' hypothesis or 'microbial deprivation' hypothesis, as also proposed by Bloomfield [**19**]. The mothers' obsessions and compulsions about contamination could be a step in the microbial hypothesis, in which less exposure to microbes is closely linked to the development of AD.

A history of infections such as hepatitis, decreased antibiotic exposure, and probiotic exposure suggest a decrease in the risk of eczema [**20**]. Hyman et al. and Dominguez et al. suggested that microbial contact for the infant is different between vaginal delivery and cesarean section. Lactobacillus in vaginal and staphylococcus in cesarean delivery are the main concominant flora. The gut microbiome, which is composed of lactobacillus, is protective for AD [**21**]. In the light of these studies,

Perders et al. suggested that the infant intestinal microbiota and probiotics play an important role in regulating immune responses. However, Ha Jung Kim et al. revealed that further studies are required to confirm the association between the gut microbiota and allergic diseases.

Moleculer and genetic studies point to the possibility that the primary defect might lie in the skin occuring early in life as a chronic pruritic skin condition than the allergic way goes through the airways (asthama, allergic rhinitis) [**22,23**]. The impaired cutaeneous barrier raised the possibility of atopic march beginning in the skin, all the way to airways; for instance variations of the flagrin gene resulting an intact barier have an important role in predisposition to atopic disease [**24**].

Toll-like receptors have been shown to be expressed by keratinocytes, and thus could have a role in the initiation and development of the atopic march [**25**].

Mutations in the human filaggrin gene (FLG) are the most significant and well-replicated genetic mutations, and other mutations associated with epidermal barriers such as SPINK5, FLG-2, SPRR3, and CLDN1 have all been linked to AD. Gene variants, including mutations in PRRs and AMPs, TSLP and TSLPR, IL-1 family cytokines and receptors genes, vitamin D pathway genes, the nerve growth factor pathway, FCER1A, and Th2 and other cytokines genes, have identified a total of 19 susceptibility loci in the pathogenesis of AD [**26,27**]. Environmental factors causing DNA methylation and microRNAs related to the immune system and skin barriers have been found to contribute to the pathogenesis of AD. Genetic variants and epigenetic alteration might be the keys for the molecular taxonomy of AD and provide background for personalized management. According to our study, using too many chemicals in cleaning could be another environmental factor related to DNA and microRNA methylation.

All of these articles are related to the genetic predisposition to atopic dermatitis. The hygiene hypothesis, or the new name microbial hypothesis, is important; however the genetic impairments would be the main etiological factor for AD in the future.

Similar to these studies, the most remarkable finding in our study was that 80% of the disease group had a history of atopy in one first-degree relative, compared with 20% of the control group. Improved genetic screening is needed in the future.

On the other hand, the other purpose of our present study was to retest the hypothesis that mothers of children with atopic dermatitis have more severe (controlling and rejecting) parental attitudes than mothers of healthy children.

We used the PARI Instrument developed by Schaefer and Bell with items modified after the types used by Mark and Shoben [**9,28,29,30,31,32**].Meads et al. evaluated the relationship between atopic dermatitis disease, its severity, and quality of life of parents [**33**].

Yeo- Jin I m et al. compared parental cognitions and relationship characteristics of mothers of children with atopic disease. The results showed that mothers who perceived their child's disease to be severe were less likely to encourage autonomy and had a lower sense of competence, more rejecting attitudes, and an external locus of control [**27**]. Teyhan et al.and Buske et al. revealed that maternal mental health could play a role in such a biological pathway, toward inflammatory diseases, and they suggested that a better understanding of the role of parental psychological well being in child health is needed [**28,29**]. In the above studies, we know little about parental attitudes of children before diagnosis of AD. In our study, maternal overprotection, rejecting attitude, authoritarian attitude, and misunderstanding between couples attitude were not statistically different in the disease group when compared with the control group. We can say that both groups (atopic disease and control group) have a democratic parental attitude with a total score of 24.96 ± 3.5 in the disease group and 24.59 ± 3.8 in the control group (p=0.5).

Schmitz et al. investigated the demographic characteristics of parents of children with atopic disease [**30**]. High and middle socio-economic status were found to be associated with atopic dermatitis; in contrast, subjects with a longer education period, higher family income, and having a job were statistically higher in the control group in this study.

These findings fail inversely with the literature in our study; this could be because of the fact that the number in the groups was small in our study, or that this factor plays a different role in understanding the hygiene hypothesis.

When we analyzed all this work, we see that the mothers of children with atopic dermatitis were spending enough time with their children, most were housewives, and there were no problems in their child-rearing attitudes; however they had financial problems and had contamination obsessions and washing compulsions.

In conclusion, AD is the most common chronic disease in children in western societies. Maternal factors and behaviors are the main environmental factor in the disease course and progression; therefore maternal and parental attitudes toward children and family life, and evaluation of obsessive-compulsive symptoms of mothers give us clues about the child's growing factors from birth to becoming a school-aged child. There was also a significant correlation between the mother's contamination obsession and compulsion behavior associated with AD children. This was the first study investigating the parental and environmental factors using the Padua Inventory and PARI instruments. In the light of this study, further well-designed studies with large cohorts involving both parents and children are needed. A better understanding of the pathogenesis of AD will definitely improve both the diagnosis and treatment of this disease.

The neccessity of using psychometric inventories in AD and in other dermatologic diseases for understanding our patients' daily lives is highlighted in this study.

References

1. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014; 70: 338-351. PMID: 24290431
2. Galassi C, De Sario M, Biggeri A, et al. Changes in prevalence of asthma and allergies among children and adolescents in Italy: 1994-2002. Pediatrics 2006; 117: 34-42. PMID: 16396858
3. Schmitz R, Atzpodien K, Schlaud M, et al. Prevalence and risk factors of atopic diseases in German children and adolescents. Pediatr Allergy Immunol 2012; 23: 716-723. PMID: 22882467
4. Karadag B, Ege MJ, Scheynius ,A et al. Environmental determinants of atopic eczema phenotypes in relation to asthma and atopic sensitization. Allergy 2007; 62: 1387-1393. PMID: 17983373
5. Strachan DP. Hay fever, hygiene, and household size. BMJ 1989; 18; 299: 1259-1260. PMID: 2513902
6. Cabana MD, McKean M, Wong AR, et al. Examining the hygiene hypothesis: the Trial of Infant Probiotic Supplementation. Paediatr Perinat Epidemiol 2007; 21: 23-28. PMID: 17935572
7. Zutavern A, Hirsch T, Leupold W, et al. Atopic dermatitis, extrinsic atopic dermatitis and the hygiene hypothesis: results from a cross-sectional study. Clin Exp Allergy 2005; 35: 1301-1308. PMID: 16238789
8. Kemény L, Szabó K. Toll-like receptors link atopic march to the hygiene hypothesis. J Invest Dermatol 2013; 133: 874-878. PMID: 23486430
9. Van Dijk M, de Vries GJ, Last BF. Parental child-rearing attitudes are associated with functional constipation in childhood. Arch Dis Child 2015; 100: 329-333. PMID: 25359759
10. Sassaroli S, Centorame F, Caselli G. Anxiety control and metacognitive beliefs mediate the relationship between inflated responsibility and obsessive compulsive symptoms. Psychiatry Res 2015; 228: 560-564. PMID: 26141603
11. De D, Kanwar AJ, Handa S. Comparative efficacy of Hanifin and Rajka's criteria and the UK working party's diagnostic criteria in diagnosis of atopic dermatitis in a hospital setting in North India. J Eur Acad Dermatol Venereol 2006; 20: 853-859. PMID: 16898910
12. Sanavio E. Obsessions and compulsions: the Padua Inventory. Behav Res Ther 1988; 26: 169-177. PMID: 3365207
13. Smári J, Olason DT, Eypórsdóttir A, et al. Psychometric properties of the Obsessive Compulsive Inventory-Revised among Icelandic college students. Scand J Psychol 2007; 48: 127-133. PMID: 17430365
14. Besiroglu L, Agargun MY, Boysan M. Obsessif-Kompulsif Belirtilerin Değerlendirilmesi: Padua Envanteri'nin Türk Toplumunda Geçerlik ve Güvenirliği. Türk Pskyatri dergisi 2005; 16: 179-189.
15. Heederik D, von Mutius E. Does diversity of environmental microbial exposure matter for the occurrence of allergy and asthma? J Allergy Clin Immunol 2012; 130: 44-50. PMID: 22502794
16. Karadag B, Ege MJ, Scheynius A et al. Environmental determinants of atopic eczema phenotypes in relation to asthma and atopic sensitization. Allergy 2007; 62: 1387-1393. PMID: 17983373
17. Zutavern A, Hirsch T, Leupold W et al. Atopic dermatitis, extrinsic atopic dermatitis and the hygiene hypothesis: results from a cross-sectional study. Clin Exp Allergy 2005; 35: 1301-1308. PMID: 16238789
18. Cabana MD, McKean M, Wong AR et al. Examining the hygiene hypothesis: the Trial of Infant Probiotic Supplementation. Paediatr Perinat Epidemiol 2007; 21: 23-28. PMID: 17935572
19. Bloomfield SF, Stanwell-Smith R, Crevel RW, Pickup J. Too clean, or not too clean: the hygiene hypothesis and home hygiene. Clin Exp Allergy 2006; 36: 402-425. PMID: 16630145

20. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 2003; 361: 1869-1871. PMID: 12788576

21. Hyman RW, Fukushima M, Diamond Let al. Microbes on the human vaginal epithelium. Proc Natl Acad Sci U S A 2005; 102: 7952-7957. PMID: 15911771

22. Spergel JM, Fogg MI, Bokszczanin-Knosala A. Correlation of exhaled nitric oxide, spirometry and asthma symptoms. J Asthma 2005; 42: 879-883. PMID: 16393728

23. Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. Allergy Asthma Immunol Res 2011; 3: 67-73. PMID: 21461244

24. Heimall J, Spergel JM. Filaggrin mutations and atopy: consequences for future therapeutics. Expert Rev Clin Immunol 2012; 8: 189-197. PMID: 22288457

25. Kemény L, Szabó K. Toll-like receptors link atopic march to the hygiene hypothesis. J Invest Dermatol 2013; 133: 874-878. PMID: 23486430

26. Hubiche T1, Ged C, Benard A, et al. Analysis of SPINK 5, KLK 7 and FLG genotypes in a French atopic dermatitis cohort. Acta Derm Venereol 2007; 87: 499-505. PMID: 17989887

27. Im YJ, Park ES, Oh WO, Suk MH. Parenting and relationship characteristics in mothers with their children having atopic disease. J Child Health Care 2014; 18: 215-229. PMID: 23818147

28. Buske-Kirschbaum A. Treating the parents to heal the child? Brain Behav Immun 2008; 22: 431-432. PMID: 18294812

29. Teyhan A, Galobardes B, Henderson J. Child allergic symptoms and mental well-being: the role of maternal anxiety and depression. J Pediatr 2014; 165: 592-599. PMID: 24952709

30. Schmitz R, Atzpodien K, Schlaud M. Prevalence and risk factors of atopic diseases in German children and adolescents. Pediatr Allergy Immunol 2012; 23: 716-723. PMID: 22882467

31. Mark JC. The attitudes of the mothers of male schizophrenics toward child behavior. J Abnorm Psychol 1953; 48: 185-189.

32. Shoben E. The assessment of parental attitudes in relation to child adjustment. Genet Psychol Monogr 1949; 39: 101-148.

33. Meads DM, McKenna SP, Kahler K. The quality of life of parents of children with atopic dermatitis: Interpretation of PIQoL-AD scores. Quality of Life Res 2005; 14: 2235-2245. PMID: 16328903