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Atopic Dermatitis; Etio-Pathogenesis, An Overview

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Abstract

Atopic dermatitis is a well-recognized clinical entity, several facets of which continue to be mystified. Accordingly, its etio-pathogenesis is largely elusive. It appears to be an outcome of interplay of several undertones, namely: genetics, maternal factor and inheritance, pregnancy/intrauterine, environmental factors, immune dysregulation, immuno-globulins, role of diet, and infection. Besides, recent innovative breakthroughs consisting of nutritional supplementation, the highlights of which were considered worthwhile to take stock of to define its current status. An endeavor to enlighten the audience has been made for their benefit.

Keywords: *Atopic dermatitis, etio-pathogenesis, prevalence*

What was known?

Atopic dermatitis is a well-recognized clinical entity, the etio-pathogenesis of which is largely elusive, contemplating future research.

Introduction

Atopic dermatitis (AD) is an itchy, chronic, and/or chronically relapsing, inflammatory dermatosis, its rash is characterized by itchy papules, occasionally vesicles which become excoriated and lichenified, and typically have a flexural distribution. It is frequently associated with other atopic conditions in the individual or other family members.[1,2,3] Atopic dermatitis/eczema for nearly two centuries has challenged neither the generation of medical scientists, who to this date have neither found a single distinguishing clinical feature nor a diagnostic laboratory test of the universally occurring disorder with an alarming rise in prevalence.[4] The clinical phenotype that characterizes AD is the product of complex interactions among susceptibility genes, the host's environment, defects in skin barrier function, and systemic and local immunologic responses.[5,6,7] Although Sulzberger and associates have been credited with devising the term atopic dermatitis in the year 1930, the condition had been described for over a century prior to this time, as disseminated neurodermatitis, pruritic rash or Besnier's Prurigo.[8,9,10]

Prevalence AD is one of the major public health problems worldwide. Its prevalence[11,12] in children varies from 0.7% to 26%, while in adults it may range from 1% to 3%. Interestingly, its prevalence is much lower in developing countries when compared with industrialized nation[13] William *et al.*[14] have

reported that in children, males show an increased incidence while in adult patients, females outnumber males. In the past 30 years, the prevalence of AD has increased two to three times, suggesting that the environmental factors are now playing a more significant role in provocation of the disease.[15] A majority of cases have been recorded to begin in early life. The disease takes a chronic course, with a clearance rate of 60% by the age of 16.[16,17,18] Severe childhood affliction, concomitant/family history of eczema and early onset indicate a worse prognosis.[16]

Etio-pathogenesis Genetics

AD is a complex genetic disease, and for obscure reasons shows a strong maternal influence.[19] The inability to demonstrate a consistent pattern of inheritance in the disorder is best explained by the presence of several genes for any given atopic phenotype interacting with each other and environment to influence disease expression.[20] A much higher disease concordance has been recorded in monozygotic twins (80%) when compared with dizygotic twins (30%)[21] Relevant to AD as part of a systemic atopic disorder, candidate genes involving immunoglobulin (IgE) and Th2 Cytokines have been identified. Studies have identified susceptibility loci on 1q21, 3p24-22, 3q21 and 17q2[22] in association with atopic dermatitis. A number of other associated loci have also been reported by further association with disease severity, IgE, or concurrent asthma, namely 3p26-24, 3q14, 4p15-14, 13q14, 15q14-15, 17q21, 18q11-12, 18q21 and 20.[23,24] A polymorphism in the gene encoding the chain of the high affinity IgE receptor FcεR1 has demonstrated a highly significant association with atopic dermatitis.[25] Genes on chromosome 5q encoding the cytokine gene cluster have been linked to atopic mucosal syndrome[26] and include associations with polymorphisms in the Interleukin 4 (IL-4) gene with atopic dermatitis.[27,28,29,30] A gene at 16p11.2-12 encoding the chain of the IL-4 receptor has been linked to atopy.[31,32,33] Variants in the RANTES gene promoter region have also been reported to be associated with atopic eczema[34] and further studies have demonstrated this variant to be associated with enhanced regulated upon activation normal T cell expressed and presumably secreted (RANTES) production.[35]

Maternal factors and inheritance

AD shows a strong maternal influence that is children of atopic mothers are more likely to be atopic than those of atopic father.[36] Cord blood IgE is high in babies whose mothers are atopic or have high IgE, whereas paternal atopy or raised IgE are not associated with raised cord blood IgE. Genes encoding IgE responsiveness, located on chromosome 11q13, are more frequently inherited from the maternal side.[37,38]

Pregnancy/intrauterine factors

For atopy, there is a positive correlation between increasing birth weight and prevalence of atopic eczema.[39,40,41] Another possible factor is the onset of immunological sensitization through intrauterine exposure to food and environmental allergens. The concentration of IgE in cord blood is a predictor for subsequent development of atopy.[42] Maternal exposure to a number of agents, including antigens, alcohol, cigarettes and other pollutants, has attracted attention, but none has emerged as a major regulatory factor.[43]

Environmental factors

A different prevalence in populations of the same genetic background separated only by geographical factors is well documented in developed countries. The two principal aspects that have attracted attention are “pollution” and “microbe”.[43]

Interaction with environmental microbes may be important in the causation of atopic eczema in a number of ways. First, early life exposure may condition the maturation of the immune system so that the apparent dysregulation associated with production of IgE antibody and formation of allergies does not occur. Secondly, in individuals with the atopic phenotype, eczema may be induced or exacerbated by staphylococcal toxins or by the presence on the skin of *Malassezia* yeasts.[43]

Early exposure to *hepatitis A virus*, *Helicobacter pylori* or *Toxoplasma gondii* is reported[44] to reduce the risk of atopy by more than 60%.

Significant differences have been observed in the prevalence of allergies between rural and urban areas within one country, which could also reflect different levels of exposure to microbes.[45] A study comparing the severity of AD in Indian children in the UK or USA, and in India revealed a less-severe form of the disease in children born and brought up in India. This study highlighted the influence of acquired factors: Temperature, humidity, food habits, clothing and psychological impacts on the clinical expression and severity of the disease.[46,47]

Immune dysregulation

In infants destined to develop infantile atopic eczema, the basal production of interferon- γ is particularly low and Th2 dominant responses persist.[48] Although development of acute lesions of atopic dermatitis is characterized by Th2 cytokines, persistence to chronic disease is associated with Th1 production as well. The reasons why the atopic immune system responds with ready generation of Th2 lymphocytes are not clear, but a hypothesis attracting much attention is the so-called hygiene hypothesis. This proposes that exposure in early life to microbes of various types, but especially those possessing lipopolysaccharide (LPS) endotoxin such as *E. coli* and other enteropathogens, is critical in pushing immune responses towards a Th1 type. The LPS activates production of IL-12 by DCs, which promotes production of interferon- γ and hence can deviate T-cell activation induced by any other antigen present at the same time towards a Th1 response.[43]

Chemokines are cytokine-like molecules which are essential for cellular recruitment to tissues in response to injury or infection. Chemokine–receptor interactions have been implicated in atopic dermatitis by demonstration of a significant role in skin homing of T cells.[43]

Immuno-globulins

Immunoglobulin E (IgE): Increased production of IgE is the main immunoglobulin abnormality in AD, about 80% of patients have increased amounts of total IgE.[43] If dermatitis is the only clinical manifestation of atopy, the amounts of total IgE may be little above the normal range, and the patients show no anaphylactic sensitivity to environmental antigens. If there is concomitant asthma or allergic rhinitis the concentrations of IgE may be very much above normal.[49,50,51]

Epithelial dendritic cells (DC) expression of fc epsilon R1 is significantly increased in individuals with AD. IgE also increases in amount with increasing severity, and extent of the dermatitis, even without respiratory allergy, and patients with high levels are likely to have a poorer prognosis.[43]

IgE is involved in autoimmune reactivity in two ways.

- Firstly, it is an antigenic target for IgG anti-IgE antibodies and
- Secondly, it can also be autoreactive, with specific city for self proteins. IgE occurs in serum in the form of immune complexes with IgG and C3, but the amounts of perceptible complexes are not related to the concentrations of serum IgE or to the severity of the skin condition.[52,53]

In a study of 102 consecutive patients, both children and adults, with AD were enrolled and 107 age- and sex-matched persons without any personal or family history of atopy were taken as controls. Patients with AD having other systemic diseases were excluded from the study. Analysis of variance was performed on parameters of severity of AD, eosinophil count and IgE levels with respect to independent variables like sex, family history of atopy either in father, mother or both, sex and associated atopic conditions bronchial asthma (BA), allergic rhinitis (AR). Each of the parameters were compared against the other using Product Moment Correlation to observe any significant covariance. The mean age at onset of AD was 4.55 (SD 3.63) years and in patients with AD, the mean absolute eosinophil count was 624 (SD 590) and the mean IgE level was 278.29 (SD 324.85); the corresponding values were 121 (SD 109) and 25.8 (SD 23.36), respectively, for the controls. The AEC and IgE levels were higher in patients with AD than in controls. They also found that both AEC and IgE levels showed significant covariance with disease severity.[54]

Another study was designed to assess these allergen-specific antibodies in the diagnosis of AD. This prospective study comprised of 50 patients of AD. Serum IgE levels were estimated and specific IgE antibodies were measured for 20 food allergens and aeroallergens. IgE was elevated in 88% of the patients,

and the highest elevation of mean IgE levels was in the 10-20 years age group.[55]

Other immunoglobulins: The amounts of IgG, IgA and IgM in atopic dermatitis are usually normal, but increases have been reported, particularly in severely affected persons. However, in patients with severe eczema complicated by cutaneous infection, an increase in IgG appears to be due to antibodies to bacteria.[42]

Although total IgG usually remains within normal limits, some patients show an increase in the subclass IgG4.[56]

It has been proposed that atopic subjects have an IgA deficiency which permits excessive absorption of allergen through mucosae, resulting in increased production of IgE.[43]

Role of diet

An open-pilot study investigated the feasibility of dietary eliminations in the Indian scenario and also assessed the effect it has on Indian children with AD. A group of 100 children were assessed for severity of itching, surface area of involvement and SCORAD (SCORing Atopic Dermatitis) index. Children without any systemic disease or those who were not on systemic corticosteroids were included in the study, and were advised to strictly adhere to a diet excluding milk and milk products, all kinds of nuts and nut-containing foods, egg and egg-containing foods, sea fish and prawns, brinjal and soyabean for a period of 3 weeks. The food items to be included freely to maintain proper nutrition were dal and dal products, rohu fish, chicken and fruits. Infants who were 6-12 months old were given protein hydrolysate formula instead of milk. All the pre-intervention parameters were measured again after 3 weeks. The male to female ratio of the study group was 0.92. There was a statistically significant reduction in severity scores after dietary elimination alone.[57]

Role of infection

The carriage state of *Staphylococcus aureus* has been a subject of interest for quite some time. Its role in the pathogenesis and management of AD were evaluated in 50 patients aged 3 months to 12 years. An equal number of age- and sex-matched controls were also studied. The positivity in patients with AD was 50% from eczematous skin, 34% from anterior nares and 26% from normal skin. In controls, the comparative figures were 14% from anterior nares and 10% from normal skin. Treatment with oral erythromycin or cloxacillin (according to sensitivity) resulted in colony counts dropping to 18% from eczematous skin, 14% from anterior nares and 8% from normal skin after 1 week and to zero after 3 weeks, and was associated with significant clinical improvement.[58] The result of this study suggests that *S. aureus* aggravates the eczematous process in patients with AD and antibiotics decrease the severity of this condition.

Innovative breakthroughs

The recent revelation that nutritional supplement (s) are incriminated in the causation of AD has triggered an innovative dialogue regarding the etio-pathogenesis. Foolad *et al.*[59] have conducted an extensive systematic review comprising of 21 randomized controlled trials/cohort studies. A total of 6859 participants, comprising infants or mothers who were either pregnant or breastfeeding, received supplements. 4134 infants or mothers served as controls. Nutritional supplementation was shown to be an effective method in preventing AD (11 of 17 studies) or decreasing its severity (5 of 6 studies). It was concluded that the best evidence for long-term prevention of AD was in favor of *Lactobacillus rhamnosus* GG. Moreover, combination of gamma linolenic acid and omega 3 acids was helpful in reducing severity of AD. Nevertheless, supplementation with an amino acid-based formula reported conflicting findings from different research groups.

Furthermore, several reports[60] have suggested a pathogenic undertone for vitamin D, through its immuno-modulatory properties. Skin infections could be prevented through enhanced expression of antimicrobial peptides by the active form of Vitamin D₃- 1,25-Dihydroxyvitamin D, particularly in AD. Another study[61] demonstrated vitamin D mediated expression of toll like receptors and production of cathelicidin. In yet another study[62] comprising 95 AD patients and 58 controls, vitamin D₃ levels were

assessed by SCORAD (scoring atopic dermatitis) in both groups. Higher frequency of bacterial infections in AD patients with lower vitamin D3 levels was found. After supplementation with vitamin D both mean objective SCORAD and SCORAD index were found to be significantly low ($P < .05$), indicating that vitamin D supplementation may help ameliorate clinical signs of AD.

What is new?

Nutritional supplements, vitamin D and its derivatives (Vitamin D3-1,25-Dihydroxyvitamin D1) through their immuno-modulatory properties are now being incriminated to prevent skin infection by enhancing the expression of antimicrobial peptides. *Lactobacillus rhamnosus* GG, too, may play a long term prevention of atopic dermatitis.

Footnotes

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Conflict of Interest: Nil.

References

1. Williams HC. Clinical practice. Atopic dermatitis. *N Engl J Med*. 2005;352:2314–24. [PubMed: 15930422]
2. Brown S, Reynolds NJ. Atopic and non-atopic eczema. *BMJ*. 2006;332:584–8. [PMCID: PMC1397720] [PubMed: 16528081]
3. Darsow U, Lübke J, Taïeb A, Seidenari S, Wollenberg A, Calza AM, et al. European Task Force on Atopic Dermatitis. Position paper on the diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2005;19:286–95. [PubMed: 15857453]
4. Leung DY, Eichenfield LF, Boguniewicz M. Atopic dermatitis (atopic eczema) In: Freeberg IM, Eausten KF, Goldsmith LA, Katz SI, editors. *Dermatology in General Medicine*. 6th ed. New York, NY: McGraw Hill; 2003. pp. 1180–94.
5. Staab D, Diepgen TL, Fartasch M, Kupfer J, Lob-Corzilius T, Ring J, et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: Multicentre, randomised controlled trial. *BMJ*. 2006;332:933–8. [PMCID: PMC1444870] [PubMed: 16627509]
6. Atopic eczema-new insights in the definition, diagnostics and disease management. Proceedings of a LEO eczema workshop. November 2003 Copenhagen, Denmark. *Acta Derm Venereol Suppl (Stockh)* 2005;7–48.
7. Consensus Conference Management of atopic dermatitis in children. Consensus Conference Management of atopic dermatitis in children. Recommendations (short version) *Eur J Dermatol*. 2005;15:215–23. [PubMed: 16048746]
8. Wise F, Sulzberger MB. Chicago, IL: Year Book Publishers; 1933. Year Book of Dermatology and Syphilology; p. 38.
9. Pascher F. Sulzberger on atopic dermatitis. *Int J Dermatol*. 1977;16:376–9. [PubMed: 326699]
10. Hill LW, Sulzberger MB. Evolution of atopic dermatitis. *Arch Derm Syphilol*. 1935;32:451–63.
11. Dotterud LK, Kvammen B, Lund E, Falk ES. Prevalence and some clinical aspects of atopic dermatitis in the community of Sør-Varanger. *Acta Derm Venereol*. 1995;75:50–3. [PubMed: 7747535]
12. Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol*. 1999;103:125–38. [PubMed: 9893196]
13. Rajka G. Berlin, Germany: Springer Verlag; 1989. Essential Aspects of Atopic Dermatitis; pp. 125–38.

14. Williams HC, Strachan DP. The natural history of childhood eczema: Observations from the British 1958 birth cohort study. *Br J Dermatol*. 1998;139:834–9. [PubMed: 9892950]
15. Vickers CF. The natural history of atopic eczema. *Acta Derma Venereol*. 1980;92:113–5.
16. Rystedt I. Long term follow-up in atopic dermatitis. *Acta Derm Venereol Suppl* (Stockh) 1985;114:117–20. [PubMed: 3859160]
17. Friedmman PS, Holden CA. Atopic dermatitis. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. *Rook's Textbook of Dermatology*. 7th ed. Oxford, England: Blackwell Sciences; 2004. pp. 18.1–31.
18. Bos JD. Immunology of atopic dermatitis. In: Harper J, Oranje A, Prose N, editors. *Textbook of Pediatric Dermatology*. 2nd ed. Oxford, England: Blackwell Sciences; 2006. pp. 202–9.
19. Ruiz RG, Kemeny DM, Price JF. Higher risk of infantile atopic dermatitis from maternal atopy than from paternal atopy. *Clin Exp Allergy*. 1992;22:762–6. [PubMed: 1525695]
20. Moffatt M, Cookson WO. Genetics of atopic dermatitis. In: Harper J, Oranje A, Prose N, editors. *Textbook of Pediatric Dermatology*. 2nd ed. Oxford, England: Blackwell Sciences; 2006. pp. 192–201.
21. Larsen FS, Holm NV, Henningsen K. Atopic dermatitis. A genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol*. 1986;15:487–94. [PubMed: 3760273]
22. Lee YA, Wahn U, Kehrt R, Tarani L, Businco L, Gustafsson D, et al. A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. *Nat Genet*. 2000;26:470–3. [PubMed: 11101848]
23. Bradley M, Söderhäll C, Luthman H, Wahlgren CF, Kockum I, Nordenskjöld M. Susceptibility loci for atopic dermatitis on chromosomes 3, 13, 15, 17 and 18 in a Swedish population. *Hum Mol Genet*. 2002;11:1539–48. [PubMed: 12045207]
24. Haagerup A, Bjerke T, Schiøtz PO, Dahl R, Binderup HG, Tan Q, et al. Atopic dermatitis – A total genome-scan for susceptibility genes. *Acta Derm Venereol*. 2004;84:346–52. [PubMed: 15370699]
25. Sandford AJ, Shirakawa T, Moffatt MF, Daniels SE, Ra C, Faux JA, et al. Localisation of atopy and beta subunit of high-affinity IgE receptor (Fc epsilon RI) on chromosome 11q. *Lancet*. 1993;341:332–4. [PubMed: 8094113]
26. Doull IJ, Lawrence S, Watson M, Begishvili T, Beasley RW, Lampe F, et al. Allelic association of gene markers on chromosomes 5q and 11q with atopy and bronchial hyperresponsiveness. *Am J Respir Crit Care Med*. 1996;153:1280–4. [PubMed: 8616554]
27. He JQ, Chan-Yeung M, Becker AB, Dimich-Ward H, Ferguson AC, Manfreda J, et al. Genetic variants of the IL13 and IL4 genes and atopic diseases in at-risk children. *Genes Immun*. 2003;4:385–9. [PubMed: 12847555]
28. Kawashima T, Noguchi E, Arinami T, Yamakawa-Kobayashi K, Nakagawa H, Otsuka F, et al. Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. *J Med Genet*. 1998;35:502–4. [PMCID: PMC1051346] [PubMed: 9643293]
29. Hosomi N, Fukai K, Oiso N, Kato A, Ishii M, Kunitomo H, et al. Polymorphisms in the promoter of the interleukin-4 receptor alpha chain gene are associated with atopic dermatitis in Japan. *J Invest Dermatol*. 2004;122:843–5. [PubMed: 15086575]
30. Oiso N, Fukai K, Ishii M. Interleukin 4 receptor alpha chain polymorphism Gln551Arg is associated with adult atopic dermatitis in Japan. *Br J Dermatol*. 2000;142:1003–6. [PubMed: 10809862]
31. Deichmann KA, Heinzmann A, Forster J, Dischinger S, Mehl C, Brueggenolte E, et al. Linkage and allelic association of atopy and markers flanking the IL4-receptor gene. *Clin Exp Allergy*. 1998;28:151–5. [PubMed: 9515586]
32. Hershey GK, Friedrich MF, Esswein LA, Thomas ML, Chatila TA. The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. *N Engl J Med*.

1997;337:1720–5. [PubMed: 9392697]

33. Kruse S, Japha T, Tedner M, Sparholt SH, Forster J, Kuehr J, et al. The polymorphisms S503P and Q576R in the interleukin-4 receptor alpha gene are associated with atopy and influence the signal transduction. *Immunology*. 1999;96:365–71. [PMCID: PMC2326760] [PubMed: 10233717]

34. Nickel RG, Casolaro V, Wahn U, Beyer K, Barnes KC, Plunkett BS, et al. Atopic dermatitis is associated with a functional mutation in the promoter of the C-C chemokine RANTES. *J Immunol*. 2000;164:1612–6. [PubMed: 10640782]

35. Bai B, Tanaka K, Tazawa T, Yamamoto N, Sugiura H. Association between RANTES promoter polymorphism -401A and enhanced RANTES production in atopic dermatitis patients. *J Dermatol Sci*. 2005;39:189–91. [PubMed: 16046258]

36. Ruiz RG, Kemeny DM, Price JF. Higher risk of infantile atopic dermatitis from maternal atopy than from paternal atopy. *Clin Exp Allergy*. 1992;22:762–6. [PubMed: 1525695]

37. Cookson WO, Young RP, Sandford AJ, Moffatt MF, Shirakawa T, Sharp PA, et al. Maternal inheritance of atopic IgE responsiveness on chromosome 11q. *Lancet*. 1992;340:381–4. [PubMed: 1353553]

38. Selnes A, Bolle R, Lund E, Lund E. Cumulative incidence of asthma and allergy in north-Norwegian schoolchildren in 1985 and 1995. *Pediatr Allergy Immunol*. 2002;13:58–63. [PubMed: 12000500]

39. Peters TJ, Golding J. The epidemiology of childhood eczema: II. Statistical analyses to identify independent early predictors. *Paediatr Perinat Epidemiol*. 1987;1:80–94. [PubMed: 3506193]

40. Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: Historical follow up by record linkage. *BMJ*. 1997;314:1003–8. [PMCID: PMC2126413] [PubMed: 9112844]

41. Godfrey K. Fetal and perinatal origins of atopic dermatitis. *Atopic Dermatitis: The Epidemiology, Causes and Prevention of Atopic Eczema*. In: Williams HC, editor. Cambridge: Cambridge University Press; 2000. pp. 125–38.

42. Tariq SM, Arshad SH, Matthews SM, Hakim EA. Elevated cord serum IgE increases the risk of aeroallergen sensitization without increasing respiratory allergic symptoms in early childhood. *Clin Exp Allergy*. 1999;29:1042–8. [PubMed: 10457106]

43. Friedmann PS, Arden-Jones MR, Holden CA. Atopic dermatitis. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. *Rook's Textbook of Dermatology*. 8th ed. UK: Blackwell Publishing Ltd; 2010. pp. 24.1–24.33.

44. Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: Epidemiological study. *BMJ*. 2000;320:412–7. [PMCID: PMC27285] [PubMed: 10669445]

45. Braun-Fahrlander C. The role of the farm environment and animal contact for the development of asthma and allergies. *Clin Exp Allergy*. 2001;31:1799–803. [PubMed: 11737027]

46. Dhar S, Banerjee R, Dutta AK, Gupta AB. Comparison between the severity of atopic dermatitis in Indian children born and brought up in UK and USA and that of Indian children born and brought up in India. *Indian J Dermatol*. 2003;48:200–2.

47. Patki A. Eat dirt and avoid atopy: The hygiene hypothesis revisited. *Indian J Dermatol Venereol Leprol*. 2007;73:2–4. [PubMed: 17314438]

48. Warner JO, Warner JA, Miles EA, Jones AC. Reduced interferon-gamma secretion in neonates and subsequent atopy. *Lancet*. 1994;344:1516. [PubMed: 7968157]

49. Ohman S, Johansson SG. Allergen-specific IgE in atopic dermatitis. *Acta Derm Venereol*. 1974;54:283–90. [PubMed: 4136514]

50. Ohman S, Johansson SG. Immunoglobulins in atopic dermatitis with special reference to IgE. *Acta Derm Venereol.* 1974;54:193–202. [PubMed: 4134128]
51. Jones HE, Inouye JC, McGerity JL, Lewis CW. Atopic disease and serum immunoglobulin-E. *Br J Dermatol.* 1975;92:17–25. [PubMed: 1156542]
52. Czech W, Stadler BM, Schöpf E, Kapp A. IgE autoantibodies in atopic dermatitis--occurrence of different antibodies against the CH3 and the CH4 epitopes of IgE. *Allergy.* 1995;50:243–8. [PubMed: 7545880]
53. Swainson JA, Wilson PB, Dore P, Pumphrey RS. Evidence for circulating complexes containing IgE in patients with atopic dermatitis. *Int Arch Allergy Appl Immunol.* 1985;76:237–42. [PubMed: 3871737]
54. Dhar S, Banerjee R. Atopic dermatitis in infants and children in India. *Indian J Dermatol Venereol Leprol.* 2010;76:504–13. [PubMed: 20826989]
55. Somani VK. A study of allergen-specific IgE antibodies in Indian patients of atopic dermatitis. *Indian J Dermatol Venereol Leprol.* 2008;74:100–4. [PubMed: 18388364]
56. Merrett J, Barnetson RS, Burr ML, Merrett TG. Total and specific IgG4 antibody levels in atopic eczema. *Clin Exp Immunol.* 1984;56:645–52. [PMCID: PMC1535979] [PubMed: 6744664]
57. Dhar S, Malakar R, Chakraborty S, Chakraborty J, Mukherjee S. An uncontrolled open pilot study to assess the role of dietary eliminations in reducing the severity of atopic dermatitis in infants and children. *Indian J Dermatol.* 2009;54:183–5. [PMCID: PMC2807161] [PubMed: 20101317]
58. Dhar S, Kanwar AJ, Kaur S, Sharma P, Ganguly NK. Role of bacterial flora in the pathogenesis and management of atopic dermatitis. *Indian J Med Res.* 1992;95:234–8. [PubMed: 1478727]
59. Foolad N, Brezinski EA, Chase EP, Armstrong AW. Effect of nutrient supplementation on atopic dermatitis in children: A systematic review of probiotics, prebiotics, formula, and fatty acids. *JAMA Dermatol.* 2013;149:350–5. [PubMed: 23682371]
60. Schaubert J, Dorschner RA, Code AB, Büchau AS, Liu PT, Kiken D, et al. Injury enhances TLR2 function and antimicrobial peptide expression through vitamin D-dependent mechanism. *J Clin Invest.* 2007;117:803–11. [PMCID: PMC1784003] [PubMed: 17290304]
61. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of vitamin D-mediated human antimicrobial response. *Science.* 2006;311:1770–3. [PubMed: 16497887]
62. Samochocki Z, Bogaczewicz J, Jeziorkowska R, Sysa-Jędrzejowska A, Glińska O, Karczmarewicz E, et al. Vitamin D effects in atopic dermatitis. *J Am Acad Dermatol.* 2013;69:238–44. [PubMed: 23643343]

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