ORIGINAL ARTICLE

A single centre study on prevalence of anemia in children and adolescents with atopic dermatitis and its associated factors

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ABSTRACT

Introduction: Chronic inflammation, food avoidance, and the use of systemic immunosuppressants are associated with anemia in patients with atopic dermatitis (AD). This study aimed to determine the prevalence of anemia among children and adolescents with AD, the type of anemia, and its predisposing factors.

Materials and Methods: This is a cross-sectional study. Patients aged ≤18 years with AD were included in the study. The exclusion criteria were malignancy, chronic organ failure, and haematological diseases. Dietary patterns and nutrient intake were determined using a 3-day dietary recall. AD severity was assessed using a scoring tool known as Scoring Atopic Dermatitis (SCORAD). Peripheral blood counts, iron studies, and serum B12 and folate levels were determined.

Results: A total of 77 patients were recruited for this study. The mean age was 8.58±5.26 years with 43(55.8%) boys and 34(44.2%) girls. Most (58.4%) were from economic bottom-tier households with incomes below RM4850. Food avoidance was common (55.8%), primarily for shellfish (37.7%), nuts (33.8%), and eggs (22.1%). The prevalence of anemia was 58.4%, and 71.1% was due to iron deficiency. Younger age, male sex, underweight, and lower intakes of iron, protein, and fat were significantly associated with anemia. There was no association between the severity with anemia.

Conclusion: The high prevalence of iron deficiency anemia in patients with AD was likely due to the lower intake of food restrictions compounded with chronic inflammation in AD.

KEYWORDS:
Anaemia, Iron, Atopic Dermatitis, Nutrition

INTRODUCTION

Atopic dermatitis (AD) is an inflammatory skin disorder that impacts around 20% of children and 10% of adults.[1] Prevalence of AD in Malaysian children was 13.4% in 2018.[2] The pathophysiology of AD is a complex interplay between genetic, immune system, skin barrier and environmental factors.[1] Nutrition is important for a healthy immune system. Micronutrients play a role in regulating immunity, improving the skin barrier function, and preventing itching in AD.[3-6]

Anemia is associated with many factors. The impact of anemia in children includes growth delays, weakened immune system, impaired motor and cognitive development, and reduced stamina.[7] In Malaysia, the reported overall prevalence of anemia was 21.3%.[8] A study conducted in Penang highlighted anemia as a public health issue among Malaysian children, with a prevalence of 22.3%.[9] A higher percentage (48.5%) of aboriginal school children aged seven to 12 years were diagnosed with anemia in a remote area of Pahang, Malaysia.10 Studies conducted in Korea and the US indicated that children with atopic conditions have a significantly higher incidence of iron deficiency anaemia[12-13]. The prevalence of anaemia among paediatric population was 3.46% in South Korea.[13] In Turkey, the rate of iron deficiency anaemia was greater in patients with AD (15%) compared to those without (5%) AD.[14] Prevalence of anaemia among the paediatric population with AD was 4.3% in South Korea.[13]

Chronic inflammation, food avoidance, and the use of systemic immunosuppressants in atopic diseases are associated with anaemia.[13-16] Parents of children with AD often restrict certain foods, favoring fruits and vegetables over dairy, meat, and fish owing to concerns about allergies.[5-6, 16] Iron loss in AD-related malabsorption and pruritus due to iron-deficiency anemia can worsen skin lesions, creating a vicious cycle.[17]

This study aimed to determine the prevalence of anemia among children and adolescents with AD. The type of anemia and its predisposing factors, including socioeconomic factors, AD severity, and dietary restriction, were assessed.

MATERIALS AND METHODS

Study Design and Participants Selection

This was a single-center cross-sectional study. Patients with AD attending the dermatology clinic at Hospital Tuanku Jaafar Seremban, Negeri Sembilan, Malaysia were screened

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and recruited from May 1, 2023, to October 31, 2023. Patients aged ≤18 years who met the diagnostic criteria for AD based on the UK Working Party were included. The exclusion criteria were malignancy, chronic or end-stage organ failure, hemoglobinopathy, bleeding disorders, menorrhagia, rheumatological disorders, inflammatory bowel disease, severe bronchial asthma, and systemic drugs that can cause cytopenia.

Data Collection

Demographic details, history of AD, comorbidities, and treatment history were obtained by interviewing patients or their caregivers and reviewing their medical records. Body mass index (BMI) was calculated and plotted using the World Health Organization (WHO) BMI for the age percentile chart. 18 Investigator Global Assessment (vIGA), ScoRing Atopic Dermatitis (SCORAD), and Dermatology Life Quality Index (DLQI) scores were calculated.[19-21] AD severity was categorized according to the SCORAD index as mild (<25), moderate (25-50), and severe (>50). 19 vIGA scores were used to categorize disease severity as mild (0-2), moderate (3), and severe (4). The DLQI scores were categorized as <10 or ≥ 10. [20-21]

Patients were asked to recall a 3-day dietary intake, which consisted of two weekdays and one weekend. This included food allergies, types of food that were avoided, types of food or beverage consumed, portion size, and cooking styles. Patients were interviewed regarding the food consumed over the past 24 hours, and portion sizes were determined using common guides such as cups, bowls, tablespoons, and teaspoons. The intake of key food groups was analyzed, including meat (chicken, beef, pork), seafood (fish, crustaceans, mollusks), vegetables, eggs, milk, peanuts, and snacks (cakes, sweets, and chips). Dietary intake was analyzed for macronutrients and micronutrients using Nutritionist Pro™ Software (Axxya Systems, the United States Department of Agriculture (USDA) Standard Reference Database, First DataBank, Inc., San Bruno, California). Malaysian food composition databases, as well as other international databases such as the USDA Food Database, Canadian Food Database, and Mexican Food Database, are included in this software.

Venous blood was obtained for peripheral blood count, iron study, and serum vitamin B12 and folate levels. Peripheral blood counts were analyzed using a Sysmex XN3000e. A Siemens Atellica Solution Analyzer was used for iron studies and measurements of serum B12 and folate levels. An iron study was performed using the colorimetric method, while folate and B12 studies were performed using a chemiluminescent paramagnetic microparticle immunoassay. These tests were conducted in the laboratory of the Hospital Tuanku Jaafar. Anemia was diagnosed based on the WHO definition: hemoglobin (Hb) <11 g/L in children aged <5 years, while for those aged ≥ 5 years, anemia was defined as <12 g/L in females and <13 g/L in males. The type of anemia was determined by a combination of hemoglobin value, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), iron, transferrin saturation, and B12 and folate levels. Comprehensive evaluations of hepcidin, erythropoietin, and transferrin levels, which may influence iron deficiency anemia, were not performed, as these are not required for the clinical diagnosis of anemia.

Sample size determination

This study was approved by the Medical Research and Ethical Committee (MREC), Malaysia, under the research code NMRR-20-00719-WZO. The sample size was calculated using the population proportion formula based on the results reported by Rhew et al.. on the association between atopic disease and anemia in children. Seventy-seven participants were required for the estimated 95% confidence level and 5% absolute precision.[22]

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 23. Descriptive statistics were used to analyze the sociodemographic and clinical characteristics of the patients. Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as means and standard deviations. Differences between categorical variables were compared using Pearson's chi-square or Fisher's exact tests. Differences between continuous variables were compared using the independent t-test or Mann-Whitney U test. Binary logistic regression was used to determine the predisposing factors for anemia. Statistical significance was set at $P < 0.05$.

RESULTS

Demographic Characteristics

A total of 77 patients participated in the study. The mean age was 8.58±5.26 years. There were 43 boys (55.8%) and 34 girls (44.2%). The majority of the patients were Malay (70.1%), followed by Chinese (19.5%), and Indian (10.4%). Most children (58.4%) were from economic bottom-tier households with income below RM4850. Nineteen (24.7%) patients had concomitant allergic rhinitis and 9 (11.7%) had bronchial asthma. Table I.

Clinical Characteristics and Laboratory Parameters

The mean BMI of the patients was 17.59 kg/m2. The majority of the study population had mild-to-moderate AD, with 53 (68.8%) categorized as mild, 19 (24.7%) as moderate, and 5(6.5%) as severe. Most patients (74%) reported minimal impact on their quality of, with a DLQI score of less than 10. All patients received topical treatment, 9.1% underwent phototherapy, and none of the patients received systemic therapy.

The mean hemoglobin level was 12.16 ± 1.51 g/dL. The mean levels of MCV, MCH, iron, and transferrin saturation were below the normal range, whereas both B12 and folate levels were normal. The prevalence of anemia in our study population was 58.4%, and 71.1% was due to iron deficiency. One patient had iron and folate deficiencies. The majority (86.6%) of the patients with anemia had hemoglobin levels of more than 10 g/dl, only 7.8% had hemoglobin levels of 9-10 g/dl. Twenty-four (31.2%) patients had high eosinophil counts. A detailed analysis of the laboratory parameters is presented in Table II.

Table I: Characteristics of the study population

Characteristics	N= 77 n (%)
Age, mean±SD	8.58±5.26
Gender	
Male	43 (55.8)
Female	34 (44.2)
Ethnicity	
Malay	54 (70.1)
Chinese	15 (19.5)
Indian	8 (10.4)
Education level	
Underage for school	16 (20.8)
Primary	38 (49.4)
Secondary	21 (27.3)
Tertiary	2 (2.6)
Household income	
B40	45 (58.4)
M40	28 (36.4)
T20	4 (5.2)
Smoking status	
No	77 (100.0)
Alcohol use	
No	77 (100.0)
Other atopic diseases	
Allergy Rhinitis	19 (24.7)
Allergy Conjunctivitis	0 (0)
Bronchial asthma	9 (11.7)

Dietary History

Nearly half of the parents (46.7%) thought that their child had food allergies, and only one patient underwent an IgE test. Food restriction was common, and 43 (55.8%) participants actively avoided certain types of food. The most common restricted foods were shellfish (37.7%), nuts (33.8%), and eggs (22.1%), whereas 10% avoided dairy products.

Factors Associated with Anemia

Age and gender were significantly associated with anemia, and younger patients were more likely to have anemia. The prevalence of anemia was higher in males than in females (p-0.006). Ethnicity, household income, concomitant allergic rhinitis or bronchial asthma, food restriction, and AD severity were not significantly associated with anemia (Table IV). Anemia was associated with lower protein, fat, iron, and folate intakes (Table V). There was high intake of carbohydrates, fat, and protein. We observed that some patients over-reported their food intake and parents tended to repeat the same main meals during the recall period.

Multiple logistic regression analyses did not reveal a significant independent risk factor for anemia other than the male gender (adjusted OR 0.27, 95%CI 0.10 - 0.70, p <0.01).

DISCUSSION

More than half of our study population had anemia and almost all were due to iron deficiency. The micronutrient status affects the risk of AD by altering cell-mediated immunity.[17,24] Iron is an important micronutrient involved in the regulation of cytokine production, cell growth, cell differentiation, and cell proliferation. The immune response in AD is dominated by type 2 cytokines including IL 4,5 and 13 which impairs the skin barrier, reduce antimicrobial peptide activity, and promote inflammation.[24] Iron modulates the differentiation and proliferation of Th cells, particularly Th1, Th2, Th17, and Treg cells.25 Iron deficiency favors a Th2 response as DNA synthesis in Th1 but not Th 2 is suppressed.[17,24] In addition, macrophages and neutrophils exhibit reduced bactericidal activity, while NK-cell's differentiation and proliferation are inhibited.[17] Adequate levels of iron enhance immune resilience and promote immune tolerance.

The prevalence of anaemia in patients with AD has been documented in previous reports.[12-14,26] The prevalence of iron deficiency anaemia (IDA) among children with AD in Turkey was 15%,[14] while in Korea, the prevalence was lower at 4.3%.[13] The prevalence of IDA or anemia due to inflammation was 57%.[26] The prevalence of anaemia among those with eczema were up to 3.0% in the 1997-2013 US National Health Interview Survey (NHIS) among 207 007 children and adolescents.[12] The adjusted odds ratio for anaemia in this survey was 1.83; 95% CI, 1.58-2.13.[12] A cross sectional study which analysed data from 1468 033 patients in the 2016 National Health Insurance Service data set found significant associations between iron deficiency anaemia and atopic conditions.[26] The odds ratios (OR) for IDA in individuals with atopic dermatitis, allergic rhinitis, and asthma were 1.40 (95% CI, 1.33–1.48; p < 0.001), 1.17 (95% CI, 1.14–1.21; p < 0.001), and 1.32 (95% CI, 1.28–1.36; p < 0.001), respectively.[26] This study also documented a higher prevalence of anaemia with higher number of atopic diseases, suggesting that the inflammatory state of atopic diseases contributes to increased risk of anemia.[26] The prevalence of anaemia in our study population was very high compared to data from other countries. However,

Table II: Clinical characteristics, treatment and laboratory parameters

Clinical characteristics	N=77 N (%) or mean ± SD
Weight, kg	29.91±18.24
Height, cm	124.08 ± 28.80
BMI, kg/m2	17.59 ± 5.31
AD severity, SCORAD score	
Mild (< 25)	53 (68.8)
Moderate (25 – 50)	19 (24.7)
Severe (> 50)	5 (6.5)
Quality of life, DLQI score	
<10	57 (74.0)
> 10	20 (26.0)
Treatment for AD	
Topical	77 (100.0)
Phototherapy	7 (9.1)
Systemic therapy	0 (0)
Laboratory parameters (normal range)	
Haemoglobin, g/dL	12.16 ± 1.51
Age < 5 years (11-15.5g/dL)	
Age ≥ 5 years	
Females (12-15.5g/dL)	
Males (13-15.5g/dL)	
Eosinophil, 103/µL (0.10-1.00 103/µL)	12.16 ± 1.51
Iron, µmol/L (11.6-31.3 µmol/L)	0.83 ± 0.75
TIBC, µmol/L (44.75-76.08 µmol/L)	11.42±5.56
Ferritin, ng/ml (22-322 ng/mL)	30.76 ± 23.18
MCV, fL (77.0-95.0 fL)	75.89 ± 7.21
MCH, pg (25.0-33.0 pg)	24.43 ± 3.00
B12, pmol/L (156-672 pmol/L)	444.65 ± 209.19
Folate level, nmol/L (> 12.19 nmol/L)	25.65 ± 12.78
TSAT, %	18.17 ± 8.69
Eosinophil count > 1 103/µL	24 ± 31.2
Anaemia status	
No	32 (41.6)
Yes	45 (58.4)
Iron deficiency, n=45	
No	13 (28.9)
Yes	32 (71.1)
B12 deficiency, n=5	
No	45 (100)
Yes	0 (0)
Folate deficiency, n=45	
No	44 (0.98)
Yes	1 (0.02)

anemia was mild in most of the patients. We postulate that the higher prevalence is due to the practice of food restriction in addition to the effect of chronic inflammation in AD. A previous local study showed that up to 61% of AD patients avoided eating three or more food groups.[16] Health practitioners caring for AD patients should be aware of the risk of not just anemia but other nutritional deficiencies as well as institute appropriate measures to diagnose and manage these conditions.

The etiology of anemia in patients with AD includes anemia of chronic disease and nutritional deficiencies (iron, vitamin B12, and folate) due to a restrictive diet and side effects of medications such as azathioprine, methotrexate, and Janus kinase inhibitors. There is limited research exploring the link between eczema and anemia. The use of systemic immunosuppressants, malnutrition, and use of alternative medicine increased the risk of anemia.[13] IDA was linked to early onset AD (< 2 years of age), history of atopy, skin infections, and comorbid allergic conditions, especially bronchial asthma.[14] IDA prevalence was 26.7% in individuals with one atopic disease and 53.3% in those with multiple atopic diseases, indicating a higher risk with more atopy.[14] the Prevalence of anemia was higher in males and younger children in a nationwide cross-sectional survey that determined the status of malaria and anemia in children between the ages of 6 months to 14 years.[25] Household income was not associated with anemia among our study population, which contradicts results from previous research.[26-28] This discrepancy may be due to the fact that most of our study participants and patients at our center were from the lower-income group.

Anemia among our patients was not associated with AD disease severity, which contrasted with the results of a study investigating risk factors for anemia in children with AD in Turkey; however.[14] Our study population did not show this association, likely because the majority of our patients had

Table III: Dietary pattern of the study population

Dietary history	N=77
	N (%)
Patient's self-diagnosed food allergy	36 (46.7)
Types of patient-reported food causing allergy	
Shellfish	20 (54.1)
Nut	1 (2.7)
Chicken	3 (8.1)
Brinjal	1 (2.7)
Egg	11 (29.7)
Yeast	1 (2.7)
Vegetarian	4(5.2)
Food avoidance	43 (55.8)
Types of Food Avoided	
Shellfish	29 (37.7)
Nuts	26 (33.8)
Egg	17 (22.1)
Dairy	8 (10.4)
Cow milk	6 (7.8)
Soy	7 (9.1)
Beef	5 (6.5)
Wheat	5 (6.5)
Poultry	5 (8.5)
Fish	5 (6.5)
Cakes & sweets	3 (3.9)
Fruits	0 (0)
Vegetables	0 (0)
Others types of food	17 (22.1)

mild AD. Chronic inflammation in AD has been shown to hinder iron absorption and utilization even if dietary intake is adequate.[12] This explains why patients with AD are at an increased risk of anemia, even in the absence of nutrient deficiencies.

Food restrictions were common among our patients. This finding was similar to a report from Korea, where the prevalence of food restriction ranged from 48.1% to 50.0%.6 A notable proportion of parents (55%) of children with AD believed their child had food allergies compared to 12% of parents of children without AD.[29] Food allergy were self-reported but not verified through clinical confirmation in our study. Thus, it is possible that many cases were not true allergies. Shellfish was the most restricted food in this study and previous studies conducted in Korea and Malaysia.[6,16] Other frequently avoided foods included milk, dairy products, eggs, and nuts.

Iron deficiency may occur in patients with AD who follow restrictive diets to avoid triggering a flare, which subsequently leads to insufficient iron intake. Our study showed that patients with anemia had a significantly lower intake of iron, protein, and fat. Thus, low iron intake is a contributing factor to iron deficiency anemia. Anemia was also associated with younger age and lower BMI; however, the only significant independent risk factor was male sex. Folate and B12 levels were slightly lower than the recommended nutrient (RNI) for Malaysia, but this was not a contributing factor to anemia in this study, as both B12 and folate levels were within the normal range and the intake for patients with and without anemia were similar. The calorie intake was adequate, whereas the intake of carbohydrate, protein, and fat was higher than the recommended nutrient intake (RNI) for Malaysia. This could be attributed to multiple factors. The validity of dietary recall depends on the accuracy of respondents' recall of their food consumption. Poor recall can lead to repetition of meals and overreporting.[30] Food insecurity, defined as limited access to safe and nutritious food, is influenced by socioeconomic, demographic, and environmental factors. Children in food-insecure households often consume energy-dense, nutrient-poor foods that leads to poor diet quality.[31-32] Studies have suggested that low income and financial constraints often lead to meal repetition, as families choose inexpensive and easy-to-prepare foods.[33] The convenience of meal preparation, especially for busy families often results in repetitive meals particularly when affordable, processed foods are readily available.[34] Many parents resorting to food exclusion diets without guidance from healthcare providers may also lead to energy dense diets.[29]

Our study is limited by the possibility of recall bias in three-day dietary recall. Future studies should consider prospective food records, 24-hour recall, or food frequency questionnaires to reduce the possibility of recall bias. However, the serum levels of micronutrients that are important for anemia were objectively measured. Concurrent parasitic infections were not assessed in this study. To further validate our findings and address the limitations of this study, a multicenter study with a larger sample size would be valuable, allowing for more comprehensive analysis and greater generalizability of the results.

CONCLUSION

The prevalence of iron-deficiency anemia is high in patients with AD. Food restriction was common with lower intakes of

Table IV: Factors associated with anaemia

Parameters	Anaemia, N=77 n (%)		Statistical test	p value
	No N= 32	Yes N= 45		
Age, mean ± SD	10.63 ±4.26	7.13±5.46	3.02 (75.0) [a]	0.003*
Gender			7.47 (1) [b]	0.006*
Male	12 (37.5)	31 (68.9)		
Female	20 (62.5)	14 (31.1)		
Ethnicity			-	0.327[c]
Malay	20 (62.5)	34 (75.6)		
Chinese	7 (21.9)	8 (17.8)		
Indian	5 (15.6)	3 (6.7)		
Education level			-	0.002[c]*
Underage for school	1 (3.1)	15 (33.3)		
Primary	19 (59.4)	19 (42.2)		
Secondary	10 (31.3)	11 (24.4)		
Tertiary	2 (6.3)	0 (0.0)		
Household income			-	0.534[c]
B40	17 (53.1)	28 (62.2)		
M40	14 (43.8)	14 (31.1)		
T20	1 (3.1)	3 (6.7)		
Food restriction			0.76 (1) [a]	0.384
No	16 (50.0)	18 (40.0)		
Yes	16 (50.0)	27 (60.0)		
BMI category			-	0.011 [c]*
Underweight	16 (50.0)	34 (75.6)		
Normal	14 (43.8)	7 (15.6)		
Overweight	1 (3.1)	4 (8.9)		
Obese	1 (3.1)	4 (8.9)		
Extreme obesity	1 (3.1)	0 (0.0)		
AD severity			1.02 (1) [b]	0.312
Mild	20 (62.5)	33 (73.3)		
Moderate to severe	12 (37.5)	12(26.6)		
Eosinophil			0.00 (1) [b]	0.990
Normal	22 (68.8)	31 (68.9)		
High	10 (31.3)	14 (31.1)		
Concomitant allergic rhinitis			0.23 (1) [b]	0.631
No	25 (78.1)	33 (73.3)		
Yes	7 (21.9)	12 (26.7)		
Bronchial asthma			-	0.152 [c]
No	26 (81.3)	42 (93.3)		
Yes	6 (18.8)	3 (6.7)		

[a] Independent t-test; [b] Pearson Chi square; [c] Fisher's exact test; [d] Mann Whitney test; * Statistically significant

Table V: Nutrient intake (% RNI) among patients with and without anemia

Dietary intake,	Anemia N=77 Median (IQR)		P value
	No N= 32	Yes N= 45	
Calorie, %	94.68 (53.10)	76.85 (28.16)	0.059[d]
Protein, %	291.66 (202.03)	211.10 (158.80)	0.036[d]*
Carbohydrate, %	170.19 (49.82)	159.44 (31.62)	0.251
Fat, %	8460.00 (6342.00)	7375.00 (2851.00)	0.009[d]*
Iron, %	138.32 (70.37)	79.94 (63.42)	0.016*
B12, %	58.50 (147.84)	40.26 (81.57)	0.079[d]
Folate, %	22.53 (24.98)	27.60 (49.12)	0.009d*
Vitamin A, %	183.08 (131.53)	210.27 (149.74)	0.189 [d]
Vitamin C, %	105.43 (131.81)	54.35 (111.64)	0.077 [d]

[a] Independent t-test; [b] Pearson's chi-squared test; [c] Fisher's exact test; [d] Mann Whitney test; *statistically significant.

protein, fat, iron, and folate among AD patients with anemia. Younger age, male sex, and underweight were factors associated with anemia. In summary, food restriction leading to inadequate iron intake may be a key factor in iron deficiency anemia among our group of patients. Chronic inflammation may also play a role in atopic eczema.

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