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Research Article

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Early and Prenatal Use of Antibiotics and Risk Atopic Dermatitis among Pre-School Children

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ABSTRACT

Overuse or misuse of antibiotics can lead to the development of antibiotic-resistant bacteria, which can be difficult to treat and can pose a serious threat to public health. In addition, antibiotic misuse can disrupt the balance of bacteria in the body, leading to an overgrowth of harmful bacteria or a decrease in beneficial bacteria. This can increase the risk of secondary infections and other health problems. Human microbiome reconstitution from antibiotic treatment is often slow and incomplete, and, in some cases, may take years to revert to naive configuration. Many studies suggested a strong correlation between the use of antibiotics and atopic dermatitis. The explanation may be linked to the microbiota changes related to antibiotic use, knowing that the microbiota influences the immune response. There is evidence showing that the early gut microbiota of children who develop atopic dermatitis later in life is different from that of children who do not develop atopic dermatitis, both in terms of composition, and diversity. This cross-sectional study was performed at Tripoli Libya and it involved 100 cases of pre-school children and 100 cases of pregnant women, in the period from January 2023 to Jun 2023 to correlate between early and prenatal use of antibiotics and the risk Atopic Dermatitis. In addition, to identify any inscrutable variables that may affect such correlations, such as environmental factors, parents' education level, etc. However, the study concluded that there were significant impacts of early and prenatal use of antibiotics at pre-school age on the evolving of atopic dermatitis (P <0.05).

Key words-*Atopic dermatitis; Microbiota; Antenatal and Prenatal.*

INTRODUCTION

Atopic Dermatitis (AD) is also called atopic eczema. Is a common chronic inflammatory skin disease affecting 20% of children.[1] Studies conducted in Libya have concluded, that the highest frequency was represented school age group, followed by pre-school age, and the lowest frequency for adults. In addition, males were finding more affected than females, with a male-to-female ratio of 1.3:1.[2-4] However, a study of South Sinai, Egypt revealed that 71.4% of the studied population had one or more skin diseases. Eczema or dermatitis was found in 25.8% of participants.[5]

The prevalence of AD is similar in the United States, Europe, and Japan and has still increased in the last few years.[6] AD has been classified into three consecutive phases: infantile, childhood, and adult, each with characteristic physical findings. Although, atopic dermatitis is characterized by a chronic, relapsing dermatitis that is pruritic, begins in the first 5 years of life of patients and usually presents with a characteristic age-dependent distribution with facial, scalp, and extensor involvement in infants and young children, and predominant flexural involvement in older children and adults. However, pruritus is universal and xerosis is a common feature in children with atopic dermatitis.[7] Furthermore, AD has a tremendously negative effect on the quality of life of patients as well as family, most commonly disturbing sleep.[8] The condition also creates a great financial burden for individuals, families, and society. However, the cutaneous manifestations of atopy often represent the beginning of the atopic march.[9]

Although, the initial manifestation of AD occurs within the first 5 years of life, Approximately a quarter of these children continue to have AD during adulthood.[10] Atopic dermatitis (AD), one of the most common skin disorders seen in infants and children, usually has its onset during the first 6 months of life.[11]

The pathogenesis of atopic dermatitis is driven by a complex interplay of genetic, immunological environmental factors.

Nowadays, early and prenatal use of antibiotics is the most considered factor for AD instigation. It is universally acknowledged that the use of Antibiotics can disrupt the balance of bacteria in the body, leading to an overgrowth of harmful bacteria or a decrease in beneficial bacteria. This can increase the risk of secondary infections and other health problems. When antibiotics are taken leads to short-term effects such as the overgrowth of harmful bacteria, in addition, a decrease in beneficial bacteria consequently compromises the body's ability to fight off infections, leading to an increased risk of secondary infections.

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However, such disruption of normal flora can also have a long-term impact on the body's immune system and overall health. Studies have shown that changes in the normal flora can contribute to the development of chronic conditions such as inflammatory bowel disease, allergies, and autoimmune disorders.[12]

Nevertheless, several lines of evidence confirm that misuse of antibiotics can result in gut microbiota dysbiosis, i.e., disturbance in composition and function.[13] Broad-spectrum antibiotics can affect the abundance of 30% of the bacteria in the gut community, causing rapid and significant drops in taxonomic richness, diversity, and consistency.[14] Dysbiosis is defined as an imbalance in bacterial composition, changes in bacterial metabolic activities, or changes in bacterial distribution within the body.[15]

The intestines of normal entities are colonized by a wide range of bacteria of over 1000 species. In healthy individuals, these bacteria are in a homeostatic balance between commensal and potentially pathogenic bacteria, and the intestinal tract does not display overgrowth of pathogenic bacteria.[16]

The microbiota offers the host protection from foreign microbes, acting as a central line of resistance to colonization by these exogenous bacteria. This protection is known as the "barrier effect", or colonization resistance. Through the mucosal surface of the intestine,[17] the microbiota interacts with the host immune system, providing the host with immune regulatory functions, like priming the mucosal immune system.[18]

Non-selective antibiotics-induced disruption of commensal microbiome community structure ''dysbiosis'' accounts for up to 20% of all AD cases.[19,20] Human microbiome reconstitution from antibiotic treatment is often slow and incomplete, and, in some cases, may take years to revert to naive configuration[21]. The gut microbiota plays a crucial role in host health regulation.

Effects of antibiotics on the host through the gut microbiome are enormous and can affect various functions including immune regulation, metabolic activities, and consequently overall health.[22]

Studies in rodent models and humans suggest an association between antibiotic exposure, especially during early stages of life, and a host propensity for a variety of long-term disorders including allergy, autoimmunity and inflammatory bowel disease.[23-28]

However, exposure to antibiotics in early life has been associated with delayed maturation of the gut microbiome, and the resulting disturbances may negatively affect bacterial diversity.[29] The gut microbiome not only regulates the gut environment but also influences the regulation of the microbiome of barrier sites such as the skin and the lungs.

The timing of dysbiosis that is likely to impact the offspring's developing immune system is not known but it has been suggested that the first 6 months after birth should be considered a time of susceptibility as the microbiome develops rapidly and may induce long-term immunological changes.[30] Supportive evidence from animal studies has shown that antibiotic exposure in neonatal mice was associated with shifts in the gut microbiome and subsequent signs of allergic asthma.[31,32]

On the other hand, research on a group of children was done in China revealing that the alterations in the microbiome by prenatal use of antibiotics may be related to atopic eczema, the risk increase associated with antibiotics may be due to changes in the host microbiota, leading to an altered development of the infant's immune system.

The explanation may be linked to the microbiota changes related to antibiotic use, knowing that the microbiota influences the immune response. There is evidence showing that the early gut microbiota of children who develop AD later in life is different from that of children who do not develop AD, both in terms of composition and diversity.[33,34] In addition, the 'revised' hygiene hypothesis states that the decrease in early childhood exposure to prototypical infections (e.g. hepatitis and tuberculosis) and, by extension, in any microbial exposure[35,36], has increased the susceptibility to allergic disease.

For AD, this hypothesis has been supported by some observations such as that the youngest among siblings has the lowest risk of AD or that AD risk is decreased in infants attending daycare during their first year of life.

However, this study is principally designed to determine and investigate the relationship between early and parental use of antibiotics and the evolving of atopic dermatitis or eczema among preschool children and to identify any confounding variables that may affect such correlations.

Consequently, to provide recommendations for clinical practicians, researchers, and parents for any interventions or future studies aimed to reduce the incidence of atopic dermatitis or eczema among studied groups.

MATERIALS AND METHODS

Study design:

The study is a cross-sectional study to address any associations between early and prenatal use of antibiotics and the risk of atopic dermatitis. It involved 100 cases of pre-school children and 100 cases of pregnant women, it was performed in the area of Tripoli city, in Libya. in the period from January 2023 to Jun 2023. The sample consisted of both gender and their age range will be from 0 days to 6 years. The study protocol was approved by the Microbiology and Immunology department.

Methods:

A parent or guardian of each child was questioned by using a questionnaire. The questionnaire consists of eight

questions about the use of antibiotics and eight questions concerning atopic dermatitis. Additional questions confirming AD are also included. The questionnaire contains questions for parents about their lifestyle, education, etc., and some important risk factors were also considered.

Statistical analysis:

Statistical analysis will be done on the statistical package for the social science program (SPSS.25), all results will be expressed as numbers and percentages, odds ratio will be calculated to show the strength of association, chi-squared tests will be used to test the significance, and *P* - value < 0.05 is considered as an indication of significant difference.

RESULTS

A total of 200 cases with a mean age of 1.41 years old take part in this study. However, this study was performed in the area of Tripoli-Libya, in the period from January 2023 to Jun 2023. The presented study is designed to address any associations between early and prenatal use of antibiotics and the risk of developing atopic dermatitis at preschool age. Also, to analysed the impact of different environmental factors, birth by C-section, and the educational level of parents on AD among preschool children. All the cases underwent medical examinations and answered the questionnaire designed for this study. The patients were classified into two groups, group 1 comprised 100 cases of children who took antibiotics before entering school, their age range between 0 and 6 years with a mean of age 1.41 years, and Group 2 comprised 100 cases of women who took antibiotics during pregnancy, with a mean of age 28.9 years old. The characteristics of participants in the study are shown in (Table 1). The prevalence rate of AD among studied groups was 42% among children, on the other hand, the incidence of AD among preschool-age children who take antibiotics was 37% compared to another group 47%.

In general, the obtained results reveal that the early and prenatal use of antibiotics is significantly associated with AD with a *P* value ≤0.05. The highest rate was among ≤ 1-year-old 19%, and the prevalence rate of AD among children with 3-4 years of age was 14%. where, 3% and 1% among 5-6 and 1-2 years old respectively. Regarding prenatal use of antibiotics, the highest rate of AD was among children whose mothers took the antibiotics in the third trimester 36%, compared to the first and second trimesters, 7% and 4% respectively. Environmental factors play an important role in the development of AD through different mechanisms, in this study 22 of the 37 children diagnosed with AD were shown to be susceptible to environmental hazards such as climate, animals, smoking, and detergents (*P* <0.05). However, the study also revealing that the type of delivery plays an important role in AD among preschool children as the cesarean delivery account for 69% of deliveries, while vaginal deliveries account for 31% (*P*<0.05). On the contrary, the

Table 1: Demographics data of the participants**.**

Parameters	Total N= 200		Male N= 36 (60%)	Female N= 24 (40%)	95% CI	P-Value
	Mean age ±SD	1.410.45±				
Age groups	< 1year	54	20	34	-.23018/ .37632	*P* <0.005
	1-2 years	46	18	28		
	3-4 years	64	25	39		
	5-6 years	36	19	17		
Eczema diagnosis	yes	84	30	54	0.641.40/	*P* <0.005
	No	116	52	64		
Types of delivery	C-sections	149	62	87	.15786/	*P* <0.005
	Normal	51	20	31		
Antibiotic use	yes	185	69	116	-20187/	*P* <0.005
	No	15	5	10		
Antibiotic use during pregnancy	1st trimester	19	..	..	.79217/ 1.30085	*P* <0.005
	2nd trimester	7	..	..		
	3rd trimester	74	..	..		

[a] chi-square test. SD, standard deviations.

Table 2: Environmental factors.

patients' group	Climate		Animals		Smoking		detergents	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Male	5	2.5%	5	2.5%	3	1.5%	5	2.5%
Female	20	10%	2	1%	8	4%	9	4.5%
P-value	*P<0.005*							

[a] chi-square tests

education level of parents hasn't any effect on AD among preschool children.

DISCUSSIONS

Atopic Dermatitis (AD) affects 20% of children.[1] The study has been conducted in Libya in 2020 concluded, that the highest frequency of AD 42.5% were represented within a school age group, followed by 26.4% young adults, and 21.8% preschool age group, and the lowest frequency was 4.6% among adults' populations. Compared to this study, we found a significant upsurge in AD incidence among preschool-age children 42%, this might be attributed to many reasons such as lifestyle, diet, and environmental factors as this study was conducted mainly in urban areas.

However, the pathogenesis of atopic dermatitis is driven by a complex interplay of genetic, environmental, and immunological factors. Regarding the impact of antibiotic use among preschool children and AD, this study revealed a significant difference in AD prevalence between the groups who did versus did not receive antibiotics in the early years of life (P <0.05). correspondingly the study revealing a correlation between such use of antibiotics among pregnant women and increasing the risk of AD amongst preschool children (P <0.05). However, the risk of atopic dermatitis among children exposed to prenatal antibiotics 47%, was greater than that among children who were not exposed and exposure to antibiotics during the first year of life 37%. The suggested mechanisms that explain such significant differences are that the exposure to antibiotics in the early years of life has been accompanied by delayed gut microbiome maturation, and the resulting disturbances may negatively affect bacterial diversity. Consequently, delaying in the maturation of children's immune systems. However, the microbiome not only regulates the gut environment but also influences the regulation of the microbiome of barrier sites such as the skin and the lungs.

Nevertheless, the timing of dysbiosis that is likely to impact the offspring's developing immune system is not known but it has been suggested that the first 6 months after birth should be considered a time of susceptibility as the microbiome develops rapidly and may induce long-term immunological changes.[30]

On the other hand, supportive evidence from animal studies has shown that antibiotic exposure in neonatal mice was associated with shifts in the gut microbiome and subsequent signs of allergic asthma.[31,32]

Research conducted in 2022 in China supports the suggestion that alterations in the microbiome by prenatal use of antibiotics may be related to atopic eczema among children.[37] It has been assumed that small intestine permeability may be increased in AD patients.[38] Although, intestinal permeability is one factor in acquired food allergy.[39]

Disturbances in the intestinal microbiome could be a risk factor for further AD development.[40] However, it is well-recognized that antibiotics drastically disturb the gut microbiota[41].

Subsequently, there have been several studies on how the use of antibiotics might affect the human immune system maturations[42]. The other suggested mechanism is that the early and prenatal use of antibiotics might increase the risk of certain respiratory tract and ear infections, these infections, in turn, may contribute to the development of AD. However, more research is required to understand the specific relationship between infections, antibiotics, and AD. Nevertheless, the influences of some environmental factors including climate, animals, and detergents on AD among preschool children are also observed, we conclude that the observed environmental factors had significant clinical impacts on AD (P<0.05) (Table 2). However, the mechanisms are not fully understood. Still, several key pathways have been proposed to elucidate how environmental factors contribute to and exacerbate AD, such as skin barrier dysfunction, allergen sensitizations, immune dysregulation, etc.

However, these findings highlight the complex interplay of such factors in the likelihood of AD evolving. The implications underscore the importance of holistic management of AD. By, incorporating such knowledge into clinical practice it's possible to improve the management and prevention of AD at preschool age.

On the other hand, the study proofs that the type of delivery also plays a significant role in atopic dermatitis evolving amongst preschool children as cesarean sections account for 69% of deliveries, while regular deliveries account for 31% (P <0.05). The antenatal intestine becomes colonized before delivery by bacterial transmission from

the mother through the placental barrier, subsequently, the mode of delivery has an additional impact on the intestinal microbiome. It has been demonstrated that delivery by the C-section section decreases the colonization by *Bacteroides* but increases the number of *Clostridia*.[43] However, the obtained results agree with a study in Sweden indicating that in sibling analyses, compared with normal delivery, in children aged <1 year, birth by caesarean section was associated with increasing the risk of atopic dermatitis. In the United States, national surveys of Children's Health birth cohort study concluded no association was observed.[44]

In the pooled European cohort study, birth by cesarean section was associated with delayed acquisition of species from families *Bifidobacteriaceae* and *Bacteroidaceae* b ut instead associated with compensatory colonization by species from the families *Enterobacteriaceae* and *Clostri diaceae*.[45,46] In addition, delayed acquisition of the *Bifido bacteriaceae* and *Bacteroidaceae* at 1 month is associated with an increased risk of atopic dermatitis in later life.[47,48] Nevertheless, children born by cesarean section had significantly lower levels of Th1-associated chemokines in the blood. The intestinal bacteria play an important role in the establishment of immune tolerance, and the lack of exposure to facultatively anaerobic bacteria that occurs during vaginal delivery may increase susceptibility to atopy and more specifically with atopic dermatitis.[49-51] There are additional factors in a study that may be related to AD among preschool children have been considered such as the education levels of the parents (P>0.05). the education level of parents can influence various aspects of a child's life. Including their health. While there is no direct causal relationship between a parent's education level and a child developing atopic dermatitis, several factors associated with parental education can contribute to its occurrence, for example, socioeconomic status, and parental education is often linked to socioeconomic status. Higher education levels typically correlate with higher incomes and access to better healthcare services. However, knowledge and awareness of parents could potentially reduce the risk or severity of atopic dermatitis in their children. It is important to note that these explanations are based on general associations and do not apply universally. Atopic dermatitis is a complex condition influenced by a combination of genetic, environmental, and immunological factors. While parental education level can play a role, it is just one of many factors that contribute to the development of atopic dermatitis among preschool children.

CONCLUSION

This study involved 100 cases of preschool children and 100 cases of pregnant women and concluded that there were significant impacts of the use of antibiotics at pre-school age (P<0.05) and prenatal (P<0.05).

It was established that the highest diagnosis of AD in children born by cesarean delivery. also, this study showed the highest significant impacts of environmental factors on AD (P<0.05).

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