Chapter 8
Disparity in Atopic Dermatitis

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Blake

Blake is a 13-year-old African American male. His mother works nights for a local chain restaurant and the patient lives in a shared home with his mother and grandparents. He presents as an acute visit to an urgent care center. Blake was diagnosed with atopic dermatitis by his pediatrician as an infant. His atopic dermatitis was previously well controlled with topical emollients and occasional topical steroids for exacerbations. However, the mother notes that since the patient started at a new middle school at age 11, his symptoms have significantly worsened. She also noted that this coincides with the patient taking on more responsibility with his own bathing, hygiene, and skin care in adolescence. Physical examination reveals erythematous papules and plaques on his bilateral arms, legs, trunk, and back. There are significant xerosis and excoriations of his skin diffusely, as well as lichenified plaques on his hands and bilateral popliteal fossa. There are also scattered areas of hypopigmentation on his cheeks and extensor forearms. The patient states that he is always up at night scratching his skin, often to the point of bleeding. He states that he is embarrassed by the physical appearance of his skin at school and also finds it difficult to concentrate. His performance at school has declined in the past year, and he attributes it to his tiredness, lack of self-esteem to contribute, and his pain and itching that make it impossible to concentrate. The mother states that she has tried to make appointments with the specialist, but because the appointments must be made so far in advance and her work schedule often changes, the patient has had multiple missed appointments. There is only one pediatric dermatologist in their

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M. Mahdavinia (ed.), *Health Disparities in Allergic Diseases*,
https://doi.org/10.1007/978-3-030-31222-0_8

region who will accept their healthcare insurance. Both the mother and the patient express frustration with his current symptoms and request an "injection to make this go away."

Introduction

Atopic dermatitis (AD) is a chronic inflammatory condition of the skin that is associated with a personal or family history of other atopic diseases, namely, allergic rhinitis and asthma. AD is most prevalent among children, but may persist into adulthood in up to one-third of individuals [1]. AD is reported to affect up to 20% of children and 3% of adults worldwide [1]. In the United States (USA), according to the 2003 National Survey of Children's Health, the prevalence of AD in those younger than 18 years was 10.7% [2]. In adults, the reported prevalence in the USA ranges from 7.2% to 10.2% [2, 3]. Affected individuals may experience refractory pruritus, poor sleep quality, secondary infections, significant psychosocial distress, and restricted participation in activities [3–5]. AD imposes a significant burden not only on affected individuals and caretakers, but also on the larger healthcare system and society [4, 6]. In one study, when considering costs of medications, physician visits, and the indirect costs of lost productivity, the annual cost of AD in the USA was over 5.2 billion dollars [7].

While AD is closely associated with asthma and allergic rhinitis, there is growing evidence that AD exhibits distinct risk factors and involves complex interactions between genetic, environmental, and lifestyle factors. While underlying genetics are certainly an important determinant of AD prevalence and severity, there is an increasing appreciation for the importance of environmental and lifestyle factors. This is highlighted by reports that there is a lack of correlation between filaggrin mutations and severity of AD [8]. The notion that AD prevalence depends considerably on the surrounding environment highlights the potential for health disparities stemming from modifiable extrinsic factors. These factors contribute to potential disparities in prevalence, severity, and management between geographic locations, as well as across socioeconomic and racial groups.

Currently Existing Disparities in Atopic Dermatitis

Prevalence

The prevalence of atopy, including atopic dermatitis, has been increasing worldwide; however, the prevalence rates vary significantly among different geographic regions [9]. According to the Internal Study of Asthma and Allergies in Childhood, an international cross-sectional study of over 500,000 school-aged children, the prevalence of AD is significantly higher in Western and Northern Europe, Australia, South America, and urban regions of Africa and lower in Eastern Europe, the Middle

East, and China [10]. In another survey of schoolchildren in Oregon, USA, by Laughter et al., a higher prevalence of AD was reported in the USA, compared to estimates from Europe or Japan [6]. A number of other studies have similarly reported a higher prevalence of AD in more developed nations [6, 11, 12]. Hypothesized explanations for this trend include the effects of urbanization, climate, diet, and varying exposure to infections and airborne allergens [1, 10].

It has been further shown that the prevalence of AD can vary significantly within the same country. The 2003 National Survey of Children's Health reported higher rates of AD among states on the east coast, compared to other regions of the USA [2]. One proposed explanation is the greater number of metropolitan cities on the east coast, compared to other regions [2]. In this study, the examination of survey data revealed that living in an urban, compared to rural environment, was associated with an adjusted odds ratio of 1.67 for AD [2]. Similarly, Laughter et al. reported higher rates of AD among surveyed children living in urban versus rural areas in Oregon [6]. Proposed deleterious effects associated with urban living include exposure to a larger quantity or more varied allergens, decreased ultraviolet (UV) light exposure, and living in more modern insulated housing [3, 13, 14].

The impact of environmental factors is further highlighted when examining immigrant populations. Multiple studies have reported that Americans who were born outside of the USA have a lower prevalence of AD than those born in the USA [2, 3]. Nevertheless, over time, the rates of AD among immigrants living in the USA increase and exceed the rates of AD from their country of origin [14]. In the 2010 National Health Interview Survey, which examined AD in American adults, foreign-born Americans exhibited decreased rates of AD when compared to those born in the USA, but after living in the USA for at least 10 years, rates of AD among immigrant groups increased. The rate of eczema in immigrants living in the USA for less than 10 years was 4.3% versus 6.7% in those living in the USA for greater than 10 years [3]. Furthermore, Silverberg et al. reported a lower prevalence of AD in American children born and living outside the USA, compared to those born in the USA [3]. Similar trends have been observed when examining Asian children born in Australia, compared to Asian children who recently immigrated to Australia [13].

Impact of Socioeconomic Factors

Numerous studies worldwide have investigated potential association between the socioeconomic status and the prevalence or severity of AD. While socioeconomic factors have been shown to be determinants of AD, there is a lack of concordance between studies on whether AD prevalence and severity are associated with higher or lower socioeconomic status. For example, Williams and colleagues examined over 8000 children across the United Kingdom (UK), stratified participants into five socioeconomic classes, and reported a significant linear trend in AD prevalence with higher social class [12]. In this study, diagnosis of AD was confirmed by physical exam and analyses were adjusted for variables, such as gender, residence, family size, ethnic group, exposure to tobacco, and breastfeeding. Of note, no similar trend

was observed when examining the prevalence of psoriasis or acne in the same cohort [12]. Furthermore, multiple separate studies, examining cohorts in the United States, Austria, Germany, and Japan, have reported an independent positive association between parental education level and AD prevalence, after adjusting for various confounding factors [3, 11, 13, 15]. Similarly, in a cross-sectional health survey conducted in Demark by Hammer-Helmich and colleagues, AD was significantly linked to higher parental education, while asthma and allergic rhinitis were associated with lower parental education [16]. Parental unemployment was also associated with a decrease in AD risk and severity [16].

Data-supported explanations for the associations between higher socioeconomic status and AD are lacking. One early hypothesis to explain the relationship between higher socioeconomic status and greater AD prevalence is the "hygiene hypothesis," or the proposed concept that increased exposure to various infectious agents confers a protective effect on the tendency to develop atopy. However, more recently, studies have reported no association between AD and factors related to the hygiene hypothesis such as larger family size and daycare attendance [15, 17]. Other explanations are that patients of higher socioeconomic class may be more likely to interact with the healthcare system and receive a diagnosis of AD, or be more likely to respond affirmatively to health surveys due to greater health literacy.

Notably, in the Danish study by Hammer-Helmich et al., while AD prevalence and severity was associated with higher parental education and parental employment, there was no association found between AD and household income, which the authors propose may relate to equivalent healthcare access in Denmark [16]. In the United States, where greater disparities in healthcare access exist, several large studies suggest that access to care may be contributing to observed trends in AD prevalence and severity. According to data from the 2010 National Health Interview Survey, the prevalence of AD was significantly associated with health insurance coverage and healthcare interaction in the past year; suggesting differences in prevalence may be related to differences in the rates of diagnosis [3]. In another study by Hanifin and Reed, an inverse relationship between household income and empirically defined AD was discovered, based on a health survey sent to a representative sample of the US population [18].

Racial and Ethnic Disparities in Atopic Dermatitis

There is a growing amount of research demonstrating that disparities in the prevalence and severity of AD exist between racial groups. Shaw and colleagues reported that based on data from the National Survey of Children's Health, African American race was associated with an increased prevalence of AD, compared to Caucasian race (15.9% vs. 9.7%, OR 1.7) [2]. In accordance, Fu et al. reported a higher prevalence of eczema in African American, compared to Caucasian children (19.3% vs. 16.1%), using 2005–2006 National Health and Nutrition Examination Survey

[20]. Williams and colleagues reported similar results in the UK in a study of nearly 700 London-born children, in which they reported a significantly higher rate of AD, diagnosed by a physician, in Black Caribbean, compared to White children (16.3% vs. 8.7%) [21]. Silverberg and Simpson also reported that based on the 2007 National Survey of Children's Health, eczema severity was reported to be associated with Hispanic or African American race in univariate analyses, although this association was no longer significant in multivariable models [8]. In a study of AD in adults using the 2010 National Health Interview Survey, a higher prevalence of AD was reported in those identifying as Hispanic or multiracial, compared to Caucasians, in multivariable models [3]. Furthermore, in a study using the National Ambulatory Medical Care Survey from 1990 to 1998, Janumpally et al. reported that the number of clinic visits for AD was significantly greater for African American (OR 3.4) and Asian/Pacific Islander (OR 6.7) patients, compared to Caucasians [14]. Of note, in this study, Caucasian individuals had a higher rate of medical visits overall, including visits for other dermatologic conditions, suggesting that the observed difference in visits for AD could not be attributed to differences in healthcare utilization in general [14].

Outcomes Related to Disparities in Food Allergy

Severity of Skin Disease

Lower socioeconomic status has been suggested to contribute to increased severity of AD. In a study by Silverberg et al., which examined data from the 2007 National Survey of Children's Health, greater AD severity, as determined from survey questions on three-point scale, was associated with lower parental education, lower household income, and poorer housing quality [8]. Proposed explanations for the relationship between greater AD severity and lower socioeconomic status include exposure to indoor pollutants in lower quality housing, greater exposure to cutaneous irritants, secondary infections, and reduced access to healthcare, resulting in poorer management and disease control [19].

Disparities among racial groups related to the severity of AD have also been identified. For example, in a study of pediatric patients with AD presenting to a tertiary care clinic, 75% of 60 African American patients qualified as having moderate–severe AD, compared to 40% among 100 Caucasian patients, based on Eczema Area and Severity Index and Investigator Global Assessment Scores [22]. In another study of 137 children with AD in the UK, the authors reported that Black children had nearly sixfold higher odds of having severe AD than White children [23]. Of note, in this study, the difference in AD severity persisted even after controlling for social class [23]. Possible causes for the differences in prevalence and severity of AD between racial groups include uneven access to care, differences in the presentation of AD in different skin types, and under-recognized differences between races in the underlying genetics and pathophysiology of AD.

Specific challenges associated with the management of AD in patients with skin of color have been described. For example, there is a higher risk of dyspigmentation associated with topical corticosteroid use in individuals with SOC. Furthermore, the dose or duration of certain treatments can depend on the race or skin type of the patient. For instance, it has been shown that the bioavailability of cyclosporine is significantly lower in African American compared to Caucasian individuals [36]. In addition, higher doses of phototherapy are required for patients with SOC [29].

Reasons for Atopic Dermatitis Health Disparities

Access to Healthcare

Access to dermatological specialty care has been suggested to be insufficient in general, stemming from a shortage of dermatologists nationally [24]. Furthermore, access to dermatology may be especially limited depending on insurance coverage, as highlighted by the results of a 2002 American Academy of Dermatology (AAD) survey reporting that only 40.8% and 51.3% of dermatologists accept new patients with Medicaid or no insurance, respectively [25]. In this report, patients receiving Medicaid comprised 5% of patients being seen at dermatology practices, significantly less than the 27% that would be predicted based on the percentage of patients receiving Medicaid in the population [25]. Differences by race in utilization of dermatological care have also been identified. In a study of the National Ambulatory Medical Care Survey, it was reported that in the USA over 90% of patients seen by dermatologists are Caucasian [26], which may reflect the inadequate treatment of AD among non-Caucasian patients. This discrepancy may relate to differences in insurance status, and in turn access to dermatology [14]. Previous studies have reported a higher rate of uninsured status among African Americans, compared to Caucasians, in the USA [14]. While this discrepancy has narrowed after healthcare reform, according to 2016 Center for Disease Control data, African American, as well as Hispanic individuals continue to demonstrate lower health insurance rates, compared to Caucasians [27].

The quality of care delivered by dermatologists for AD may also vary across racial groups due to differences in disease presentation and inadequate focus on these differences during physician training. In one survey of US dermatology chief residents, only 25.4% reported having had expert lectures on topics related to skin of color (SOC) and only 30.2% reported having a specific rotation during which experience in treating patients with SOC was obtained [28]. In another survey, 47% of dermatologists and dermatology residents reported feeling that their training was inadequate in conditions affecting individuals with SOC [24]. The lack of specialized training may contribute to disparities in diagnosis and management between patients of different racial groups and contribute to the observed differences in AD severity. In a study of 137 pediatric patients with AD in the UK by Ben-Gashir and col-

leagues, it was discovered that a lack of ability to appreciate erythema on the physical exam of Black patients resulted in an underestimate of AD severity [23]. In this study, AD severity was compared between Black and White children using the SCORAD scale, which relies on factors such as erythema, edema, excoriation, and lichenification. Initially, the authors discovered a nonsignificant greater severity among White patients; however, once erythema scores were omitted from the severity assessment tool, it was reported that Black children showed a significantly higher rate of severe AD than White children (OR 5.93, $p = 0.002$) [23]. After controlling for erythema scores, physician severity assessments became more aligned with parental severity scores. Adjustment of other factors, such as edema, excoriation, or lichenification, did not produce a difference in severity outcome. The authors emphasize that reliance on erythema, which is included in a number of severity measures, may result in a falsely low impression of AD severity in SOC [23]. Disparities in accurate diagnosis may further result from the potential for AD in SOC to present with more subtle lesions, different morphology, or with an atypical distribution. For example, AD in African Americans may present with follicular, papular, or lichenoid lesions, or with a greater involvement of extensor instead of flexural surfaces [1, 22, 29]. Consequently, these differences may result in delayed diagnosis, counseling, and appropriate management.

Genetic Beyond differences in the phenotypic expression of AD between skin types, there is emerging evidence that there may be racial differences in the underlying genes involved in AD. Several studies have reported that the prevalence of filaggrin null mutations is significantly lower in African American, compared to Caucasian, patients with AD [30, 31]. In one study of 857 children with AD by Margolis et al., at least one filaggrin null mutation was detected in 27.5% of Caucasian, compared to 5.8% of African Americans [31]. In another study, it was reported that two common FLG mutations in patients with European ancestry, namely, R501X and 2282del4, were absent in individuals of African or Asian ancestry [32]. These findings suggest that there are distinct genetic mechanisms underlying AD in different racial groups, which may contribute to differences in AD severity. A number of other physiologic differences important in AD differ by race. It has been reported that, compared to Caucasians, African Americans have higher serum levels of immunoglobulin E, larger mast cell granules, and polymorphisms in pruritus receptors [22, 29, 33, 34]. Further, African American patients may have a higher tendency toward xerosis, as it has been shown that African American skin at baseline demonstrates higher transepidermal water loss and a lower ratio of ceramide to cholesterol, compared to Caucasian or Asian skin [22].

Racial variations in the underlying immunologic phenotype for AD may exist as well, which may contribute to disparities in targeted treatments. In one study, lesional and nonlesional biopsies were performed on 30 patients with AD and reverse-transcriptase-polymerase chain reaction (RT-PCR) and immunochemistry were employed to make comparisons between Caucasian, African American, and control patients. Biopsy specimens from African American patients showed greater

infiltration with dendritic cells with the high-affinity IgG receptor, compared to specimens from Caucasians [29]. In addition, while both European and African patients with chronic AD showed upregulation of Th2-related cytokines, African Americans demonstrated decreased expression of Th1- and Th17-related markers, suggesting that Th1 skewing in chronic AD may not occur uniformly across racial groups [29]. Nodal et al. analyzed biopsy samples of European American and Asian individuals with AD and reported that the immunologic phenotype of AD in Asian patients demonstrated a distinct profile, compared to European patients [35]. In this study, AD severity scores were equivalent between European and Asian patients. While both groups showed increased Th2 expression, Asian patients with AD demonstrated significantly greater Th17 activation, along with greater acanthosis, parakeratosis, and Ki67 counts. The authors suggest that racial differences in immune phenotypes require greater attention during the use and development of targeted therapies [35].

Conclusions

AD is complex in its etiology, challenging to treat, and significantly impacts the quality of life of those affected. Those individuals affected by the disparities in AD often do not achieve adequate control of their symptoms and treatment of their condition. It is important for health practitioners to recognize these disparities when evaluating and treating patients with atopic dermatitis. There is ongoing research on the identification of these unique patient factors and implementation of novel treatment modalities. This includes therapy targeted at the various immunologic mechanisms and phenotypes that exist in atopic dermatitis. The first such biologic therapy, Dupilumab, a monoclonal antibody that binds to interleukin-4 receptor subunit alpha (IL-4Rα) and subsequently blocks the Th2 immune response, has been approved in adults. Current studies are underway examining Il-31 as a molecular target to reduce the immune response associated with pruritus. The development of biomarkers, specific molecules which can identify the phenotype and clinical presentation of the disease, is the next step in creating targeted, individualized therapies in AD.

Going back to our case, severe AD has impacted this child's quality of life, performance at school, and potentially his future. His uncontrolled disease is impacted by lack of access to specialty care and inadequate treatments. The treatment of AD relies on daily care and use of multiple topical medications, which is only possible through education, close relation with healthcare providers, and teamwork. Furthermore, other factors, such as exposure to indoor pollutants, cutaneous irritants and allergens, and secondary infections, need to be assessed and addressed by specialist. As the pathogenesis of AD becomes better understood particularly among different populations and treatment options for AD evolve, efforts are also needed to develop programs for patients with limited resources. With the use of these programs along with novel treatment modalities, there is hope that the gap in AD disparities will narrow.

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