The Shape of Atopic Dermatitis


What do we really mean when we talk about flares or waxing and waning presentations?

BY NEHA CHANDAN, MPH AND PETER A. LIO, MD

>> Atopic Dermatitis (AD) is a highly prevalent, complex, chronic inflammatory skin condition that is thought to be caused by immune dysregulation and skin barrier dysfunction. Similar to many chronic skin diseases, AD is characterized by a relapsing and remitting nature, with periods of relative improvement interspersed with periods of flares or exacerbations over years.[1] The etiology of this waxing and waning disease is multifactorial, with interactions between one's genetics, environment, and immune system influencing disease severity. This complex interplay of factors is undoubtedly different for each patient, and thus no two disease courses will look the same. Specifically, the conception of a flare-up, as well as the frequency, number, timing, and severity of flare-ups, varies from patient to patient, adding not only to the complexity of the pathophysiology behind AD but to its clinical course and treatment, as well.

This brief review seeks to initiate a discussion about the wide range of disease patterns that accompany AD. Herein, we focus on what "waxing and waning" really means and its unique presentation in patient populations. We also seek to define what is meant by a "flare" and "remission" and how these definitions can change at different points in time. Additionally, we discuss AD's convoluted relationship to environmental factors and exposures. While this is clearly not an exhaustive collection of disease presentations, we hope it will serve as a useful reference, inspiring further investigation into individual AD profiles.

In the US[6]:

Overall, office visits for AD peak in the spring.

Avg. number of visits in May is 3.4.

In the South, AD visits peak in the summer.

DEFINING AD

The Hanifin-Rajka criteria and the UK Working Party refinement are the two most commonly used validated criteria to reliably identify established cases of AD. Using the Hanifin-Rajka criteria, at least three out of four of the major criteria must be met to qualify as a case of AD:

1. the presence of eczema,
2. typical distribution,
3. pruritus,
4. a relapsing and remitting course.[2]

The UK criteria further specify that a child must have had an itchy skin condition in the past 12 months. In both criteria, the concept of "relapsing and remitting" is left to the discretion of the patient or provider, leaving much room for interpretation.

So what does relapsing and remitting really mean? The answer is: it depends on the patient. In keeping with the variability of the disease itself, different patterns of relapse and remission can be present in AD. Patients who have mild AD may be more likely to experience a true relapse and remission, in which control is lost for a brief, specified time period (constituting the relapse) and then regained, and the patient returns to his/her original baseline prior to the flare (constituting the remission). The opposite may also occur, wherein patients with severe AD may experience high disease activity throughout their course that represents sustained relapses, intermittently broken by brief, non-sustained periods of remission.[1]

While the Hanifin-Rajka criteria and the UK Working Party refinement assist in reliably identifying established AD cases, no such standardized criteria exists to date for defining an incident case. One systematic review found a large degree of variability in the methods used to define an incident case of AD and also discovered that 25 percent of studies altogether failed to report any form of definition whatsoever.[2] Furthermore, many studies have shown that oftentimes eczematous rashes that appear in infants are transient, and these children do not necessarily go on to develop

true AD. It has thus been recommended that modification to the UK Working Party criteria be made to include a time requirement of four weeks that the eczema be present to be considered AD.[2] This time requirement should increase specificity of AD diagnoses, as well as allow for a diagnosis to be made even if the rash is treated early in its course.

Once an incident case has been identified, a baseline must be established. A common misconception is that a baseline is what may be considered "normal" or "stable." In reality, due to the relapsing nature of the disease, baselines in AD will fluctuate following each inciting event.[3] In any given week, month, or season, a patient may develop a new baseline that will be identified by the level of control over their symptoms in light of the severity of their disease. These baselines ought to be flexible and can improve with effective, long-term treatment as well as worsen with irritants or other triggers.

WHAT IS A FLARE?

The complex process of defining a flare must also be undertaken. Currently, disease flares are defined as an increase in disease activity as observed by the patient in relation to his/her previous experiences. A review that sought to understand the most commonly used definitions of a flare found that these definitions can be broadly categorized into three overarching themes:

1. composite definitions including at least two different factors (symptoms, severity duration, or treatment),
2. score thresholds or changes in score severity using indexes, such as Investigator Global Assessment (IGA) or Scoring Atopic Dermatitis (SCORAD), and
3. behavioral definitions, such as the use of rescue therapy.[3]

Combining these themes, Langan et al. recommended a flare be defined as an episode requiring an escalation of treatment or seeking additional medical advice.[3] Such behavior may include the need to increase potency of medication or increase frequency of application. Additionally, a decreased level of control with the same medication regimen may constitute a flare, as this, too, is a deviation from the patient's recent baseline.

Measures from the Global Initiatives for Asthma/National Institutes of Health guidelines model can also be adopted to help define flares. This model focuses on the concept of "totally controlled weeks" and "well-controlled weeks" as a means of determining long term disease control. These definitions ought to be individualized to each patient. For example, in patients with mild AD, a totally controlled week may be a week in which the patient has zero days with symptoms, whereas in patients with moderate to severe AD, a totally controlled week may be a week in which the patient does not require additional "rescue" treatment on top of the usual regimen, including but not limited to the use of more potent topical steroids or the need to visit a dermatologist. Similarly, a well-controlled week may be a week in which the mild patient only has symptoms for one or two days and the moderate/severe patient only requires rescue treatment for one or two days.[3]

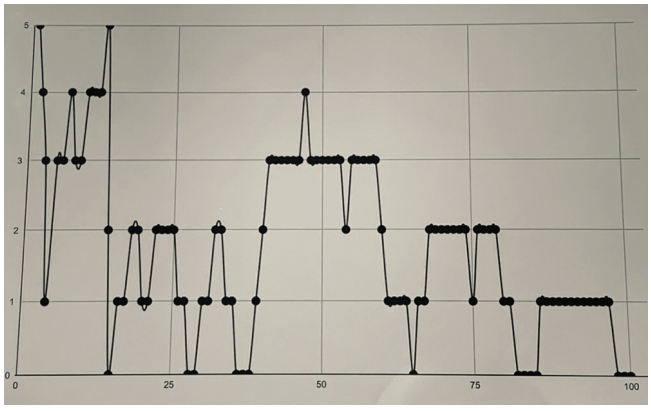

Fig 1. Actual patient-plotted chart of eczema severity over time.

In summary, we recommend maintaining an ever-changing definition of a baseline that is modified with the disease. From here, we can define a flare as a change in that new baseline and a relapse as a return to the baseline prior to the flare, rather than a return to the original state (Fig 1).

SEASONALITY IN AD

Seasonality is just one of the many environmental factors that can influence the course of AD. A seasonal fluctuating course is a well-known feature in patients with AD, although there does not seem to be one strict pattern of exacerbation. Climatic conditions, such as temperature, humidity, and ultra violet (UV) radiation, are strong components of seasonality, with low temperatures enhancing skin irritability, low humidity increasing skin roughness, and exposure to UV radiation reducing symptom severity of AD.[4] Allergen exposure may also induce or exacerbate symptoms, with pollen exposure predominantly occurring in spring and summer. It is important to take into account the patient's pattern of behavior. as well, as recreational activities change with the seasons. For example, warmer temperatures may be associated with increased frequency of swimming in chlorinated waters, increased contact with outdoor animals, and changes in diet.

A 1996 population-based study of 39 children with AD in Augsburg, Germany found significant variations in seasonal patterns, with 21 children (53.8 percent) exhibiting symptoms mainly in the winter and 19 children (48.7 percent) exhibiting more symptoms in summer.[4] Symptoms included itch and extent of disease per 15-degree Celsius increase or

> "AD ought to be thought of as a spectrum of disease that should be studied in light of one's genetics, environment, and lifestyle."

decrease in temperature. These results provide evidence for at least two different seasonal patterns of AD: a summer-type pattern with temperature increases worsening symptoms, and a winter-type pattern, with temperature increases decreasing symptoms. Additionally, this near equal split demonstrates that consideration of the individual type of AD is important in predicting disease pattern.

Here in the US, we experience a wide range of climatic factors between different geographic regions. With all these different weather patterns, it is no surprise that we observe many different AD seasonal patterns. A 19-year study seeking to investigate the relationship between US ambulatory AD office visits and seasonality found that as ambient air temperature increases, the likelihood of an AD visit rises. In the US overall, the number of visits was highest in the spring, specifically in the month of May, with an average number of 3.4 visits/month.[5] This pattern held true across the Midwest and West, but in the South, where US climate is the hottest on average, AD visits were highest in the summer. It is possible this difference can be attributed to the extreme heat and humidity of Southern summers. Both heat and humidity may provoke perspiration, which may have an irritant effect on the skin, leading to increased pruritus.[6] Although the greatest numbers of visits occurred in May and June, smaller peaks were also observed in January and October; remarkably, however, not a single region in the US demonstrated clear evidence of a winter flare of AD.[5]

Another study from Korea, analyzing the relationship between seasonality and aggravation of AD in children, found that symptoms increased significantly in spring, autumn, and winter relative to summer, with skin symptoms being the worst in April.[7] These strikingly different results from Krämer et al's 2005 study, Fleischer's 2019 study, and Kim et al's 2017 study serve to remind us that influences of AD extend well beyond temperature, and the many different shapes this disease can take are testaments to its multifactorial etiology.

THE GEOGRAPHY OF ATOPIC DERMATITIS

It is important to consider geographic location when studying AD. Epidemiological evidence points to an increased prevalence of AD at higher latitudes. Interestingly, vitamin D deficiency is also more prominent at higher latitudes, as exposure to UV radiation is significantly less in these regions. We know that vitamin D deficiency can contribute to altered barrier function, immune dysregulation, and inadequate bacterial defense in AD. Thus it has been proposed that oral vitamin D supplementation may be the solution to winter-related AD that is often seen in these high-altitude, low UV areas. As one Boston study found, vitamin D supplementation for patients who noted worsening in the winter months led to improvement of disease severity in 80 percent of subjects vs. 17 percent of subjects in the placebo group.[8] Additional studies in the Boston area found that serum 25-hydroxyvitamin D levels were inversely associated with AD status in adults, and diets of adults with AD were lower in vitamin D than those of controls.[8] Correcting for low vitamin D levels may be a step toward correcting for the geographical disparities of AD.

The prevalence of AD also appears to be higher in wealthier, developed regions compared with developing regions.[6] This brings us back to the hygiene hypothesis, which maintains that early life exposure prior to maturation of the immune system to a variety of pathogens can decrease allergic inflammation. Simply put, this translates into increased exposure to dirt and other environmental pathogens being protective against the development of AD, and thus the decreased prevalence of AD in developing countries. Children born outside the US have dramatically lower odds of AD than those born in the US, and farm and rural children have lower odds of AD than suburban and urban children.[6] These findings can be attributed to increased exposure to protective pathogens, such as manure, dogs, and unpasteurized milk, as well as protective microbial exposures, such as to bacterial endotoxins, helminths, and common viral infections. In fact, a single episode of systemic viral infections such as varicella-zoster virus when acquired in the first eight to 10 years of life is inversely associated with subsequently developing AD.[6,9] Interestingly, the protective effects of these early exposures are not permanent and may wear off, as evidenced by the increasing odds of AD after residing in the United States for 10 or more years.[6]

As with all things, a flip side exists, and there are also microbial exposures that increase the risk of AD. One important element of the Hanifin-Rajka minor criteria is predisposition to cutaneous viral infections, with a diagnosis of AD being associated with an increased risk of a subsequent diagnosis

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of Molluscum Contagiosum (MC).[10] MC, a common pediatric viral infection of the skin and/or mucous membranes, can trigger the onset of AD as well as aggravate existing AD. Children with AD onset triggered by MC infection were more likely to have flexural localization of MC and AD lesions, while children with AD flares triggered by MC infection were more likely to have lesions of the popliteal region and legs.[9] It is unclear why this distribution occurs. Interestingly, flares could not be prevented by treatment of MC.

Other observed associations between cutaneous infections and AD exist. It has been postulated that infections with Malassezia, herpes simplex, and Coxsackie virus in patients trigger AD, outside of their secondary infections of eczema herpeticum and eczema coxsackium, respectively.[6,9] Still, larger studies are needed to further assess these relationships.

CONCLUSION

As clinicians seek to discover more about AD, it becomes clear that this complex disease does not stand alone but rather is intertwined with and influenced by a number of modifiable and non-modifiable factors. AD ought to be thought of as a spectrum of disease that should be studied in light of one's genetics, environment, and lifestyle. There remains much to be learned about this multifactorial and heterogeneous disease, but looking at the shape of disease activity curves on an individual basis may allow for better subtyping of AD. In this way, both the clinician and the patient can better understand the course and treatment outcomes of AD. ■

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