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Original Article

'Measuring' eczema in children: what actually are we measuring?

兒童濕疹的評估：我們用甚麼衡量?

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The disease activity and severity of atopic dermatitis (AD) may be measured clinically and biochemically. There are at least thirteen clinical scoring systems for the assessment of disease severity in AD. Each system has its problems with inter-observer and intra-observer variability. They focus on the various symptoms and signs of this chronically relapsing disease. There are also various non-specific biochemical markers of disease severity. The markers for type 1 T helper (Th1) lymphocyte-mediated immunity, usually associated with infective process, are depressed in AD and their levels may be altered with eczema treatment whereas Th2 markers are associated with allergic inflammation and may be elevated in AD. Interleukin-18, a pleiomorphic marker, plays important roles in both Th1 and Th2 immunity. Cutaneous T cell-attracting chemokine (CTACK), on the other hand, is a skin-specific chemoattractant cytokine which may correlate with AD severity and obviate the issue of observer reliability. We share our experience in some of these markers and discuss the potential clinical significance of their measurement.

異位性皮炎病情的輕重和活躍性可以透過臨床或生物化學的方法去評估。臨床上最少有十三個評估計分系統用於評估異位性皮炎病情的輕重，但每個系統均各有其不足，存在著不同評估者之間及同一評估者不同評估時間之間的差異。這些系統著眼於此症的症狀和體徵。此外，有很多非特異性的生化標記物可反映病情的輕重。一型輔助性T淋巴細胞仲介免疫反應(Th1)的標記物通常伴隨感染發生，在異位性皮炎患者中水平下降，並隨治療有所改變，另一方面，二型輔助性T淋巴細胞仲介免疫反應(Th2)的標記物則伴隨過敏性炎症發生，在異位性皮炎患者中水平升高。白血球介素-18為一多形標記物，對一型及二型輔助性T淋巴細胞仲介免疫反應均起重要作用。皮膚T淋巴細胞吸引趨化因子(CTACK)為皮膚特異性化學吸引細胞因子，能客觀反影異位性皮炎病情輕重，避免評估者的主觀判斷差異。我們將討論這些標記物的潛在臨床意義及其衡量方法。

Keywords: Atopic dermatitis, CTACK

關鍵詞：異位性皮炎，皮膚T淋巴細胞吸引趨化因子

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Introduction

Atopic dermatitis (AD) is a common disease in children and affects nearly 20% of Hong Kong schoolchildren.[1,2] We surveyed all the new referrals to the paediatric dermatology clinic of Prince of Wales Hospital in the year 2000 and found that one third of these were eczema.[3] The financial

burden to our hospital system is tremendous. Recent report suggested that its incidence has been on the rise in the last decade.[4]

Clinical assessment of AD activity

Physicians in their busy clinics often claim to be able to take a glance at the patients and be able to determine the disease severity by their experience. This is neither objective nor evidence-based. There are at least thirteen scoring systems and indices for the assessment of disease severity in children with AD but many of these have not been adequately tested.[5] We share our experience in two of the scoring systems in children. The SCORing Atopic Dermatitis (SCORAD) is a comprehensive index utilised extensively in Europe as a research tool for the assessment of AD severity.[6] It is the only severity index for which published data could be found on validity, reliability, sensitivity, and acceptability, although problems occurred with inter-observer variation.[5] It consists of observations of signs and the assessment of symptoms and takes approximately ten minutes to perform by trained physicians who recognise the various components of this score. The SCORAD is weighted toward paediatric populations and is a rather complex tool not regularly used by the general practitioners. Though not the gold standard, it has been validated and widely quoted as a reliable research and clinical tool for the assessment of AD severity.[6] Scratching and sleep disturbance are subjective symptoms that are difficult to study. Some scoring systems, therefore, have bypassed the assessment of sleep loss and pruritus and adopt a more objective approach. Kunz and coworkers, for instance, suggested that the modified SCORAD index (without the pruritus and sleep-loss components) is more objective and accurate in defining the disease severity of AD.[7] The Nottingham Eczema Severity Score (NESS) is a three-part score developed for population-based research in the United Kingdom and has the advantage of being very easy to perform.[8] It is a less comprehensive scoring system and only gives a final grading of the severity of AD as being mild, moderate or severe. In the Chinese population, there has not been a validated clinical or research tool for the assessment of severity of AD. We translated the NESS into a self-administered Chinese questionnaire.[9] There were good agreement and correlation among the NESS scores, severity grades and the SCORAD. The correlation (r^2) between SCORAD and NESS as assessed by parents with children younger than ten years, parents with children 10 years or older and for patients who self-evaluated was 42.1%, 47.5% and 49.8% respectively. The self-administered questionnaire in Chinese enables the non-English speaking Chinese with AD to be assessed. We further modified the questionnaire to improve its clarity.[10] For instance, additional instructions were added and the diagram was enlarged. Our results showed that 92 percent of moderate-to-severe AD as defined by SCORAD could also be identified by NESS. It appears that NESS is good at detecting moderate-to-severe AD but is insensitive at assessing children with mild disease.[10] It is uncertain if this is due to the weighting given to the symptoms of pruritus and sleep loss in the SCORAD index. Alternatively, our data suggest that AD in patients with moderate-to-severe AD by SCORAD would remain severe in the longer run, whereas patients with mild disease might just be in remission at the time of assessment. When compared with our previous study,[9] the modified NESS with enhanced clarity correlates even better with the SCORAD.[10] Further study is underway to assess whether this modified NESS in Chinese can be used as a user-friendly tool for population-based research in Hong Kong.

Measuring AD activity in blood

As mentioned above, problems with inter- and intra-observer variability become an unavoidable issue when using any of these subjective clinical

indices. Thus, it would be useful for clinicians to have an objective laboratory marker that correlates with the various clinical aspects of AD, especially the inflammatory intensity of the disease.[11] This is even more important to evaluate any novel therapeutic agent in the research setting. There are various biochemical markers of AD severity.

The type 2 T helper (*Th2*) *lymphocyte-related markers* are associated with allergic inflammation and may be implicated in the pathogenesis of AD.[12-14] There has been tremendous research activity in assessing the usefulness of these Th2 cytokines and chemokines as markers of disease severity. Thymus and activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC) are two Th2 chemokines that specifically act on chemokine receptor CCR4[15] to attract Th2 cells into sites of allergic inflammation.[15-18] Eotaxin is another chemokine involved specifically in Th2-type immune responses.[19] Plasma eotaxin levels were increased in children with AD compared with controls.[20]

Interleukin (IL)-18, a *pleiomorphic marker*, plays important roles in both Th1 and Th2-mediated immunity. Monocyte chemotactic protein 1 (MCP-1) also played a role both in Th1 and Th2 antigen-induced granuloma formation.[21]

The cutaneous T cell-attracting chemokine (CTACK), on the other hand, is a skin-specific chemokine which may correlate with AD severity. CTACK functions by providing a skin-specific signal involved in localisation of cutaneous lymphocyte-associated antigen (CLA) memory T cells to skin and provides a potential target to regulate cutaneous T cell trafficking.[22] These findings also support the hypothesis that the nonrandom re-circulation of subsets of memory T cells relies not only on restricted expression of specific vascular adhesion molecules, but also on microenvironmentally restricted activation chemokines.[22,23]

In two recent publications, we demonstrated that serum concentrations of MDC, TARC, eotaxin, IL-18, but not MCP-1 correlated with the intensity of AD.[24,25] Serum MDC concentrations correlate with SCORAD, its extent and intensity components, whereas serum TARC concentrations showed significant correlation only with the extent and intensity of AD but not with overall SCORAD. MDC appeared to be better in terms of evaluating the disease severity of AD compared with TARC. However, these inflammatory markers are susceptible to the influences of other atopic disorders.[26,27] Thus, serum concentrations of these two Th2 chemokines may not be accurate in reflecting AD severity in children with concurrent and poorly controlled asthma or allergic rhinitis.[26-28] In another study of 37 patients, we showed there were significant correlations between SCORAD ($r=0.394$, $p=0.016$), its area ($r=0.528$, $p=0.001$) and intensity components ($r=0.429$, $p=0.008$) with the serum levels of CTACK.[11] Serum concentrations of CTACK were increased in our AD patients as compared to 13 controls (median, IQR: 1145, 774-1688 pg/ml versus 558, 485-592 pg/ml; $p<0.0001$). Serum CTACK concentrations in patients with moderate and severe AD were also significantly higher than those with mild AD. The median (IQR) CTACK levels in the mild, moderate and severe groups were 1026 (676-1221) pg/ml, 1487 (787-1999) pg/ml and 1289 (1013-2124) pg/ml, respectively.

The serum concentrations of inflammatory markers MDC and TARC also correlated with the CTACK concentrations ($r=0.618$, $p<0.001$ and $r=0.587$, $p=0.001$, respectively). Therefore, serum CTACK concentration appears to be a useful skin-specific and objective marker for AD severity even in patients with coexisting atopy. In fact, serum CTACK concentrations showed significant correlation with those of MDC and TARC in our AD patients.[11] These findings in paediatric AD are similar to those reported in adults.[22] We can possibly eliminate the

confounding effects from other atopic disorders on serum chemokine measurement by using CTACK to monitor the disease activity of AD.

Measuring AD activity in urine

Leukotriene E4 (LTE_4) is a cysteinyl leukotriene which is excreted in the urine and represents a product of the final common pathway of cysteinyl metabolism. It is elevated in adults with AD. Hishinuma and colleagues reported that urinary LTE_4 levels were higher in 20 adults with AD as compared to 17 controls. Increased urinary LTE_4 was also seen in subjects with higher serum total IgE levels. However, they did not look at whether this marker has any significant correlation with the disease severity of AD.[29] We evaluated if urinary LTE_4 as a noninvasive marker correlates with clinical indices of disease activity in AD.[10] Disease severity over the preceding three days was evaluated by the SCORAD index, whereas the longer term (12 months) severity of AD was evaluated by the NESS in Chinese. When compared with normal subjects without atopy, we demonstrated that urinary LTE_4 was significantly elevated in 126 AD children. There was also a significant correlation between urinary LTE_4 concentration and (i) overall and objective SCORAD, (ii) extent of skin involvement and (iii) intensity components; but not the subjective symptoms of sleep loss and pruritus (Table 1). As this investigation is totally non-invasive, serial urinary LTE_4 measurements may be useful to supplement the SCORAD for following the longitudinal changes in AD severity with different forms of anti-inflammatory treatments. There is no correlation of urinary LTE_4 levels with the NESS score which evaluates the more chronic symptomatology of AD, suggesting that LTE_4 is probably an acute disease marker.

Summary: correlations between these markers

The correlations between SCORAD and its components and the various blood and urine markers are summarised in Table 1. It is important to understand what is being measured when one measures AD. The SCORAD, for instance, measures the extent, intensity, pruritus and sleep loss over the preceding three days. The symptoms of pruritis and sleep loss over the preceding three days probably reflect acute symtomatology. On the other hand, the extent component would reflect both acute and subacute sign of disease activity. The intensity component is a complex element and reflect acute and chronic signs. For instance, erythema and weeping are acute signs of

Table 1. The correlation between SCORAD and inflammatory markers in blood and urine

	Serum Concentrations								Urine Concentration	
	CTACK[11]		MDC[11]		TARC[11]		IL-18[25]		LTE_4[10]	
	r	p	r	p	r	p	r	p	r	p
Total SCORAD	0.917	0.001	0.867	0.002	0.750	0.020	0.502	0.029	0.270	0.002
SCORAD components										
Extent	0.950	<0.001	0.900	0.001	0.733	0.025	0.633	0.004	0.185	0.038
Intensity	0.937	<0.001	0.810	0.008	0.836	0.005	0.371	0.118	0.247	0.005
Sleep loss	0.728	0.026	0.879	0.002	0.485	0.185	0.443	0.057	0.240	0.007
Pruritis	0.798	0.010	0.824	0.006	0.555	0.121	0.311	0.194	0.223	0.012

r, Correlation coefficient ; p, p value; CTACK, Cutaneous T cell-attracting chemokine; MDC, Macrophage-derived chemokine; TARC, Thymus and activation-regulated chemokine; IL-18, Interleukin-18; LTE_4, Leukotriene E4

inflammation and lichenification reflect chronic inflammation. It is a weighted index, with less weight on the extent (by multiplying a factor of 0.2) but more emphasis on the intensity (by a factor of 3.5) and symptomatology of pruritus and sleep loss (by a factor of 1).[6] The NESS, on the other hand, relies heavily on the reported symptoms of sleep and pruritus over the preceding twelve months as well as the extent of AD.[8] We now have evidence that Th2 chemokines, especially CTACK, are involved in the inflammatory process.[11] Our findings concur with the hypothesis that CTACK, being a skin-specific immune marker, correlates with the objective features (extent and intensity) but not the subjective features (pruritus and sleep loss).

As the inflammatory process in AD is complex, it may be impossible to characterise the disease with a single clinical score or marker. Quantifying the various markers and correlating their levels with clinical scores may lead to a better understanding of AD and improve research in its management.

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