Original article

CED
Clinical and Experimental Dermatology

Atopic dermatitis characteristics and medication-use patterns in school-age children with AD and asthma symptoms

M. van der Lee,[1] A. Arabkhazaeli,[1] F. C. van Erp,[2] J. A. Raaijmakers,[1] C. K. van der Ent,[2] C. A. F. M. Bruijnzeel-Koomen,[3] M. S. de Bruin-Weller,[3] S. J. H. Vijverberg[1] and A. H. Maitland-van der Zee[1,4]

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht University, Utrecht, The Netherlands; [2]Department of Paediatric Pulmonology and Allergology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands; [3]Department of Dermatology and Allergology, University Medical Centre Utrecht, Utrecht, The Netherlands; and [4]Department of Respiratory Disease, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

doi:10.1111/ced.13111

Summary

Background. Atopic dermatitis (AD) and asthma often coexist. Both diseases can have a major impact on the lives of children with AD and their caregivers.

Aim. To investigate the association of patient characteristics, comorbidities and impact of AD on children who have both asthma and AD.

Methods. Children with AD (n = 140) were selected from a larger cohort of children with a reported use of asthma medication. The Children's Dermatology Life Quality Index (CDLQI) was used to assess Quality of Life (QoL), and the Self-Assessed Eczema Area and Severity Index (SA-EASI) was used to measure AD severity. Characteristics assessed included: age, sex, and the number and type of atopic comorbidities. Medication use for AD was defined using the total number of AD prescriptions, the number of different topical AD prescriptions and the highest potency topical corticosteroid (TCS) used. Determinants of AD severity and QoL were evaluated using Spearman rank tests.

Results. The following factors were most strongly associated with a lower QoL: characteristics of AD lesions (Spearman R_s = 0.61–0.69, $P < 0.01$), a higher SA-EASI score (R_s = 0.54, $P < 0.01$) and a larger number of different topical AD prescriptions (R_s = 0.38, $P < 0.01$). The following factors were correlated with more severe AD: age (R_s = −0.36, $P < 0.01$), larger number of different TCS preparations used (R_s = 0.27, $P < 0.05$) and larger number of TCS prescriptions (R_s = 0.25, $P < 0.05$).

Conclusion. In children with asthma and AD, the number of TCS preparations used is associated with lower QoL and increased AD severity.

Introduction

Atopic dermatitis (AD) is a chronic skin disease with a high prevalence (7–9% for children), and it often coexists with asthma.[1] Genetic predispositions seem to play a role.[1,2] Children with asthma and AD display more severe symptoms compared with children who have only one atopic disease, and therefore this is a subgroup that requires attention.[1] Asthma and AD are diseases that can have a major impact on quality of life (QoL).[3] Few studies have investigated factors related to the QoL of children with AD. Most studies have focussed on the prevalence of AD, but did not look at severity or at populations with asthma.[4–6] It has not conclusively been shown that AD severity influences QoL,[7,8] but it is likely to do so.

Topical treatment of AD usually consists of an emollient, a topical corticosteroid (TCS) or a combination of

Correspondence: Dr Anke-Hilse Maitland-van der Zee, Department of Respiratory Disease, Academic Medical Center (AMC), University of Amsterdam (UvA), PO Box 22660, 1100 DD, Amsterdam, the Netherlands
E-mail: a.h.maitland@amc.uva.nl

Conflict of interest: SJHV was supported by an unrestricted grant from GlaxoSmithKline (GSK). JAMR is a part-time professor Utrecht University, was Vice-President for External Scientific Collaborations for GSK in Europe and holds stock in GSK. A-HMvDZ received an unrestricted grant from GSK. CKvdE received unrestricted grants from GSK and Grunenthal. The remaining authors declare that they have no conflicts of interest.

Accepted for publication 16 October 2016

both. For therapy-resistant AD, or in the case of TCS-related adverse events, topical calcineurin inhibitors (TCIs) can be used. Guidelines recommend treating more severe AD with more potent TCS preparations.[9,10] The number of topical AD therapies dispensed might also be associated with AD severity and QoL.

In this study, we aimed to assess whether clinical factors are associated with AD-related QoL and AD severity in children using asthma medication. Furthermore, we aimed to assess whether pharmacy dispensing data can be used as a measure of AD severity and AD-related QoL.

Methods

Participants

We used data collected in the PACMAN (Pharmacogenetics of Asthma medication in Children, Medication with ANti-inflammatory effects) cohort study and the Electronic Portal (EP) for children with respiratory and allergic symptoms. The PACMAN study was approved by Medical Ethics Committee of the University Medical Centre Utrecht. Written, informed consent for all participants in the study was obtained from either the participants themselves or, where participants were minors, a parent or guardian.[11,12]

In the PACMAN study, children aged 4–12 years old, who regularly used asthma medication, were selected from Dutch community pharmacies. Parents and children were asked to complete a questionnaire about asthma symptoms, risk factors and atopic comorbidities.[12] All diagnoses were parent-reported. All responders were then asked to take part in a digital follow-up, the EP, which contains questionnaires regarding general wellbeing and the presence and severity of atopic diseases. By now the children could be older than 12 years.[11]

The children were selected for the study based on a positive answer to the question: 'Are you currently experiencing symptoms of eczema?'.

Questionnaires

Severity of AD was assessed by the Self-Assessed Eczema Area and Severity Index (SA-EASI), ranging from 0 (very mild AD) to 72 (extremely severe AD).[11–13] AD-related QoL was assessed using the Children Dermatology Life Quality Index (CDLQI), ranging from 0 (no impact on QoL) to 30 (severe impact on QoL).[11,14,15]

Children were directed to the CDLQI questionnaire if they gave a positive answer to the question': 'Did you (your child) have an itchy rash in the past 12 months?', and to the SA-EASI questionnaire, if the question 'Do you currently have eczema complaints?' was answered positively.

Pharmacy data

Pharmacy dispensing records were collected for all patients. In the Netherlands, individuals are usually registered at a single pharmacy, which provides a full record of that patient's medication use.[16] TCS preparations are prescribed by a physician and cannot be bought over the counter.

From the dispensing data, all topical AD medication [Anatomical Therapeutic Chemical (ATC) codes; D07, D02AX, D11AH01 and D11AH02] dispensed in the 12 months prior to the EP was collected. The ATC system subdivides active substances into groups based on their therapeutic indication.[17] The therapies were subdivided into the following categories: emollients, TCS and TCI. The TCS preparations were further subdivided into potency classes (1 being least potent and 4 most potent) according to the European classification system.[18,19] The total number of AD prescriptions, the number of different topical AD prescriptions and the highest potency TCS used were evaluated. The dispensed amount of TCS in preparations is generally 30 g (72.1% of the prescriptions in our study). In the Netherlands, a pharmacist is only allowed to dispense for 3 months at a time; the rest of the prescription is kept at the pharmacy to be dispensed at a later date.

Statistical analysis

The correlation between age, sex and the number of comorbidities in relation to the SA-EASI and CDLQI score was investigated using Spearman rank test and Mann–Whitney *U*-test. The appearance of AD lesions and their correlation with the CDLQI, the association between the number of medications and the SA-EASI/CDLQI scores, and the correlation between the individual CDLQI questions compared with the final score of the CDLQ were analysed using Spearman rank test. To assess the influence of body areas affected, the population was divided into two groups, with the cut-off being 10% of the individual body area affected. The effect on QoL was assessed using the Mann–Whitney *U*-test. Analyses were performed using SPSS for Windows (v20.0; IBM, Armonk, NY, USA).

Table 1 Demographic characteristics.

	Overall study population (n = 140)	Population for medication analyses (n = 94)*	P
Age, years; mean ± SD	10.1 ± 2.4	10.0 ± 2.5	0.71
Male, %	58.6	59.6	0.73
Questionnaires			
SA-EASI, median (IQR) (n)†	0.8 (0.0–4.1) (118)	0.8 (0–4.0) (85)	0.96
CDLQI, median (IQR) (n)†	1.0 (0–4.0) (139)	1.0 (0–4.0) (93)	0.92
Comorbidities, % (n/N)‡			
Atopic dermatitis	89.2 (124/139)	93.6 (88/94)	0.02
Asthma	79.3 (111/140)	78.7 (74/94)	0.81
Hay fever	50.0 (70/140)	52.1 (49/94)	0.47
Food allergies	37.4 (52/139)	41.9 (39/93)	0.12
Therapies			
Emollients	–	24.5	–
TCS class 1	–	9.6	–
TCS class 2	–	16.0	–
TCS class 3	–	7.4	–
TCS class 4	–	1.1	–
TCI	–	2.1	–
Coal tar	–	1.1	–
Any therapy	–	29.8	–
TCS potency, median (IQR)	–	2.0 (1.0)	–
No. of different therapies, median (IQR)	–	0.0 (1.0)	–
Total no. of prescriptions, median (IQR)	–	0.0 (1.0)	–

CDLQI, Children's Dermatology Life Quality Index; SA-EASI, Self-Assessed Eczema Area and Severity Index; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid. *All children with a fully up-to-date dispensing record available; †not all questionnaires were completed; ‡comorbidities were self-reported for children aged ≥ 12 years (as this was a follow-up study, some could have been older than the age at which they were originally enrolled into the PACMAN study) and parent-reported for children < 12, out of a total of four comorbidities.

Results

Patient characteristics

In total, 140 children were enrolled in the study: of these, 117 completed both questionnaires, while 22 completed the CDLQI only, and 1 completed the SA-EASI only. The majority (58.6%) of the children were boys (see Table 1). Half of the children (50%) reported having hay fever currently or previously, and 37.4% had food allergies.

The majority (> 77%) of children reported having ≥ 10% of different body areas affected (Table S1). One child reported > 90% body surface area (BSA) affected on their hands and arms, while another reported > 90% BSA on the neck only. The genital/anal areas were the only areas with < 10% BSA affected in all the children.

Complete pharmacy dispensing data was available for 94 of the 140 children in the study. Self-reported diagnosis of AD was the only factor that was different in the overall study population compared with the study population with up-to-date medication data (Table 1). Almost 70% of the children had not received a topical AD prescription in the past 12 months. The most commonly used treatments were emollients (used by 24.5%) and class 2 TCS preparations (16.0%), while TCIs were used by 2.1%.

Severity of atopic dermatitis

Median AD severity (SA-EASI) score was 0.8 [interquartile range (IQR) 0.0–4.1]. The SA-EASI was negatively correlated with age (Spearman $R_s = -0.36$, $P < 0.01$) and positively correlated with the number of different AD therapies ($R_s = 0.27$, $P = 0.01$) (Table 2) and the total number of AD prescriptions ($R_s = 0.25$, $P = 0.02$), but there was no statistically significant correlation with sex ($P = 0.66$), TCS potency ($R_s = -0.10$, $P = 0.67$), number of comorbidities ($R_s = 0.14$, $P = 0.15$), or presence of any of the other atopic comorbidities [hay fever ($P = 0.95$) and food allergies ($P = 0.28$)].

Atopic dermatitis-related quality of life

Median CDLQI in the population was 1.0 (IQR 0.0–4.0). There was no statistically significant correlation between the CLDQI and either age ($R_s = -0.01$, $P = 0.92$) or sex ($P = 0.13$), but there was a significant positive correlation with the presence of

Table 2 Correlations between atopic dermatitis severity and quality of life measurements in children with AD and asthma.

	SA-EASI			CDLQI		
	n	R_s	*P*	*n*	R_s	*P*
Maximum TCS potency	22	−0.10	0.67	23	0.15	0.50
No. of different therapies	85	0.27	0.01*	93	0.38	< 0.01†
Total no. of prescriptions	85	0.25	0.02*	93	0.36	< 0.01†
Age	118	−0.36	< 0.01†	139	−0.01	0.92
No. of atopic comorbidities	116	0.14	0.15	137	0.26	< 0.01†

CDLQI, Children's Dermatology Life Quality Index; SA-EASI, Self-Assessed Eczema Area and Severity Index; TCS, topical corticosteroid. *Significant; †highly significant. Correlations were assessed with Spearman rank test. Comorbidities were asthma, atopic dermatitis, hayfever and food allergies.

additional atopic diseases (hay fever or food allergy) (R_s = 0.26, P < 0.01). Children with hay fever scored higher on the CDLQI than children without (mean score of 3.4 vs. 1.8, respectively), and the same was true for food allergies (3.4 vs. 1.4, respectively). Children with hay fever were slightly older than those without (10.36 vs. 9.49 years, P < 0.05), whereas there was no statistically significant difference in age for children with or without food allergies (Table 3).

For all body areas there was a statistically significant difference in CDLQI between children with < 10% BSA affected by AD and those with > 10% BSA affected (Table S1).

The CDLQI was not correlated with TCS potency (R_s = 0.15, P = 0.50), but there was a moderate correlation with the number of different therapies (R_s = 0.38 P < 0.01) and the total number of AD prescriptions (R_s = 0.36 P < 0.01) (Table 2).

Correlation between the questionnaires

There was a statistically significant correlation between the SA-EASI and the CDLQI results (*Rs* = 0.54, P < 0.01) (Fig. 1). All lesion characteristics were statistically significantly correlated with the CDLQI (R_s 0.61–0.69, P < 0.01) (Table S2).

Table 3 Influence of atopic comorbidities on atopic dermatitis severity (AD) and AD-related quality of life in children with AD and asthma symptoms.

	CDLQI			SA-EASI		
Presence of:	Median	IQR	*P*	Median	IQR	*P*
Hay fever						
Yes	1.5	0.0–6.0		0.8	0.0–5.0	
No	0.0	0.0–2.0	< 0.01	1.0	0.0–3.8	0.95
Food allergies						
Yes	1.0	0.0–5.0		2.2	0.0–8.2	
No	1.0	0.0–3.0	0.04	0.8	0.0–3.5	0.28

CDLQI, Children's Dermatology Life Quality Index; IQR, interquartile range; SA-EASI, Self-Assessed Eczema Area and Severity Index.

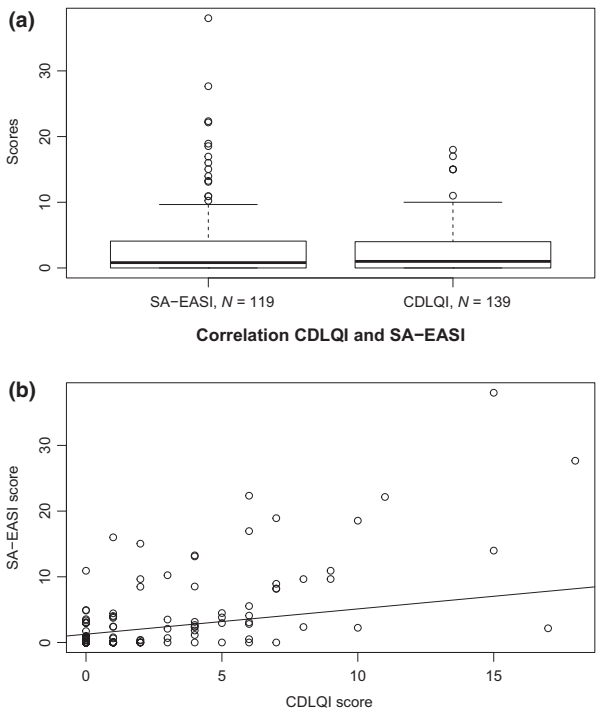

Figure 1 (a) Severity distribution of the Self-Assessed Eczema Area and Severity Index (SA-EASI) and the Children's Dermatology Life Quality Index (CDLQI) in our study population. The thick lines represent the average score and the boxes the inter quartile ranges. (b) Correlation between the SA-EASI and CDLQI scores in children with AD and asthma symptoms. *Rs* = 0.54, P < 0.01. SA-EASI ranges from 0 to 72, CDLQI ranges from 0 to 30.

Discussion

In this study, we found that QoL in children with AD and asthma is correlated with the clinical characteristics of the lesions, and with AD severity and AD medication use. Furthermore, the number of topical

therapies used might be a marker for AD-related QoL and AD severity, whereas TCS potency is not a marker.

We found that the number of atopic comorbidities correlated with QoL but not with AD severity. Having more comorbidities might cause the child to experience their AD symptoms as being more impairing. Some of the symptoms might also be due to other comorbidities, e.g. an allergic rash.

Children with hay fever or food allergies scored higher on the CDLQI but not on the SA-EASI. The children with hay fever were slightly older than the ones without, but there was no link between the CDLQI and age, which suggests that age was not a confounding factor. A strong association between hay fever and AD severity and prevalence has been shown previously.[20–22] Silverberg *et al.* studied the link between AD and atopic comorbidities, and reported an association between severe hay fever and AD, and between food allergies and AD.[20] We were not able to replicate these results, which might be due to our study population having a mainly mild AD population or to preselection of our population by the use of asthma medication. Asthma itself is linked to more severe AD and a higher prevalence of AD;[20,21] however, even though our study population had a high prevalence of asthma, it was still a population with relatively mild AD, which is the most likely explanation.

Even though guidelines recommend treatment with TCS preparations with higher potencies for more severe AD,[9,10,23] we did not find a correlation between TCS potency and AD severity or QoL. A possible explanation might be that physicians are hesitant to treat children with a higher potency TCS, or are not following the guidelines, possibly because of concerns about steroids. This might be leading to undertreatment of these patients.

Both the number of different topical AD therapies and the total number of topical AD prescriptions correlated with AD severity and more strongly with QoL. The number of different AD therapies used seems to be the most suitable parameter to be used as a marker in epidemiological studies for AD severity and AD-related QoL.

Of the 140 children, 8 received a total of 14 systemic prescriptions corticosteroids in the study period. None of the prescriptions was prescribed concurrently with AD medication. As asthma medication was prescribed concurrently for 10 of the 14 children, it is very likely that these corticosteroid prescriptions were used for asthma and not for AD.

Records of medication used in the past 12 months might not necessarily reflect current medication use, but owing to the small sample size of this study it was not possible to focus on a shorter time frame. An explanation for the correlation between medication use and AD-related QoL might be that the children find the application of the therapies difficult or bothersome. However, we did not find a strong correlation between QoL and the CDLQI question about AD treatment.

One of the major strengths of this study was the detailed data available on AD severity and AD-related QoL in combination with complete pharmacy dispensing data. One of the limitations of this study is the fact that analyses were performed with correlation tests rather than (linear) regression, which would have allowed for correction of confounders. The reason for this was the non-Gaussian distribution of the outcomes and the residuals, even after transformation. Another limitation was that the diagnoses might have been confounded as they were parent-reported and not all were confirmed by physicians. However, in the PACMAN study, the agreement between parent-reported and physician-reported diagnoses was high.[24]

Conclusion

This study provides valuable information about the correlation of atopic comorbidities, age and medication use with AD severity an AD-related QoL. TCS potency was not correlated with AD severity or QoL, whereas the number of different therapies and the total number of prescriptions were correlated, thus these last two parameters might serve as a measure for AD severity and AD-related QoL. In addition, it seems that children with multiple atopic disorders experience AD as more impairing, thus interventions specifically targeted at this group might empower these children and improve QoL.[25]

What's already known about this topic?

- Few studies have investigated factors related to the QoL of children with AD.
- Most studies investigating factors such as age or comorbidities that might be associated with AD have focused on the prevalence of AD, but did not study severity of AD or populations with AD and asthma.

What does this study add?

- This study showed that QoL in children with AD and asthma is correlated with clinical

characteristics of the AD lesions, AD severity and AD medication use.
• The number of atopic comorbidities was correlated with the QoL but not with AD severity.
• In children with asthma and AD, the number of topical corticosteroids children use were associated with a lower quality of life and an increased AD severity.

References

1 Arabkhazaeli A, Vijverberg SJ, van Erp FC *et al.* Characteristics and severity of asthma in children with and without atopic conditions: a cross-sectional study. *BMC Pediatr* 2015; **15**: 172.
2 Palmer CN, Irvine AD, Terron-Kwiatkowski A *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–6.
3 O'Connell EJ. The burden of atopy and asthma in children. *Allergy* 2004; **59** (Suppl): 7–11.
4 Odhiambo JA, Williams HC, Clayton TO *et al.* Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009; **124**: 1251–8. e2.
5 Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003; **361**: 151–60.
6 Thomsen SF. Atopic dermatitis: natural history, diagnosis, and treatment. *ISRN Allergy* 2014; **2014**: 354250.
7 National Collaborating Centre for Women's and Children's Health (UK). *Atopic Eczema in Children: Management of Atopic Eczema in Children from Birth up to the Age of 12 Years*. London: RCOG Press, 2007.
8 Ben-Gashir MA, Seed PT, Hay RJ. Quality of life and disease severity are correlated in children with atopic dermatitis. *Br J Dermatol* 2004; **150**: 284–90.
9 Nederlands Huisarten Genootchap, NHG–Standaard Eczeem [NHG Standard for Eczema] (in Dutch). Available at: https://www.nhg.org/standaarden/volledig/nhg-standaard-eczeem (accessed 6 August 2016).
10 Nederlandse Vereniging voor Dermatologie en Venereologie. Richtlijnen [Guidelines] (in Dutch). Available at: http://www.nvdv.nl/wp-content/uploads/2014/08/Richtlijn-Constitutioneel-Eczeem-2014.pdf (accessed 6 August 2016).
11 Zomer-Kooijker K, van Erp FC, Balemans WA *et al.* The expert network and electronic portal for children with respiratory and allergic symptoms: rationale and design. *BMC Pediatr* 2013; **13**: 9.
12 Koster ES, Raaijmakers JA, Koppelman GH *et al.* Pharmacogenetics of anti-inflammatory treatment in children with asthma: rationale and design of the PACMAN cohort. *Pharmacogenomics* 2009; **10**: 1351–61.
13 Housman TS, Patel MJ, Camacho F *et al.* Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: results of a validation study. *Br J Dermatol* 2002; **147**: 1192–8.
14 Holm EA, Wulf HC, Stegmann H *et al.* Life quality assessment among patients with atopic eczema. *Br J Dermatol* 2006; **154**: 719–25.
15 Lewis-Jones MS, Finlay AY, Dykes PJ. The Infants' Dermatitis Quality of Life Index. *Br J Dermatol* 2001; **144**: 104–10.
16 van Boven JF, Hiddink EG, Stuurman-Bieze AG *et al.* The pharmacists' potential to provide targets for interventions to optimize pharmacotherapy in patients with asthma. *Int J Clin Pharm* 2013; **35**: 1075–82.
17 WHO Collaborating Centre for Drug Statistics. ATC/DDD Index. Available at: https://www.whocc.no/atc_ddd_index/ (accessed 23 October 2015).
18 Sterry W, Paus R, Burgdorf W. *Dermatology – Thieme Clinical Companions*. Stuttgart, New York: Georg Thieme Verlag, 2006: 597.
19 Farmacotherapeutisch Kompas. Middelen bij huidaandoeningen [Drugs for disorder] (in Dutch). Available at: https://www.farmacotherapeutischkompas.nl/bladeren-volgens-boek/inleidingen/inl-middelen-bij-huidaandoeningen (accessed 6 August 2016).
20 Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. *Pediatr Allergy Immunol* 2013; **24**: 476–86.
21 Ballardini N, Kull I, Lind T *et al.* Development and comorbidity of eczema, asthma and rhinitis to age 12**:** data from the BAMSE birth cohort. *Allergy* 2012; **67**: 537–44.
22 Ben-Gashir MA, Seed PT, Hay RJ. Predictors of atopic dermatitis severity over time. *J Am Acad Dermatol* 2004; **50**: 349–56.
23 Ring J, Alomar A, Bieber T *et al.* Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol* 2012; **26**: 1045–60.
24 Pieters L, Vijverberg S, Raaijmakers J *et al.* Astmadiagnose bij kinderen. *Huisarts Wet* 2014; **57**: 446–51.
25 Ahrens B, Staab D. Extended implementation of educational programs for atopic dermatitis in childhood. *Pediatr Allergy Immunol* 2015; **26**: 190–6.

Supporting Information

Additional Supporting Information may be found in the online version of this article:
Table S1. Quality of life related to areas affected in children with atopic dermatitis and asthma.
Table S2. Atopic dermatitis characteristics and the correlation with quality of life.

