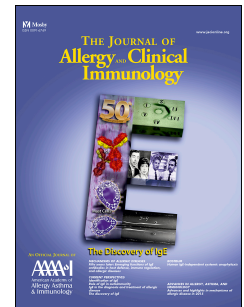


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Childhood Chronic Prurigo: interest of Patch tests and delayed reading Skin prick tests to environmental allergens

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Capsule summary:

Childhood chronic prurigo is rarely studied in particular for allergic components. We propose a clinical classification according to seasonality of prurigo in three groups to help identifying causal agents and guide allergy testing with delayed readings tests.

Key words: prurigo, *papular urticaria*, children, skin prick tests, patch tests

Abbreviations used:

AD - Atopic dermatitis

cDLQI - Children's Dermatology Life Quality Index

D.pter - *Dermatophagoides pteronyssinus*

D.far - *Dermatophagoides farinae*

HDM- House dust mites

LS - Laboratory Standards

P-VAS Pruritus Visual Analogue Scale

SD- Standard derivation

SPT- Skin prick tests

PT- Patch Test

sIgE - Serum specific IgE antibodies

tIgE - Total IgE

88 *To the Editor:*

89 Prurigo is defined clinically by symmetrical pruritic, papular, or papulovesicular
90 erythematous skin lesions.¹ It may be acute, subacute or chronic.² In children, prurigo is
91 mainly described as *prurigo strophulus* or *papular urticaria*, and viewed as a subacute
92 delayed hypersensitivity reaction to insect bites arising between 2-7 years old in up to 5% of
93 pediatric dermatology consultations.³
94 However, in our experience, prurigo in children may run a chronic course lasting several
95 months to years, triggered and maintained by environmental allergens, but remains poorly
96 studied.

97 The goal of the study was to describe the clinical features of childhood chronic prurigo
98 and define different clinical forms after analysis of sensitization profiles to various
99 environmental allergens. We also assessed the quality of life of these children and the
100 relevance of allergy testing.

101 We conducted a prospective, multicenter study in 11 French Dermatology outpatients
102 units between April 2015 and March 2016. Consecutive patients younger than 16 years old
103 with typical pruritic lesions lasting for more than 6 weeks continuously or with intermittent
104 flares were included. We collected demographic data, seasonal influence, clinical
105 characteristics, quality of life index (cDLQI)⁴ and pruritus scores (P-VAS)⁵. Results of skin
106 prick tests (SPT) and patch tests (PT) to seven environmental allergens (house dust mites,
107 storage mites, mosquito, cockroach, cat and dog dander), eosinophil counts, total and specific
108 serum specific IgE were analyzed. The evaluation of the SPT was done after 20 minutes as
109 usual, but also at 48 hours for evaluation of delayed reactions, and again at 96 hours. Allergy
110 testing and data analysis are detailed in the Methods section in this article's Online
111 Repository. A control group of patients without prurigo was constituted (patient's
112 characteristics are showed in Table E1 in the Online Repository).

113 The study was approved by the Hospital ethical committee (DC2016/09). For each
114 child, informed consent was obtained from the parents for participation in the study.

115 A total of 102 children were enrolled in the study (57% boys, mean age of 5.9 years).
116 According to seasonality, three subgroups were identified: perennial, summer and non-
117 summer prurigo. Clinical characteristics are summarized in Table I. The most frequent
118 affected areas in the three subgroups were legs and forearms in 84% and 74%, respectively.
119 Figure E1 in the Online Repository shows the clinical phenotype in each subgroups. The most
120 prevalent types of lesions in all three groups were papules for 85% of patients and
121 excoriations for 72 % of patients. The mean cDLQI was 6.1/30 (+/- 5.8; range 0-25) and mean

P-VAS was 3.7/10 (+/- 3.0; range 0-10). The full panel of allergy investigations was done in 56 patients. Their general characteristics were similar to those of the total population of 102 patients (see Table E2 in the Online Repository).

In the summer prurigo subgroup, 14 children (52%) had a positive SPT to mosquito at 48 hours compared to 2 (7%) after 20 min ($p=0.007.10^{-1}$). Moreover, SPT at 48 hours were more sensitive than patch tests at 48 hours to mosquito ($p=0.01.10^{-2}$).

PT to *D.pter*, *D.far* were positive at 48 hours for 45% and 40% of perennial prurigo patients respectively. For all patients, positivity to HDM patch tests was higher than positivity to SPT at 48 hours to *D.pter* ($p=0.01.10^{-1}$) and to *D.far* ($p=0.009.10^{-1}$). Other results of SPT and patch tests are detailed in Table E3 (in the Online Repository). The delayed positivity of tests to mosquito, HDM and cockroach was specific to children with chronic prurigo because late readings were negative in the control group of 24 children (see Table E1 in the Online Repository). Patients with prurigo had negative sIgE antibodies for *D.pter*, *D.far* in 59% of cases, and for mosquito and cockroach in 73% of cases. Details of blood investigations are shown in Table E4 in the Online Repository.

This is the first and largest study of childhood chronic prurigo. The seasonality is a simple way to classify prurigo, because possibly linked to its cause, such as mosquito bites reported as the main cause of summer prurigo in children.⁶ Perennial prurigo is mainly represented by atopic prurigo (80% of perennial prurigo cases). It occurs most of the time in patients with a past medical history of atopic disorder (AD, asthma, allergic rhinitis). However, 60% of patients with atopic prurigo had no medical history of characteristics skin lesions of AD. Atopic prurigo could thus be considered as a newly recognized clinical form of AD, and is clearly associated with a delayed HDM sensitization. Summer prurigo is the most frequent subtype of childhood chronic prurigo with a recurrent evolution. It is most often associated with delayed hypersensitivity to mosquito bites, best explored by SPT assessed at 48 hours. One can understand that the SPT mimics an insect bite, which the PT does not do. Non-summer prurigo may be related to other environmental factors, such as flea bites or other bugs we were not able to assess.

Unlike chronic prurigo of adults, the association with systemic diseases is exceptional.

Results of SPT and PT emphasize the importance of late readings at 48 hours. A reading at 96 hours is not mandatory because results were similar to 48 hours readings, but remains recommended if at 48 hours the reading is negative or uninterpretable (e.g. "angry back"). Our results showed that sIgE antibodies are not useful in practice, because the majority of the results were not significant in our study (<0.10 KUI/L).

This is also the first study assessing the quality of life of children with prurigo. By showing that the P-VAS and the cDLQI scores are as high as those observed in atopic dermatitis, this study emphasizes the need to study and develop ways to treat these affected children^{7,8}.

Among limitations of our study, allergy investigations were not exhaustive as other biting insects can be involved.

In conclusion we present the first study of chronic prurigo of childhood, a common but neglected disease impacting quality of life. Our major result is that a simple investigation with delayed readings of SPT and patch testing with a limited battery of allergens allows the distinction between allergic (delayed and persistent lesions) and non-allergic (recurrent acute prurigos) forms. We propose a pragmatic classification based on seasonality (see Figure 1). With this classification in mind, the causal agent is more easily identified, unnecessary allergy tests are avoided and specific treatment (such as specific immunotherapy) may be proposed in the future.

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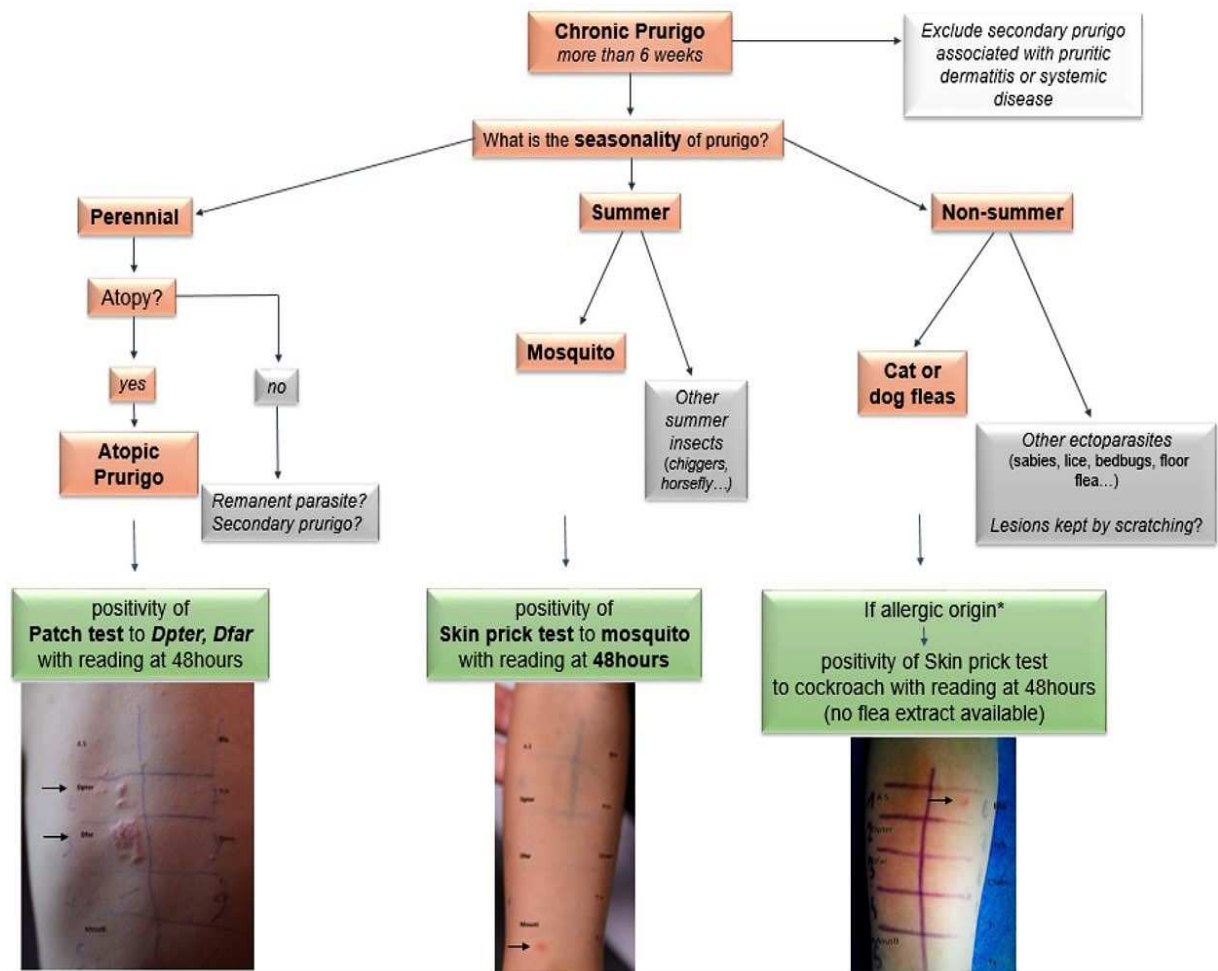
Legend of Figure:**Figure I: Classification of childhood chronic prurigo according the seasonality**

Each subgroup is associated with a sensitization to a dominant allergen, but sometimes non-exclusive. Thus we could propose to explore allergic prurigos with at least skin prick tests to mosquito and cockroach with reading at 48 hours, and patch tests to *Dpter*, *Dfar*.

*allergic origin is suspected if delayed lesions occur several hours after exposition and persist for up to one week. In non-summer prurigo a cross reactivity between cockroach and flea is possible, as suggested by a study performed in dogs⁹. Cockroach extract could also be used as a substitute to flea, since flea antigen is not currently available.

Table I: Main Clinical Characteristics of patients with chronic prurigo

Number of patients	102		
male	58 (57%)		
female	44 (43%)		
Age (years)	mean= 5.9 (+/- 3.6) range= 0.5-16		
2 to 6 included	46 (45%)		
Past medical history			
Atopic dermatitis	30 (29%)		
Allergic rhinitis	18 (18%)		
Asthma	11 (11%)		
Urticaria or dermographism	9 (9%)		
<i>Other</i>			
viral or bacterial infection (<i>including hepatitis B, C, HIV, atypical mycobacteria</i>)	2 (2%)		
metabolic or inflammatory diseases (<i>type 1 diabetes, thyroid, kidney or liver disease, enteropathy...</i>)	2 (2%)		
child psychiatric disease	1 (1%)		
Type of prurigo according to seasonality	Perennial prurigo	Summer prurigo	Non-summer prurigo
	38 (37%)	45 (44%)	19 (19%)
Evolution of prurigo			
permanent prurigo 49 (58%)	33 (87%)	0	16 (84%)
recurrent prurigo 53 (52%)	5 (13%)	45 (100%)	3 (16%)
Age of onset disease (years): mean= 4.1 (+/- 3.2)	3.8 (+/-2.8)	4.2 (+/-4.6)	4.5 (+/-2.5)
Past medical history of atopic dermatitis	17 (45%)	11 (24%)	2 (11%)



Supplemental text file

Methods and Allergy testing

Seven allergens were tested using skin prick tests (SPT) and patch tests (PT) for house dust mites (HDM, namely *Dermatophagoides pteronyssinus* and *farinae*), storage mites (a mix of *Glyciphagus domesticus*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, *Acarus siro*), mosquito, cockroach, cat and dog dander.

SPT were performed on uninvolved skin of the flexural surface of the right forearm with standardized allergen extracts (Stallergènes*) for the seven allergens mentioned above. Histamine phosphate and physiological saline solution were used as positive and negative controls, respectively. The cutaneous response was scored 20 minutes after the challenge and also at 48 and 96 hours. SPT was positive at 20 minutes if the wheal diameter was at least 3mm and superior or equal to the positive control.¹ At 48 and 96 hours a positive response was defined by the presence of a wheal whatever the size, and in the absence of reaction of the controls.

PT were performed on clinically uninvolved back skin with extracts of the aforementioned allergens in petrolatum vehicle (Chemotechnique; Destaing*) and Patch test Chambers (IQ Ultrat Chemotechnique; Destaing*). PT with the vehicle served as negative control. Readings were done at 48 and 96 hours and were considered positive from ++ (i.e., erythema, papules, and/or vesicles) onwards according European Society of Contact Dermatitis Guideline for Diagnostic Patch Testing.²

Blood samples were obtained at enrollment and included eosinophil count (*Laboratory Standards* (LS): 40-700/mm³), total IgE (LS: 0-156 kUI/L) and specific IgE antibodies for *D.pter*, *D.far*, mosquito and cockroach (LS: positive > 0.10kUI / Phadia Thermo Scientific*). Patients were instructed not to take antihistamines, topical corticosteroids and any systemic corticosteroid treatment for at least one week before the tests.³

Data Analysis

Descriptive characteristics were analyzed according to the seasonality of prurigo, a simple way to classify prurigo, possibly linked to its cause and previously described.⁴ Perennial prurigo was defined by permanent or recurrent lesions all year round. Summer prurigo was defined by prurigo occurring during the warm season between May to October in France and between October to May in Reunion and Mauritius. Non-summer prurigo was defined by lesions occurring during a continuous period of less than 12 months and not

exclusively during the previously defined warm season. Basic summary statistics, such as proportions, means and SDs were used to characterize population attributes. Means and SDs were rounded to the upper decimal. Comparisons of qualitative data were made with Fisher test and quantitative data with Student test.

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Legend of supplementary figure

Figure E1 on the Online Repository: Clinical presentations of childhood chronic prurigo

Three clinical pattern defined by the association between the most frequently affected areas (in yellow) and more specifically affected areas (in brown).

Nodules, papular and excoriated lesions on armholes (wrists and ankles) are common in atopic perennial prurigo (a-b). Lesions on the face (c), vesicles and bullous (d) in summer-prurigo due to mosquitoes. Linear lesions suggest bedbugs (e); vesicles grouped on the elastic of sleeve in a non-summer prurigo due to cat flea (f).

Table E1: Clinical and allergologic characteristics of 24 patients without prurigo

Number of patients	24
Gender	
Female	12 (50%)
Male	12 (50%)
Age (years): mean= 6.1 (+/-3.3). range= 1.5-2	
2 to 6 included	9 (38%)
Past medical history	
Atopic dermatitis	8 (33%)
Asthma	4 (17%)
Allergic rhinitis	6 (25%)
Urticaria or dermographism	8 (33%)
Other (<i>Neurofibromatosis type 1</i>)	1 (4%)
Reason for consultation in allergology	
food allergy	6 (25%)
palmar and plantar chronic dermatitis/ contact dermatitis	5 (21%)
atopic dermatitis	5 (21%)
asthma or perennial rhinitis	2 (8%)
aluminium granuloma	1 (4%)
<i>unspecified</i>	5 (21%)

	Skin prick tests		Patch tests
	Day 0 N(%)	48hours N(%)	48hours N(%)
Storage mite	0	0	0
<i>Dpter</i>	2 (8%)	0	5 (21%)
<i>Dfar</i>	2 (8%)	0	4 (17%)
Mosquito	0	1 (4%)	0
Cockroach	0	1 (4%)	2 (8%)
Cat dander	2 (8%)	0	1 (4%)
Dog dander	0	0	0

Table E2: Descriptive characteristics of 56 patients with chronic prurigo

Gender	
Male	33 (59%)
Female	23 (41%)
Age (years): mean= 5.4 (+/-3.2) range= 1-14	
2 to 6 included	27 (48%)
Past medical history	
Atopic dermatitis	13 (23%)
Asthma	10 (18%)
Allergic rhinitis	7 (13%)
Urticaria or dermographism	4 (7%)
<i>Other</i>	
viral or bacterial infection (<i>including hepatitis B, C, HIV, atypical mycobacteria</i>)	1 (2%)
metabolic diseases (<i>type 1 diabetes, thyroid disease, kidney or liver disease, enteropathy ...</i>)	1 (2%)
child psychiatric disease	1 (2%)
Type of prurigo according to seasonality	
perennial prurigo	20 (36%)
summer prurigo	27 (48%)
non-summer prurigo	9 (16%)

Table E3: Results of skin prick tests and patch tests of 56 explored patients with chronic prurigo

PRICK TESTS	Total Prurigo (N=56)			Perennial Prurigo (N=20)			Summer Prurigo (N=27)			Non-summer Prurigo (N=9)		
	Day 0	48hours	96hours*	Day 0	48hours	<i>p</i>	Day 0	48hours	<i>p</i>	Day 0	48hours	<i>p</i>
<i>Dpter</i>	10 (18%)	7 (13%)	6 (11%)	6 (30%)	4 (20%)	0.72	2 (7%)	2 (7%)	1	2 (22%)	1 (11%)	1
<i>Dfar</i>	8 (14%)	3 (5%)	3 (5%)	4 (20%)	3 (15%)	1	2 (7%)	0	0.49	2 (22%)	0	0.47
Mosquito	5 (9%)	27 (48%)	27 (48%)	2 (10%)	8 (40%)	0.06	2 (7%)	14 (52%)	0.007.10⁻¹	1 (11%)	5 (56%)	0.13
Cockroach	2 (4%)	17 (30%)	14 (25%)	1 (5%)	4 (20%)	0.34	1 (4%)	8 (30%)	0.02	0	5 (55%)	0.03

PATCH TESTS	Total Prurigo		Perennial Prurigo	Summer Prurigo	Non-summer Prurigo
	48hours	96hours*	48hours	48hours	48hours
<i>Dpter</i>	23 (41%)	17 (30%)	9 (45%)	10 (37%)	4 (44%)
<i>Dfar</i>	17 (30%)	14 (25%)	8 (40%)	8 (30%)	1 (11%)
Mosquito	8 (14%)	9 (16%)	0	7 (26%)	1 (11%)
Cockroach	7 (13%)	8 (14%)	1 (5%)	4 (15%)	2 (22%)

*results at 96hours in each group were similar than results at 48hours and thus not detailed.

Results of tests with storage mites, cat and dog dander were not shown because no relevant.

Table E4: Eosinophils, total IgE and specific IgE antibodies of 56 patients with chronic prurigo

	Total Prurigo (N= 56)	Perennial Prurigo (N=20)	Summer Prurigo (N=27)	Non- summer Prurigo (N=9)
	mean (SD) min/max values	mean (SD) min/max values	mean (SD) min/max values	mean (SD) min/max values
Eosinophils (/mm3)*	556 (+/- 393) 0-1860	685 (+/- 379) 310-1860	539 (+/- 426) 30-1540	358 (+/- 245) 0-800
total IgE (KU/L) **	901 (+/- 1188) 3-5171	1207 (+/-1276) 3-5171	891 (+/- 1243) 3-4725	281 (+/-478) 29-1534

* laboratory standards: 40-700/mm3

**laboratory standards: 0-156 KUI/L

	Total Prurigo			Perennial Prurigo			Summer Prurigo			Non- summer Prurigo		
	< 0,10 (N(%))***	0,1-100 (N (%))	>100 (N (%))	< 0,10 (N(%))	0,1-100 (N (%))	>100 (N (%))	< 0,10 (N(%))	0,1-100 (N(%))	>100 (N (%))	< 0,10 (N(%))	0,1-100 (N(%))	>100 (N (%))
sIgE Dpter (KU/L)	33 (59%)	19 (34%)	4 (7%)	10 (50%)	8 (40%)	2 (10%)	17 (63%)	9 (33%)	1 (4%)	6 (67%)	2 (22%)	1 (11%)
sIgE Dfar (KU/L)	33 (59%)	22 (39%)	3 (5%)	9 (45%)	11 (55%)	2 (10%)	17 (63%)	10 (37%)	0	7 (78%)	1 (11%)	1 (11%)
sIgE mosquito (KU/L)	41 (73%)	15 (27%)	0	13 (65%)	7 (35%)	0	20 (74%)	7 (26%)	0	8 (89%)	1 (11%)	0
sIgE cockroach (KU/L)	41 (73%)	15 (27%)	0	12 (60%)	8 (40%)	0	21 (78%)	6 (22%)	0	8 (89%)	1 (11%)	0

***sIgE positive > 0,1 KU/L

Perennial prurigo**Summer prurigo****Non-summer prurigo**