

Review Article

Sesquiterpene lactone dermatitis in the young: is atopy a risk factor?

EVY PAULSEN¹, AKSEL OTKJÆR² AND KLAUS E. ANDERSEN¹

¹Department of Dermatology, Odense University Hospital, University of Southern Denmark, DK-5000 Odense C, Denmark, and ²The Skin Clinic, Bredgade 30, DK-7400 Herning, Denmark

Screening for Compositae contact allergy has documented fairly high prevalence in adults, and recent studies indicate that the allergy may be more common in children than previously believed. However, detailed information on sensitization in this age group is sparse. The objective of this study was to present another 2 cases in children and review the literature. Screening with sesquiterpene lactone (SL) mix has shown prevalence of 0.5% and 1.8% in 2 studies, while screening with 2 different Compositae mixes detected 4.2% and 2.6% positives among children and adolescents. All individual case reports describe sensitization in atopic children, and the largest screening study showed a prevalence of Compositae mix sensitization that was significantly higher in children with atopic dermatitis compared with non-atopics. Compositae sensitization should be considered in children with a family or personal history of atopy, summer-related, or -exacerbated dermatitis of any kind, and a history of plant exposure. Screening with SL mix is recommended but should be supplemented with plant extracts based on exposure history. Compositae weeds, especially dandelions, seem to be important sensitizers in children.

Key words: adolescents; children; Compositae mix 5% pet.; Compositae mix 6% pet.; contact dermatitis; dandelion; patch testing; plants; SL mix. © Blackwell Munksgaard, 2008.

Accepted for publication 30 November 2007

Traditionally, Compositae dermatitis is claimed to spare children (1–3). This notion seems to be based on some of the original clinical studies on ragweed dermatitis in North America, Parthenium dermatitis in India, and Australian bush dermatitis, all of which were mainly observed in adult males (4–6).

Screening studies for Compositae allergy have shown fairly high prevalences of sensitization in the past decades, even in younger age groups (7–11), but the number of case reports on true sesquiterpene lactone (SL) dermatitis in children and adolescents is sparse: only 1 case from the USA and 2 from Europe (12–14). The striking common feature of these children is that they are atopics. Based on our results with Compositae screening from 1990, we here report some additional cases in the young and review the literature.

Case Report 1

In May 2002, a 13-year-old girl was referred to our department for light testing and possibly photo-

patch testing. She had a personal history of atopic dermatitis (AD) from infancy but never any mucosal symptoms. In May 1992, when the patient was 3 years old, she was seen by a dermatologist because of a widespread, excoriated dermatitis of the face, trunk, flexures, and hands. She was treated with topical corticosteroids and antibiotics, and after at least one relapse in June, the dermatitis, which was considered to be AD, disappeared completely by August 1992. In the following years, the eczema recurred in April, typically involving shins, popliteal areas, elbows, volar and dorsal aspects of forearms, and back of the hands as well as the face and lasting for the early part of the summer. When the patient was 5 years old, she was seen by another dermatologist who suspected that she suffered from polymorphic light eruption.

In April 2002, she was seen by a third dermatologist who prescribed topical corticosteroids and from June cyclosporin 100 mg daily, which proved to be very effective in controlling the eczema. Patch testing prior to referral showed

positive reactions to colophonium, nickel sulfate, and cobalt chloride. The patient had noticed that the dermatitis appeared concurrently with her use of T-shirts with short sleeves and short skirts, whereas sun exposure did not seem to be an aggravating factor.

Table 1 shows the results of patch and photopatch testing in October 2003 after cyclosporin had been discontinued for 9 months using Finn Chambers® (Epitest Ltd, Helsinki, Finland) on Scanpor® (Scanpor Alpha AS, Oslo, Norway). Readings were made on D3 according to the guidelines of the International Contact Dermatitis Research Group (15).

The 2+ reaction to cobalt chloride was of unknown relevance, while the strongly positive Compositae reactions were considered to be of both current and old relevance. The patient had always liked playing in the garden, and she used to make wreaths of dandelions and daisies (*Bellis perennis*) as well as fresh and dried bouquets of Compositae weeds.

The minimal erythema doses for ultraviolet (UV)A and UVB were within normal limits. Prick tests with standard inhalant allergens, latex, and *Pityrosporum ovale* showed positive reactions to birch, grass, and mugwort pollen.

Table 1. Distribution of positive patch test reactions to standard and Compositae allergens in 2 Compositae-sensitive children (D3 readings unless otherwise stated)

Allergen	Case 1	Case 2
Potassium dichromate	++	–
Sesquiterpene lactone mix 0.1% pet.*	++	++
Alantolactone 0.1% pet.	–	–
Costunolide 0.1% pet.	++	++
Dehydrocostus lactone 0.033% pet.	+	++
Isoalantolactone 0.1% pet.	NT	–
Parthenolide 0.1% pet.	++	++
Compositae mix 6% pet.†	++	++
Arnica 0.5% pet. (<i>Arnica montana</i>)	NT	–
German chamomile 2.5% pet. (<i>Chamomilla recutita</i>)	NT	++
Yarrow 1% pet. (<i>Achillea millefolium</i>)	NT	++
Tansy 1% pet. (<i>Tanacetum vulgare</i>)	NT	++
Feverfew 1% pet. (<i>T. parthenium</i>)	NT	++
Chrysanthemum 3% pet. (<i>Dendranthema indicum</i> hybrid)	NT	++
Marguerite daisy 3% pet. (<i>Argyranthemum frutescens</i>)	NT	++
Stinking mayweed 1% pet. (<i>Anthemis cotula</i>)	NT	++
Dandelion 2.5% pet. (<i>Taraxacum officinale</i>)	++ at D7	++
Scentless mayweed 10% pet. (<i>Tripleurospermum inodorum</i>)	NT	–
Lettuce oleoresin 1:10 w:v alcohol (<i>Lactuca sativa</i>)	NT	+

pet., petrolatum; NT, not tested.

*Consisting of alantolactone 0.033%, costunolide 0.033%, and dehydrocostus lactone 0.033%.

†Consisting of short ether extracts of arnica (*A. montana*) 0.5%, German chamomile (*C. recutita*) 2.5%, yarrow (*A. millefolium*) 1%, tansy (*T. parthenium*) 1%, and feverfew (*T. parthenium*) 1%.

In the summer of 2004, the patient's Compositae dermatitis was well controlled by avoidance of contact with Compositae plants combined with use of topical corticosteroids.

Case Report 2

A 10-year-old boy was referred for further testing in August 2004 after being diagnosed with Compositae contact allergy. He had a strong family history of atopy: his maternal grandmother had 'eczema', while his mother and 2 brothers had or had had AD. His child-minder had noticed a tendency to hand eczema in the patient from 1999. He had no symptoms of hay fever or asthma.

In 2001 or 2002, the patient developed a severe vesicular hand eczema lasting from May to September and involving the volar aspects of hands and fingers, mainly on the right side. In the following years, the eczema recurred every spring, sometimes also spreading to feet, knee, and the periorbital area. Treatment with potent topical corticosteroids, antibiotics, and potassium permanganate soaks were of limited value, and the complete clearing of the eczema in winter, observed in the beginning, was later replaced by winter-related improvement without disappearance of the hand eczema. Thus, at the first examination in our clinic in November 2004, the patient presented with erythema of both palms and dried-up dyshidrotic vesicles on the right side.

The patient lived in a small town, and the family's garden adjoined the countryside. He was not interested in plants but was engaged in outdoor activities such as mowing lawns, helping out with firewood, and riding on his bicycle. Occasionally, he picked dandelions for his cousin's pet rabbit.

The patient had been patch tested with the European baseline series prior to referral, and the SL mix was the only positive (2+) reaction. Table 1 shows the results of additional testing with Compositae test materials at our department.

Prick tests with the standard inhalant allergens supplemented with latex, *P. ovale*, pollens of German chamomile (*Chamomilla recutita*), and *Dahlia* (Soluprick®; ALK-Abello A/S, Hørsholm, Denmark) showed positive reactions to grass pollen and *Cladosporium* of unknown relevance.

In view of the clinical features, photosensitivity was considered unlikely and accordingly, the boy was not light or photopatch tested.

On the basis of the strongly positive reactions to several weeds, the patient was advised to stop mowing lawns and wear gloves for other outdoor activities. Ingestion of lettuce was not considered an exacerbating factor, according to the medical history.

However, the patient still has severe summer-exacerbated hand eczema, and it was necessary to treat him with systemic corticosteroids in the summer of 2007. The fact that the patient spends much more time in a rural area, including working in a cowshed after school, was considered a contributory factor to his recalcitrant hand eczema.

Discussion

The fact that 25 000 Indian students from schools and colleges participated in the famous 'Destroy Parthenium' campaign in 1974 without developing Parthenium dermatitis apparently supported the view of age-dependent sensitization (16). However, none was patch tested.

The first large-scale study on Compositae sensitization in both adults and children was the 4-year report on screening with the SL mix in London: Ross et al. (8) patch tested 7420 patients, 135 of whom were SL mix positive. Only 5 of these were 20 years or younger, the youngest being 13 years old (8). Likewise, Wakelin et al. detected only one SL mix-positive child after testing 187 children (0.5%) from January 1992 to August 1996 (14). Contrary to these relatively low prevalences are the findings of Heine et al. who reported on screening with the Compositae mix 6% petrolatum (pet.) (Trolab, Reinbek, Germany) in a German multicentre study: among 285 children (6–12 years old) and 2175 adolescents (13–18 years old) tested between 1995 and 2002, 4.2% and 3.1% tested positive, respectively (10). This prevalence is slightly lower than the one detected in adults in the same study (4.6%), but on a par with a previously reported prevalence of 3.1% when performing routine patch testing with the Compositae mix 6% pet. (7). However, it is well known that the advantageous detection rate of the Compositae mix 6% pet. carries a risk of false-positive reactions or even active sensitization compared with that of the SL mix (17, 18). Hausen, in his study on the German Compositae mix, saw no cases of sensitization, probably because of the fact that the mix was applied to the back for 1 D only (19). In the German multicentre study, 29 of 40 centres applied the patch test materials for 2 D, which may have caused false-positive reactions to the Compositae mix as pointed out by the authors (10). Furthermore, positive reactions to the fragrance mix occurred in about 6% of children and adolescents, and some of the reactions may reflect cross-reactivity between fragrance terpenes and Compositae plant extracts (20) rather than true Compositae sensitization.

In principle, the higher frequency of positives to Compositae mix compared with SL mix may be

because of (1) a higher content of SLs in the former or (2) its content of allergens of non-lactone origin, or (3) false-positive reactions. The relative contribution of each of these possibilities has not been clarified. However, because short ether plant extracts contain SLs as well as polyacetylenes/thiopenes and because each individual extract of the Compositae mix may elicit strongly positive reactions on its own, it is hardly surprising that testing with this mixture of allergens in a fairly high concentration means that we obtain more reactions of unknown relevance (9). Whether the amount of SLs in the Compositae mix exceeds that of the SL mix is not known, but the diversity of SLs is higher in the Compositae mix, probably making this mix a better screening agent for SL allergy than the SL mix. Furthermore, some of the reactions of unknown relevance may reflect cross-reactivity rather than false-positive reactions (9, 20).

The German Compositae mix was discontinued in 2006, but another Compositae mix 5% pet. (Chemotechnique, Malmö, Sweden) is still commercially available. In contrast to the German Compositae mix, the latter contains the SL parthenolide instead of an extract of feverfew (*Tanacetum parthenium*) and an extract of Roman chamomile (*Chamomilla romana* = *Chamaemelum nobile*) instead of an extract of German chamomile (*C. recutita*). Belloni Fortina et al. used the Compositae mix 5% pet. in their paediatric screening series and found positive reactions in 17 of 641 (2.6%) consecutive children and adolescents (11). 12 of these were considered relevant, and even if some of the above-mentioned reservations concerning 2 D application of plant extracts to the skin may apply to this study too, especially in view of the many (41%) positive reactions to cocamidopropyl betaine, the summer exacerbation, lack of fragrance contact allergy, and clinical features suggest genuine Compositae sensitization.

The SL mix was included in our standard series in 1990 and the SL parthenolide 0.1% pet. in 1995. In the period from January 1995 to December 2006, 281 children and adolescents younger than 17 years old were patch tested with both substances, and 5 tested positive to either 1 or both. However, in 2 patients, the reactions were considered to be because of cross-reactions to the primary sensitizer *p*-phenylenediamine (21). The third patient had a 1+ reaction to SL mix on D3 of unknown relevance, but she also had a doubtful positive reaction to *p*-phenylenediamine. The overall prevalence of SL mix positivity (1.8%) may reflect the prevalence in the latest European multicentre study (1.0%) (22) taking the number of patients into consideration, but it is lower than

the prevalence of 2.8% among adults in our area (9). For comparison, the Compositae mix 6% pet. was included in our standard series from October 1998 to March 2001, and on the basis of computerized data, 72 patients under the age of 17 years were tested. Among these, 2 (2.78%) were weakly positive (1+) on D3 and doubtfully positive on D7, while 11 tested doubtfully positive. The relevance was unknown in the 2 children with positive reactions, although a 1+ reaction to balsam of Peru in 1 of them may have caused cross-reactivity to the Compositae mix. A strongly positive reaction to the SL mix in a child is more convincing evidence of Compositae sensitization than a positive reaction to a plant extract and of course a prerequisite for diagnosing a true SL dermatitis. However, in both previous and present case reports, the children tested positive to an array of Compositae extracts, including dandelion (*Taraxacum officinale*) (12, 14). This plant is considered a weak and rare sensitizer (23) and, even when used for aimed patch testing, elicits positive reactions in only 25.5% of patients tested (24). The 2+ reactions seen in the children [(12, 14) and Table 1] are therefore remarkable but probably reflect a higher degree of direct exposure compared with that of adults who handle the plant like a weed rather than like a flower using gloves and tools when removing it. Likewise, Belloni Fortina et al. mention that some of their children experienced exacerbations in their dermatitis after picking dandelions (11). As pointed out by Lovell and Rowan (25), only 2 of 7 dandelion-sensitive subjects tested positive to the SL mix; therefore, testing with selected plant extracts, based on exposure history, is necessary when suspecting Compositae dermatitis in a child.

Even if children with AD are more sensitive to skin irritants, which is probably reflected in the results of the Italian study (11), the strongly positive reactions to the other Compositae extracts in the Danish and British children (14) are considered to be because of their SL allergy, evidenced by their 2+ reactions to the SL mix that is so rarely seen in children.

The clinical features in the 4 detailed case reports (Table 2) are less distinctive, but they have one feature in common: they all had hand eczema,

and 3 of 4 had volar involvement. It is difficult although to establish whether the hand eczema in itself is a risk factor for the development of subsequent Compositae allergy or is caused by Compositae sensitization. However, both children presented here had summer-related eczema from the beginning, indicating a causal relation to the Compositae sensitization. Dyshidrotic eczema is not mentioned in the cases from the USA and UK, but the boy in case 2 was clinically diagnosed with this rare type of hand eczema. Apparently, his direct plant contact was much less than that of the girl in case 1 who had exposed skin pattern with involvement of the thin skin on the backs of the hands rather than the palms. This is the pattern typically seen in florists and gardeners (26). The boy had no other contact allergies, and one possibility is that he had a genuine dyshidrotic eczema – which is often worse in summer, and at least in previous studies, related to atopy – with a secondary Compositae sensitization. Another possibility is that his eczema was provoked by inhalation or ingestion of ubiquitous Compositae allergens in the rural environment.

In the Italian study, the authors state that most of their patients had an airborne contact dermatitis pattern with exacerbations in late spring or summer (11). Thus, even though it may be difficult to distinguish AD from Compositae dermatitis, there seems to be 2 main patterns: volar hand eczema with more or less widespread dermatitis and an airborne pattern involving exposed skin of face, extremities, and the backs of the hands. Both patterns are summer-related or -exacerbated. However, localized eczema of hands or face was also observed by Belloni Fortina et al., indicating that the variability of clinical features in Compositae dermatitis, well known among adults, may also be found in children (11, 27).

Clayton et al. pointed out that the localization of the primary eczema could not be used to predict which children would develop positive patch test results (28). They concluded that any child with persistent eczema should be patch tested, and we would like to change that statement to 'persistent or recurrent' (28).

Another common clinical feature is a personal history of atopy. Mitchell in his review on

Table 2. Distribution of Compositae dermatitis in detailed case reports

Case	Sex/age in years	Face/neck	Hand eczema	Palms	Arms	Feet	Legs	Flexural eczema
Guin and Skidmore (12)	M/9	X	X	X	X*			X*
Wakelin et al. (14)	M/7		X	X	X			X
Case report 1	F/13	X	X		X	X	X	X
Case report 2	M/10	X	X	X		X	X	

*Only involvement of antecubital areas.

Compositae dermatitis from 1969 quoted 3 studies that reported an apparent association of ragweed oil dermatitis and AD (4). Guin, in a later review, stated that it was 'most unusual' to see Compositae dermatitis in persons with atopic disease, although Compositae dermatitis might mimic AD (2). However, Warshaw and Zug in their thorough 1996 survey quoted 6 studies with atopy prevalences of 17–38% (3). This percentage may be even higher in children. In the German multicentre study of contact allergy in children and adolescents, Heine et al. reported the prevalence of AD to be 37.5% in children ($n = 285$) and 36% in adolescents ($n = 2175$) compared with 7.8% in adults ($n = 7408$) (10). However, details on the prevalence of AD in children with positive patch test reactions to Compositae mix 6% pet., which ranked no.10 among the top 10 list of contact allergies in this age group, were not reported (10). In the Italian study, 12 of the 17 children who tested positive to Compositae mix 5% pet. had AD and the sensitization was significantly higher than that in children without AD (11). The relevance of the Compositae allergy was current or past in 8 of these 12 children (11). 14 of the 17 children had other contact allergies, and although, as mentioned previously, some of these reactions, especially to cocamidopropyl betaine and Compositae mix, might be because of irritancy, they may also reflect a propensity to development of contact sensitization because of genetic or constitutional factors. Whether the prevalence of allergic contact dermatitis in patients with AD is similar to that in non-atopics is not clarified, but in 2 of the detailed case reports, the patients were sensitized to Compositae only, and in the third (12), the boy had one additional contact allergy, namely to common ivy (*Hedera helix*).

The 2 Danish children and the British boy (14) featured both plant protein and hapten sensitization – in case report 1, both caused by members of the Compositae family. This concurrent sensitization may be purely coincidental – positive prick tests to standard inhalant allergens is after all one way of defining atopy – or, as suggested by Heine et al. (10), the positive Compositae reactions may be caused by a localized immunoglobulin E-mediated eczema in persons with a type I sensitization from Compositae.

Another interesting feature is the age distribution: in the case reported by Guin and Skidmore (12), the boy was 2 or 3 years old when his dermatitis first appeared, while the girl in our case report 1 had symptoms from the age of 3–4 years. In the case reported by Wakelin et al. (14), the 7-year-old boy had had 'long-standing' hand eczema, and the boy of case report 2 likewise

had had hand eczema from the age of 5 years. Belloni Fortina et al. detected Compositae sensitization in 9 children aged 5 years or younger, the 2 youngest being 2 years old (11). Thus, Compositae sensitization may occur in even small children.

In conclusion, both screening studies and individual case reports support that a history of personal atopy in children seems to be a risk factor for developing a contact sensitization to Compositae. The allergy should be suspected in even small children with a personal or family history of atopy and summer-related or -exacerbated dermatitis of any kind as well as a history of plant exposure. Screening with the SL mix is safe but should be supplemented with ether extracts based on the individual exposure history. Compositae weeds, and especially dandelions, seem to be important sensitizers in this age group.

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Address:
Evy Paulsen
Department of Dermatology
Odense University Hospital
University of Southern Denmark
Sdr. Boulevard 29
DK-5000 Odense C
Denmark
Tel: + 45 6541 2705
Fax: + 45 6612 3819
e-mail: evy.paulsen@ouh.regionsyddanmark.dk