

Patch Testing with the Swedish Baseline Series in Two Countries

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Abstract

Patch testing is a very effective mean to investigate causes of allergic contact dermatitis (ACD), but results obtained in different countries is usually hard to compare due to reading of patch tests. The aim of the study was to examine the prevalence of contact allergy to substances present in the Swedish baseline series and to compare results between the clinics in Vilnius and Sweden when the patch test procedure is similar in both countries.

Consecutive patients with suspected ACD were tested with the Swedish baseline series at the university hospitals in Malmö, Sweden, and Vilnius, Lithuania in the years 2010–2012.

Positive patch test reactions to at least one allergen was observed in 115 (53.7%) in Lithuania and in 237 (55.4%) in Sweden. The top 5 most frequent allergens (and respective prevalence rates) in Lithuania were as follows: nickel sulphate (25.7%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (10.3%), cobalt chloride (7.5%), potassium dichromate (6.1%), formaldehyde (6.1%). The most prevalent positive patch tests reactions in Sweden were to nickel sulphate (18.9%), cobalt chloride (6.3%), *M. pereirae* resin (5.6%), MCI/MI (4.9%), Amerchol L 101 (4%). Statistically relevant differences were seen in sensitization to preservatives (3.7% in Lithuania and 1.8% in Sweden, $p < 0.001$) and metals (13.1% in Lithuania and 9.3% in Sweden, $p < 0.03$).

In conclusion, this multicenter study provides some information on the prevalence of contact allergy to the most common contact allergens in two countries, although it is not possible to establish if the different prevalence was due to the difference in atopic background or allergen exposure. This should be further investigated.

Keywords: Patch testing; Contact allergy

Introduction

Patch testing is a complex but very effective mean to establish contact allergy although the diagnosis of allergic contact dermatitis comes from the combination of patch-test results (which allow to identify contact allergy) and clinical data (which helps the clinician to establish if a positive patch test reaction is relevant for the diagnosis). However, different countries and centers usually have their own patch test traditions despite the efforts to standardize the procedure by international societies (e.g., the European Society of Contact Dermatitis). This makes it difficult to compare results obtained in different countries [1].

In the present article, we summarize and discuss the results obtained with the Swedish baseline series in testing consecutive dermatitis patients in the department of Occupational and Environmental Dermatology, Malmö, Sweden, and in the Allergy Center, Vilnius, Lithuania in the years 2010–2012. One of the authors had spent some time in the clinic in Malmö and was taught how to perform patch testing and reading. After returning to her clinic in Lithuania she used her skills and the Swedish baseline series to patch test consecutive dermatitis patients in order to compare results with the clinic in Malmö.

Methods

Patients

Demographic data are displayed according to MOAHLFAP (male, occupational, atopic, hand, leg, foot, age > 40 years, percent positive) guidelines [2,3].

For every Lithuanian case two controls were selected from the database of all dermatitis patients patch tested with in Malmö department between January 2010 and June 2012 with the Swedish baseline series. Matching was done by sex and age. All patients both in Vilnius and Malmö were Caucasians.

Patch testing

Allergens were provided by Chemotechnique Diagnostics (Vellinge, Sweden). The same batch was used in both clinics. Two additional allergens not present in the Swedish baseline series at that time were also tested, i.e. a textile dye mix (TDM 3.2% w/w) composed of 8 disperse dyes [4] and gold sodium thiosulphate [5]. TDM is already inserted into the Swedish (as well as into the European) baseline series since 2015 [6]. The patch test results for these additional allergens will be presented elsewhere. Finn Chambers® (Ø8 mm, Epitest Ltd, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Venne, Norway) were used for patch testing. 15 µl of test solution was applied with a micropipette to the filter paper discs in the chambers or 20 mg

of test preparation in petrolatum to each test chamber [7,8]. The chambers were left on the back for 48 hrs and the readings were performed on day (D) 3 or 4 and D7 by a dermatologist (in Malmö) or allergologist (in Vilnius), trained to perform patch testing. This allergologist was responsible for performing all the tests and reading the results from the patients in Lithuania in this study.

The patch test reactions were scored according to the guidelines of the International Contact Dermatitis Research Group [9]. For the present analysis, the maximal patch test reaction from either D3/D4 or D7 was considered as the outcome. The results of the first reading could be different according to the selected day. Reactions + to +++ were classified as positive, and negative, irritant and doubtful reactions as non-positive.

Statistical analysis

The Fisher's exact test was used and we regarded $p < 0.05$ as statistically significant. Sensitization frequencies are given directly as age- and sex-matched prevalence, accompanied by a 95% confidence interval (CI). Data analysis was performed by using IBM SPSS Statistics version 20 package. No alpha adjustment had been employed in the exploratory statistical analysis.

Results

Patient characteristics

The demographics of the patch-tested patients are summarized in Table 1. The most common body locations of dermatitis were hands (47%), face (26%), legs (26%), scattered/generalized pattern (13%) in Sweden and face (55.6%), hands (28.5%) and legs (15.9%) in Lithuania.

Of the 214 patients tested, 115 (53.7%) had at least 1 positive reaction in Lithuania and of the 428 patients tested, 237 (55.4%) in Sweden.

Allergen frequencies

The top 10 most frequent allergens (and respective prevalence rates) in Lithuania were as follows: nickel sulphate (25.7%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI)

(10.3%), cobalt chloride (7.5%), potassium dichromate (6.1%), formaldehyde (6.1%), fragrance mix I (5.7%), *Myroxylon pereirae* resin (4.7%), colophony (4.7%), p-phenylenediamine (4.2%), and Quaternium-15 (2.3%).

The most prevalent positive patch tests reactions in Sweden were to nickel sulphate (18.9%), cobalt (6.3%), *Myroxylon pereirae* resin (5.6%), MI/MCI (4.9%), Amerchol L 101 (4%), fragrance mix II 3.9%), colophony 3.3%, fragrance mix I (3.3%), thiuram mix (2.9%), and potassium dichromate (2.8%).

Characteristic	n (%)	
	Lithuania	Sweden
Male*	26 (12.1)	47 (11.0)
Occupational	0 (0)	210 (57.7%)
Atopic dermatitis	155 (72.4)	119 (27.8)
Hand	61 (28.5)	203 (47.4)
Leg	34 (15.9)	23 (5.4)
Face	119 (55.6)	113 (26.4)
Age>40 years*	84 (39.3)	167 (39.0)
Positivity rate (≥ 1 positive reaction)	115 (53.7)	237 (55.4)

*patients were age- and sex-matched

Table 1: MOAHLFAP characteristics of the two tested populations in Lithuania and Sweden.

Prevalence rates for allergens in Lithuania as compared to Sweden

As shown in Table 2, the positive allergic reaction rates significantly differ for 3 allergens: formaldehyde, Amerchol L 101 and MCI/MI. When grouping allergens, it is visible that in the Lithuanian center, the prevalence of contact allergy to metals (nickel, potassium dichromate and cobalt) and preservatives is higher than in the Swedish center (Table 3).

Patch test allergen	Lithuania			Sweden			p-value
	N	Positive reaction n, (%)	95% CI	N	Positive reaction n, (%)	95% CI	
Potassium dichromate 0.5% pet	214	13 (6.1%)	2.8-9.2	428	12 (2.8%)	1.4-4.6	0.052
p-Phenylenediamine 1.0% pet	214	9 (4.2%)	1.4-6.6	428	10 (2.3%)	0.7-3.3	0.21
Thiuram mix 1.0% pet	214	1 (0.5%)	0-2.3	428	12 (2.8%)	1.4-4.6	0.07
Neomycine sulphate 20.0% pet	214	4 (1.9%)	0.1-3.9	428	1 (0.2%)	0.1-1.9	0.052
Cobalt (II) chloride hexahydrate 0.5% pet	214	16 (7.5%)	4.4-11.6	428	27 (6.3%)	3.8-8.3	0.62
Quaternium-15 1.0% pet	214	5 (2.3%)	0.1-3.9	428	3 (0.7%)	0.1-1.9	0.12
Nickel (II) sulphate hexahydrate 5.0 % pet	214	55 (25.7%)	20.1-31.2	428	81 (18.9%)	15.3-22.7	0.052
Quinoline mix 6.0% pet	214	2 (0.9%)	0-2.3	428	0	-	0.1
Colophonium 20.0% pet	214	10 (4.7%)	2.1-7.9	428	14 (3.3%)	1.4-4.6	0.38

Paraben mix 16.0% pet	214	2 (1.0%)	02.3	428	1 (0.2%)	0.1-1.9	0.26
Black rubber mix 0.6% pet	214	3 (1.4%)	0-2.3	428	2 (0.5%)	0.1-1.9	0.34
Sesquiterpene lactone mix 0.1% pet	214	1 (0.5%)	0-2.3	428	3 (0.7%)	0.1-1.9	1
Mercapto mix 2.0% pet	214	1 (0.5%)	0-2.3	428	3 (0.7%)	0.1-1.9	1
Epoxy resin 1.0% pet	214	3 (1.4%)	0-2.3	428	4 (0.9%)	0.1-1.9	1
Myroxylon pereirae resin 25.0% pet	214	10 (4.7%)	2.1-7.9	428	24 (5.6%)	3.8-8.3	0.7
4-tert-Butylphenol formaldehyde resin 1.0% pet	214	2 (0.9%)	0-2.3	428	6 (1.4%)	0.1-1.9	0.7
Fragrance mix II 14.0% pet	214	4 (1.9%)	0.1-3.9	427	17 (3.9%)	2.1-5.9	0.24
Formaldehyde 1.0% aq.	213	13 (6.1%)	2.8-9.2	428	9 (2.1%)	0.7-3.3	0.01
Fragrance mix I 14.0% pet.	213	12 (5.7%)	2.8-9.2	427	14 (3.3%)	1.4-4.6	0.2
Phenolformaldehyde resin 1.0% pet	214	1 (0.5%)	0 – 2.3	414	6 (1.4%)	0.1-1.9	0.43
Diazolidinyl urea 2.0% aq.	214	4 (1.9%)	0.1-3.9	428	6 (1.4%)	0.1-1.9	0.74
Methylchloroisothiazolinone/ Methylisothiazolinone 0.02% aq.	214	22 (10.3%)	5.9-14.0	428	21 (4.9%)	2.9-7.1	0.01
Amerchol L-101 50.0% pet	214	0		428	17 (4.0%)	2.1-5.9	0.001
Caine mix II 10.0% pet	214	1 (0.5%)	0-2.3	428	4 (0.9%)	0.11.9	0.67
Lichen acid mix 0.3% pet	214	2 (0.9%)	0-2.3	428	3 (0.7%)	0.1-1.9	1
Tixocortol-21-pivalate 0.1% pet	214	1 (0.5%)	0-2.3	428	7 (1.6%)	0.7-3.3	0.28
Toluensulfonamide formaldehyde resin 10.0% pet	214	2 (0.9%)	0-2.3	428	0	-	0.11
Budesonide 0.01% pet	214	2 (0.9%)	0-2.3	428	2 (0.5%)	0.1-1.9	0.6
Methylidibromo glutaronitrile 0.5% pet	214	2 (0.9%)	0-2.3	428	8 (1.9%)	0.7-3.3	0.51
H 5.0% pet.	214	3 (1.4%)	0-2.3	394	5 (1.3%)	0.1-1.9	1

N: Number tested to specific allergen; n- number of positive patients

Table 2: Frequencies of positive reactions to the Swedish baseline series as age- and sex-matched percentage with 95% confidence intervals for proportions and p values for the differences between Lithuania and Sweden.

Allergen group	Lithuania	Sweden	p value
	% (Positive test reactions/total tests)	% (Positive test reactions/total tests)	
Preservatives	3.7 (48/1283)	1.8 (45/2568)	0.0003
Metals	13.1 (84/642)	9.3 (120/1284)	0.029
Fragrances	3.2 (41/1283)	3.0 (77/2532)	0.84
Corticosteroids	0.7 (3/428)	1.1 (9/856)	0.76
Rubber chemicals	1.6 (14/856)	1.6 (27/1712)	1

Table 3: Rates and differences of positive patch tests to common contact allergens in the Lithuanian and Swedish centers.

Regarding contact allergy to preservatives (Table 4), those with atopic dermatitis were positive more frequently to formaldehyde and formaldehyde-releasers (F/FR) and to MCI/MI in Lithuania than in

Sweden, and in both centers more atopic patients were positive to both MCI/MI and F/FR.

Regarding nickel allergy, 26.9% women with atopic dermatitis were positive to nickel in Lithuania versus 17.5% in Sweden. For those without atopic dermatitis, the figure is 47.1% nickel allergy for women in Lithuania versus 21.9% in Sweden.

		Positive patch test reactions (No)						Total positive to F/FR and/or MCI/MI
		F/FR*		MCI/MI*		Both**		
Atopic dermatitis (+)	Lithuania n 155	19	<i>P</i> =0.01	21	<i>P</i> =0.04	5	<i>P</i> =0.06	40
	Sweden n 119	4		6		10		10
Atopic dermatitis (-) ^a	Lithuania N 59	3		1		1		14
	Sweden n 305	14	15	2		29		

F/FR: Formaldehyde/formaldehyde releasers (Quaternium-15, diazolidinyurea); MCI/MI, and methylchloroisothiazolinone/methylisothiazolinone; ^asolely positive to F/FR or MCI/MI, respectively; **positive to both F/FR and MCI/MI; *p*>0.05, when comparing Sweden and Lithuania

Table 4: Contact allergy to the preservatives of interest among patients with atopic dermatitis in Lithuania and Sweden.

Discussion

The present descriptive analysis of contact allergy prevalence's in patients patch tested for suspected allergic contact dermatitis in two countries was performed attempting to reduce the impact of inter-departmental variation in patient characteristics and the potential for variation in defining positive reactions. The standardized readings in multicenter studies is of utmost importance when comparing results and getting valid comparisons. There are several prerequisites that should be fulfilled when performing a multicenter study to guarantee the highest quality. The patch test system should be the same, the patch test substances should be the same and from the same batch, application of volatile sensitizers to test chambers should be done just before application to the back off the tested person, defined doses should be used, the same occlusion time and reading times should be used, control of adhesiveness of the test system to the test area after 48 hours should be done, the same classification system for reading should be adopted, calibration of reading patch tests should be performed [10]. Therefore, according to the proposed quality ranking of multicenter patch test studies, the total score of the current study justifies a ranking equivalent to that of an excellent quality.

The patients have been matched for age and sex in this analysis, following guidelines [2,3]. The patient characteristics according to the MOAHLFAP index differed in some aspects between centers. High proportion of occupational dermatitis and hand dermatitis in Malmö could be explained by the specialization of the department in occupational dermatology. In the Lithuanian center patients with facial dermatitis and atopic dermatitis are over-represented. This could be related to the different traditions in referring patients. In Lithuania as in the most Eastern European countries atopic dermatitis is considered to be mainly an allergic disease (both by patients and clinicians). Thus, almost all patients diagnosed with atopic dermatitis are referred firstly to allergologists and later to dermatologists. In Scandinavia and most Western European countries atopic dermatitis is diagnosed and treated mostly by dermatologists. That is partly confirmed by the study performed in dermatological clinic in Lithuania, where atopic dermatitis prevalence among patch-tested patients was 17% [11].

While comparing prevalence rates, two allergen groups differed on a statistically significant level between the centers, namely metals and preservatives. Patch test results from testing nickel, cobalt and chromate showed higher frequencies in Lithuania, although these differences did not reach a statistically significant level. Concerning nickel allergy, one plausible explanation could be a different exposure. The Nickel Directive in Lithuania is adopted since 2003, while a kind of restriction in nickel exposure has been present in Sweden already since 1991 [12,13] when nickel-containing piercers or rings were banned if the alloy contained more than 0.05% nickel. Another explanation could be that atopic dermatitis patients become more easily sensitized to metals, especially nickel [14]. Some studies have shown that patients with atopic dermatitis are more likely than non-atopic patients to acquire and manifest contact allergy [15,16]. However, in our study there was no difference in nickel allergy between those with atopic dermatitis and those without in Sweden (17.5% versus 21.9%) and even more women without atopic dermatitis were sensitized to nickel (47.1% vs 26.9%) in Lithuania.

Concerning chromate, there has been a legislation in Sweden since 1983 regulating the level of hexavalent chromate in cement, thus reducing the exposure to this allergenic salt, but in Lithuania this regulation did not come into force until 2003, when a similar legislation was adopted in the EU.

Regarding contact allergy to preservatives in Lithuania there was a statistically significant difference compared to Sweden. Interestingly, Lithuanian patients allergic to F/FR and MI/MCI were mostly atopics, while in Sweden these were without atopic dermatitis. Among those patients who were positive to all preservatives, most of them had atopic dermatitis. There was an overrepresentation of atopic dermatitis patients and face dermatitis patients in the Lithuanian center. Thus, one may speculate that exposure through cosmetics and emollients containing these preservatives are more common in this patient population. Whether atopics are more likely than non-atopics to react to F/FR is unclear. A study of pathologists who were frequently exposed to formaldehyde showed no tendency for atopic pathologists to be more sensitive to formaldehyde than non-atopic pathologists, but on the other hand, one study found formaldehyde

exposure associated with an increased prevalence of atopic eczema [17,18]. Moreover, some studies have shown that there is no significant difference in prevalence of allergic reactions to F/FR between atopic dermatitis populations and non-atopic populations [17].

There was no statistically significant difference with respect to positive reactions to parabens in our study. This supports past studies that found parabens to be relatively non-sensitizing preservatives, even in the atopic population [15].

Contact allergy to lanolin (Amerchol L 101) was significantly more common in Sweden than in Lithuania. This is hard to explain as patients were matched according to their age, and reading standards were the same (readings were also performed on D7), and leg dermatitis was not more prevalent in the Swedish patients.

Some allergens such as *Myroxylon pereirae* resin, colophony, hydroxyisohexyl 3-cyclohexene carboxaldehyde, or budesonide yielded very similar contact allergy frequencies in spite of differences in tested populations (e.g., more occupational dermatitis cases in Sweden and more atopic dermatitis patients in Lithuania). When comparing the Lithuanian results of this study with the dermatology clinic in Lithuania, where data from consecutively patch-tested dermatitis patients were reported [11], significantly lower rates of positive reactions were found to metals, F/FR and MCI/MI and higher rates of positive reactions to fragrances, *Myroxylon pereirae* resin, colophony, MDBGN, paraben mix and lanolin in the dermatology clinic. For MCI/MI a lower concentration tested (dose mg/cm²) may be one explanation [19].

It has been stated that the contact allergy prevalence in consecutively tested patients should normally exceed 0.5–1% for an allergen to be eligible for inclusion in the baseline series [20]. From this background Amerchol L 101 could be removed from the Lithuanian baseline series, and toluensulfonamide formaldehyde resin and quinoline mix could be removed from the Swedish baseline series, but low frequency of positive patch test reactions may simply reflect the relatively small number of tested patients included in the study or be related to the low concentration of the actual allergen in the patch test preparations due to degradation.

The work presents a limit that albeit the Lithuanian author has been trained in Sweden, the inter-operator bias remains.

Conclusion

This multicenter study provides some information on the prevalence of contact allergy to the most common contact allergens in two countries. Methodological differences, which may contribute to between-center variations, were minimized. In view of an apparently higher prevalence of atopic dermatitis and higher proportion of sensitization to F/FR and MI/MCI in Lithuanian center it could be speculated that atopic dermatitis patients are more likely to become sensitized to some preservatives (MI/MCI and F/FR), although it is not possible to establish if the different prevalence was due to the difference in atopic background or allergen exposure. This should be further investigated.

Conflicts of Interest

The authors declare no conflict of interests.

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References

1. Bruze M (1990) What is a relevant contact allergy? Contact Dermatitis 23: 224-225.
2. Uter W, Schnuch A, Gefeller O; ESCD working group: European Surveillance System on Contact Allergies (2004) Guidelines for the descriptive presentation and statistical analysis of contact allergy data. Contact Dermatitis 51: 47-56.
3. Uter W, Schwitulla J, Thyssen JP, Frosch PJ, Statham B, et al. (2011) The 'overall yield' with the baseline series - a useful addition to the array of MOAHLFA factors describing departmental characteristics of patch tested patients. Contact Dermatitis 65: 322-328.
4. Ryberg K, Isaksson M, Gruvberger B, Hindsén M, Zimerson E, et al. (2006) Contact allergy to textile dyes in southern Sweden. Contact Dermatitis 54: 313-321.
5. Möller H, Svensson A, Björkner B, Bruze M, Lindroth Y, et al. (1997) Contact allergy to gold and gold therapy in patients with rheumatoid arthritis. Acta Derm Venereol 77: 370-373.
6. Isaksson M, Ryberg K, Goossens A, Bruze M (2015) Recommendation to include a textile dye mix in the European baseline series. Contact Dermatitis 73: 15-20.
7. Bruze M, Isaksson M, Gruvberger B, Frick-Engfeldt M (2010) Recommendation of appropriate amounts of petrolatum preparation to be applied at patch testing. Contact Dermatitis 2010: 63: 284-288.
8. Frick-Engfeldt M, Gruvberger B, Isaksson M, Hauksson I, Pontén A, et al. (2010) Comparison of three different techniques for application of water solutions to Finn Chambers®. Contact Dermatitis 63: 284-288.
9. Fregert S (1981) Patch testing. In: Manual of Contact Dermatitis (2nd edn.) Munksgaard, Copenhagen, pp. 71-81.
10. Svedman C, Isaksson M, Björk J, Mowitz M, Bruze M (2012) 'Calibration' of our patch test reading technique is necessary. Contact Dermatitis 66: 180-187.
11. Beliauskienė A, Valiukeviciene S, Uter W, Schnuch A (2011) The European baseline series in Lithuania: results of patch testing in consecutive adult patients. J Eur Acad Dermatol Venereol 25: 59-63.
12. General advice regarding ear piercing. National Board of Health and Welfare, Sweden. SOSFS 1989, June 27.
13. Lietuvos higienos norma HN36:2002. Draudžiamos ir ribojamos medžiagos. Lietuvos Respublikos sveikatos apsaugos ministro 2002 05 27 isakymas Nr. 239.
14. Malajian D, Belsito DV (2013) Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis. J Am Acad Dermatol 69: 232-237.
15. Shaughnessy CN, Malajian D2, Belsito DV3 (2014) Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis: reactivity to topical preservatives. J Am Acad Dermatol 70: 102-107.
16. Gittler JK, Krueger JG, Guttman-Yassky E (2013) Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. J Allergy Clin Immunol 131: 300-313.
17. Matsunaga I, Miyake Y, Yoshida T, Miyamoto S, Ohya Y, et al. (2008) Ambient formaldehyde levels and allergic disorders among Japanese pregnant women: baseline data from the Osaka maternal and child health study. Ann Epidemiol 18: 78-84.
18. Sasseville D (2004) Hypersensitivity to preservatives. Dermatol Ther 17: 251-263.
19. Bruze M, Goossens A, Isaksson M (2014) Recommendation to increase the test concentration of methylchloroisothiazolinone/methylisothiazolinone in the European baseline patch test series - on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. Contact Dermatitis 71: 35-40.

20. Bruze M, Condé-Salazar L, Goossens A, Kanerva L, White IR (1999) Thoughts on sensitizers in a standard patch test series. *The European Society of Contact Dermatitis. Contact Dermatitis* 41: 241-250.