

Variability in patch test reactions – first report from the Norwegian Patch Test Registry*

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Background: A nation-wide Norwegian Patch Test Registry (NOLAR) was established in 2005 as a collaboration between six dermatology departments. International, multi-centre studies have documented great variability in the frequency of positive patch test reactions, considered as mainly due to heterogeneity of test populations.

Objectives: To analyse the variability of positive test reactions by studying patch tests performed at the six collaborating departments, using standardized procedures.

Materials and methods: Data from all patch tests ($n = 2089$) performed in 2007–2008 as registered in the NOLAR program. Differences between centres were analysed using Exact Pearson χ^2 test.

Results: Between the centres, positive test reactions (+, ++, or +++) varied significantly for 8 of the 26 allergens in the European Baseline Series. When considering strong reactions (++ or +++) only, the differences were statistically significant for six of these allergens, i.e. cobalt chloride, potassium dichromate, *p*-phenylenediamine, formaldehyde, paraben mix, and mercaptobenzothiazole.

Conclusion: The results indicate regional differences in the prevalence of sensitization to certain allergens within the Norwegian population, although inter-observer differences cannot be ruled out as a factor.

Key words: allergic contact dermatitis; European Baseline Series; quality control; variability. © John Wiley & Sons A/S, 2010.

Conflict of interests: The authors have declared no conflicts.

Accepted for publication 16 January 2010

The Norwegian Patch Test Registry (in Norwegian: *Norsk lappetestregister*; NOLAR) was established in 2005 to monitor patch test reactions and allergen sensitization in the Norwegian population. All university departments of dermatology in Norway, covering every health region in the country, participate in the program.

Reports from the European Surveillance System of Contact Allergies (ESSCA) have shown large variations in the proportion of positive reactions

in patch testing (1–3). This high between-centre variability has been explained by possible differences in study populations, standard series definition, test indications, and interpretation of study results, as well as weak reproducibility.

With relative homogenous populations, low-selection bias and standardized procedures, the NOLAR registry should be well suited to explore the variability in patch test reactions. In this article, the first from the NOLAR collaboration, we report the proportion of positive patch test results and sensitization using graded reactions and discuss possible explanation for differences between centres.

*All authors have participated sufficiently to take public responsibility for appropriate portions of the work.

Materials and Methods

All European baseline series patch tests performed at the departments of dermatology in Oslo (i.e. Rikshospitalet and Ullevål University Hospital), Stavanger, Bergen, Trondheim, and Tromsø between 1 January 2007 and 31 December 2008 were included. In September 2007, the two departments in Oslo were merged to one department.

All centres reported the results of the European baseline series patch tests as defined in early 2007, which included 26 allergens (Chemotechnique Diagnostics®, Vellinge, Sweden). Test substances were applied in Finn Chambers® (Epitest Ltd Oy, Tuusula, Finland) on Scanpor® tape (Alpharma AS, Oslo, Norway). Data registration was performed through an internet-based Access (MICROSOFT®) database. Information on sex, age, diagnosis, test results after 3 days with graded reactions, and the doctor's assessment of positive test results being relevant or not relevant, was recorded. We used a modified ESSCA reading scale with grading defined as: negative = no erythema or erythema without infiltration; + = erythema with infiltration (homogenous or spotty); ++ = erythema, infiltration, and vesicles; and +++ = erythema, infiltration, and vesiculo-bullous reaction.

Statistics

Differences between centres were tested using Exact Pearson χ^2 test and, in case of insufficient memory, using a Monte Carlo simulation of the exact *P*-value. A difference was considered statistically significant if *P* < 0.05. The statistical analyses were performed using Statistical Package for the Social Sciences (SPSS 16.0, SPSS Inc, Chicago, Illinois, USA).

Results

During the 2-year registration period, 2089 test results were recorded (Table 1). Missing data ranged from 2% (sex) to 53.6% (clinical relevance). All centres had missing data, but two centres had more than the other four.

Data on sex were available in 2047 tests (98%), of which 1278 tests (62.4%) were on women. Data on age were available in 1733 tests (83%), with mean age of tested persons being 43.4 years; 44.0 years in women and 42.4 years in men. Diagnosis was recorded in 1301 tests (62.3%), with hand eczema (*n* = 494; 38.0%) and dermatitis of the face (*n* = 184; 14.1%) being the most frequent diagnoses. The probability of a positive test was highest in patients with dermatitis of the face, with 56% of the tests being positive. Dermatitis of the face was more prevalent among women; other diagnoses were equally distributed among men and women (data not shown). Dermatitis of the shins was more prevalent in the older age groups; mean age being 61.1 years.

In total, 1045 tests (50.0%) had positive reactions to at least one allergen, ranging from 39.3% to 57.9% among the six centres. There was no association between the number of tests performed and the proportion of tests with at least one positive reaction. Two hundred and eighty-eight tests (27.6%) were positive to four or more allergens, and 113 tests (10.8%) were positive to five or more allergens. Nickel sulfate, cobalt chloride, fragrance mix I, potassium dichromate, and *Myroxylon pereirae* resin (balsam of Peru) had the highest proportion of positive test results, both overall (Table 2) and among patients with hand eczema or dermatitis of the face (data not shown).

The difference in proportion of positive results between the six centres was statistically significant for 8 of the 26 allergens (Table 3). When considering strong positive reactions (++ or +++) only, the difference was statistically significant for cobalt chloride, potassium dichromate, *p*-phenylenediamine, formaldehyde, paraben mix, and mercaptobenzothiazole.

Nickel tests were positive in 440 tests (21.1%). The highest proportion of nickel contact allergy was found in Tromsø (25.7%). More women than men had nickel allergy (29.2% versus 10.0%; *P* < 0.001). Stratification according to the quartiles of the age distribution showed differences in the proportion of patients with nickel allergy, but were statistically significant (*P* = 0.018) only for women (24.6%

Table 1. Patch testing at six participating dermatology hospital departments in the NOLAR programme in 2007–2008

	Population size in geographical region	Number of patch tests (%)	Tests with at least one positive reaction
Oslo (Rikshospitalet)	1 600 000	453 (21.7)	239 (52.8%)
Oslo (Ullevål)	1 000 000	135 (6.5)	66 (48.9%)
Bergen	700 000	308 (14.7)	121 (39.3%)
Trondheim	700 000	290 (13.9)	134 (46.2%)
Tromsø	300 000	140 (6.7)	81 (57.9%)
Stavanger	300 000	763 (36.5)	405 (53.1%)
Total		2089 (100)	

Table 2. Proportion of 2089 patch tests in six dermatology departments in Norway in 2007–2008 being positive for the 26 allergens in the European Baseline Series patch tests (+, ++, or ++++)

	Total (range)
Nickel sulfate	21.1 (16.6–25.7)
Cobalt chloride	12.5 (3.7–25.0)
Fragrance mix I	9.1 (5.8–12.2)
Potassium dichromate	7.7 (3.6–14.3)
<i>Myroxylon pereira</i> (balsam of Peru)	5.7 (2.1–7.6)
Colophonium	3.9 (2.2–4.9)
<i>p</i> -Phenylenediamine	3.2 (0.6–5.2)
Formaldehyde	3.1 (0.3–5.9)
Methyldibromo glutaronitrile	2.6 (1.0–3.8)
Thiuram mix	2.0 (0.0–3.4)
Methylchlorisothiazolinone (and) methylisothiazolinone	2.0 (0.7–3.1)
Quaternium-15	1.9 (0.7–3.7)
Neomycin sulfate	1.4 (0.6–2.9)
Clioquinol	1.4 (0.0–2.0)
Epoxy resin	1.4 (0.0–2.1)
Budesonide	1.4 (0.9–4.3)
Paraben mix	1.2 (0.0–5.0)
Tixocortol-21-pivalate	1.2 (0.0–3.0)
Sesquiterpene lactone mix	1.1 (0.0–2.0)
N-isopropyl-N-phenyl-paraphenylenediamine (IPPD)	1.0 (0.0–1.7)
4- <i>tert</i> -Butylphenol formaldehyde resin	0.9 (0.6–2.2)
Benzocaine	0.7 (0.0–1.1)
Lanolin alcohols	0.5 (0.0–0.9)
2-Mercaptobenzothiazole	0.5 (0.0–2.1)
Primin	0.4 (0.0–0.6)
Mercapto mix	0.3 (0.0–0.7)

for <28 years; 34.5% for 28–41 years; 32.7% for 42–56 years; and 25.1% for >57 years).

Discussion

In this report from six departments of dermatology covering all health regions in Norway for the period 2007–2008, the proportion of patch tests with at least one positive reaction was somewhat

higher than reported in other European multi-centre studies. The proportion of positive test results varied between centres. Sensitization to specific allergens showed a similar variability, even when considering strong reactions only.

The overall proportion of patch tests with at least one positive result was higher than that reported by ESSCA (2, 3). This is probably because of a stricter indication for patch testing among Norwegian dermatologists. We find it unlikely that a higher proportion of the Norwegian population has contact allergy than other European populations. One centre, i.e. in Stavanger, performed about one-third of all the patch tests despite serving a modest part of the general population in the country. This centre covers a region with no other patch test services. The proportion of tests with at least one positive reaction in this centre was close to the average for all six departments, indicating a similar practice regarding patch test indications. In the ESSCA reports, between-centres variability is partly explained by the heterogeneity of the populations served by participating centres. Our populations are probably more homogenous, and consequently other explanations should be considered.

Patch test techniques and interpretation were standardized during the study period. Nevertheless, inter-observer differences could be a source for between-centre variation. An unpublished survey among our dermatology residents on how to evaluate patch test results indicated a need for improved instruction on patch test evaluation, especially on the interpretation of weak positive reactions. Also, conflicting interpretation of test results being relevant or not underlined a need for improved quality control and improvement. We have planned further initiatives to improve the quality of patch test readings among our dermatologists.

However, to elucidate whether the variability could be explained by inconsistent interpretations of weak reactions, we re-analysed the data on substances that differed significantly between centres,

Table 3. Allergens showing statistically significant between-centre differences in the proportion of patch tests being positive

	Proportion being positive (+, ++, or ++++)		Proportion being strongly positive (++ or ++++)	
	% (range)	<i>P</i> -values	% (range)	<i>P</i> -values
Cobalt chloride	12.5 (3.7–25.0)	<0.001	6.1 (3.0–17.9)	<0.001*
Fragrance mix I	9.1 (5.8–12.2)	0.009	5.5 (2.9–7.1)	0.390
Potassium dichromate	7.7 (3.8–14.3)	0.001	3.5 (0.7–10.0)	<0.001
<i>Myroxylon pereira</i> (balsam of Peru)	5.7 (2.1–7.6)	0.024	2.7 (0.7–4.4)	0.108
<i>p</i> -Phenylenediamine	3.2 (0.7–5.2)	0.039	2.3 (0.3–5.3)	0.026
Formaldehyde	3.1 (0.3–5.9)	0.002	1.7 (0.3–5.2)	0.018
Paraben mix	1.2 (0–5.0)	<0.001	0.43 (0–4.3)	<0.001
Mercaptobenzothiazole	0.5 (0–2.1)	0.004	0.53 (0–2.1)	0.009

*Using a Monte Carlo simulation of the exact *P*-value.

now using proportions of strong reactions only. The differences between centres persisted for six out of eight substances (although one calculation was based on few observations), indicating a real difference in the prevalence of sensitization in patients in different parts of the country.

Another possible factor explaining variability is the time interval between testing and reading. Evaluating test reactions after 2 days only may lead to false negative results, as shown in other studies (4, 5). Evaluating test reactions on 2 consecutive days, as is often recommended, is impractical for most out-patients. Others recommend the morphological reaction after 3 days as the standard outcome in single reading of patch test reactions (6), as used in this study. Reactions to certain allergens, such as *p*-phenylenediamine, neomycin, bacitracin, corticosteroids, and blue disperse dyes, may develop even later (7). Only *p*-phenylenediamine had a statistically significant difference in the proportion of patients with positive reactions.

Tests performed with allergens from different commercial suppliers may show different results (8). In our study, every centre used allergens from the same supplier. Low reproducibility of test reactions may be another factor (9), even when the production of test substances is standardized. All the participating centres in our study perform patch testing regularly, storage procedures are standardized, and test substances are stored for a limited time to ensure the quality of the allergens.

The proportion of patch tests that were positive to at least four substances was rather high. We did not explore whether these tests included allergens with known cross-reactivity or if they could be the result of an angry back reaction.

Nickel was the most common contact allergen, as in many other patch test studies (2, 10, 11). In a recent ESSCA report, Gentofte in Denmark had the lowest proportion of nickel positive reactions among the 31 European participating centres in 2004 (9.7%) (2). This was explained by a conservative reading of doubtful or weak reactions and a long-standing and efficient nickel regulation in Denmark. In an earlier ESSCA report from 2002 to 2003 (3), Gentofte was the centre reporting the lowest proportion of patients being positive to at least one allergen, indicating a conservative reading of test reactions or liberal indication for testing. For comparison of single allergens to be meaningful, some kind of adjustment for proportion of positive patients is necessary. Denmark passed legislation in 1990 to reduce nickel release from consumer products, resulting in lower levels of nickel sensitization in younger age groups (12). Similar European Union legislation from 1994 was implemented in Norway in 1997. In our study, the proportion of positive

reactions to nickel was lower in the youngest age group than among the middle aged, especially in women, but the point-prevalence study design does not permit any conclusion whether the new nickel legislation has had any effect in Norway.

In Tromsø, situated in Northern Norway, one out of four patients was nickel positive, one out of four was cobalt positive, and one out of seven was chromate positive. A high prevalence of nickel sensitization in the general population of Northern Norway has previously been shown by Dotterud and Smith-Sivertsen (13). This was partly explained by more common use of ear piercing in Northern Norway, although the extent of ear piercing in different regions of Norway is unknown. The prevalence of cobalt and chromate sensitization in the same population was 2.8% and 0.8%, respectively (13). Similar prevalence of chromate sensitization has been found in Denmark (14). It has been suggested that cobalt sensitization requires both dermatitis and co-sensitization to nickel (15). The high level of cobalt sensitization could consequently be secondary to the level of nickel sensitization. Chromate allergy is usually a result of occupational exposure, including leatherwork, construction work with wet cement, and machine operation or repair. In Norway, for many years ferrous sulfate has been added to cement to reduce chromate to the trivalent state. However, data on occupational exposure to potential allergens were not included in our study.

Our reading scale was a modification of the one recommended by ESSCA, but used in several reports. As a result of a high proportion of missing data, we decided not to analyse data on clinical relevance in our report.

In this report, we have described the proportion of positive patch test reactions in patients tested at all six university departments of dermatology in Norway in 2007–2008 and discussed possible explanations for the variability of patch test reactions. Our results indicate that there may be differences in the prevalence of sensitization to certain allergens in different geographical regions of Norway, although inter-observer differences cannot be ruled out as a factor. This will be explored further by improving patch test readings and data registration and by including more data in the NOLAR database.

Acknowledgements

We thank Endre Madsbu for technical assistance and the NOLAR nurses Bente Torvund and Elin Wennberg for filling in test results.

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