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Latex allergy in healthcare workers: prevalence and characteristics in Ghent University Hospital

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Abstract: *Objective:* Much research has already been conducted on the consequences of an allergy to latex in patients. Our study will focus on the consequences for healthcare workers and describe characteristics at Ghent University Hospital.
Background: Healthcare workers remain at risk of developing an allergy due to their exposureto latex since surgical latex gloves became widely spread in the '80s as protection against emerging infectious diseases.
Methods: After approval of the internal Ethics Committee (B.U.N.: B67Q202000Q690 – September 15 2020 – Ethics Committee of Ghent University Hospital and Ghent University) an e-survey was sent out among healthcare workers of Ghent University Hospital. The survey consisted of 21 multiple-choice questions and was available for one month, from October 22nd 2020 to November 18th 2020. Data collection was done via SurveyMonkey and statistical analysis through SPSS Software version 26.
Results: 112 respondents answered the survey. 7.9% of respondents reported being latex allergic, 5.0% responded that they were possibly. 10.7% reacted allergically after contact with latex-containing materials and 14.3% had a food allergy, all specified known to be have a crossallergy to latex. In general, cutaneous symptoms were dominant. 8.7% adjusted their professional activities, 6.5% limited their activities and 2.2% had to make a career change due to their allergy. 82.6% continued their latex-exposured environment without any adjustment.
Discussion and Conclusion: With 7.9% of healthcare workers at Ghent University Hospital proclaiming to be allergic to latex, our survey approaches prevalence rates among healthcare workers as described in the literature. Primary prevention of latex sensitization remains paramount and should happen through education and avoidance of unnecessary use of latex- containing materials. The exclusion of powdered gloves and the introduction of low-protein gloves have reduced the number of de novo sensitization. Additional research on the feasibility of being 'latex-safe' within this hospital should be done.

Keywords: Latex hypersensitivity; health personnel; surveys and questionnaires.

Introduction

History and context

Latex is the milky substance extracted from the rubber tree, Hevea Brasiliensis. The product is an emulsion of natural rubber (polymer of isoprene) in water and 1-2% protein. More than 240 polypeptides have been identified, 15 of which are officially recognized as latex allergens (1). Latex is one of the main raw materials in modern industry and has a wide range of uses in the medical world. It is used for surgical gloves, certain catheters, blood pressure cuffs, rubber bottle tops and many dental materials may also contain latex. A more comprehensive list has been compiled by the Premier Safety Institute (2). Around 1980, the use of protective latex gloves increased dramatically due to an increased awareness and need for protection against infectious diseases, particularly HIV and Hepatitis C. This translated into a series of preventive measures established by the Centers for Disease Control and Prevention (CDC) in 1987 (3). Secondary to the increased use of surgical gloves, latex allergy became an important and widespread phenomenon among healthcare workers.

Ebo et al. (4) analyzed, over a span of 17 years, data of patients referred with a suspected perioperative hypersensitivity reaction. Although the proportion of latex as a suspect agent decreased from 25% (2001-2011) to 18% (2001-2018), it remained the most common perioperative trigger,

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after neuromuscular blockers. Similar data from Dong et al (5) from a French multi-center survey, where latex also ranked second with 20%; This contrasts with the British NAP6 study, where no latex-induced anaphylaxis was reported (6).

Although the peak of the epidemic seems to be behind us in industrial countries, latex remains a prominent etiological agent in allergic reactions in healthcare. That healthcare workers have an increased risk of sensitization and of developing an allergy to latex due to their increased exposure has only been confirmed in recent literature. The reason for this is mainly to be found in the high degree of heterogeneity between the studies and insufficient uniformity in diagnostic criteria and tools. Also regional differences seem to exist; Prevalence rates vary widely from 3.3% in Japan, 13.6% in Jordan, 0.9%-17% in Europe, 0.7% in Canada, 2.9-30% in the United States, 4% in Mexico, 17.3% in Argentina and 6-8% in Brazil (7).

A recent systematic review by Bousquet et al. (8) put the prevalence rates at 4.32% and 1.37% for healthcare providers versus the general population, respectively. A 2016 review by Wu et al (9) of studies, published in the past 5 years, found a prevalence rate of 9.7% in healthcare providers and 4.3% in the general population.

Sensitization to latex - pathways

Sensitization to latex may occur via various pathways.

Direct exposure to latex through the skin is an important pathway to sensitization. In particular, when the natural barrier of the skin is already damaged, e.g. by irritant contact with cornstarch or pre-existing contact dermatitis; This appears to facilitate sensitization to latex (10).

A second important pathway occurs via contact with aerosolized latex particles. These particles spread into the room when surgical gloves are put on and taken off. The cornstarch, used as a lubricant, binds the latex particles and promotes this process. Inhalation of these particles can thus lead to sensitization via the respiratory tract.

A cross-allergy or secondary allergy of latex to certain fruits is known. Kiwi, banana, avocado, potato and chestnut have the strongest association and many other – mainly tropical – fruits have been described. Latex IgE antibodies, which bind to structurally similar epitopes of fruit species that are phylogenetically related, are responsible for this cross-reactivity. 30-50% of individuals with an allergy to latex have an associated hypersensitivity to one or more of these fruits. This is described as the "Latex-Fruit Syndrome" (11).

An entirely different entity of allergic cross-reactivity is the Oral Allergy Syndrome (OAS). OAS is also an IgE-mediated immune response and includes cross-reactivity of pollen with certain vegetables, fruits and legumes. Clinically, this is usually expressed as orobuccal symptoms such as itching and swelling around the mouth, but anaphylaxis cannot be ruled out. Cross-reactivity between latex allergy and OAS has been reported rarely, but should be considered as separate entities (12).

Types of latex reactions

The clinical presentation of a reaction to latex varies widely.

Irritant contact dermatitis is a non-allergic reaction, which is mainly caused by friction or maceration of the skin, secondary to wearing powdered gloves or insufficient drying of the hands after washing/disinfecting.

It also occurs due to an irritant reaction to certain chemicals such as cornstarch, detergents or the use of alkaline gloves. Characteristics of irritant contact dermatitis are dry, cracked and red skin. Itching is also possible. Skin affected by irritant contact dermatitis is more prone to eczematization and possibly to develop an allergic reaction to latex. Two types are distinguished:

— *Delayed-type hypersensitivity reaction type IV* ; a T-cell mediated reaction, mostly to added chemicals in the production process.
— *Immediate-type hypersensitivity reaction type I* ; An IgE-mediated reaction to latex allergens.

Delayed-type (type IV) hypersensitivity reaction at the level of the skin causes a so-called *allergic contact dermatitis*. This hypersensitivity reaction typically has a delayed course with the onset of symptoms 24-48h after exposure. This process is a *T-cell mediated* immune response. Although the symptoms can be disabling, they are usually limited to local redness, pruritus and the development of small vesicles or blisters on the affected skin, the development of systemic symptoms cannot be excluded. Such immune responses usually occur to added components in the production process of latex, antioxidants or accelerators of the vulcanization process, such as thiurams, carbamates and benzothiazoles. Type IV hypersensitivity reactions to latex allergens has been described but is usually rather rare (13).

Immediate-type (type I) hypersensitivity reaction differs from the previously mentioned in both clinical presentation and underlying immunological process (13). Symptoms occur within seconds to minutes of contact with the agent.

The immune response is *IgE-mediated* and exposure in sensitized individuals leads to mast cell degranulation with release of mediators such as histamine. Antibodies are being produced to one or more of the latex allergens. The clinical presentation is variable and can affect multiple organ systems, ranging from (generalized) contact urticaria, pruritus, angioedema (skin and mucosa), asthma, dyspnea, bronchospasm and rhinoconjunctivitis (respiratory) to fulminant anaphylaxis with cardio-respiratory arrest.

Type 1 and type IV hypersensitivity reactions are not mutually exclusive and can thus occur simultaneously (10).

The "allergic potential" of latex gloves

Natural rubber latex (NRL) consists of more than 240 polypeptides, of which the International Union of Immunological Societies (IUIS) have officially recognized 13, Hev b1 until Hev 13, as latex allergens (1). Of these allergens, Hev b1, Hev b3 and Hev b7 have the strongest link to patients with spina bifida; Hev b2, Hev b5, Hev b6.01 and Hev b13 are linked to latex allergy in healthcare workers (14).

Several studies have shown a correlation between the amount of extractable proteins in latex gloves and the risk of allergic reaction or sensitization. Although the total amount of extractable proteins is not a measure of the amount of latex allergens since it does not distinguish between allergens and non-allergens, selection based on a low concentration of extractable proteins is thought to reduce de novo sensitization to latex (15). As no scientific threshold in exposure to latex allergens with regard to the risk of sensitization can be determined, no safe lower limit can be drawn for their use. Thus, the "as low as reasonably practicable" (ASARP) principle is applied. This implies that the term hypoallergenic has no clinical value and may lead to a false sense of security for people who are already sensitized (15). The European Commission has established a guideline for the use of latex-containing medical materials in 2004, as well as some European quality standards for medical gloves:

EN 455-1: porosity, breach detection

EN 455-2: resistance to externally applied force

EN 455-3: protein titration, which consists of determining the total amount of proteins (micrograms/gram glove).

Diagnosis of latex allergy

The diagnostic tools for an IgE-mediated allergic response to latex are cutaneous prick tests or the detection of NRL-specific IgE in the serum. Prick tests are considered 1st line detection due to the high sensitivity of the test and are inexpensive to perform. Several commercial extracts are available and although they may differ in sensitivity and specificity, comparative studies are lacking. However, only one commercial extract is available in Belgium.

Serological testing for Natural Rubber Latex (NRL) IgE is done via immunoassays, in particular ELISA and RAST. Several commercial detection techniques, e.g. alaSTAT, autoCAP, are available with similar results regarding sensitivity and specificity. The emphasis of these tests is mainly on their high specificity. The lower sensitivity, which is around 70%, makesserological testing less applicable as a screening method. The reason for this lower sensitivity may be the absence or already established denaturation of certain latex allergens, such as Hev b5, which are not picked up by NRL IgE antibodies (16).

The role of in vivo provocation testing seems to be mainly reserved for individuals with both a negative prick test and a negative serological test but with a clinical picture strongly suggestive of latex allergy. Despite the high sensitivity and specificity of this type of test, its use is ratherlimited and should be considered individually. The safety of the patient is the main concern and the risk assessment should be taken into account (16).

Consequences for healthcare workers

Due to their professional activities, healthcare workers frequently come into contact with latex-containing materials, and although this is not exclusively occupational, we observe a higher incidence of latex sensitization and allergy among this group. Healthcare workers are exposed to latex in different ways: direct skin contact, exposure of the respiratory system through inhalation of aerosolized latex particles bound to the coating of surgical gloves.

Furthermore, the manufacturing process of surgical gloves, in which the glove is coated with cornstarch, provides an ideal breeding ground for bacteria. Although the bacteria themselves are

destroyed during the sterilization process, endotoxic cell wall lipopolysaccharides from gram-negative bacteria can cause dermatitis of the hands, which facilitates sensitization to latex (17).

A second important risk factor for the development of latex hypersensitivity is atopy. Healthcare workers with atopy develop significantly more latex hypersensitization than colleagues who are not (17).

Finally, a concomitant allergy to certain fruits (cfr. supra) is also a risk factor because of structurally similar epitopes with certain latex allergy and therefore risk of cross allergy.

Measures

Latex allergy remains an important medical and professional problem among healthcare workers. Healthcare workers sensitized to latex are three times more likely to leave their jobs than non-sensitized colleagues (18). Primary prevention of sensitization and reduction of exposure to latex continue to play a primary role in the fight against latex allergy. Latex allergy education remains one of the most effective ways to reduce allergy-related symptoms in the workplace (19). The Medical Devices Agency (MDA) in the United Kingdom have set out a number of priorities in their policy advice; education of healthcare workers, provision of alternative materials and monitoring of reactions following contact with latex-containing materials (20).

Substitution of powdered latex gloves by powder-free gloves, non-NRL gloves or both have been shown to significantly reduce the airborne load of latex particles and even bring it below the detection limit (21).

A prospective study by Kelly et al. (18) analyzed and evaluated the exposure and sensitization to latex of 805 healthcare workers. The intervention consisted of replacing all powdered latex gloves with a non-powdered latex alternative and avoiding latex gloves in those already foundto be sensitized. As a result of the intervention, the number of new-onset sensitization was reduced by a factor of 16. In addition, several healthcare workers with a previously positive prick test tested negative after the intervention. Although the number of new-onset sensitization was significantly reduced, the intervention could not be reduced to zero due to continued exposure to latex material. Aerosolized latex particles thus appear to be an important medium for sensitization.

Finally, the role of immunotherapy for latex allergy is not yet clear due to a highly variable success rate within the published studies. This therapy also carries a risk of severe allergic reactions such as anaphylaxis (22).

Methodology

This study was conducted by means of an e-survey. The design of the survey was aimed at healthcare providers, particularly doctors, nurses, dentists and midwives. Our intention was tocreate a sample frame that was representative for healthcare workers.

Initially, a broad audience of Belgian doctors and nurses was addressed; unfortunately, the Order of Physicians could not comply with the request to distribute the survey among its members due to GDPR legislation. The General Union of Nurses of Belgium (AUVB) was contacted at various times but did not respond to our correspondence. Thus, it was decided to focus on the care providers of the institute where the research was conducted, being the Ghent University Hospital. Permission was obtained from the internal Ethics Committee as well as from hospital management. The survey was distributed to the hospital staff through the hospital management's internal mailing list.

The study was conducted in accordance with Good Clinical Practice (ICH/GCP) guidelines and the most recent version of the Declaration of Helsinki, drawn up to protect clinical trial participants. All participants were informed about the principal investigator and the purpose of the study. MonkeySurvey, online cloud-based software for survey development, served as the hosting website and was used in an initial data analysis. Participation in the study was entirelyvoluntary and not associated with any (financial) benefits or costs. The time frame for data collection was one month, from 22 October 2020 to 18 November 2020.

The duration of the survey was estimated to be about 8 minutes for 21 multiple-choice questions. Only completed questionnaires were used for analysis. Statistical analysis was carried out using SPSS software, version 26, via Athena UGent. Concerning the time in the operating theatre in relation to latex allergy, due to the non-parametric responses and 3 (>2) unpaired samples, the Kruskal-Wallis test was chosen to support the hypothesis. For the time in the operating theatre in relation to an allergic reaction to latex-containing material, the Mann- Whitney test was used because of two unpaired samples. The relationship with age of the respondent was performed similarly, with additional use of the Mann-Whitney test for a relationship with

food allergy. For all statistical analysis, a p-value less than 0.05 was considered significant.

Results

112 respondents completed the survey. All participants (100%) gave informed consent for participation in the study as this was a requirement.

The profile was as follows: 69 (61.6%) were physicians, 37 (33.0%) were nurses, 2 (1.8%) midwives, 3 (2.68%) dentist, 1 person was retired (0.9%) and worked on a voluntary basis but his profession was not known. Among the physicians, 11 (16%) had a surgical specialization, 9 (13%) had a mixed medical/surgical specialization, 17 (25%) were anesthesiologists, 4 (6%) emergency doctors, 18 (26%) had an internist specialization, 6 (9%) pediatricians, 1 (1%) anatomical pathologist, 1 (1%) radiologist and for 2 (3%) the specialization was not known.

9 respondents were excluded from the analysis of nurse specialists because they belonged to a different professional category. Amongst the nurses, 4% were instrumentalists, 4% worked atthe PAZA, 6% in a health care department, 4% with Vlaamse Kruis, 4% in mental health care, 44% had an administrative function as head or deputy head nurse and for 16% of the respondents, the specialization was not known.

Of the 112 respondents, 36 (32%) indicated that they worked in the operating theatre. Among them, 6 (17%) worked less than 10 hours per week in the operating theatre, 9 (25%) between 10 and 20 hours per week, 10 (28%) persons worked 20 to 40 hours per week, 4 (11%) between 40 and 60 hours per week and finally 7 (19%) indicated that they worked 60 hours or more perweek in the operating theatre.

The number of years of exposure to the working environment and consequently to latex has a wide distribution in the study population. 59 (52.7%) respondents were female, 33 (29.5) respondents were male. Data on gender were missing for 20 (17.9%) persons. The different age categories were all represented. 7.9% of the respondents said they were allergic to latex, 5.0%said they might be and the remaining 87.1% were not allergic to latex. The persons who indicated to be allergic to latex had the following complaints; 1 (7.1%) person reported developing cardiovascular symptoms, in particular anaphylactic shock, arrhythmias, hypotension or cardiorespiratory arrest. 3 (21.4%) subjects had respiratory symptoms, defined as asthma, dyspnea, cough, bronchospasm or desaturation.13 (92.9%) had cutaneous complaints being urticaria, erythema or other rash, oedema at the level of the skin or mucous membranes.1 (7.1%) person reported digestive complaints, such as nausea, vomiting or diarrhea. Finally, 3 (21.4%) presented with symptoms of OAS, being rhinitis, conjunctivitis or swelling/ itching of the lips.

Out of 112 respondents, 12 (10.7%) persons reported to develop symptoms after contact with latex-containing products.

The clinical presentation after contact with latex-containing products was distributed as follows; 1 person (8.3%) presented with cardiovascular symptoms. 2 (16.7%) had respiratory symptoms. 10 persons (83.3%) had cutaneous symptoms. 1 (8.3%) had symptoms of a digestive nature, being nausea, vomiting and diarrhea. Finally, 2 (16.7%) presented with symptoms of OAS.

Of the 112 respondents, 16 (14.3%) reported developing symptoms after eating certain food products. 11 of them specified the product and all of them could be associated with a cross allergy to latex. 5 persons reacted to certain food products but did not specify to which products.

The clinical presentation after eating certain food products was distributed as follows; 1 person (6.3%) presented with cardiovascular symptoms. 2 (12.5%) had respiratory symptoms. 10 persons (62.5%) had cutaneous symptoms. 1 (6.3%) had symptoms of a digestive nature, being nausea, vomiting and diarrhea. Finally, 8 (50%) presented with symptoms of OAS.

As mentioned earlier, the consequences of a latex allergy can be significant for professional activities. In our study, 8.7% of the respondents who indicated that they were allergic to latex had to modify their professional activities. 6.5% had to restrict their professional activities and 2.2% had to make a career change. 82.6% did not make any change or adjustment in their professional activities.

Statistical analysis

A possible association between the time spent in the operating theatre per week and the presence of a latex allergy was examined. Based on the respondents' time spent in the operating room per week, no significant difference (p=0.285) could be shown between the groups with self- reported latex allergy, possible latex allergy and no latex allergy, as well as between the groups who had or did not have an allergic reaction after contact with latex-containing products (p=0.633).

A possible association between the age of the respondent and the presence of a latex allergy was also examined. No significant (p=0.538) difference could be shown based on age betweenthe groups with self-reported latex allergy, possible latex allergy and no latex allergy, as well as between the groups who had or did not have an allergic reaction after contact with latex- containing products (p=0.773). Also for the group with a food allergy that was specified and linked to the latex fruit syndrome, no significant difference (p=0.510) was found.

Discussion

Occupational allergy is an important clinical and socio-economic problem (18, 23). Therefore, it is essential to identify individuals at risk or already sensitized to latex in order to take appropriate and timely measures. The most important tool to identify employees who are at risk is their medical history. The following questions should be asked:
the healthcare professional have known allergies to certain food products or medications?

– Does the healthcare professional have a history of asthma or eczema?
– Have there ever been complaints after contact with balloons, condoms, rubber, or after a visitto the dentist?
– Have there been previous surgical procedures and if so, were there any complications?
– Have allergy tests ever been taken and if so, for which products and what was the result?

Positive answers to any of the above questions may help identify healthcare workers at risk of developing hypersensitivity to latex (10). Although prevalence rates of latex allergy and sensitization among healthcare workers vary widely due to high inter-study heterogeneity, Wu et al. (9) in a review of the recent literature found that 9.7% of healthcare workers had a latex allergy compared to 4.3% in general population. These figures are roughly in line with the results of our survey at the Ghent University Hospital, where 7.9% of respondents stated that they were allergic to latex. In addition, 5% of the respondents stated that they might be allergicto latex.

10.7% had symptoms after contact with latex-containing products, of which a majority (83.3%) were cutaneous complaints. 14.3% had symptoms after eating certain food products. All specified products had a known cross allergy to latex. Here again, cutaneous symptoms were predominant (62.5%), although 50% presented symptoms fitting an Oral Allergy Syndrome. Interpretation of the latter group should be done with caution, since it may indicate both a latex-fruit syndrome or a pollen-fruit syndrome.

It is important to differentiate between allergic contact dermatitis and an IgE-mediated immune response. Whereas the symptoms of allergic contact dermatitis are generally limited to the site of contact and may be disabling, they rarely elicit severe systemic reactions. The T-cell mediated immune response is delayed and manifests as a local rash with papules and/or vesicles. In contrast, IgE-mediated immune response to latex is usually immediate and does frequently involve severe systemic reactions. Although these reactions are not predictable and may vary after each exposure, the trend is often incremental.

After statistical analysis of the data collected from the survey of healthcare workers at the Ghent University Hospital, there appeared to be no significant difference in terms of time in the operating room between the persons with self-reported latex allergy, possible latex allergy andno latex allergy, nor between the persons who reported to have an allergic reaction after contactwith latex-containing products. Also with regard to the age of the respondent, no significant difference could be found between the above groups, nor for the group with a food allergy where the product was linked to the latex fruit syndrome. Limitations of this study were the limited size of the sample population with 112 respondents. 66% of the respondents were physicians, 25% of whom were anesthesiologists, which may not be representative for the entire population of healthcare workers at Ghent University Hospital. The prevalence of latex allergy was only determined on the basis of self-reporting without additional prick and/or serum tests. A potential bias of this survey is the risk of selection bias in responders who are, possibly due to their allergy to latex, keen on participation. Therefor overestimation of our prevalence can not be ruled out.

A general limitation of such studies is the so-called “healthy worker effect”, which implies that healthcare workers with latex allergy may have already left their work environment due to complaints and thus the prevalence figure is an underestimation of the reality (24).

In our study, the consequences on the professional life turned out to be significant; 8.7% of therespondents who reported an allergic reaction to latex had to limit their professional activities and 2.2% were forced to change careers. However, a

majority (82.6%) did not make any specific changes to their work environment, possibly due to only mild symptoms, but continued to be exposed to latex. A latex-safe environment aims first of all to prevent sensitization to latex and – if sensitization occurs – to minimize symptoms and health risks for the healthcare worker.

The most effective and cost-efficient technique to achieve this is prevention by banning all products containing latex. However, avoiding unnecessary use of latex products as well as a latex-free alternative to surgical gloves can already significantly reduce exposure. Replacing powdered latex gloves with an unpowdered alternative seems to reduce the degree of de novo sensitization to latex and in some cases may even reverse it. Although the total amount of extractable proteins is only an indirect measure of the allergic potential of surgical gloves, a lower concentration also seems to lead to less sensitization and thus the 'as low as reasonably practicable' (ASARP) principle applies.

The economic aspect of a switch to a latex-safe working environment is a real concern among hospitals, yet some examples can be found in the literature where this switch was not accompanied by additional expenditure; An example is the Mayo Clinic in Rochester, Minnesota, where savings of 200,000+ dollars were recorded after the switch to a latex-safe environment. Several other hospitals also concluded no additional costs were associated with this change, including savings on the purchase of expensive hypoallergenic gloves (10).

In conclusion, latex allergy remains an undeniable occupational disease with a potentially very strong disabling impact on both the medical and professional context of the healthcare provider. Our survey with healthcare workers from the Ghent University Hospital had similar prevalence figures for latex allergy as described in the literature. Neither age nor time spent in the operating theatre as a measure of exposure had any influence on the prevalence of latex allergy, allergic reaction to latex-containing material or food allergy, related to latex fruit syndrome, although our sample group was rather limited.

Prevention of latex sensitization remains paramount, yet a number of measures seem to be effective in reducing the number of de novo latex sensitization. The European Commission recommends, among other things, the exclusion of powdered gloves in favor of a non-powdered variant with a low quantity of extractable proteins, according to the "as low as reasonably practicable" principle. Projects in several international hospitals have also shown that creating a latex-safe hospital environment does not necessarily require additional financial efforts and thus seems feasible. However, the most efficient protection against latex allergy remains a completely latex-free hospital environment.

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