Susceptibility to hand eczema in high risk occupations: Contribution of genetic and environmental factors
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SUMMARY

General introduction

Occupational Contact Dermatitis (OCD) is a highly prevalent work-related disease, that is induced by skin exposure to irritants or allergens. In the workplace, irritant contact dermatitis (ICD) is the most common form of OCD. High risk occupations are in health care, hairdressing, the food sector and the metal industry. OCD tends to become chronic; persistent OCD often results in impaired quality of life and loss of work ability.

In addition to environmental exposure, the development of OCD is influenced by personal susceptibility. The uppermost layer of the skin, the Stratum Corneum, forms an effective barrier against penetrance of chemical and biological agents and prevents water loss from the skin. Some individuals have an intrinsically impaired skin barrier, for example, individuals with atopic dermatitis (AD). AD is a chronic inflammatory skin disease characterized by dry skin, pruritus, and erythematous lesions, often including flexural eczema. In the European population, AD is prevalent in 10-20% of children and up to 10% in adults, and it is a firmly established risk factor for ICD. Furthermore, it has recently been discovered that ‘filament aggregating’ epidermal protein filaggrin has an important function in the skin barrier. Loss-of-function mutations in the filaggrin gene (FLG), present in approximately 7-10% of the Western European population, result in a decreased amount of filaggrin in the skin and increase the susceptibility to AD and, possibly, to ICD.

The primary purpose of this thesis was to study the contribution of FLG loss-of-function mutations, AD, and occupational exposure in the causation of OCD. A second goal was to explore whether it would be recommendable to include FLG genotyping in susceptibility screening programs for OCD, in addition to the usual examination of present or past AD. In this context, also the attitude of apprentice nurses towards genetic susceptibility screening for OCD was studied.

Wet work

‘Wet work’, i.e. frequent contact with water, soap, detergents, or prolonged use of occlusive gloves, is a major cause of OCD. The German guidance TRGS 401 recommends that the duration of wet work should not exceed 2 h/day. This highlights the need for a reliable method to assess duration and frequency of wet work.

In Chapter 2.1, the use of a recently developed wet-work sampler was evaluated in a healthcare setting, using direct observation as reference. The sampler uses the temperature difference, generated by evaporative cooling, between a sensor on the skin and a second one 2 mm above the skin. Twenty-six nurses wore the sampler on the volar side of the middle finger for approximately 2 hours during their regular daily tasks, while being observed by a researcher. Sampler results were evaluated using various threshold values for the temperature difference to identify wet events of the hands. The optimal temperature difference to discern wet and dry skin
varied considerably between individual nurses. Individual results yielded a median sensitivity of 78 and 62% and a median specificity of 79 and 68% for indicating wet skin and glove use, respectively. As agreement between observed wet work and device-reported wet events was not high, further developments are required.

In Chapter 2.2, wet work exposure and its influence on the risk of developing hand eczema were investigated in a prospective cohort study among Dutch apprentice nurses, who were starting their practical training in different healthcare sectors, e.g., hospitals and nursing homes. Participants recorded wet work exposure and symptoms of hand eczema using specially designed diary cards. Seven hundred and twenty-one apprentices were included; for 533 participants, a follow-up time of 1–3 years was completed. Diary cards were supplied by 383 participants.

The 1-year period prevalence of hand eczema was 23% in the first year of follow-up, 25% in the second year and 31% in the third year. Eighty-one new cases of hand eczema developed, most of which occurred during the first year of follow-up. In approximately one-third of the participants, wet work exposure exceeded the Dutch national guideline of 2h/day or 20 wet work events/day. Frequent hand washing during traineeships [odds ratio (OR) 1.5; 90% confidence interval (CI) 1.0–2.3], frequent hand washing at home (OR 2.3; 90% CI 1.5–3.7) and having a side job involving wet work (OR 1.6; 90% CI 1.0–2.4) were independent risk factors for hand eczema.

**Influence of AD and FLG mutations**

In Chapter 3.1, the contribution of FLG mutations and AD on the risk of OCD was investigated in German patients with severe, chronic irritative OCD and in controls (vocational school apprentices). 634 Patients and 393 controls were genotyped for the most common FLG mutations (R501X, 2282del4, R2447X and S3247X). Current or past flexural eczema was used as an indicator of AD.

FLG mutations were found in 16% of the patients with OCD and in 8% of the controls, with a crude OR of 2.1 (95% CI 1.3–3.3) for the combined genotype. The OR for FLG mutations, adjusted for AD, was 1.6 (95% CI 1.0–2.6). Subjects with AD had an OR, adjusted for FLG mutations, of 2.9 (95% CI 2.1–4.0). There was no evidence of interaction between these two risk factors.

In Chapter 3.2, the contribution of FLG mutations and AD, together with wet work, on the development of hand eczema was studied in a prospective cohort study in Dutch apprentice nurses. At inclusion, history of AD and hand eczema were assessed by questionnaire, and genotyping was performed for the four most common FLG mutations. Exposure and hand eczema prevalence during traineeships were assessed with diary cards.

The prevalence of hand eczema during traineeships was higher among subjects with a history of hand eczema at inclusion. Hand washing during traineeships and at home increased the risk of hand eczema (OR=2.2 and OR=1.8, respectively). Adjusted for the effects of exposure and FLG mutations, an OR of 2.5 (90% CI 1.7–3.7) was
found for AD. Subjects without a history of AD showed no increased risk of hand eczema conferred by FLG mutations, but subjects with concomitant FLG mutations and AD had an OR of 3.6 (90% CI 1.7-7.5), adjusted for wet work exposure.

**Opinion of apprentice nurses on genetic testing for susceptibility to OCD**

Genetic research has opened up possibilities for identification of persons with an increased susceptibility for occupational disease. However, regulations considering the ethical issues that are inevitably associated with the use of genetic tests for susceptibility for occupational diseases are scarce. The question is whether the opinions of intended stakeholder groups are sufficiently addressed by existing recommendations.

In Chapter 4, attitudes and opinions of Dutch student nurses as a stakeholder group toward a genetic test for susceptibility to OCD were studied in a qualitative setup, using focus groups, interviews and electronic questionnaires. The results were compared with guidelines and recommendations extracted from the literature.

Sixty-nine percent of the student nurses said they would partake in a genetic test for susceptibility to OCD when available. The main arguments in favour of testing were curiosity about one’s susceptibility and the intention to take preventive measures based on the test result. Concerns were expressed regarding the difficulty of interpreting test results, the utility of the test result in practice and the necessity of genetic tests for non-severe diseases. For the issue of privacy and confidentiality, the students expressed few worries and much confidence that this would be well organized. The existing guidelines largely covered the students’ opinions. Still, two important issues were missing in the guidelines, namely: (1) the need for good risk communication considering difficulties with interpreting risk information, and (2) the need for practical advice accompanying test results.

**General discussion**

In Chapter 5 the main findings of the thesis are discussed. The most important finding is that FLG mutations mainly appear to increase the risk of OCD in the presence of concomitant AD. It seems that some extra stimulant may be needed to predispose for AD and OCD in FLG mutation carriers. It might also be possible that some FLG mutation carriers are able to compensate for the reduced amount of filaggrin in their skin, counterbalancing their predisposition to develop AD and OCD.

The usefulness of FLG genotyping will depend on the context in which it would be used. Possible scenarios are diagnosis and treatment, pre-employment medical screening, and career counselling.

Many apprentices in our cohort study were hardly aware of the health risks associated with wet work exposure and had a rather careless attitude towards skin protection. This stresses the importance of education.
On the basis of the results of this thesis, the following conclusions and related recommendations are presented:

1. Apprentice nurses are still at substantial risk of developing hand eczema during traineeships. Education and encouragement to prevent hand eczema should be intensified, giving attention to alternatives for the use of water and soap and to skin care. The effectiveness of such activities should be assessed.

2. Adjusted for AD, FLG mutations significantly increased the risk of chronic irritant OCD (OR=1.6) in our case-control study, but had no distinct effect on the risk of hand eczema in apprentice nurses. Individuals with concomitant FLG mutations and AD appear to have the highest risk of OCD.

3. Including FLG genotyping in addition to the anamnesis of AD as susceptibility screening for OCD in all applicants for a high risk job is not recommended. However, FLG genotyping of individuals with AD may aid in diagnosis and more tailored therapy and prevention. Furthermore, in view of the high risk of OCD in AD+/FLG+ individuals, renouncing from entering a high exposure job may be considered for this group.

4. Guidelines on genetic screening for susceptibility to occupational diseases show a deficiency concerning risk communication and the need of practical advice accompanying individual test results. The guidelines should be improved in this respect. In the preparation of such a screening, these elements can be elaborated by deploying focus groups or interviews with stakeholders.