Susceptibility to hand eczema in high risk occupations: Contribution of genetic and environmental factors
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5 GENERAL DISCUSSION
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This thesis primarily aimed to investigate the contributions of loss-of-function mutations in the filaggrin gene (FLG), atopic dermatitis (AD), and occupational exposure to development of contact dermatitis in high risk jobs. An underlying thought was the question whether FLG genotyping would be feasible to use in susceptibility screening programs for occupational contact dermatitis (OCD). Furthermore, we investigated the attitude of apprentice nurses toward susceptibility testing. In this chapter, the main results are summarized, and interpretations of the results and some methodological considerations are discussed. Finally, recommendations for practice and further research are given.

MAIN FINDINGS

On the basis of the studies described in this thesis, we have found that:

- **Apprentice nurses are at substantial risk of developing hand eczema already during traineeships (Chapter 2.2).** In the cohort study, the 1-year period prevalence of HE was 21% - 31% during follow-up. Among participants without a history of hand eczema, 18% developed hand eczema during their traineeship.

- **Regarding exposure, frequent hand washing during traineeships was the main risk factor for hand eczema in apprentice nurses (OR = 2.2), while the use of hand alcohol gel rubs and occlusive gloves did not increase the risk. In addition to occupational exposure, hand washing at home was a significant risk factor (OR = 1.8) (Chapter 2.2).**

- **A history of AD increases the risk for OCD (Chapter 3.1 and 3.2).** In the case-control study of occupational irritant contact dermatitis (ICD) the OR for AD, adjusted for FLG mutations, was 2.9. In the prospective cohort study of hand eczema the OR for AD, adjusted for wet work exposure and FLG mutations, was 2.5.

- **Adjusted for AD, FLG mutations increased the risk for OCD in the case-control study, but not in the prospective cohort study (Chapter 3.1 and 3.2).** In the case-control study an increased risk of occupational ICD conferred by FLG mutations alone was found (OR=1.6). In the prospective cohort study, FLG mutations in absence of AD had no effect on the risk of hand eczema.

- **Individuals with concomitant FLG mutations and AD appear to have the highest risk of developing OCD (Chapter 3.1 and 3.2).**

- **The opinion of apprentice nurses towards genetic testing for susceptibility to hand eczema is incompletely covered by existing guidelines on genetic screening for susceptibility to occupational diseases (Chapter 4).** Issues missing in the guidelines were: (1) the difficulty with interpreting risk information and (2) the need for practical advice accompanying test results.
METHODS USED TO ASSESS WET WORK EXPOSURE, ATOPIC DERMATITIS AND HAND ECZEMA

In addition to the methodological issues discussed in the respective studies, the following issues deserve some extra attention:

Measurement of wet work exposure

Because of the relevance of wet work exposure in the development of OCD, we aimed to perform a thorough exposure assessment in our cohort study. Several exposure measurement techniques are available for this purpose, each with their own advantages and disadvantages. The use of observations or questionnaires (self-report) are two common methods for the assessment of wet work exposure. Observations of the subjects performing wet work are time-consuming, which makes them unsuitable for large cohorts, and have the drawback of inducing behavioral changes in the workers observed. On the other hand, self-report can be subject to recall bias. Some more objective techniques exist for the measurement of dermal exposure, e.g. absorbing patches, rinse or wipe techniques, but none of these are suitable for sampling exposure to water. Another challenge for the assessment of wet work exposure is its complexity. According to the German TRGS guideline, the total duration of wet work should not exceed 2 hours a day, and a Dutch expert group recommended that the total number of wet work events (all added together) should not exceed 20 times a day. In order to uphold these guidelines, both the cumulative duration and frequency of contact with irritants (including water) should be measured as well as the use of occlusive gloves. The wet work sampler described in Chapter 2.1 seemed promising in this respect, but unfortunately, it appeared not to be suitable in assessing wet work exposure in nurses. In our cohort study, we therefore chose to use diary cards. Earlier studies focusing on wet work exposure in nurses have found that when using questionnaires, nurses tend to overestimate the duration and underestimate the frequency of their wet work activities. In our study, the participants were asked to fill in the cards on several days of each traineeship period to obtain more reliable estimates in the case of fluctuations in wet work activities. The exposure estimates obtained by using the diary cards showed good agreement with the data from other observational studies among (apprentice) nurses, suggesting that our results were reliable at least on a group level.

Case definition for AD

The definition of AD in research is still a point of debate. In preceding studies that investigated AD as a risk factor for OCD, diverging criteria have been used. In several studies, the categorization of AD was based on a positive answer on questions like “Have you ever had atopic dermatitis?” or “Has a physician ever told you that you had atopic dermatitis?”, whereas in other studies, symptom-based definitions were used, usually including the presence or a history of flexural eczema, asthma, allergic rhinitis,
or general allergic symptoms like hay fever\textsuperscript{9-14}. In our prospective cohort, we used a set of criteria based on the UK Working Party Diagnostic Criteria\textsuperscript{15} “Question-only” version, whereas in our case-control study we based the diagnosis of AD on the current or past presence of ‘flexural eczema’. Despite this difference in the case definition of AD, the prevalence of AD among both the Dutch and German apprentices (24% and 19%, respectively) is in the range of what has been found in other epidemiological studies\textsuperscript{16-19}.

\textbf{Case definition for hand eczema}

As opposed to our case-control study, where the diagnostics was based on clinical examination, questionnaires and exposure history, our prospective cohort study used a symptom-based definition to assess self-reported hand eczema. Although we initially intended to have a clinical examination of all suspected hand eczema cases, from practical reasons this turned out to be impossible. Based on the reported symptoms, we could not classify the hand eczema as irritant, allergic or atopic. As \textit{FLG} mutations are reported to have little influence on allergic contact dermatitis\textsuperscript{20-24}, the presence of allergic hand eczema cases may have influenced the observed low association between \textit{FLG} mutations and hand eczema in our cohort.

\textbf{ROLE OF FLG LOSS-OF-FUNCTION MUTATIONS AND AD IN SUSCEPTIBILITY TO OCD}

Previous studies have convincingly shown that present or past AD increases the risk of developing OCD\textsuperscript{9,10,25-27}, an effect that was confirmed in our case-control study as well as in our prospective cohort study. The mechanisms by which AD modifies the risk for OCD is not clear yet. A general enhanced immune reactivity in AD skin may explain part of the increased susceptibility to OCD. Another explanation might be an impaired skin barrier function, which is a major hallmark of AD. Skin barrier failure in AD may be due to reduced amounts of filaggrin, but it can also be caused by other factors, for example, an impaired organization and structure of the skin lipids, altered enzyme activity involved in desquamation, or changes in the levels of the proteins of tight junctions and the cornified envelope\textsuperscript{28-35}. Intrinsic filaggrin deficiency is not only dependent on \textit{FLG} mutations but also on copy number variations in the \textit{FLG} gene\textsuperscript{36}. Reduced levels of filaggrin can also be a secondary effect of disease itself, as the Th2-mediated cytokine milieu in AD skin has been shown to suppress the expression of filaggrin\textsuperscript{37-40}. It is likely that in heterozygous carriers of \textit{FLG} mutations, the levels of filaggrin are further decreased by the processes related to AD, which might explain the highest susceptibility of the individuals with concomitant AD and \textit{FLG} mutations in our studies.

In the case-control study, we found a small but significant effect of \textit{FLG} mutations on the risk of OCD, adjusted for the history of AD. In the cohort study, we did not
find a distinct effect of FLG mutations on the risk of hand eczema. This might partly be explained by the differences in disease status between these two studies (chronic, rather severe irritant contact dermatitis versus early symptoms of hand eczema of all subtypes, which may have included atopic and allergic hand eczema), as discussed earlier. Our two studies agree in the finding that individuals with concomitant AD and FLG mutations had the highest risk of OCD. A large cross-sectional study among the general population in Copenhagen found a similar result: FLG mutations were associated with hand eczema in subjects who also had AD (OR=2.98; 95% CI 1.27 – 7.01) but not in subjects without AD (OR=0.82; 95% CI 0.41 – 1.67) 13.

In the studies described in this thesis, the contribution of FLG mutations and AD to the development of OCD each was calculated while adjusting for the other risk factor, a common procedure to eliminate confounding. However, AD is not only an independent risk factor for OCD, but is also – in part of the subjects with FLG mutations – an element in the etiological pathway from FLG to OCD. Thus, the etiological contribution of FLG mutations may be somewhat underestimated in our studies. FLG mutations are associated with more severe AD 41-45 but on the other hand, less than half (approximately 40%) of the FLG carriers develops AD 46,47. Thus it seems that in addition to FLG mutations, some extra stimulus is needed to predispose for AD and subsequently OCD. The exact nature of these internal or external stimuli is as yet unknown, but a specific cytokine milieu and environmental exposure to allergens or irritants at a young age may be involved. It might also be that part of the FLG mutation carriers somehow are able to compensate for the reduced filaggrin levels in their skin via yet unknown mechanisms, which enable them to (partly) restore their skin barrier function and protect them against developing OCD as well as AD. More research into skin barrier properties of this subgroup of FLG carriers and into possible predisposing stimuli is warranted, as it might open up possibilities to better protect individuals from AD and OCD.

SOCIAL IMPLICATIONS

Predicting the risk of OCD

One underlying reason behind the investigations in this thesis was the question whether FLG genotyping can be used as a test for susceptibility to OCD, in addition to assessment of the presence of the known risk factor AD. Different answers to this question may apply according to the precise aims and context for which FLG genotyping would be used. Possible scenarios could be, for example: 1) use as part of the diagnosis in OCD-patients aiming at more targeted prevention and therapy, 2) use as part of a pre-employment medical examination, or 3) use in career or educational counseling.

In the first scenario, as part of diagnosis, FLG genotyping can add to the understanding of the individual disease aetiology and can influence treatment and prevention measures. Recently, it has been found that topical application of recombinant filaggrin restores filaggrin levels in the skin of FLG-deficient (‘flaky tail’) mice and restores their Ichtyiosis Vulgaris phenotype towards normal skin 48. This may
be a starter to the development of new topical treatment aimed at restoring filaggrin levels in the FLG mutation carriers.

In the second and third types of intervention, FLG genotyping is used as a tool to assess susceptibility, which implies that some considerations are needed in addition to the criteria for diagnostic tests. One reason is that a positive result on a susceptibility test does not mean that the disease will occur with certainty; the probability of the development of the disease is influenced also by other factors than susceptibility, such as the ‘background’ risk of the disease in the population and the exposure characteristics. As discussed in Chapter 4, the positive predictive value of a test is one of the key criteria to select and decide on the implementation of a screening test. It displays the probability that a person will develop the disease, given a positive test. Also for a screening test with a high positive predictive value, however, the decision on application of the test depends on the context in which it would be used: the supposed gain due to more targeted prevention has to be balanced against the efforts and costs of testing and ethical issues associated with using the test, such as potential exclusion from the job for people with a positive test result and potential violation of privacy or confidentiality. Furthermore, the possibilities for and the effectiveness of preventive measures that can be taken upon a positive test result may differ per situation.

In pre-employment medical examination according to the Dutch OCD guideline, individuals with AD in combination with chronic hand eczema are regarded as unfit for working in jobs with frequent wet work exposure. Individuals with AD without a history of hand eczema are advised to pay extra attention to skin care and are monitored by the occupational physician. Our results indicate that among individuals with AD, the subgroup with concomitant AD and FLG mutations have a substantially increased risk of developing OCD. Moreover, a longitudinal follow-up of the OCD patients from our case-control study revealed that AD+/FLG+ patients had more persistent disease associated with the worst prognosis and the lowest rate of return to their job. These prognostic data emphasize that this particular group should receive special attention in the pre-employment medical examination. In the scenario of education or career counseling, it might be considered to advise only the most susceptible, AD+/FLG+, individuals to avoid high-risk jobs, while non-carriers with a history of AD can pursue a career in a high-risk job when desired – provided that they take extra preventive measures. As already mentioned in Chapter 4, good risk communication – including practical advices – is of crucial importance in this scenario. Ideally, the expectations and perceptions of the intended target groups regarding susceptibility testing should be surveyed, so that risk communication can be tailored for each group concerned. A qualitative study by our group has shown that the best method to achieve this is by using interviews or focus groups.

Prevention of OCD: perceptions, behavior and possible interventions

In addition to the measured effects of exposure and susceptibility factors, our prospective cohort study has yielded some other interesting results regarding
behavior of the apprentice nurses towards wet work exposure and skin protection and regarding dealing with skin complaints.

Through communication with study participants during our prospective cohort study, we have noticed that many students were not aware of the skin damaging effects of wet work. For example, most apprentices did not know that hand washing results in more skin damage than disinfection with alcohol gel. Some of them actually perceived the opposite, because the alcohol may give a stinging or burning sensation, especially on already compromised skin. The idea that the use of alcohol gel rubs is worse to the skin than the use of water and soap seems to be a frequently occurring misconception; two German questionnaire surveys revealed that 60-70% of the nurses regarded hand alcohol gel rubs as more damaging to the skin than hand washing. In addition, students working outside hospitals in e.g. nursing homes or homecare sometimes did not have access to alcohol gel rubs at their workplace, so they had to use water and soap. The same applied for the availability of protective gloves.

Another observation from our cohort study revealed that the majority of apprentices who reported hand eczema did not consult the occupational physician, even if they were actively invited to an easily accessible, free consultation by telephone. The invitation included the message that the occupational physician would give professional advice about skin care and protection. Still, approximately two-third of the students who were offered such a consultation did not make use of it. Especially if the symptoms were relatively mild, they were regarded as ‘not worth bothering a physician with’. Among healthcare employees with self-reported hand eczema who were invited to consult a specialized occupational dermatology nurse, a slightly higher attendance rate of 46% was observed. The importance of skin protection measures is often not recognized by workers, even if they already have OCD. Such a rather careless attitude towards OCD symptoms is undesirable, because early intervention can prevent the progression from mild symptoms to severe, chronic OCD.

Obviously, the first step in the prevention of OCD is education. Students pursuing a career in healthcare or other high risk occupations should be informed on the effects of skin exposure and the importance of adequate skin care and early recognition of symptoms, especially if they have a history of AD. This means that knowledge on occupational exposure, skin care and prevention of OCD should be disseminated to vocational schools and become an integral part of the curriculum. The role of personal susceptibility should be brought under attention among (prospective) students while they still have the option to choose between different specializations; educational or career counsellors should play a more proactive role in this. Furthermore, education should not stop after finishing the vocational training; workers should be reminded of the importance of preventive measures and should be stimulated to report early skin symptoms to their occupational physician or occupational health nurse. Employers in healthcare should be educated about the skin damaging effects of different hand hygiene measures, the costs associated
with hand eczema (e.g. in terms of sick leave, but also increased risk of infections) and adequate prevention measures. As skin irritation forms a major reason for noncompliance with hand hygiene rules, which is estimated to cause one-fifth of healthcare associated infections, implementation of the Dutch OCD guideline will kill two birds with one stone. Not only hospitals, but also nursing homes and similar healthcare institutions should receive this information, so that the availability of alcohol gel rubs and protective gloves can be promoted.

Education and training as part of secondary and tertiary prevention programs (aiming at improving skin condition in workers with OCD) has already been shown successful according to a few intervention studies in Germany and Denmark. However, to our knowledge, studies describing interventions aiming at primary prevention of OCD are lacking. It would be recommendable to develop educational programs for primary prevention and assess their effectiveness in longitudinal studies.

CONCLUSIONS AND RECOMMENDATIONS

In summary, the results of this thesis lead to the following conclusions and recommendations:

Conclusions
1. Apprentice nurses are at substantial risk of developing hand eczema during traineeships; the most important exposure factor is frequent hand washing at the workplace as well as at home.
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 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. Guidelines on genetic screening for susceptibility to occupational diseases show a deficiency concerning risk communication and the need of practical advice accompanying the test results for the individuals undergoing genetic screening.

Recommendations for further research
1. More research is needed into skin barrier function of FLG mutation carriers without AD, to reveal possible compensatory mechanisms.
2. Future studies should further investigate the relative risk for OCD conferred by FLG mutations. In view of the relatively small number of FLG carriers among the population, multicenter studies of starting employees in high risk occupations are to be preferred.
3. Intervention studies should be set up on the effects of primary prevention of OCD by education and training programs, preferably embedded in a comprehensive preventive program.
Recommendations for practice

1. Education and encouragement to prevent hand eczema should be intensified, not only for workers but also for vocational students, giving attention to alternatives for the use of water and soap, to skin care, and to early recognition of signs and symptoms. Occupational and regulatory health professionals, employers and vocational schools should facilitate exposure reduction measures, promote skin care and give attention to high risk groups.

2. 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. 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.

3. In the process of implementing any screening tool, attention should be paid to difficulties with interpreting risk information by the person undergoing the test and to practical advice accompanying the test results. The best way to prepare such an intervention is by deploying focus groups or interviews with stakeholders.

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