CHAPTER 1

INTRODUCTION
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Hand eczema is defined as an inflammation of the skin (‘dermatitis’) confined to the hand(s). We define the hands as the part of the arm, distal of the wrist, including the fingers. The point where the wrist ends and the hand starts, is visible as a fold in the skin. Hand eczema may spread to the wrists and the forearms, or occur in conjunction with foot eczema. However, in cases with eczema predominantly on other parts of the body than the hands, it would be best to use the term eczema with hand involvement.\textsuperscript{1}

The word ‘eczema’ is derived from the Greek word εκζεμα: ‘to boil out’. Its first use is attributed to Aëtius of Amida, who was writer and physician to the Byzantine Court, and who lived from 502 to 575. It is said to have been the name given by ancient physicians to any fiery pustule on the skin.\textsuperscript{2} This inaccuracy continued to some extent for centuries and prompted the writer Norman Walker to refer to the word ‘eczema’ in 1913 as a “chaotic conglomeration” and a “cloak for ignorance”.\textsuperscript{3} In the following decades nomenclature has gained more precision, although confusingly the term ‘dermatitis’ is now frequently used interchangeably with ‘eczema’, especially in the USA. Dermatitis however, is a broader descriptive term that implies an inflammation of the skin and therefore encompasses more than eczema alone. In Europe the term ‘hand dermatitis’ is preferred for those cases in which the eczema is caused by contact with irritants or allergens. In this thesis only the term ‘hand eczema’ will be used, regardless of the clinical manifestation or aetiology.

The special interest for eczema of the hands is justified because it is common and long lasting with a chronic relapsing course, and because it may have severe consequences to the patient and others. In the next paragraphs these points will be addressed, in addition to other general aspects of hand eczema.

Epidemiology
Hand eczema is a common disease. Exact prevalences however, are unknown. There are many reasons for this: it is not a notifyable disease, there is no universally accepted definition, no clear delineation from slightly damaged skin and not all patients seek medical attention. Research on the topic has usually focused on the prevalence in certain populations, especially with an occupational interest, e.g. hairdressers and nurses. The value of population-based questionnaires is limited by the imprecision in the definition of hand eczema and the self-assessment by those in the sample. Finally, comparing point prevalences, one-year prevalences and life-time prevalences may be difficult.

Exemplary for the fact that most hand eczema prevalence studies are from the Nordic countries, the 1987 paper of Meding reported a one-year prevalence.
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of 9% for men and 15% for women among a random sample from the Gothenburg population (Sweden). The point prevalence in 1983 was 5.4%. The same population was examined again in 1996. This follow-up showed a decrease in one-year prevalence to 7.0% for men and 12.3% for women. In Stockholm in 1997 the self-diagnosed one-year prevalence was 6% for men and 10% for women. A self-reported life-time prevalence of hand eczema among Danish twins was 12% for men and 21% for women. This rise in prevalence over the decades, in contrast to Meding’s findings, was confirmed by Nielsen, who reported a rise in self-diagnosed hand eczema in the 1990’s. The life-time prevalence was 10.1% for men and 23.3% for women in 1990; in 1998 these numbers were 18.4% and 32.4% respectively.

The incidence of hand eczema was 4.0 new cases per 1000 person-years for men and 7.1 for women. Interestingly, there was no difference in incidence between men and women over the age of 30 years.

The male to female ratio seems to be slightly under 1:2. However, a 2000 paper from St. John’s contact dermatitis clinic reported a male to female ratio of 4:5.

Given the practical limitations of a medical examination of large populations, many of these studies combine the validity of a clinical diagnosis with the easy applicability of self-administered questionnaires. In (another) example of such a study, a set of three questions was developed, asking about symptoms of hand eczema, their duration and whether these were recurrent. The validity was evaluated among 109 nurses and compared with a medical diagnosis made by a dermatologist. A diagnosis of hand eczema, defined as one or more symptoms with a recurrent character or lasting for more than three weeks, had a sensitivity of 100% and a specificity of 64%, resulting in a positive predictive value of 31%. This indicates that use of a questionnaire alone would result in a significant overestimation of the prevalence. This might explain the wide range of prevalences found in the above-mentioned studies, including some very high prevalences. Medical examination of only those who responded positively, to exclude false-positive cases, would, however, increase the specificity while maintaining the high sensitivity. A Swedish study showed that the use of the self-diagnosis term ‘hand eczema’ seems to be valid, although it was difficult for the individual to identify skin signs compatible with the clinical diagnosis of hand eczema.

Aetiology

The aetiology of hand dermatitis is usually multifactorial and can be divided in endogenous and exogenous causes. Rarely, hand eczema is caused by one single factor.
In 1953, the typical patient with hand eczema was described as “a young matron, who must keep house, cook, wash dishes, do the laundry, raise her children and hold her husband.”\textsuperscript{14} This clearly illustrates the importance of a few commonly encountered irritants: water, food products, soaps and detergents. Other examples are chemicals, dry and cold air and friction. A sequence of repetitive insults with contact irritants may disrupt the epidermal barrier and inhibit its repair, thus leading to hand eczema after repeated exposure.\textsuperscript{15} Irritants are the commonest exogenous cause of hand eczema.\textsuperscript{16} Sweat, due to hyperhidrosis, can also be an irritant. Although the reasons for the different prevalence in hand eczema between men and women are unknown, the greater exposure of women to wet work is probably significant.

The other exogenous cause of hand eczema are contact allergens. These substances result in a type IV delayed type cell mediated hypersensitivity. They can be related to occupation, to hobbies or to domestic work. The role of oral ingestion of allergens remains controversial.\textsuperscript{17} Alternatively, type I immediate type IgE mediated hypersensitivity to proteins may provoke hand eczema in certain individuals.\textsuperscript{18}

Atopy may be both the cause and a contributing risk factor for hand eczema.\textsuperscript{19} Similar to atopic eczema of the body, lesions limited to the hands may develop. More commonly, the increased susceptibility of atopics to contact irritants will result in irritant contact eczema of the hands.\textsuperscript{20}

Occupational factors, both irritant and allergic, can precipitate and perpetuate hand eczema, especially in atopics. Hand eczema now accounts for an estimated 90\% of occupational skin diseases.\textsuperscript{21}

Bryld observed in a population-based twin cohort hereditary factors despite a presumable substantial individual-specific environmental variation.\textsuperscript{7} Although the significance of psychosomatic factors to hand eczema remains speculative at best, there is considerable interest in them.\textsuperscript{1} Probably there is no aetiological relation, although emotional factors and psychological stress may aggravate hand eczema. One case report proposes an aetiological relation between waterpipe smoking and hand eczema.\textsuperscript{22}

In contrast to what has been proposed in the past, there is no dysfunction of the acrosyringium and no relationship with sweat gland obstruction or hyperhidrosis in vesicular hand eczema.\textsuperscript{23} Therefore, dyshidrotic hand eczema is actually a misnomer. It is also frequently referred to as pompholyx (from the Greek word for ‘bubble’).

**Clinical features**

Itching, and to a lesser extent burning, stinging, and pain, may be the most prominent and disturbing symptoms. In acute hand eczema signs are erythema, oedema, papules and vesicles, sometimes with superimposed weeping and
crusting due to secondary bacterial infection. Secondary viral infection, usually in atopics, is less common. The vesicles may coalesce to form bullae. Chronic forms usually present with less erythema, no vesicles and more scaling, sometimes even significant hyperkeratosis with fissuring (tylotic hand eczema or eczema hyperkeratoticum et rhagadiforme). The palmar epidermis is thicker than the skin of the back of the hands and the fingers. Therefore, the first signs may be visible on the latter parts of the hands.

Hand eczema tends to run a long lasting and chronic relapsing course, probably due to its multifactorial origin. Only in those relatively few cases where there is a single, easily avoidable contact factor, the prognosis is good.

Classification
The classification of hand eczema is complex, leading to considerable confusion. In addition, no single classification is satisfactory. The simplest is into acute, subacute and chronic. As this is usually not refined enough for clinical use, more commonly a combination of morphology (e.g. dyshidrotic hand eczema), aetiology (e.g. allergic contact eczema) and sometimes anatomical localisation (e.g. palms or fingers) is used.

The commonest aetiological hand eczema category is irritant contact eczema (35%), followed by atopic hand eczema (22%) and allergic contact eczema (19%).

It is important to realise that a single cause can sometimes produce different morphological patterns. Reversely, a certain clinical pattern, does not necessarily imply one single cause.

Making the diagnosis
In most cases the diagnosis can be made upon evaluation of clinical features and symptoms, such as itch, or pain in cases of fissuring hyperkeratotic hand eczema. Sometimes there is a history of provoking factors, such as irritants (e.g. detergents) or allergens (e.g. nickel). However, some patients do not report such factors, even when explicitly asked. Therefore, epicutaneous allergy tests (patch tests) for type IV delayed type cell mediated hypersensitivities, the gold standard for determining contact allergens, is an essential part of the diagnostic work-up. Finding an allergen holds the tantalising promise of a cure. Unfortunately, when allergies are found, the relevance is not always clear. Scrutinous anamnnesis, based upon the test’s results, is then needed. In some selected cases, a visit to the work place may elucidate the role and relevance of these allergies. A (family) history of asthma, childhood eczema or hay fever may suggest an atopic diathesis. This can be confirmed by measuring total or specific IgE antibodies and eosinophilic granulocytes in the serum, and by performing intracutaneous allergy tests.
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The main differential diagnostic points are psoriasis and tinea manuum. Examination of other parts of the body may hold evidence for psoriasis or tinea manuum: especially the feet and toes for tinea manuum, and the elbows, knees, scalp and nails for psoriasis. In addition, family history of psoriasis should be taken, as well as skin scrapings for fungal examination. In rare cases, lichen planus and discoid lupus erythematosus may mimic hyperkeratotic hand eczema. An unusual presentation of bullous pemphigoid limited to the hands may be confused with dyshidrotic hand eczema. Differentiation between dyshidrotic hand eczema and pustulosis palmaris can be facilitated by the presence of the characteristic brown marks, which remain after resolution of the pustules in pustulosis palmaris.

Finally, those cases with mild signs and symptoms, such as only mild chapping, can pose a problem. Should they be classified as hand eczema or as a variation in the condition of otherwise normal skin? Do those cases require treatment? As there is no universally accepted definition for hand eczema, these questions are hard to answer. It is in fact up to the individual clinician to make an assessment, in which other signs and symptoms, a previous history of eczema, a possible role of irritants and allergens and an atopic diathesis should be taken into account.

Histopathology
In hand eczema spongiosis in the lower epidermal layers can be seen, with the possibility of confluence, resulting in intraepidermal vesicles. These can be visible clinically as vesicles or papules, the latter especially on the palms of the hands due to its characteristically thick stratum corneum. There is a sparse, superficial infiltrate of lymphocytes with some exocytosis. In allergic contact dermatitis mild spongiosis adjacent to the vesicles may be present, in combination with eosinophilic granulocytes in the inflammatory infiltrate. The histopathology of hyperkeratotic hand eczema is similar to other forms of hand eczema. But in addition, it shares psoriasiform hyperplasia with compact hyperkeratosis and focal parakeratosis with psoriasis. Hand eczema usually lacks, however, neutrophilic granulocytes in the infiltrate.

Management
As hand eczema is an inflammatory dermatosis, anti-inflammatory agents are the mainstay of therapy. Topical corticosteroids have replaced coal tar derivatives as the first-line of treatment in the mid 1900s. Other important measures are avoidance of irritants and allergens, and frequent application of bland emollients to restore the disruption of the skin barrier. A supportive measure in cases with vesiculation is soaking the hands in water with added
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For hyperkeratotic hand eczema keratolytic agents (salicylic acid, lactic acid, urea in petrolatum) may provide relief.

Short bursts of oral steroids are useful in a few severe cases only. Other second-line treatments are phototherapies with UVB, UVA, or UVA with psoralens (PUVA) either oral or as soak, and ciclosporin. They have proven to be effective and are relatively frequently used. The following therapies have or are being used for hand eczema: retinoids, methotrexate, ionising radiation, mycophenolate mofetil, iontophoresis, azathioprine, diets or chelating agents, and intradermal botulinum toxin. The efficacy of some, but not all of them, has been evaluated in randomised controlled trials. Topical calcineurin inhibitors, tacrolimus and pimecrolimus, are the latest addition to the dermatologist’s therapeutic arsenal.

Preventive measures are important, especially for those at high risk, such as hairdressers and those with an atopic diathesis. Organisational adaptations are required for occupational cases. Obviously, protective measures such as protective gloves, barrier creams and emollients, are recommended.

Outcome parameters

The outcome parameters in intervention studies for hand eczema are usually based on a clinical assessment (severity). There are many ways to make this assessment, none of which are validated. Examples are: clinical judgement, objective signs only (e.g. vesiculation, scaling, erythema), subjective signs only (e.g. itch and pain), both objective and subjective signs, combination of area and severity, and treatment related (e.g. grams of corticosteroids used per week). Rarely one will find a paper in which the patient is asked if he feels better.

Other outcomes may include an economical evaluation, or other burden of disease related parameters. These also, are rarely the primary outcome.

Recently, two studies investigated, respectively, the value of a photographic scale and a numerical scale as instruments to rate the overall severity of hand eczema; they found high levels of intra- and interobserver reliability. They did not validate these scales (content, construct, criterion validity). At present, a validated instrument to assess the severity of hand eczema is still lacking. So, rigorous validation studies are needed.

Consequences

“The hands are the organs of doing things with things. They pick at, pry at, rub and investigate.” In addition, the hands are important tools for communication and expression. It is therefore easy to understand that any impairment in form and function may result in major psychosocial problems, e.g. anxiety, low self-esteem and social phobia. The itching is another major problem. It may interfere
with sleep for patients and also their spouses. A vicious cycle of symptoms and skin damage (the itch/scratch/itch cycle) can aggravate the patient’s problems.32

Painful cracks and blisters can prevent or severely complicate manual work leading to significant disability, economic loss to both individuals and State, and distress to the affected patients. The economic impact may be direct or indirect. Direct costs include medical costs, social security and medical litigation; indirect costs may arise from absence from work and loss of productivity.13

AIMS OF THIS THESIS

As the title of this thesis indicates, it describes studies on two closely related themes: interventions for hand eczema and its burden of disease. First, we shall focus on interventions for hand eczema. Chapter 2 will describe the characteristics of intervention studies for hand eczema and discuss their quality. Chapter 3 will give an overview of the papers dealing with interventions for hand eczema, from a clinical, problem-oriented perspective. Chapter 4 describes a systematic review on interventions for hand eczema. A randomised controlled trial comparing two PUVA treatments for hand eczema will be presented in chapter 5. A case report of a patient with a rare side effect due to one of these PUVA treatments is described in appendix 2.

Second, the burden of disease is the central theme in chapter 6 and appendix 1. In chapter 6 data from the study which is described in chapter 5, will be used to compare patient-rated and physician-rated severity scores with a burden of disease questionnaire. As the economic impact of a disease is another component of burden of disease,33 appendix 1 also uses the data from the study described in chapter 5, to make an economic evaluation of the two PUVA treatments.

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