Dissertation

Hereditary Ichthyosis. Causes, Skin Manifestations, Treatments and Quality of Life

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Agneta Gånemo defended her thesis on April 5, 2002 at the Department of Medical Sciences, Uppsala University, Uppsala, Sweden. The external examiner was Associate Professor Åke Svensson *(left)*. Professor Anders Vahlquist *(second from left)* served as supervisor and Associate Professor Magnus Lindberg *(third from left)*, professor Per-Olow Sjödén *(right)* and Associate Professor Christina Lindholm *(second from right)* served as co-supervisor.

Ichthyosis is a descriptive name for a group of skin disorders that encom-pass 20–30 different forms with different patho-aetiologies. Hereditary ichthyosis ranges in frequency from common (1/300) to very rare (<1/100 000) and is either present at birth or develops in early childhood. It is characterised by more or less generalised dryness, hyperkeratosis, scaling and other symptoms such as erythema, blisters, ectropion, keratodermia and anhidrosis. The signs and symptoms differ in different types of ichthyosis. The four main groups of ichthyosis are lamellar ichthyosis (LI) syn: autosomal recessive congenital ichthyosis (ARCI), bullous ichthyosis syn: epidermolytic hyperkeratosis (EHK), X-linked recessive ichthyosis (XRI) and ichthyosis vulgaris (IV). The treatment of ichthyosis is symptomatic and aims to give the skin a more normal appearance. The basic principles of the therapy are the same irrespective of whether the patient has a common ichthyosis (XRI or IV) with mild to moderate symptoms or a rare form (LI) with moderate to severe symptoms. The treatment is often very time-consuming and may include baths once or twice a week and application of topical emollients several times a day.

The overall aim of this investigation was to gain further knowledge into the aetiologies, signs and symptoms of ichthyosis, its influence on the patient's life and the possible treatments. The patients with ichthyosis were identified and recruited via the Swedish Ichthyosis Association, via dermatology departments in Uppsala and in several other cities around Sweden, as well as from Tartu University Clinics, Estonia (study I).

In the first paper 83 patients (72 families) who fulfilled the criteria for ARCI participated. The patients were clinically examined, using a standardised protocol in which the degrees of ichthyosis and erythema were scored as 0–4 in 9 different body regions. Blood DNA was prepared and analysed for TGM1 mutations, and a punch biopsy specimen was taken and processed for transmission electron microscopy (EM). The patients (or parents) completed a questionnaire concerning their past and present skin symptoms and/or reduced sweating or general malaise in a hot climate, and what type of therapy they preferred.

On the basis of DNA analysis and the clinical phenotypes we subdivided the patients into three groups. The largest group (A, *n*=44) comprised patients with TGM1 mutations who had typical LI or congenital ichthyosiform erythrodermi (CIE), except in two cases that showed only mild or focal ichthyosis. Group B (*n*=19) comprised patients with a clinical appearance similar to that in group A, but without TGM1 mutations; some of these patients were erythrodermic. The patients in group C (*n*=20) also lacked a TGM1 mutation, but had mild skin symptoms at the time of investigation; we named this phenotype Congenital Ichthyosis with Fine or focal Scaling (CIFS). The ichthyosis score was significantly higher in group A than in groups B and C, whereas the erythema score was highest in group B. A great variation of clinical symptoms was found within the three groups. Anhidrosis was a problem in 80–100% of all patients, and 35–80% were born as collodion babies. They also suffered from ectropion, alopecia and keratodermia palmoplantaris. The EM analysis showed type I in 36 cases in the groups, 20 cases of type II in group A, 3 cases each of type III and Harlequin-ichthyosis in group B, and 2 cases of type IV in group C.

All patients used some type of topical therapy, which was usually applied once or twice a day but varied greatly in degree. The most popular cream additives were urea, various alpha-hydroxy acids, and lactic acid/propylene glycol (LPL). About 20% of the patients (mainly in groups A and B) also used oral retinoids. In conclusion, this study showed that the clinical spectrum in Sweden and Estonia is broad and the aetiologies numerous. However, by using a combination of genetic blood tests, careful clinical characterisation and EM analysis it is often possible to make an adequate diagnosis of certain subtypes of the disease, thus allowing proper information to be given to the patient.

In the second paper 144 patients with LI, XRI or IV were invited to participate. The aim was to investigate the Health-Related Quality of Life (HRQoL) of patients with ichthyosis. We used the following questionnaires: socio-demographic questions, the Dermatology Life Quality Index (DLQI), the generic quality of life instrument Short Form-36 (SF-36) and a subjective measure of disease activity using a visual analogue scale (VAS). Of the 144 patients, the questionnaires were completed by 121, aged 17–78 (LI=37; XRI=36; IV=48). There were no significant differences between the three diagnostic groups (LI, XRI and IV) regarding age, marital status, education, employment or geographical area of residence.

The mean total score for DLQI was 6.1, significantly higher (worse) for LI (7.70) than for XRI (4.17). The SF-36 showed significantly lower (worse) scores for the study group in four of the eight dimensions compared to age- and gender-adjusted Swedish norm scores. No differences in SF-36 were found between men and women or between the different groups of ichthyosis. We used a VAS method to assess the patients' perception of their own skin symptoms at the time of the survey and how the respondent perceived these symptoms when they were at their worst. During the time of the survey, patients with IV had significantly higher scores for 'dryness' than those with XRI. It was surprising that patients with LI do not score higher in scaling than the other groups of patients. We also assessed the correlations between the VAS and the two quality of life instruments. The DLQI domains correlated well with the skin symptoms of 'scaling' and 'dryness', but less well with erythema. In conclusion, these results show that patients with ichthyosis have a reduced quality of life as reflected by the DLQI and by some domains of the SF-36. In some of the DLQI dimensions and in the subjective measure of disease activity (VAS), we also detected some gender differences.

In the third paper, ten persons with LI (*n*=9) and EHK (*n*=1), 56–80 years old, participated. The specific aims of this study were to investigate the life-time perspective and the quality of life in middle-aged and elderly persons with congenital ichthyosis in order to learn more about the influence of the disease on different phases of life. The Nottingham Health Profile (NHP) was used to

investigate quality of life and a face-to-face interview was performed concerning childhood and adulthood. Interview data was analysed using content analysis. The interview material was structured into two categories, childhood and adulthood, and into 16 themes. All the interviewees reported that their skin disease had affected them negatively to varying degrees during their entire lives and that the most problematic period was childhood. Coping strategies used during childhood were to hide the skin and to be naturally shy. When the NHP scores were compared with age- and gender-adjusted scores for the general population, the participants showed a lower quality of life in all areas. The results of this study confirmed that individuals with congenital ichthyosis have a reduced quality of life.

In the last paper, 20 patients with LI, aged 16–64, participated. The aim of this study was to evaluate the effects of a newly invented keratolytic cream formulation for the treatment of LI in a clinical trial. The investigation was designed as a double-blind within-patient study for comparing the following cream formulations: 5% urea in Locobase® fatty cream, 20% propylene glycol in Locobase® fatty cream, 5% lactic acid/20% propylene glycol in Locobase® fatty cream (LPL) and 5% lactic acid/20% propylene glycol in Essex® cream (LPE). Before and after applying the creams twice daily on each of the four extremities for 4 weeks, the following investigations were performed: scoring xerosis, scaling and erythema, measurements of skin hydration (capacitance) and transepidermal water loss (TEWL). All four creams reduced xerosis, but LPL and LPE significantly more so. Scaling was reduced only by LPL and LPE, which also caused a slight increase in the erythema score. The patients' weekly evaluation of symptoms showed that LPL produced the most rapid effect. Skin hydration and TEWL were both significantly increased by LPL and LPE, whereas skin roughness was reduced most by LPL. This investigation confirmed that a combination of low concentrations of lactic acid and propylene glycol in a semiocclusive cream base has the advantage of being both highly effective and well tolerated.

List of original publications

I. Gånemo A, Pigg M, Virtanen M, Kukk T, Raudsepp H, Rossman-Ringdahl I, et al. Autosomal recessive congenital ichthyosis in Sweden and Estonia: Clinical, ultrastructural and genetic findings in 83 patients. Accepted in Acta Derm Venereol 2003; 83: 24–30.

II. Gånemo A, Sjödén P-O, Johansson E, Vahlquist A, Lindberg M. Health-related quality-of-life among patients with ichthyosis. Submitted

III. Gånemo A, Lindholm C, Lindberg M, Sjödén P-O, Vahlquist A. Quality of life in adults with congenital ichthyosis: A life-time perspective on an inherited skin disease. Submitted.

IV. Gånemo A, Virtanen M, Vahlquist A. Improved topical treatment of lamellar ichthyosis: a double-blind study of four different cream formulations. Br J Dermatol 1999: 141; 1027–1032.