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Burden of itch in ichthyosis: a multicenter study in 94 patients

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ABSTRACT

Background. From clinical experience, we know that itch is a major concern for many ichthyosis patients. Nonetheless, no previous studies specifically addressed the issue of itch in ichthyosis.

Objective. The objective of this study was to specifically address the burden of itch and all its dimensions in ichthyosis patients.

Methods. Ninety four ichthyosis patients from 4 different centers were recruited to participate in this cross-sectional, questionnaire-based study. All participants completed the Leuven Itch Scale, a multidimensional self-report instrument that quantifies the frequency, duration, severity, distress, consequences and surface area of itch.

Results. Participants included 18 keratinopathic types, 55 autosomal recessive congenital ichthyoses (ARCI), 11 X-linked recessive ichthyoses (XLRIs), 6 Netherton's ichthyoses, 1 Sjögren-Larsson type, 1 locrin ichthyosis and 2 unknown subtypes. Itch occurred in 93% of all patients. In patients with itch, 63% reported that it was often or always present, although most itch episodes were short in duration. Itch, in all its dimensions, was worst in patients with Netherton syndrome. Patients with XLRI had in general a lower itch profile. About half of all ichthyosis patients reported to experience flares during a change in weather, in a hot environment or in stressful situations, whereas a cold environment led to itch in only 26% of patients. The most significant consequences of itching were lesions from scratching, difficulties in falling asleep, bad mood and loss of concentration.

Conclusions. Itch is a major concern in patients with ichthyosis, with significant impact on daily life. Research on future treatments should therefore take itch into consideration and itch should be evaluated in clinical studies. Among the studied subgroups, Netherton patients experienced the most severe consequences.

INTRODUCTION

The congenital ichthyoses form a large heterogeneous group of mendelian disorders of cornification. Clinically, skin changes are characterized by hyperkeratosis, scaling and different grades of erythema. In keratinopathic forms, blisters and erosions are seen as well. The current classification of ichthyoses remains clinically based, with “syndromic” versus “nonsyndromic” forms providing a major subdivision.¹ Within the nonsyndromic forms, the group caused by keratin mutations is referred to by the term “keratinopathic ichthyosis”, whereas “autosomal recessive congenital ichthyosis” (“ARCI”) is an umbrella term for harlequin ichthyosis, lamellar ichthyosis and the congenital ichthyosiform erythroderma group. In the ARCI group, the genetic background is variable with until now more than 10 genes known to be involved.² Recessive X-linked ichthyosis (RXLI) exists in a syndromic as well as a non-syndromic form and is, in its non-syndromic form together with ichthyosis vulgaris, comprised in the group of the “common ichthyoses”. The fourth group of nonsyndromic ichthyosis is referred to as “other forms” and includes rare variants. The second major group, i.e. the syndromic forms, encompasses the X-linked ichthyosis syndromes and the autosomal ichthyosis syndromes, including among others Netherton and Sjögren-Larsson syndrome.¹

Whereas the clinical skin changes that are typical for ichthyosis have been well studied and documented, less is known about itch in ichthyosis. Nonetheless, clinical experience learns that itch is a major problem in ichthyosis patients. In the current study, we aimed to assess the burden of itch in several types of ichthyosis.

MATERIALS AND METHODS

Study population

This was a cross-sectional multi-center study in patients with ichthyosis from 4 different dermatology centers in Europe: University Hospitals Leuven (Belgium), Hospital Infantil Niño Jesús, Madrid (Spain), Hôpital Larrey, Toulouse (France) and Ludwig-Maximilians-Universität München (Germany). Patients were eligible for inclusion if they were diagnosed with congenital ichthyosis; if Dutch, Spanish, German or French was their native or second (fluently spoken) language; if they were older than 12 years of age; and if they provided written informed consent. We excluded ichthyosis vulgaris as this type is frequently associated with atopic dermatitis, which could be an important confounding factor.

Data on itch in atopic dermatitis patients were included as a reference. These data were obtained from our previous study, where the LIS was validated.³ This group consisted of 63 atopic dermatitis patients (36 males, 27 females, mean age 33,4 years) with moderate atopic dermatitis (some severe) only receiving local therapies (ie. emollients, topical corticosteroids or topical calcineurin inhibitors) but no systemic therapies.

Variables and measurement

We conducted a multi-centered, questionnaire-based survey using the Leuven Itch Scale (LIS) to measure different aspects of itch (appendix 1).³ The LIS is a multidimensional self-report instrument that assesses symptom occurrence (frequency, duration, severity and circumstances), distress, management and location, sensory perceptions of the symptoms as well as consequences of the itch over the previous 4 weeks (the LIS is available as a supplementary file). Using specific algorithms, subscale scores on 6 domains (itch frequency, duration, severity, distress, consequences and surface area) can be calculated by summing the raw scores and transforming them to a scale ranging from 0 to 100. Higher scores represent more itching. The subscale scores allow the determination of a comprehensive profile of itch for individual patients or for groups of patients, and can be expressed using radar graphs.⁴ The LIS has been tested for its validity, reliability and responsiveness in patients with different dermatological conditions, such as burns, atopic dermatitis, chronic urticaria and epidermolysis bullosa.^{3,5} The LIS has been translated and validated into different languages, including Dutch, French, English and Spanish.

Procedure

From the databases of the participating centers, we retrieved a list of patients with ichthyosis who met the inclusion criteria. A package comprising the informed consent document, the LIS and the clinical research form for demographic and clinical information was either sent to the patients via surface mail or provided to patients visiting the center where they were followed. Patients who received the package at home were asked to complete the three documents and return them to us via surface mail. Data were collected throughout 2017 and 2018. The study was approved by the ethics committee of the University Hospitals Leuven, Belgium (Reference MP12592) and was conducted according to the latest version of the Declaration of Helsinki.⁶ Clinical information on the genetic background was given by the physician in charge of the patient. Data were collected by a study coordinator not involved in the final analysis of the data.

Statistical analysis

Data analysis was performed using SPSS 25 (IBM, Armonk, NY, USA). For descriptive statistics of the subscales, means and standard deviations were calculated. Descriptive statistics for nominal variables are expressed in absolute numbers and percentages. Differences between the 4 subtypes of ichthyosis were assessed using the Kruskal-Wallis test. Correlations between the subscale scores were calculated using Pearson correlation coefficients. Two-sided tests were used, and the level of significance was set at $P < 0.05$.

RESULTS

We obtained 94 questionnaires between January 2017 en August 2018, including 18 keratinopathic types, 55 ARCI, 11 XLRI, 6 Netherton, 1 Sjögren-Larsson and 1 Iocrin ichthyosis. Two patients did not know which type of ichthyosis they suffered from. Patients were 35 men and 59 women. Mean age was 37.5 years old (range 13-74 years). According to nationality, we obtained questionnaires from 44 French, 20 Belgian, 17 Spanish, 8 German and 1 Italian, 1

Chinese, 1 Moroccan, 1 Polish and 1 South Korean patient. The latter 5 patients were fluent or native speaking in either French, Spanish or English.

Itch occurred in 87 out of 94 patients (93%) (17/18 KP; 52/55 ARCI; 9/11 XLRI; 6/6 Netherton; 1/1 Sjögren-Larsson; 1/1 Iocrin ichthyosis; 1/2 unknown types). Fifty-five out of 87 (63%) patients with itch reported to experience itch often or always. Only 7 ichthyosis patients never experienced itch. Table 1 provides information on the profile of itch in the total sample and in the subgroups. When itch occurred, it lasted shortly in most cases: out of 87 patients with itch, 71 reported that an episode lasted less than 30 minutes or between 30 and 60 minutes. However, 3 out of 6 Netherton patients reported that the itch episodes lasted longer than 1 hour. Moreover, 5 out of 6 Netherton patients reported that itch was often or always present. In fact, in patients with Netherton syndrome, itch in all its dimensions was generally the worst. Patients with XLRI had in general a lower itch profile than the other subgroups. Our single patient with Sjögren-Larsson syndrome reported itch often. The entire itch profile of the different groups is expressed in Fig. 1. Within the ARCI group, a subgroup analysis was performed according to the involved gene (data not shown). Due to the small number of patients within all groups, it was impossible to perform significant statistical calculations. Despite this, it is noteworthy to mention both ARCI patients carrying a CYP4F22 mutation reported to have itch always.

In Table 2, the circumstances, consequences and sensory characteristics of itching are expressed. In the total sample, about 50% of patients experienced itch during a change in weather, in a hot environment or in stressful situations, whereas a cold environment led to itch in only 26% of the total sample. Interestingly, a different trend was noted in the XLRI subgroup, where 44% experienced itch in a cold environment and only 11% in a hot environment.

The most significant consequences of itching were lesions from scratching, difficulties in falling asleep, bad mood and loss of concentration. These observations held for the total sample and were moreover uniform through all the subgroups. Patients in the Netherton subgroup suffered the most for all consequences that were addressed, apart from the lesions from scratching.

In all subgroups as well as in the total sample, a tickling, a prickling and a burning sensation were most frequently reported as characteristic for the itch. A tingling or a stinging sensation were only reported in a minority of cases.

The correlogram (Fig. 2) clearly shows that the frequency, the severity, the distress, and the consequences of itch are highly interrelated, with correlations ranging between 0.55 and 0.77. In particular the severity and distress of the itch were highly correlated with the consequences.

Finally, we obtained data on the genetics of the different types of ichthyosis in our patient population. Within the ARCI group, there were 11 patients of whom the genetic subtype was unknown and 21 patients with a mutation in the *TGM1* gene. The other reported mutations within the ARCI group were in *ALOXE3*, *PNPLA1*, *CYP4F22*, *ABCA*, *NIPAL4* or *ALOX12B*, corresponding to between 1 and 6 patients in each group. Due to the small number of patients

for each genetic subgroup, no statistical analysis were performed. However, for the larger group with mutations in the *TGM1* gene (21 patients), we learned that only 2 patients never reported itch, whereas 5 and 7 patients experienced itch always and often, respectively. Three patients reported itch rarely and 4 patients sometimes. Regarding the severity, the mean (median) value of itch in the *TGM1* group was similar to the mean (median) in the ARCI group as a whole.

DISCUSSION

Itch has been recognized as a feature negatively influencing quality of life in patients with inherited ichthyosis.⁷ A previous questionnaire-based study with the aim to determine which factors were mostly associated with impaired quality of life in 158 adult ichthyosis patients revealed that all the 6 DLQI areas were affected, the strongest impairment being on “symptoms and feelings” (86% of patients).⁸ The items “daily activities”, “treatments”, “work”, “leisure” and “personal relationships” were all relevant as well, albeit to a lesser extent. Based on univariate regression analysis, pruritus appeared to be the factor with the second most important impact on quality of life, following cutaneous pain. The mean VAS score for pruritus was 4.14 ± 2.9 . In multivariate regression analysis, cutaneous pain and scales appeared the most relevant. Recently, an expert group on ichthyosis concluded that itch was considered the third most important item that should be prioritized for further research, given its impact on the life of afflicted patients.⁹ Nonetheless, little is currently known about the severity of itch in ichthyosis. The exact pathophysiology of itch in ichthyosis remains to be elucidated, but it may be related to skin inflammation.¹⁰

No studies have been reported that specifically investigated the issue of itch in ichthyosis. However, itch has occasionally been reported as an additional parameter in several studies, for instance when investigating the effect of topical therapies in ichthyosis. In a study where an emollient cream was used to reduce the severity of ichthyosis, the cutaneous xerosis evolution was assessed as a primary criterion using the SRRC score and pruritus was assessed as a secondary criterion.¹¹ On a visual analogue scale (VAS ranging from 0 (no itch) to 10 (very severe)), pruritus at baseline was scored 3.41 and 3.76 in the vehicle and treatment group, respectively. At day 84 post treatment, the scores were reduced to 1.07 and 0.78 respectively. No separate data were available for the different types of ichthyosis (ichthyosis vulgaris, X-linked recessive ichthyosis, ARCI and other types). Another study to assess the efficacy of a specific hydrotherapy on quality of life (using the DLQI score) and on clinical symptoms in ichthyosis patients showed that the DLQI scores were significantly improved at the end of the treatment but also at 3 and 6 months after the therapy.¹² Pruritus was assessed as part of an “ichthyosis score”, where pruritus carried a weight of 10% to the total score. At baseline, pruritus was scored 4.9 ± 2.4 on a VAS scale. At 3 months post treatment, a 39% mean reduction was noted in the severity of pruritus. A study assessing the quality of life in Swedish children with congenital ichthyosis revealed that “itchy or painful skin” was one of three items with the highest impact.¹³ Pruritus in particular was considered problematic in 5 out of 15 children. In a study on the efficacy of oral liarozole in lamellar ichthyosis, itch was measured as a secondary

outcome variable. At baseline, pruritus scores were between 13.3 and 14.7 on a maximum scale of 36.¹⁴ Treatment with oral liorzole failed to reduce pruritus scores.

Treatment of pruritus in ichthyosis is mainly symptomatic, as a specific cure is not at hand. Topical skin care, using emollients, remains the basis of treatment. Antihistamines, oral retinoids or other systemic therapies (eg. antidepressants) can be tried in case of persistent pruritus, although they have usually little or no effect.¹⁵

To our knowledge, this is the first study particularly addressing the issue of itch in ichthyosis patients in a comprehensive way by assessing different dimensions of itch. This study demonstrates that itch is a significant issue for most forms of congenital ichthyosis, influencing several aspects of daily life. It is important to mention however, that only in Netherton patients the frequency, duration and severity of itch is comparable to that of patients with atopic dermatitis. For the other subtypes of ichthyosis, the parameters associated with itch appeared to be less severe (Fig. 1A).

Unpublished data in this paper learned that itch is not only related to the severity of disease but depends also on the underlying genetic defect. Future studies should focus on underlying itch mechanisms. Moreover it would also be important in the design of new drugs for treatment of ichthyosis that they are evaluated for their capacity to control itch, especially in those forms where it has important consequences in daily life. These results are important, on the one hand for a better understanding of the diseases, on the other hand because this should be considered when developing new therapies for ichthyosis patients.

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Figure 1. Panel A. Radar graph expressing the itch profile of the 4 ichthyosis subgroups. Six domains of itch were calculated by summing raw scores and transforming them to a scale ranging from 0 to 100. Higher scores represent more itching. Itch scores of patients with atopic dermatitis are included as a reference. Data on the surface area of patients with atopic dermatitis are lacking, as surface area was not assessed in the version of the LIS that was used for atopic dermatitis patients (data from our previous study)³. **Panel B. Itch severity in the 4 ichthyosis subgroups, including patients with atopic dermatitis as a reference.** Data are expressed as boxplots, ranging from the first quartile to the third quartile. A vertical line goes through the box at the median. The whiskers go from each quartile to the minimum or maximum.

Figure 2. Correlogram of the dimensions of itch, reflecting the degree to which 2 variables are intercorrelated. All correlations were statistically significant at the level of 0.01.

Table 1: Itch profile in 87 patients with ichthyosis who experienced itch. Using specific algorithms, subscale scores on 6 domains (itch frequency, duration, severity, distress, consequences and surface area) can be calculated by summing the raw scores and transforming them to a scale ranging from 0 to 100. Higher scores represent more itching.

Itch parameter	Total sample	ARCI	Keratinopathic	XLRI	Netherton
Frequency	61.4 +/- 29.5	65.9 +/- 27.8	56.9 +/- 28.2	40.9 +/- 30.2	75.0 +/- 27.4
Duration	21.5 +/- 33.7	22.4 +/- 34.8	13.72 +/- 29.0	18.5 +/- 24.2	50.0 +/- 45.9
Severity	42.4 +/- 25.5	43.3 +/- 23.6	40.5 +/- 30.8	24.5 +/- 13.1	57.6 +/- 24.7
Distress	34.7 +/- 29.0	33.9 +/- 27.8	38.9 +/- 32.7	17.9 +/- 20.8	43.7 +/- 27.5
Consequences	24.2 +/- 19.0	23.5 +/- 17.6	26.1 +/- 21.4	17.9 +/- 11.6	33.6 +/- 30.4
Surface area	42.9 +/- 30.5	44.0 +/- 28.4	39.7 +/- 39.0	33.0 +/- 15.6	66.0 +/- 36.4

Values are mean $\pm$ SD

Table 2: Circumstances, consequences and sensory characteristics of itching in 87 patients with ichthyosis. Values are expressed in absolute numbers or percentages.

	Total sample n (%)	ARCI n (%)	Keratino- Pathic n (%)	XLRI n (%)	Netherton n (%)
<u>CIRCUMSTANCES IN WHICH ITCH OCCURS</u>					
During a change in the weather	40 (46.0)	22 (42.3)	8 (47.1)	4 (44.4)	4 (66.7)
During spells of pain	21 (24.1)	10 (19.2)	5 (29.4)	1 (11.1)	4 (66.7)
When making a movement	10 (11.5)	4 (7.7)	2 (11.8)	2 (22.2)	1 (16.7)
When sweating	28 (32.2)	14 (26.9)	7 (41.2)	2 (22.2)	4 (66.7)
In a hot environment	42 (48.3)	27 (51.9)	7 (41.2)	1 (11.1)	5 (83.3)
In a cold environment	23 (26.4)	12 (23.1)	5 (29.4)	4 (44.4)	1 (16.7)
When standing up after sitting or lying down	15 (17.2)	11 (21.2)	3 (17.6)	0 (0)	0 (0)
When I was stressed out	45 (51.7)	28 (53.8)	9 (52.9)	2 (22.2)	5 (83.3)
On contact with air	16 (18.4)	12 (23.1)	1 (5.9)	2 (22.2)	1 (16.7)
When touching the skin	20 (23.0)	9 (17.3)	7 (41.2)	3 (33.3)	0 (0)
<u>CONSEQUENCES OF ITCHING</u>					
Lesions from scratching	83.3%	82.4%	93.7%	75.0%	66.7%
Reduced social contact due to itching	32.9%	36.0%	20.0%	25.0%	50.0%
Reduced quality of life due to itching	59.0%	58.8%	56.2%	62.5%	60.0%
Disturbed my routine activities due to itching	46.3%	49.0%	37.5%	50.0%	50.0%
Difficulties in falling asleep due to itching	69.4%	66.7%	76.5%	62.5%	83.3%
Waking up due to itching	54.8%	49.0%	56.2%	62.5%	66.7%
Needed sleeping pills due to itching	22.2%	16.3%	31.2%	12.5%	40.0%
Loss of appetite due to itching	12.0%	8.0%	12.5%	12.5%	33.3%
Bad mood due to itching	61.9%	62.7%	56.2%	62.5%	66.7%
Changes in behavior toward others due to itching	50.0%	49.0%	37.5%	62.5%	66.7%
Loss of concentration due to itching	61.4%	60.0%	62.5%	62.5%	66.7%
<u>SENSORY CHARACTERISTICS OF ITCHING</u>					
A tickling sensation	41 (48.2)	29 (55.8)	7 (43.8)	3 (37.5)	1 (16.7)
A tingling sensation	11 (12.6)	9 (17.3)	1 (5.9)	0 (0)	0 (0)
A prickling sensation	36 (41.9)	22 (42.3)	5 (31.3)	3 (33.3)	5 (83.3)
A stinging sensation	12 (13.8)	9 (17.3)	0 (0)	1 (11.1)	2 (33.3)
A burning sensation	37 (42.5)	19 (36.5)	8 (47.1)	4 (44.4)	5 (83.3)