*Clinical study*

# ICHTHYOSES IN SLOVENIAN POPULATION PRELIMINARY REPORT

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## ABSTRACT

*Introduction.* Ichthyoses are a heterogeneous group of disorders, up to now no generally accepted classification exists. Additionally to the recessive x-linked ichthyosis (RXLI) in certain families of patients with lamellar ichthyosis (LI) the metabolic defect was elucidated. As known from previous studies the palmoplantar keratodermas and other genodermatoses are quite frequent in Slovenia. As there are no data on prevalence of ichthyosis in our country we decided to carry out a pilot study.

*Methods.* Out- and in-patients' records were studied in the University Department of Dermatology in Ljubljana as well as in the dermatology departments of General Hospitals in Maribor and Celje. In Ljubljana data for a 20-year-period, in Maribor for a 10-year period and in Celje for an even shorter period were collected.

*Results.* In Ljubljana 190 cases were recorded: 167 cases of ichthyosis vulgaris (the documentation did not allow a differentiation between the autosomal dominant ichthyosis and RXLI), 19 of non-bullous ichthyosiform erythroderma (NBIE) and 4 cases of LI. In Maribor there were 95 cases of ichthyosis vulgaris and 5 of NBIE. In Celje were registered 36 cases of autosomal dominant ichthyosis (ADI), 8 of RXLI, 4 of NBIE and 1 with neurological implication. Altogether 339 patients were recorded.

*Discussion.* Although the material obtained is not suitable for an exact statistical analysis, the total of 339 cases of ichthyoses represents a rather high figure for a population of barely 2 million. The result includes only a minor number of affected family members.

*Conclusion.* As the study is still in course, a substantially higher number of ichthyosis cases is to be expected.

*KEY WORDS*

*ichthyosis, epidemiology, Slovenia*

## INTRODUCTION

In the literature there are some data on the prevalence of various types of ichthyoses based mainly on observations by clinicians and mostly not collected according to strict statistical rules. A further disadvantage is that there is no generally accepted classification of ichthyoses in order to make the data

*Table 1. Ichthyosis patients diagnosed at the Department of dermatology, University Medical Centre, Ljubljana.*

| DIAGNOSIS TYPE OF ICHTHYOSIS | TOTAL |
|---|---|
| ADI | 167 |
| RXLI | |
| NBIE | 19 |
| LI | 4 |
| with neurological symptoms | |
| TOTAL | 190 |

LEGEND:
ADI *autosomal dominant ichthyosis vulgaris*
RXLI *recesive x-linked ichthyosis*
NBIE *non-bullous ichthyosiform erythroderma*
LI *lamellar ichthyosis*

*Table 2. Ichthyosis patients diagnosed at the Department of dermatology, General Hospital Maribor.*

| DIAGNOSIS TYPE OF ICHTHYOSIS | TOTAL |
|---|---|
| ADI | 95 |
| RXLI | |
| NBIE | 5 |
| LI | |
| with neurological symptoms | |
| TOTAL | 100 |

LEGEND:
ADI *autosomal dominant ichthyosis vulgaris*
RXLI *recesive x-linked ichthyosis*
NBIE *non-bullous ichthyosiform erythroderma*
LI *lamellar ichthyosis*

by various authors comparable. During the last five years facts have been accumulating revealing that ichthyoses are a rather heterogeneous group of disorders characterized by generalized persistent scaling, but caused by different pathogenetic mechanisms. The problem is additionally complicated due to manifold non-cutaneous manifestations relatively often accompanying skin symptoms.

## PREVALENCE

Autosomal dominant ichthyosis vulgaris (ADI) is characterized by high penetrance and is the most common condition in this group of disorders with an estimated prevalence of 1:250 to 1:320 (1). It seems to be more frequent in certain areas in India (2). Recessive X-linked ichthyosis (RXLI) is in principles restricted to males, however female carriers may demonstrate some of the features. Its prevalence has been recorded in the literature at 1:6000 (3), in Israel 1:9500 (4) and in Spain 1:4125 (5). By screening maternal sera for Down syndrome in 15375 pregnancies in Germany, 5 in 7500 male births were affected by steroid sulfatase (STS) deficiency which is a reliable marker for RXLI (6), giving the prevalence rate of 1:1500 in this selected group. Prevalence of severe autosomal recessive lamellar ichthyosis (LI) is estimated at 1:200 000 (7).

## PATHOGENESIS

The clinical diagnosis of ichthyosis includes a number of pathogenetically different conditions clinically displaying often a more or less similar appearance. The underlying metabolic or molecular-biologic mechanisms have been elucidated up to now (at least partially) only in a few of these conditions:

In 1978 Shapiro et al demonstrated the deficiency of the enzyme steroid sulfatase (STS) in cultured fibroblasts of patients with RXLI (8). The action of this enzyme which splits cholesterol sulfate into cholesterol and sulfate in the upper stratum corneum (SC), is essential for normal shedding. An increased content of cholesterol sulfate seems to be responsible for formation of scales in RXLI.

In certain patients with severe LI it was possible to prove complete linkage to several markers within a 9.3 cM region on chromosome 14q (7). Transglutaminase 1 (TGM-1) which is responsible for cross-linking of proteins during formation of cornified cell envelope CE), maps to this interval. In a study of 23 families with severe LI Parmentier et al detected a linkage of the disease to TGM-1 in 10 families, while in further 13 families TGM-1 was not linked to the disease (9). They concluded that LI is genetically a heterogeneous disorder, it not in all instances linked to a TGM 1 deficiency.

Biochemical analysis of ichthyotic scales revealed an increase of cholesterol sulfate in scales from RXLI patients (10), and an increase of n-alkanes in scales of patients with NBIE (11). A more detailed explanation of pathogenesis was given earlier (12).

*Table 3. Ichthyosis patients diagnosed at the Department of dermatology, General Hospital Celje.*

| DIAGNOSIS TYPE OF ICHTHYOSIS | TOTAL |
|---|---|
| ADI | 36 |
| RXLI | 8 |
| NBIE | 4 |
| LI | |
| with neurological symptoms | 1 |
| TOTAL | 49 |

LEGEND:
ADI *autosomal dominant ichthyosis vulgaris*
RXLI *recesive x-linked ichthyosis*
NBIE *non-bullous ichthyosiform erythroderma*
LI *lamellar ichthyosis*

*Table 4. Ichthyosis patients diagnosed in Slovenia.*

| DIAGNOSIS TYPE OF ICHTHYOSIS | TOTAL |
|---|---|
| ADI | 298 |
| RXLI | 8 |
| NBIE | 28 |
| LI | 4 |
| with neurological symptoms | 1 |
| TOTAL | 339 |

LEGEND:
ADI *autosomal dominant ichthyosis vulgaris*
RXLI *recesive x-linked ichthyosis*
NBIE *non-bullous ichthyosiform erythroderma*
LI *lamellar ichthyosis*

## MATERIALS AND METHODS

Out- and in-patients' records were studied in the University Department of Dermatology in Ljubljana as well as in the dermatology departments of the General Hospitals in Maribor and Celje. All three mentioned departments are staffed with competent dermatologists. In Ljubljana a 20-year period was covered, whereas due to technical difficulties in Maribor a 10-year and in Celje a 2-year period. The dermatology department in Ljubljana is covering an area of approximately 800 000, the one in Maribor 450 000 and in Celje 250 000 inhabitants. Total population of Slovenia is close to 2 million.

The existing clinical classifications of ichthyosis are unsatisfactory, which is due to the fact that the etiopathogenesis of various forms is still not elucidated. We have used the one which is compatible with the one by Griffiths et al (12) and by Williams (13), it was elaborated in details as already mentioned in a previous publication (12)

Unfortunately in the existing records there were often not sufficient data for separation of the ADI from RXLI. LI was not an accepted as a diagnostic entity years ago, while erythrodermia ichthyosiformis non-bullosa (NBIE) was diagnosed relatively frequently.

## RESULTS

The data from Ljubljana are presented in table 1, data from Maribor in table 2 and from Celje in table 3. Altogether, ichthyosis was diagnosed in Slovenia in 339 instances. There were 306 ADI and RXLI patients which corresponds to a combined prevalence of 15.3 in 100 000. The diagnosis NBIE was made in 28 cases giving a prevalence of 1.4 in 100 000. and LI in 4 cases. Table 4.

## DISCUSSION

Desquamation is a process in which corneocytes are detached from the skin surface in the terminal differentiation stage of the epidermis. It is still poorly understood and the nature of pathological desquamation of SC in ichthyosis remains unsolved. In RXLI there is evidence that the presence of cholesterol sulfate in the outer SC due to deficient activity of the STS might be responsible for the formation of scales (10).

Recent studies have shown that desmosomes also play a vital role in SC adhesion and that their degradation may be a prerequisite for normal SC desquamation. It was reported that desmoglein 1 (DSG-1) which is a desmosome protein is associated with corneocyte adhesion in plantar SC (15). Suzuki et al incriminate the decreased activity of both the trypsin-like and chymotrypsin-like serine proteases in the ichthyotic SC and the following decreased degradation of DSG-1 for the abnormal desquamation (16).

Many efforts were dedicated to the study of LI. The terminal differentiation in the granular layer

and the transition to corneocytes results in formation of a cornified envelope filled with a keratin matrix. Transglutaminase (TGM) catalyzes the calcium-dependent cross-linking of proteins through the formation of Ne(gama glutamyl) lysine isopeptide bonds. In the epidermis involucrin and loricrin are known to be cross-linked by TGMs in the process of formation of the CE. The newly synthesized protein undergoes post synthetic fatty acid acylation resulting in attachment of the fatty acids and ceramides derived from lamellar bodies to the surface of the envelope (16). TGM-1 plays a key role in the process of terminal differentiation and formation of the CE. Further studies stressed the importance of TGM-1 in the pathogenesis of LI specially in linking LI to a chromosom 14q region maping for TGM-1 (18), but further studies may reveal additional pathogenetic mechanisms

This short review reveals how difficult it is to establish a classification of ichthyoses suitable for every day clinical use and at the same time reflecting all the new achievements.

## CONCLUSIONS

1. The preliminary aim of the study in course is to gather data for future genetic counseling. Previous investigations concerning various palmoplantar keratodermas and cutaneous porphyrias which have been carried out years ago, have shown that genetic defects are relatively frequent in the population of Slovenia.

2. The modern genetic counseling is based on sophisticated biochemical and molecular-biologic techniques, which have to a great deal supplemented the methods used before.

3. New techniques are complicated, time consuming and expensive, the biologic material (usually blood) has to be taken from patients as well as from their affected and unaffected family members. For this reason a careful case selection is necessary.

4. Clinical classification of various types of ichthyoses has to take into consideration the latest developments in the pathogenesis but still to be relatively simple and suitable for routine clinical work.

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