Original paper

High frequency of primary hereditary ichthyoses in the North-East region of Cairo, Egypt

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Abstract

Introduction: Inherited ichthyoses are caused by mutations in various genes important for keratinocyte differentiation and epidermal barrier function. Although ichthyoses are rare disorders, they require costly long-term medical management, and thus there is a need for efficient preventive and therapeutic strategies.
Aim: We performed a retrospective study to determine the frequency, types, clinical presentation and associated genomic errors of primary hereditary ichthyoses in Egyptian patients and their relatives consulting the Genetics Clinic, Pediatric Hospital, Ain Shams University.
Material and methods: The outpatient log books of patients between January 2000 and December 2014 were reviewed, and diagnosis of new patients was confirmed through examination by a dermatologist. All epidemiologic, demographic, and clinical data were extracted and recorded in especially designed data collection forms.
Results: The occurrence rate of primary hereditary ichthyoses in our study was 25.7% of genodermatosis patients attending the genetics clinics and 1 per 2359 patients attending the Pediatric Hospital. The commonest type of ichthyosis in our study was Lamellar ichthyosis (38%), followed by congenital ichthyosiform erythroderma (26.8%). Consanguineous marriage was reported among the parents of 79% of patients and positive family history was reported in 72% of patients.
Conclusions: To the best of our knowledge, this preliminary study is the first report on the clinico-epidemiological features of primary hereditary ichthyoses in Egypt. The high rate of prenatal consanguinity among parents of our patients may account for the high frequency of these genodermatoses in Egypt. This highlights the importance of genetic counselling and prenatal diagnosis in Egypt.

Key words: Egypt, frequency, hereditary, ichthyosis, primary.

Introduction

Inherited ichthyoses, defined as the generalized form of Mendelian disorders of cornification, are characterized by visible scaling and/or hyperkeratosis of most or all of the skin. This etiologically and phenotypically heterogeneous group of conditions is caused by mutations in various different genes important for keratinocyte differentiation and epidermal barrier function [1]. More than 25 genes have been identified that encode a wide spectrum of epidermal proteins, including enzymes of lipid metabolism and of peptide cross-linking, proteases and their inhibitors, epidermal structural proteins, and proteins involved in cellular communication, signaling and gene transcription. Abnormalities in any of these components result in a rather stereotypic epidermal response with epidermal hyperplasia and the formation of excess stratum corneum (SC) accompanied by abnormal delayed and/or disordered desquamation, with visible accumulation of scales on the skin surface [2, 3].

Over the years much progress has been made in defining the molecular causes of ichthyosis, however there is no internationally accepted classification and terminology. It was agreed that classification remains clinically based and distinguishes between syndromic and non-syndromic ichthyosis forms [1, 4, 5]. Distinguishing between specific subtypes requires careful assessment of clinical features. Associated cutaneous and extracutaneous features, as well as disease onset and clinical course, provide important diagnostic clues. In all forms of Mendelian Disorders of Cornification (MeDOC), the clinical presentation may be variable in both severity and in the expression of associated features, and at times

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additional laboratory testing including microscopy and genetic analyses is required [1, 6–8].

There is limited clinico-epidemiologic information on primary hereditary ichthyoses (PHI) in Egypt. Given this background, the objective of this study was to illustrate phenotypic variability and frequency of various types of PHI in an ethnically fairly homogeneous country like Egypt. Herein, we conduct a retrospective study to determine the frequency, types, clinical presentation and associated genomic errors in PHI patients and their relatives in the Genetics Clinic, Pediatric Hospital, Ain Shams University. This hospital is located in the northeast section of Cairo, and is the second largest hospital in Egypt. It has a high standard of health care, so nearly all patients in this area attend this hospital for consultation. Also patients come nearly from all regions of Egypt to obtain good health care. So, the frequency and characteristics of ichthyosis in this hospital will represent that in the general population to a great extent.

Material and methods

The present study comprised 284 index patients with PHI out of 1106 index patients with genodermatoses who were registered at the Genetics outpatient clinic, pediatric hospital, Ain Shams University, and 670,000 patients attending the whole pediatric hospital between January 2000 and December 2014.

The outpatient department log books of these patients were reviewed by a geneticist and a dermatologist, and diagnosis of new patients was confirmed through examination by a dermatologist. The medical records of these patients were reviewed and all the epidemiological, demographic, and clinical data were extracted and recorded in especially designed data collection forms.

Diagnosis depended on typical findings at clinical examination, detailed patient and family history, age of onset, sex, scales distribution, presence or absence of erythema, atopic dermatitis, ectropion, mental retardation, convulsions, speech defect and other neurological manifestations. Index pedigree design including parental relationship, and laboratory work up when needed for some patients were also done or reviewed through medical records.

Patients with extra cutaneous findings were also examined by other specialists to assess the possibility of syndromic ichthyosis. Patients prone to infection were examined for the presence of lipid droplets in leucocytes indicating Chanarin-Dorfman syndrome.

Statistical analysis

The collected data were subsequently entered into a computer database and analyzed statistically using the SPSS program (SPSS Inc. Chicago, IL, USA). This study was approved by the local ethics committee, and all new patients or parents gave informed consent before enrollment in the study.

Results

Epidemiological features and clinical findings of 284 patients with PHI are summarized in Table 1.

Occurrence rate

Out of 1106 new genodermatosis patients attending the Genetics outpatient clinics during the period of the study, 284 patients had the diagnosis of PHI confirmed clinically and after full investigations. The occurrence rate was 25.7% of genodermatoses, and 1 per 2359 patients attending the Pediatric hospital, Ain shams University, Cairo, Egypt.

Epidemiological profile

Of the 284 patients with ichthyosis 138 (48.6%) were males and 146 (51.4%) were females, giving a male to female ratio of 0.9 : 1. Consanguineous marriage was reported among the parents of 224 patients out of 284 (79%), being most noticeable in lamellar ichthyosis (LI) parents (92 out of 284, 32.4%). Family history of a similarly affected sib or other relative was reported among 204 out of 284 patients (71.6%).

Age of onset

In ichthyosis vulgaris (IV) group, all patients had their presentation after the third month of life. In the X-linked ichthyosis (XLI) group, most of the patients presented at birth with collodion membranes (70%). In the LI and congenital ichthyosiform erythroderma (CIE) group, all patients presented at birth with a collodion membrane. Most of our Sjogren-Larsson syndrome (SLS) group (75%) presented after the first month of life with diffuse erythema and scaling.

Clinical phenotypes and skin findings

The commonest type of ichthyosis in our study was LI 108/284 (38%), followed by CIE 76/284 (26.8%), IV; 38/284 (13.4%) and XLI; 30/284 (10.6%). Sjogren-Larsson syndrome was detected in 32/284; 11.3% of our patients.

Of the 284 patients with PHI in our study, 196 (69%) were born with a collodion membrane. These comprised all babies with LI and CIE, and 12 babies with XLI (4.2%) who were born with exaggerated skin desquamation and peeling at birth. Thirty two babies out of 284 (11.3%) with SLS were born with diffuse erythema and scaling. In LI and CIE, the scales were mostly generalized and ranged from fine and white (in CIE) to thick, dark and plate like (in LI). While in patients with IV, the scales were small, greyish-white and semi-adherent. In XLI, the scales were large, dark, mainly on the trunk and extensors. The flexures were spared both in IV and XLI patients. In SLS

patients, the scales were fine with generalized erythema. Severe scaling of the scalp (dandruff) was found in 72 patients of the 284 (25.3%): 40 with CIE (14%), 15 with IV (5.3%), 10 with LI (3.5%) and 7 with XLI (2.5%). Palmoplantar keratoderma (PPK) was seen in 42 (15%) patients of the 284, 25 (9%) patients with CIE, and 17 (6%) patients with LI. Nail abnormalities were observed in 22 cases of the 284 (4.6), 13 with CIE (4.6), and 9 with LI (3.2). Atopic dermatitis was reported in 38 patients out of 284, all of them had IV.

Ocular findings

Ectropion was observed in 12/108 (11%) of patients with LI, and 24/76 (31.6%) of patients with CIE. Corneal opacity was observed in 16/30 (53%) patients with XLI. Recurrent conjunctivitis mostly of the bacterial type was

Table 1. Epidemiological features and clinical findings in 284 patients with hereditary ichthyosis

Clinico-epidemiologic data	Ichthyosis vulgaris (IV) (%)	X-linked ichthyosis (XLI) (%)	Lamellar ichthyosis (LI) (%)	Congenital ichthyosiform erythroderma (CIE) (%)	Sjogren-Larsson syndrome (SLS) (%)	Total (%)
Patients, number (%)	38 (13.4)	30 (10.6)	108 (38)	76 (26.8)	32 (11.3)	284 (100)
Egyptian nationality	13.4	10.56	38	26.76	11.26	100
Sex: male	5.63	9.85	15.49	11.26	6.33	48.59
Positive parental relationship	9.15	7.39	32.39	21.83	8.09	78.87
Positive family history	10.17	7.36	31.22	18.94	3.85	71.57
Age of onset:						
Onset at birth/neonatal period	–	7.4	38	26.8	2.9	75
Onset after 1 month of life (1–3 m)	13.4	3.2	–	–	8.5	25
Skin lesions:						
Collodion baby or exaggerated skin desquamation and peeling at birth	–	4.2	38	26.76		69
Diffuse erythema and scaling					11.3	11.3
Generalized scales, which range from fine and white to thick, dark and plate like	–	–	15 Coarse plate-like scales	16 Fine grey white scales		31
Adherent brown scales/extensor surfaces	13.4	10.6	–	–	–	24
Preserved flexures	13.38	10.56	–	–	–	24
Dandruff	5.3	2.5	3.5	14		25.3
Palmoplantar keratoderma			6	9		15
Nail abnormalities			3.2	4.6		7.7
Atopic dermatitis	13.4					13.4
Corneal opacity		5.6				5.6
Ectropion	–	–	4.2	8.4	–	12.7
Recurrent conjunctivitis		2.5	4.2	3.2		9.9
Mental retardation/learning difficulties	–	2.8	–	3.2	11.3	17.3
Seizures/muscle spasms	–	–	–	–	11.3	11.3
Speech defect	–	–			6	6
Growth retardation/short stature	–	–	15	5	2	21.4
Eclabion			19.4	6		25.4
Alopecia	–	–	3.5	6	–	9.5

observed in 9/76 (12%) patients with CIE, 12/108 (11%) patients with LI and 7/30 (23%) of patients with XLI.

Other medical associations

Forty-nine (17.3%) of our PHI patients were reported to have mental retardation (MR) or learning difficulties compared with their unaffected siblings or peers. All SLS patients had mental retardation or learning difficulties. Eight XLI patients (8/30; 27%), and 9 CIE cases (9/76; 12%) had also learning difficulties. Seizures or muscle spasms were reported in all patients with SLS. Speech defect was reported in 17 patients with SLS (17/284; 6%). Of the 284 patients, 61 (21.4%) were below the third percentile for weight or height; 42 (15%) had LI, 14 had CIE (5%), and 5 patients with SLS (2%). Alopecia areata (AA) was reported in 17/76 patients with NBCIE (22.4%) and 10/108 patients with LI (9.3%). Eclabion (eversion of the lips) was seen in 72 cases; 55 with LI and 17 with CIE.

Table 2. Associated medical conditions defined among relatives of 284 patients with PHI

Associated medical conditions among relatives	Number	%
Polydactyly	6	6.316
IDDM	3	3.158
Glaucoma	1	1.053
Osteogenesis imperfecta	1	1.053
Isolated growth hormone deficiency	1	1.053
Goitre	1	1.053
Congenital heart diseases	4	4.211
GMME	14	14.737
Hypertension	11	11.579
Bronchial asthma	3	3.158
Anencephaly	1	1.053
Squint	1	1.053
Allergic dermatitis	4	4.211
Psoriasis	3	3.158
Vitiligo	2	2.105
Tumors	6	6.316
Peptic ulcer	1	1.053
Mental deficiency	12	12.632
Infertility	7	7.368
Talipus equinovarus	4	4.211
Deaf mutism	4	4.211
Speech defect	2	2.105
Short stature	2	2.105
Hydrocephalus	1	1.053
Total	95	100.000

Associated medical conditions among relatives

Ninety-five associated medical conditions were defined among relatives of 284 patients with ichthyosis (33.5%) (Table 2).

Discussion

Although ichthyoses are rare disorders, they require costly long-term medical management, and thus there is a need for efficient preventive and therapeutic strategies [9]. Prevalence rates among Middle Eastern populations are unknown; however, the high frequency of consanguineous marriages characteristic of these populations suggests that due to their mode of inheritance, these diseases may be particularly common in this region [8, 10]. There is limited clinico-epidemiological information on PHI outside of North America and Europe [11, 12]. To our best knowledge, there are no recent published reports in the medical literature about the incidence of PHI in Egypt. We present a preliminary survey of PHI in the population of the Eastern Province of Egypt.

Our study shows that the occurrence rate of PHI was 25.7% of genodermatosis patients attending the genetics clinics and 1 per 2359 patients attending the Pediatric Hospital, Ain Shams University, Cairo, Egypt. The occurrence rate of PHI in the Eastern Province of Saudi Arabia study was 0.67% or 7 per 1000 new dermatology cases [6]. In addition, another study stated that the incidence of moderate to severe ichthyosis is 5 to 10 per 100,000 people every year in the United States [12]. The high occurrence rate in our study probably reflects a high incidence of PHI in Egyptian population, which is possibly secondary to high consanguinity rates in the parents of Egyptian patients. Male to female ratio in our study was 0.9 : 1. This was different from other studies, in which a male predominance was found [6, 13].

Consanguineous marriage was reported among 79% of the parents of our patients, which was significantly high being most noticeable in LI parents (32%). Our results were similar to those of Shawky *et al.*, who stated that the rate of consanguineous marriage is high in Egypt (35.3%), especially among first cousins (86%) [14]. Consanguineous marriage was also reported among 64% of Egyptian ichthyosis patients in another study [13]. The high frequency in these two studies was attributed to the traditional intrafamilial cousin first degree marriage in Egyptian families. On the other hand, a study in 2008 reported that parental consanguinity was noted in 60% of Tunisian patients [15]. Our study showed a high proportion of patients with a positive family history (72%). Similar results were reported by another study (75%) [6], while it was 25.7% in a Tunisian study [15].

The commonest type of ichthyosis in our study was LI (38%) followed by CIE which constituted 26.8% of all cases. This was in agreement with Shawky *et al.* [13] who performed a study on genodermatoses prevalent among

Egyptian children. The most common type was ichthyosis (26.5%), of whom LI was the most common (88%) followed by IV (12%). Inherited as an autosomal recessive trait, the high rate of LI and CIE in the Eastern Province of Egypt possibly reflects high rates of consanguinity in this region. On the other hand, the incidence of LI was 5.6% in a study done in Saudi Arabia, 2006 [7]. This was in contrast to the results of other studies that considered CIE a rare or uncommon inherited ichthyosiform dermatosis [16–19].

In our study, the frequency of IV was 38/284 (13.4%) and XLI was 30/284 (10.6%). SLS was detected in 11.3% of our patients. This was in contrast to another study which reported that the commonest type of ichthyosis was IV (44.7%), followed by CIE (29.6%), XLI (16.9%), LI (5.6%) and EH (4.2%) [7]. In addition, a study in 2006 reported that IV is the most common inherited disorder of keratinization [20]. These different incidences that are characteristic for each geographic region, may be reflected in the genotypes of specific ethnic groups [11, 16].

Dandruff was found in 25% of our patients and PPK in 15%. Our findings are consistent with observations in the literature [4, 6, 20]. Atopic dermatitis mostly accompanied by asthma and pruritus, was reported in 13.4% of our patients, all of them had IV which is considered the most common type of PHI reported to be associated with atopic dermatitis in the medical literature [20, 21].

Forty-nine (17.3%) patients of our PHI group were reported to have mental retardation (MR) or learning difficulties compared with their unaffected siblings or peers. All SLS patients had mental retardation or learning difficulties. Eight XLI patients (8/30; 27%), and 9 CIE cases (9/76; 12%) had also learning difficulties. A study in 2005 reported that mental retardation can be seen in some XLI patients and is thought to be due to deletions encompassing neighboring genes [22]. Speech defects were reported in 17 patients with SLS (17/32; 6%). Speech defects are a common finding in SLS cases [23]. Twenty-one percent of our patients were below the third percentile for weight or height. These findings were also reported previously [20]. Alopecia was reported in 17/76 patients with CIE (22.4%) and 10/108 patients with LI (9.3%). This finding was consistent with previous reports [4, 20]. Eclabion was seen in 55 cases with LI and 17 cases with CIE. Eclabion is a characteristic clinical feature of LI [4, 6].

Ninety-five associated medical conditions were defined among relatives of 284 (33.5%) patients with ichthyosis. Genealogic analysis of pedigrees of index patients with ichthyosis revealed an apparently high incidence of other genetic anomalies which manifested simultaneously or segregated randomly among many of proband's relatives. The identification of isolated ichthyosis as well as isolated deafness or mental deficiency among certain index kindreds, could advocate the possibility of linkage of mutant gene loci mediating both types of anomalies.

Due to the recent advances in our understanding of the genetic defects underlying severe congenital ichthyosis, it has become possible to make DNA-based prenatal diagnoses for congenital ichthyosis families by sampling chorionic villus or amniotic fluid in the earlier stages of pregnancy. That lowers the risk to fetal health and reduces the burden on mothers compared with prenatal diagnoses by fetal skin biopsy [24]. Molecular diagnosis is a crucial diagnostic tool and has become in some countries the gold standard for the diagnosis of the ichthyoses and Mendelian disorders of cornification (MEDOC) in general [4]. Several powerful tools for the treatment of genetic disorders, such as siRNA gene silencing technology, read-through compounds to read through nonsense mutations, and improved corrective gene transfer techniques have been introduced. Fortunately, the skin is the most easily accessible organ for these novel treatment approaches. Thus, the development of novel, highly effective therapeutic methods in the near future is expected [24].

Conclusions

This study shows that the occurrence rate of PHI was 25.67% of genodermatosis patients attending the Pediatric Clinic, Ain Shams University, Cairo, Egypt between January 2000 and December 2013. The male to female ratio was of 0.9 : 1. Consanguinity among the parents was significantly high being most noticeable in LI parents. The commonest type of ichthyosis in our study was LI followed by CIE. Sixty-nine percent of our patients were born with collodion membranes. Our survey reflects the geographic and ethnic variation in the incidence and clinical features of this group of genodermatoses and highlights the importance of prenatal diagnosis in this region.

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This study was conducted at the Pediatric Hospital, Ain Shams University, Cairo Egypt.

Conflict of interest

The authors declare no conflict of interest.

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