Autosomal Dominant Ichthyosis and X-linked Ichthyosis

Comparison of their Clinical and Histological Phenotypes

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The clinical and histologic distinction between X-linked recessive and autosomal dominant ichthyosis was studied by evaluating 12 classical differential parameters in 85 patients. Thirty-three of them had X-linked and 52 autosomal dominant ichthyosis. Eight of these parameters were generally helpful in the differential diagnosis: age of onset, severity of involvement, scale size, chapping of hands and feet, atopic background, influence of warm weather, corneal opacities and state of the granular layer. Involvement of skin folds, keratosis pilaris, increased palmo-plantar markings and improvement with age were unreliable. In the literature, age of onset and corneal opacities were additionally found unreliable; the histology was of limited value in two reports. Therefore, we concluded that the herein evaluated differential criteria seem to be valid mainly when considering groups of patients. For the individual case, an error in diagnosis, particularly in X-linked ichthyosis, is not rare when relying solely on these criteria. When in doubt, determination of steroid sulphatase activity is mandatory. ***Key words: Genodermatoses; Keratinization; Steroid Sulphatase; Corneal opacities.***

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The vulgaris-type ichthyoses are the most common ones. Although they are inherited either as an autosomal dominant or an X-linked recessive trait, they may resemble each other clinically. Differential criteria between X-linked recessive (XL) and autosomal dominant ichthyosis (AD) were published by a group of British investigators in the late 1960s (1–4). According to these criteria (1, 2), XL appears earlier, is more severe, has larger scales, shows more often involvement of skin folds and neck but less often chapping of hands and feet, is not accompanied by keratosis pilaris and never affects the front and sides of the face or the palms and soles; an atopic background is less common in XL and while it improves more often in warm weather it does not do so with advancing age. Histologically, compared with AD, the granular layer in XL is prominent or thickened (3). Finally, punctate corneal opacities are much more common in XL (4). These differential guide-lines have been adopted by many authors and are referred to here as the "classical differential criteria or parameters" (1–4).

In 1978, XL was shown to be deficient in steroid sulphatase, as opposed to other ichthyoses (5); this deficiency has since been used as a biochemical marker of XL. Finally, in 1981 it was demonstrated that XL can also be diagnosed by routine lipoprotein electrophoresis which reveals an abnormally rapid mobility of low-density lipoproteins (6).

There has been disagreement in the literature about the reliability of some of the clinical and histological differential criteria between XL and AD. The biochemical method to correctly diagnose XL and rule out AD has helped to better evaluate the validity of these criteria. The purpose of this paper is to evaluate the reliability of the classical differential criteria (1–4) in our group of patients with XL and AD, as well as those in the literature.

MATERIALS AND METHODS

Patients were selected according to two basic criteria:

1. A genotype compatible with an autosomal dominant or X-linked recessive mode of inheritance. Seven sporadic cases were also selected on the basis of a deficient steroid sulphatase activity.
2. A clinical phenotype not corresponding to the following known types of ichthyosis: autosomal recessive ichthyoses, congenital bullous ichthyosiform erythroderma and the recently described dominant lamellar ichthyosis (7).

Table I. *Reliability of classical differential parameters (1–4) between XL and AD in our group of patients (33 with XL and 52 with AD)*[a]

Parameter	Present predominantly in	*p*-value[b]	
Earlier onset	XL	= 0.02	(**)[c]
Severe expressivity	XL	= 0.0001	(***)
Large scales	XL	≃ 0.0002	(***)
Involvement, skin folds	XL	< 0.001	(***)
Chapping, hands-feet	AD	< 0.0001	(***)
Keratosis pilaris	AD	< 0.0001	(***)
Increased palmo-plantar markings	AD	< 0,0001	(***)
Atopic background	AD	< 0.0001	(***)
Better/absent in warm weather	XL	< 0.008	(**)
Improving with age	XL	< 0.001	(***)
Corneal opacities	XL	< 0.0001	(***)
Granular layer, prominent/thickened	XL	< 0.001	(***)

[a]XL = X-linked recessive ichthyosis; AD = autosomal dominant ichthyosis.
[b]Significance of difference in distribution between XL and AD.
[c]*** indicates significance ($p < 0.004$); **indicates only a tendency ($p < 0.05$).

In 7 sporadic cases and 42.4% of familial cases of XL, we confirmed the diagnosis by demonstrating a deficient steroid sulphatase activity in cultured skin fibroblasts (8). Steroid sulphatase activity was also checked in 9.6% of patients with AD. Lipoprotein electrophoresis was performed in only a few patients.

According to the two selection criteria there were 52 individuals with AD: 24 females and 28 males. Their ages at examination ranged between 3 and 70 years (average, 29 years). Thirty-three males had XL and their ages ranged between 3 and 69 years (average, 24 years). Of the total of 85 subjects, 68 were of Swiss extraction.

Topical medications were stopped one week prior to examination. However, most patients admitted to continuing use of topicals on the face and neck. Therefore these two regions were omitted from our study. Clinical and histological examination of all patients was performed by one of us. The great majority were examined between October and May and most were seen once only. Biopsies were taken from one of the regions most severely affected and tissue was routinely processed and stained with hematoxylin and eosin. A slit lamp examination of the cornea was performed by an ophthlmologist in 61% of cases with AD and in 76% of those with XL.

We evaluated the degree of reliability of 12 classical differential parameters between XL and AD (1–4). In comparing the phenotypes of AD and XL, the difference in the incidence of each studied parameter was analysed statistically. Depending on the number of patients examined for a given variate, either the Fischer or X^2-test was used. $p < 0.004$ was required for results to be significant; $p < 0.05$ indicated only a tendency; $p > 0.05$ denoted insignificance.

The extracutaneous manifestations of XL, except for corneal opacities, were not considered in the present work.

RESULTS

Table I summarizes our results. For 10 parameters the difference in distribution between XL and AD was statistically significant. In particular, as shown in Table II, not all XL patients were free of keratosis pilaris or palmo-plantar involvement and improvement with age was more common in XL; moreover, skinfold involvement was very common in AD. The great majority of our subjects had a histological picture corresponding to the classical description (3); however, 8% of cases of AD showed a granular layer compatible with XL, while 6% of XL patients revealed a granular layer suggesting the diagnosis of AD.

Finally, when examining an individual patient without relying on biochemical data, we were in doubt or made the wrong diagnosis in 24% of XL cases and in 6% of those with AD.

Table II. *Clinical parameters in our study at variance with the classical differential criteria (1, 2)*

	X-linked rec. ichthyosis			Autos. dom. ichthyosis	
	Involv. palms-soles	Kerat. pilar.	Improv. with age	Improv. with age	Involv. skin folds
Wells & Kerr[a] 1966 (1)	0%	0%	6%	38%	2%[b]
Merrett et al.[a] 1967 (2)	0%	0%	5%	43%	–
Our results[a]	21%	21%	45%	12%	44%

[a]The differences between the two ichthyoses in the study were statistically significant.
[b]Clinical criteria were different from ours.

DISCUSSION

Contrary to two classical, statistically analysed studies (1, 2), among our patients XL improved with age significantly more often than AD (Table II). The rest of our findings were generally in agreement with those of the British authors (1–4). Nevertheless, for three other parameters, our results were sufficiently different to be of practical importance (Table II). In particular, the presence of palmo-plantar involvement or of keratosis pilaris could not rule out XL, and involvement of skin folds was very common in AD.

In most other reports the distribution of variates in XL and AD is expressed as a percentage, without statistical analysis. The following are some of the important departures from the classical concept (1–4). One study in Israel found onset at birth in 64% of cases of AD and an about equal tendency to improve with age in both ichthyoses (10). In Germany, Hofbauer & Schnyder (11) found corneal opacities in only 12% of XL cases. In another region of Germany, von Voss & Jünemann (15) and in Spain, Unamuno et al. (12), did not observe corneal opacities in XL. Working in Japan, Buzou et al. (13) found keratosis pilaris in 7% of patients with XL, while Okano et al. (16) reported palmo-plantar involvement in 11% of XL cases and ichthyotic skin folds in 31% of those with AD. Histologically, the granular layer in XL was found compatible with AD in 7% (9), 28% (17) and 45% (16) of the cases. On examination of an individual patient without relying on biochemical data Okano et al. (16) recorded doubt or error in diagnosis in 27% of XL and 31% of AD cases. Bousema et al. (18) were in doubt or wrong in 28% of XL cases. No doubt, this significant variability in findings is at least partially attributable to differences in methodology. It should also be pointed out that the studies considered here were performed with different ethnic groups and in various geographic regions; such differences may have an influence on the expressivity of the autosomal dominant and X-linked recessive genes.

Our results showed that 4 of 12 classical differential parameters between AD and XL were unreliable. In the literature, additional parameters were found to be of little or no differential value. Therefore, the classical differential criteria between AD and XL (1–4) seem to be valid mainly when one considers groups of patients. For the individual patient, a doubt or error in diagnosis, particularly in XL, is not rare when relying solely on these criteria. When in doubt about a given patient with ichthyosis of the vulgaris type, determination of steroid sulphatase activity is the best test to arrive at the correct diagnosis. In the great majority of cases of XL, lipoprotein electrophoresis can be used instead of steroid sulphatase assay to establish a definitive diagnosis. However, at least one report (19) has suggested that this test may not be 100% reliable.

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