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MINIREVIEWS

X linked recessive ichthyosis: Current concepts

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Abstract

In the present review, we describe the most important aspects of the X-linked ichthyosis (XLI) and make a compilation of the some historic details of the disease. The aim of the present study is an update of the XLI. Historical, clinical, epidemiological, and molecular aspects are described through the text. Recessive XLI is a relatively common genodermatosis affecting different ethnic groups. With a high spectrum of the clinical manifestations due to environmental factors, the disease has a genetic heterogeneity that goes from a point mutation to a large deletion involving several genes to produce a contiguous gene syndrome. Most XLI patients harbor complete *STS* gene deletion and flanked sequences; seven intragenic deletions and 14 point mutations with a complete loss of the steroid sulfatase activity have been reported worldwide. In this study, we review current knowledge about the disease.

Key words: *STS* gene; X-linked ichthyosis; Steroid sulfatase; Gene deletion; Contiguous gene syndrome; Genodermatosis

Core tip: In the present study we describe the current knowledge of historical, clinical, epidemiological, physiopathological and molecular data in the X-linked ichthyosis (XLI). We consider that this review is important due to XLI is one of the most frequent genodermatosis that affects similarly to different ethnic groups worldwide.

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HISTORY

The term ichthyosis has been used for over 2000 years

and comes from the Greek root "ichthys" meaning fish. In the nineteenth century, the Indians and Chinese referred to the disease as "a condition of snakeskin or fish scales" and at the time of the Arab physician Avicenna as "nigra albarras". The first description of ichthyosis documented in the medical literature was in the work "On cutaneous diseases" by Wilan[1] in 1908. Cockayne[2] in 1933, was the first to describe cases of ichthyosis in males and used the genetic classification. In 1965, Wells *et al*[3] could distinguish the X-linked ichthyosis (XLI) from the dominant ichthyosis vulgaris. They suggested that the onset of dominant form was present after three months with a less body affection. In 1978, Koppe *et al*[4] and Webster *et al*[5] identified the absence of the steroid sulfatase (STS) enzyme in fibroblasts of patients with XLI.

EPIDEMIOLOGY AND ETIOLOGY

XLI (OMIM 308100) is a genodermatosis caused for STS deficiency[4,5]; it is characterized by abnormal desquamation and hiperqueratosis in the skin[6], and is due excessive amounts of cholesterol sulfate in the epidermis[7]. XLI has a frequency of one to two in 6000 men[8]. With respect to the genetics of X-linked recessive disorders, these diseases are generally restricted to males, these ones transmit the affected gene only to females (obligated carriers). Carriers of the X-linked gene defect have a risk of 50% to have affected males or carriers females.

The STS protein has 583 amino acids with a molecular weight of 62 kDa. The first 22 amino acids correspond to the leader peptide, which is cleaved post-translationally to give rise to the mature enzyme[9]. STS protein has 4 glycosylation sites[10]. The STS enzyme is attached to the rough endoplasmic reticulum and hydrolyzes the sulfate groups of the sulfated 3 β-hydroxysteroids such as dehydroepiandrosterone sulfate (DHEAS), cholesterol sulfate, pregnenolone sulfate and androstenediol 3 sulfate[11-13], metabolites that serve as precursors for estrogens, androgens, and cholesterol. STS is expressed on placenta, breast, immune system, brain, liver, reproductive tract and blood cells[10]. In placenta, STS deconjugates DHEAS, a previous step for the oestrogen synthesis during pregnancy. STS enzyme is upregulated by tumor necrosis factor α and interleukin (IL)-6, while IL-1β and interferon-γ downregulate it by inhibiting nuclear factor-kappa-B and activiting glucocorticoid receptor. Retinoids and 1,25(HO)$_2$-vitamin D3 induce its activity and expression[14,15].

The STS gene is located in the Xp22.3 region[16,17], and has 10 exons, 2 untranslated regions (at the 5' of 206 bp and at the 3' of 668 bp), and one open reading frame of 1752 bp[18-20]. The Xp22.3 region escapes to X-inactivation[16,21]. More than 90% of XLI patients present a complete *STS* gene deletion and flanked sequences, the remainders have showed 7 intragenic deletions[22-28] whereas 14 point mutations with a complete loss of the STS activity[29-38] have been reported. Contiguous gene deletions around the STS leading to a more complex phenotype associated with short stature, chondrodysplasia punctata, Kallman syndrome and ocular albinism[39].

One explanation for the deletion of the *STS* gene and flanking sequences on the short arm of the X chromosome is the presence of families of repeated sequences in low copy number (G1.3 and CRI-S232) on both sides of the *STS* gene[40-43]. In women, the presence of these sequences could produce an unequal homologous recombination; however, another proposed mechanism is a mismatch by sliding DNA chains as shown the paternal origin of the affected X chromosome[22,44-46].

CLINICAL FEATURES

Mothers of affected fetus con XLI may present delayed or prolonged labor due the absence of STS enzyme in the placenta[47]. Onset of symptoms of the XLI is in the first months of life by the presence of polygonal, loosely adherent translucent scales with a generalized distribution[48]. The scales predominantly are in anterior abdomen, preauricular area, neck, axillae and extension zones of the limbs[3,49-52]. The scalp is affected in childhood and this affection disappears in the adulthood. Generally, scales spare palms, soles, popliteal and antecubital fossae and the mid-face[52-54]. Clinical manifestations are worse in cold/dry weather. XLI patients have low sweat production due to a decrease numbers of sweat gland[55]. Filaggrin mutations may be associated with ichthyosis vulgar, xerosis and atopic dermatitis exacerbating the XLI phenotype[56,57]. Extracutaneous manifestations, such as ocular defects, have been observed in 10%-15% of patients and up to 25% of carrier mothers[58]. Diffuse deposits in the corneal stromal and descemet membrane[59], may appear at any time of life, they predominate in the 2nd and 3rd decade without affect visual acuity[60,61]. Back embryotoxon, deuteranopia, corneal erosion[62,63] has also been observed. Cryptorchidism is observed in 20% of cases[64], with a cancer high risk of testicular germ cells[65]. Neurological alterations have been observed in patients with XLI, such as epilepsy, electroencephalogram abnormalities, mental retardation, hyposmia[66], attention deficit hiperactivity disorder, autism and speech deficit; these manifestations have been attributed to altered sterol metabolism in the central nervous system[67,68] frequently associated with contiguous gene deletion. Others anomalies less frequent are seizures, psychological disorders[69,70], pyloric hypertrophy[71,72], abdominal wall defects, leukemia, nodular heterotopia periventricular[73,74] and steroid-resistant nephrotic syndrome[75].

PHYSIOPATHOLOGY

Cholesterol sulfotransferase (SULT2B1b) generates cholesterol sulfate (CS) in lower nucleated cell layers

(stratum basal) of the epidermis, increasing the concentration of CS from 1% to 5% on the stratum granulosum[52]. STS enzyme decreases CS to 1% in the stratum corneum (outer epidermis)[52,76,77]. The increase of CS induces the expression of the skin barrier protein filaggrin and plays a role in the differentiation of normal keratinocyte[78,79]. Rupture of CS cycle by STS defect produces an increase of CS from 1% to 10%-12% in the stratum corneum of the epidermis[7]; this results in: (1) a decrease barrier function with a failure of the normal liquid-crystalline transition phase of intercellular lipids; and (2) an abnormal corneocyte retention stimuling the hyperplasia epidermal-inflamation and a thickened stratum corneum. The increase of CS is in relation with the decrease of the activity serine protease and the increase of Ca^{2+}, producing corneodesmosomal retention[6,52,80]. Besides, the dark color of the scales could be explained by the presence of large amounts of melanosomes in the corneal cells[81].

LABORATORY DIAGNOSIS

Prenatal diagnosis can be carried out through the study of triple marker in second trimester of pregnancy which detects low or absent serum levels of estriol. The suspect of a fetus with XLI is associated with a decrease level of estrogen and the presence of unhydrolyzed steroid sulfates in maternal urine[82-84]; a history of prolonged labor and delivery increases this possibility. The analysis of the *STS* gene through southern blot, *in situ* hybridization, polymerase chain reaction can be made on chorionic villi or amniotic liquid when the familial genetic defect is known[85]. Determination of steroid sulfatase activity and polymerase chain reaction, fluorescence *in situ* hibridation and DNA of the *STS* gene analyses allow to discard XLI[31,32,34,41,86]. New techniques as MLPA, DNA microarrays, total exome sequencing is helping to prove the complete deletion, partial deletions or point mutations in the *STS* gene. Histopatological study is not useful for the diagnosis of XLI, however it may be useful in the differential diagnosis of XLI with other specific histopathology entities[6].

DIFFERENTIAL DIAGNOSIS

XLI differential diagnosis mainly is with ichthyosis vulgaris and others ichthyosis like lamellar ichthyosis[50,54,87]. Ichthyosis vulgaris (IV) is characterized by symmetric light gay scaling, generally after 3 mo of age; flexion zones are affected and inheritance pattern is dominant autosomal, nevertheless in some cases it can be acquired. Biopsy studies of skin appear similar in both cases. In sporadic cases is most difficult to stablish the correct diagnosis, because it is not present a specific inheritance pattern. In familiar cases, genealogy is an important tool to correctly identify XLI from IV. The determination of STS activity is the golden standard in the differential diagnosis of both diseases but molecular studies of *STS* or *FLG* genes are also useful to perform the correct diagnosis.

MANAGEMENT

XLI has not definitive treatment, but fortunately, except for the aesthetic appearance, rarely affects normal life function. XLI mainly affects the skin that is exacerbated in winter, but improves in summer. Lubricants, humectants and keratolytic agents are indicated when there is excessive large scale or keratinization[88]. There are few studies on the treatment of XLI, one study used tazarotene 0.05% and glycolic acid 70% in a patient with a large deletion of the *STS* gene, with good response, but with a remission to the 8 and 2 mo, respectively[89], another study used calcipotriol in 8 cases with XLI and 11 patients with congenital ichthyosis and showed reduction of scaling and roughness[90]. On a heterogeneous study[91], liarozole *vs* oral acitretin were compared with no significant differences[92]. Generally, XLI treatment is based upon studies in other groups of congenital or heterogeneous ichthyoses[93-95]. In neonates and infants, keratolytics should be handled with caution because they are absorbed due to the immature skin barrier causing toxicity. Any treatment regimen works for everyone, and the best therapy for each patient may be the result of months or years of painstaking effort on both the physician's and the patient's behalf. It is important to keep in mind the cost of the topical treatments[88]. Multidisciplinary management with various specialists such as dermatologists, geneticists, ophthalmologists, psychologists, gynecologists should be considered.

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