Ichthyosis in Cattle: Clinical, Pathological and Management Insights

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SUMMARY

In this descriptive review we aimed to provide succinct yet comprehensive overview of ichthyosis (IT) in cattle, focusing on clinicopathological presentations, genetic aetiology, and potential management strategies.
IT is an inherited disorder characterised by excessive keratinization and scaling of the skin. Two major forms with known causal variant have been identified in bovine species: Ichthyosis Fetalis (IF) and Ichthyosis Congenita (IC).
IF is widely recognised as the most severe form, associated with foetal death, stillbirth or death in the first days of life. IF is autosomal recessively inherited, with clinicopathological characteristics of hyperkeratosis, scaling of the epidermis, alopecia, eclabium, ectropion and microtia. The *ABCA12* gene has been associated with IF in Chianina, Shorthorn, and Polled Hereford breeds. The frequency of the IF allele has been estimated at 3.8% in the Shorthorn population and less than 3% in the Chianina population.
IC is a less severe form of IT, observed in different breeds. In Scottish Highland cattle the IC presents clinicopathological characteristics which include hyperkeratosis, epidermal hyperplasia, diffuse alopecia, and keratoconjunctivitis. These manifestations are associated with a recessively inherited missense variant in the *DSP* gene. Similar clinicopathological findings are present also in the Italian Chianina cattle. In addition, Chianina IC-affected animals can also show cystitis and urolithiasis. In this breed IC is caused by a recessively inherited variant in the *FA2H* gene with an allelic frequency of 7.7%.
Foetal and calf mortality, stillbirth and euthanasia of severely affected animals may have significant economic and welfare impact. Additionally, complications such as dystocia and secondary skin infections (e.g. pyodermitis) also in milder forms may adversely affect longevity, productivity and health. Additional economic damages are due to the compromised quality of the leather products also in the cases of mild disease of IC. So far, no specific treatments are available for both IT, with symptomatic dermatological treatments being the only option currently available.
Genetic testing and selective breeding programmes are the best strategies for addressing recessively inherited disorders like IT.

KEY WORDS

Bovine; Ichthyosis Fetalis; Ichthyosis Congenita; Chianina; Genodermatoses.

INTRODUCTION

Genodermatoses are a heterogenous group of inherited skin disorders in both humans and livestock, usually following a genetic monogenic mode of inheritance . These conditions can affect the structure, function, and appearance of the skin, leading to a wide range of phenotypical presentations, such as the presence of keratinization disorders, blistering, alopecia, pigmentation abnormalities and inflammation .
Ichthyosis (IT) belongs to the group of keratinization disorders and is characterized by an abnormal terminal keratinocyte differentiation resulting in hyperkeratosis and scaling. IT encompasses a large spectrum of clinicopathological forms with a heterogenous molecular basis. In human medicine, IT is classified into two major categories: non-syndromic and syndromic forms . The non-syndromic forms are when the clinical findings are limited to the skin while syndromic forms involve additional organs . In humans, IT has been associated with pathogenic variants in more than 30 genes that are involved in several cellular functions, such as DNA repair, lipid biosynthesis, adhesion, desquamation, and formation of the hydrophobic barrier .
In veterinary medicine, IT has been reported in buffalo , pigs (OMIA:002238-9823) , sheep (OMIA:002193-9940) , dogs (OMIA:001980-9615) , greater kudu (OMIA:001993-9946) (30), and cattle (OMIA:002238-9913) . In sheep, and greater kudu the underlying genetic cause of IT has not been determined. In dogs of different breeds, four recessively inherited deleterious variants have been reported to be associated with IT affecting the *TGM1* (OMIA 000546-9615), *PNPLA1* (OMIA 001588-9615), *NIPAL4* (OMIA 001980- 9615), and *SLC27A4*

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(OMIA 001973-9615). Furthermore, two dominantly inherited forms of IT in dogs have been reported to be associated with variants in *KRT1* (OMIA:002425-9615) and *ASPRV1*(OMIA 002099-9615) .

In cattle, IT has two main phenotypic presentations: Ichthyosis Fetalis (IF) and Ichthyosis Congenita (IC) (20, 21). In this descriptive review, we aim to summarize the current state of the art of IT in cattle, focusing on clinicopathological presentations, genetic aetiology, and potential management strategies. Emphasis is given to the Chianina breed.

Ichthyosis Fetalis in cattle

IF is a lethal form of IT and it can lead to late abortion or stillbirth. Born calves may die during or shortly after calving. The dermatological clinical findings (Figure 1&2) include rigid, horny, leathery, and thick skin with alopecia, accompanied by scaly plates separated by deep reddened fissures covering over 80% of their body. Additional findings are eclabium (lip eversion), ectropion (eyelid eversion), and microtia.

Histopathological findings present follicular (including dermal root sheath of hair follicles), epidermal and diffuse hyperkeratosis, with thickened stratum corneum and laminated anuclear keratin. In the dermal layers, apocrine glands show a mild epithelium attenuation, and they are dilated . Focal mild parakeratosis and severe lamellar granules can also be noticed . Due to massive lamellar orthokeratosis, the stratum corneum is 10-20 times thicker than normal. The hair follicle infundibula are also affected, and both the sweat gland ducts and hair follicles are usually dilated. A diffuse and intense hyperkeratosis with no inflammation in the dermis is observed .

Figure 1 - Stillborn calf with ichthyosis fetalis, showing diffuse, thickened, and fissured hyperkeratotic skin with rigid folds and limb contracture.

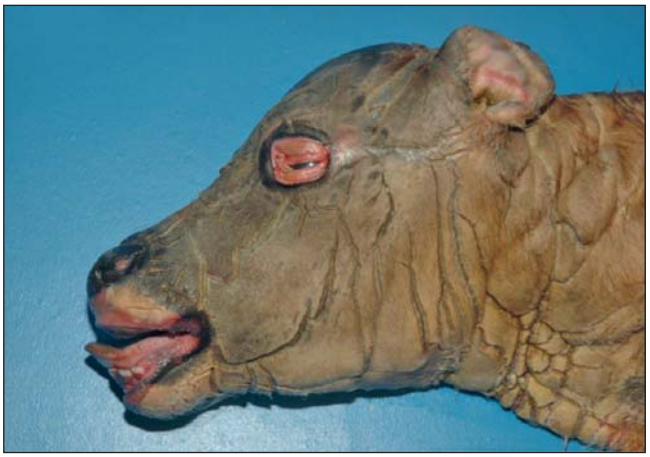

Figure 2 - Craniofacial abnormalities in ichthyosis fetalis, including severe hyperkeratosis, ectropion, microtia, fissured skin, and a rigid open-mouth posture.

IF has been reported in Polled Hereford , Shorthorn , Belgian White, Red cattle and Chianina cattle (21).

This form of IT is recessively inherited and is caused by pathogenic variants *ABCA12* in the Chianina, Shorthorn, and Polled Hereford breeds (OMIA 002238-9913) whereas the molecular aetiology of IF in Belgian White and Red cattle is still unknown. Previous studies have identified three different variants in the *ABCA12* gene associated with IF. They are missense variants in Chianina and Shorthorn breeds and an insertion in Polled Hereford . A summary of these variants is presented in Table 1. The IF allele frequency has been estimated to be 3.8% in the Shorthorn and less than 3% in Chianina populations respectively .

The *ABCA12* gene belongs to the superfamily of ATP-binding cassette transporter family. This gene is a keratinocyte transmembrane lipid transporter protein associated with the transport of lipids in lamellar granules to the apical surface of granular layer keratinocytes. Pathogenic variants affecting this gene frequently result in the accumulation of intracellular aggregates of defective lamellar body contents, resulting in severe hyperkeratosis.

Ichthyosis Congenita in cattle

IC has been reported in different breeds including the Scottish Highland , Chianina (Table 1) and Holstein with different clinicopathological presentations.

Ichthyosis congenita in Scottish Highland

In Scottish Highland cattle, IC is characterized by diffuse alopecia (covering about 90% of the body surface), keratoconjunctivitis (corneal defect), accompanied by easily pulled hairs found on the cephalic, appendicular, and caudal regions. In addition, the skin presents multiple folds, and thick layer of keratin covers the lichenified hyperkeratotic skin, displaying large scales . While the eyelids present hyperkeratosis, the mucocutaneous junctions are normal. Moreover, the nasal bridge alongside areas lateral to the metacarpi, dorsal and tarsi are covered with flat crusts.

Histopathological findings of IC in Scottish Highland consist of necrotic debris covering the tongue surface highlighting acantholysis, mild to moderate hyperplasia of the epidermis covered with multifocal crusts and laminated keratin. Multifocal deep fissures can be observed on the tongue mucosa, which also presents parakeratotic hyperkeratosis. Other significant features include hair shaft dysplasia, and mild infiltration of lymphocytes and plasma cells in the lamina propria .

This form of IC is caused by a deleterious homozygous missense variant in the *DSP* gene (OMIA 002243-9913, 2022) . The IC allele frequency has been estimated to be 1.2% in the Scottish Highland population . The *DSP* gene, which is involved in the formation of desmosomes, primarily codes for the protein Desmoplakin . Desmosomes play a critical role in maintaining strong adhesion between keratinocytes, and abnormalities in desmosomal cadherins - transmembrane proteins essential for this adhesion - are a key factor in the development of this condition.

Table 1 - Summary of ichthyosis forms in cattle with a known genetic cause.

Disorder	Phenotype	Codon	Protein	Gene	OMIA	Type of Variant	Breeds	Ref
Ichthyosis Fetalis (IF)	Lethal. Hard white plaques like scales, small ear, averted lips, and eyelids. Hyperkeratosis, dermal layers apocrine glands dilation. Scattered and perivascular lymphocyte within the epidermis. Thickened stratum corneum	c.5804A>G	p.(H1935R)	*ABCA12*	002238-9913	Missense	Chianina	(21)
		c.6776T>C	p.(L2259P)	*ABCA12*	002238-9913	Missense	Shorthorn	(16)
		c.5689_5690 insC	p.(S1784Ifs*33)	*ABCA12*	002238-9913	Insertion (≤ 20) (Frameshift)	Polled Hereford	(17)
Ichthyosis Congenita (IC)	Sub-lethal. Severe skin lesions, epidermal hyperplasia, acantholysis of the tongue, corneal defect, alopecia, multiple folds on skin, lichenified hyperkeratosis. Sebaceous gland hyperplasia	c.6893C>A	p.(A2298D)	*DSP*	002243-9913	Missense	Scottish highland	(27)
	Sub-lethal. Skin xerosis, hyperkeratosis, multifocal alopecia around the muzzles, eyelids, ear, and inner thigh region. Severe lesions, retarded growth. Wrinkles and fold on the skin. Urinary bladder inflammation	c.9dupC	p.(A4Rfs*142)	*FA2H*	002450-9913	Insertion (≤ 20) (Frameshift)	Chianina	(19)

Ichthyosis Congenita in Chianina

In Chianina cattle, IC is characterized by multifocal alopecic lesions mostly localized around the eyelids, muzzle, ears, neck, rump, and inner regions of the limbs. Scaling, skin xerosis and hyperkeratosis are evident features . Affected animals can also show multiple folds and wrinkles and occasionally they may develop pyoderma. Some animals develop urolithiasis and cystitis (Figure 3&4).

Histopathological findings of IC in Chianina include severe and diffuse orthokeratotic and hyperkeratosis on cutaneous lesions (Figure 5). The adnexal structures present a normal appearance. However, intracytoplasmic, spindle-shaped, optically empty clefts are present with the sebocytes indicating hyperplasia of the sebaceous glands. The sweat glands are filled with basophilic homogenous material and are often dilated. In addition, cystitis can also be observed in some affected animals . This form of IC is caused by a deleterious frameshift insertion in *FA2H* gene (OMIA 002450-9913, 2021) The IC allele frequency has been estimated to be approximately 7.7% in the Chianina population . FA2H protein is responsible for the synthesis of glycosphingolipids and sphingolipids which are involved in the formation of epidermal lamellar bodies critical for skin permeability barrier . Glycosphingolipids are important for regulating hair follicle homeostasis while sphingolipids are important for regulating lipid mobility. The pathogenic variants in *FA2H* gene may impair lipid synthesis leading to reduced keratinocyte proliferation and persistent skin dehydration.

Ichthyosis Congenita in Holstein

In Holstein, IC is characterised by fissures over large areas of the body, thickening of the epidermis, alopecia, thick horny scales, deep cracks with lack of flexibility in the gluteal, shoulder or knee area. Microtia, eclabium and ectropion may also be present.

Figure 3 - Chianina calf with Ichthyosis Congenita, showing xerosis, patchy alopecia, and hyperkeratotic plaques on the hindlimb.

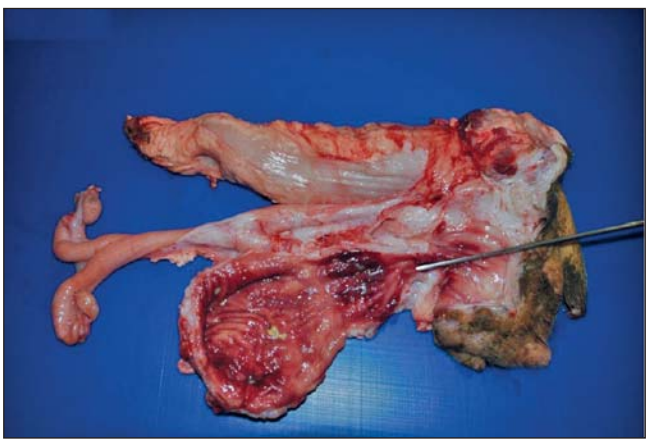

Figure 4 - Cystitis in an Ichthyosis Congenita-affected calf. The bladder mucosa exhibits marked congestion, ulceration, and fibrinous exudation, indicative of secondary bacterial infection.

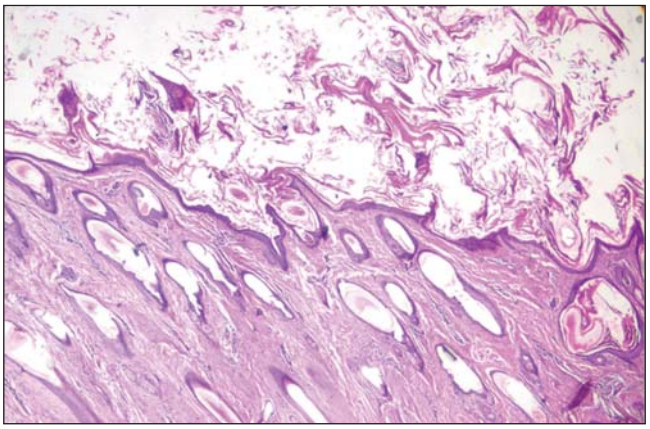

Figure 5 - Haired skin. Severe orthokeratotic hyperkeratosis and follicular keratosis. Hematoxylin and eosin stain, 2x magnification.

Pathological examination reveals seborrhoea, hyperkeratosis and dermal collagen dysplasia. Other observations include hypergranulosis, oedema, mild perivasculitis. Hyperaemia and haemorrhage may be evident in the subcutaneous muscles (28). No information on a potential genetic variant has been reported.

Economic and welfare impact of IT in cattle

Cows' longevity, productivity, health, and calving ease remain crucial selection criteria for optimal herd performance. Genodermatoses such as IT can significantly impact these desired traits directly or indirectly.

IF is associated with foetal death, stillbirth or death shortly after birth, representing therefore a direct loss for the farmer. Moreover, foetal death and stillbirth may lead to dystocia that may predispose to different gynaecological conditions, such as metritis and retained placenta. Complications associated with dystocia significantly impact the cow reproductive and productive lifespan, negatively affecting profitability .

Epidermal abnormalities may be susceptible to secondary infection. Frequent use of antibiotics to treat these secondary infections may contribute to antimicrobial-resistance thereby, posing a public health problem. Furthermore, persistent occurrence of IT contributes to increased culling rate, reduction in the population of high-quality breeding stock, reduced productivity (e.g. meat, leather). Additionally, IT management inflates production costs incurred from special management of affected cattle, and results in corresponding lower market value for the affected cattle. The combined effect of these impacts contributes to wasted resources and substantial economic losses for cattle producers .

Chianina, an autochthonous beef breed native to central Italy, is considered the tallest breed of cattle in the world (38) with a well know marbled meat quality and valuable leather. The spreading of IT alleles in the population poses a great threat if no control strategies are implemented (19). Beyond leather, there is an inevitable compromise in the Chianina meat quality which could be attributed to increased stress and overall poor welfare conditions translating into poor growth performance. IT induced alterations in the integument may significantly affect muscle development and marbling characteristics of the meat. This detrimental effect poses a significant threat on the economic viability and cultural significance of Chianina breed (33, 35).

Management strategies to prevent and control the occurrence of IT in cattle

Routine genotyping of animals should be performed to prevent mating risk between carriers of these deleterious alleles. Implementing genotyping protocols would be instrumental in selective breeding of carrier cows and identification carrier bulls entering the gene pool. On farm rapid and effective genotyping assays should be developed to ensure the easy, accurate and efficient diagnosis of this disorder. Breeders and breeders' association should be trained on various genetic disorder to prevent genetical defect in the seedstock herd. Organizing genetic training and counselling session for cattle producers and practicing veterinarian to keep them abreast on evolving abnormalities and management/therapy to be administered should be considered .

The ANABIC (National Association of Beef Cattle Breeders) in Italy has implemented a selective breeding program against Ichthyosis Fetalis, which has resulted in a significant reduction of the allele frequency in Italian beef cattle (18). Despite this success, Ichthyosis Congenita (IC) in Chianina cattle has not yet been incorporated into the breeding program. The allelic frequency for IC remains moderate among top sires, and the continued use of carrier sires presents a risk of increasing the prevalence of this deleterious allele within the Chianina population. This highlights the need for consistent breeding management to prevent its spread.

Hence, Cattle breeders and veterinarians should continuously emphasize the importance of integrating IC into the ongoing breeding strategies to safeguard cattle health and industry sustainability.

Topical application of moisturizing, emollient, eventually with antibiotics cream might be indicated as symptomatic therapy in the case of the IC. Moreover, improving management practices are very important: among these the environmental temperature control as affected animals have difficulties in coping with extreme temperatures. Ensuring that hygienic and disinfection of the environment is maintained, together with respect of general biosecurity procedures are other very useful measures.

CONCLUSION

Note that there is no known therapy for this disorder in cattle. Hence, early detection through genetic approach is important. Upon identification or suspicion, animals should undergo testing, with cases submitted to diagnostic and research centres for confirmation. Selective breeding or culling of affected animals is imperative. For recessive diseases, avoiding risk mating is the most effective strategy for prevention. While genetic approaches offer potential advantages, they are costly and may not improve the welfare of affected animals. Conclusively, rapid and precise diagnostic practices are urgently needed to prevent the increase of this allele frequency in the cattle population, which poses a threat to food sustainability, producers' livelihoods, and animal welfare.

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