

Photosensitization and its management in Livestock

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Abstract

Photosensitivity is a condition in which animal becomes hyper-reactive to sunlight irradiation. Photosensitization disease can cause production-reproduction losses and animal welfare losses worldwide, resulting in to great economic losses to farmers. Animals in countries like India and other South Asian countries which fall on or near the equator are very much prone to photosensitization. Photosensitization majorly affects the skin, hair and eye of the animals. Animals with pigmented skin are less likely to be affected by photosensitization. Young, sick, non-pigmented or hairless animals are more prone to dermal photosensitization than those are mature, healthy, pigmented or hairy. Photosensitization in a biological system such as the epidermis leads to oxidative or other chemical change in a molecule in response to light-induced excitation of endogenously or exogenously-delivered molecules within the tissue. Hence, to discuss various types of photosensitization, its pathogenesis, diagnosis, treatment protocol and probable preventive measures, this review paper is placed on record.

Keywords: Irradiation; Livestock; Photosensitization; Sunlight

Introduction

Photosensitization is a syndrome developed when animal at a state of photosensitivity is exposed to sunlight (Clare, 1953). Photosensitivity is caused by activation of photodynamic agent by light energy (280-790 nm wavelength) leading to abnormal sensitivity of superficial layers of unpigmented or light skinned areas of body to ultraviolet and visible light, in peripheral circulation resulting in tissue necrosis and inflammation (Sarigson *et al.*, 2012). Photo-oxidation can also occur in the plant itself apart from animals, resulting in the generation of reactive oxygen species, free radical damage and eventually DNA degradation. Similar cellular changes occur in affected herbivores animal and are associated with an accumulation of photodynamic molecules in the affected dermal tissues or circulatory system of the animal (Quinn *et al.*, 2014). The condition is commonly differentiated from other similar conditions producing similar signs like sunburn, mycotic dermatitis, big head of rams caused by clostridium novyii and haemoglobinuria and myoglobinuria observed in other metabolic diseases (Ritz *et al.*, 2008). Photosensitization is not equivalent to 'sunburn' although its appearance can be superficially very similar. Sunburn is caused by extended exposure of normal skin to damaging ultraviolet rays, while photosensitivity manifests as a rapid reaction of cells in the skin to both visible and ultraviolet irradiation through stimulation in the associated light spectrum. Both ultraviolet and visible irradiation can cause photo-excitation of light reactive molecules in plants like *lantana camera* resulting in photosensitivity. In contrast, sunburn typically results from excessive ultraviolet exposure while premature aging is particularly exacerbated by ultraviolet irradiation due to its ability to penetrate the skin more deeply thereby causing cumulative photo damage to skin (Smith *et al.*, 2012).

Pathogenesis

There are two routes by which photosensitizing products can enter the skin either through direct contact or by systemic transport via the bloodstream. These agents may cause damage to skin cells directly via cytotoxic mechanism (also referred to as photocytotoxicity), or much less commonly by the induction of an immune system (photoallergic) response. Photocytotoxic photosensitization can show highly variable onset. It can occur within minutes of exposure to the toxic substance by direct contact, within hours (via contact or ingestion) of deposition of the primary photosensitizing agent, or days after exposure due to activation of secondary photosensitizers (following liver damage and deposition of phytoporphyrin into skin). Photoallergic photosensitization may also take days to manifest clinically with either direct or systemic deposition, and is not well characterized in grazing herbivores (Quinn *et al.*, 2014).

In photosensitization, unstable, high-energy molecules are formed when photons react with a photodynamic agent. These high-energy molecules initiate reactions with substrate molecules of the skin, leading to the release of free radicals that in turn result in increased permeability of outer cell and lysosomal membranes. Damage to outer cell membrane leads to leakage of cellular potassium and cytoplasmic extrusion. Damaged Lysosomal membrane releases lytic enzymes into the cell. This can lead to skin ulceration, necrosis and edema. The time interval between exposure to the photodynamic agent and the onset of clinical signs depends on the type of agent, its dose and the exposure to sunlight (Barrington, 2017).

The sensitivity of grazing herbivorous animals to dermal toxins or photosensitizing compounds is governed by a number of factors. These include species, breed, skin pigmentation, fur or hide thickness, age, health status of the animal and localized environmental conditions such as temperature, humidity and rainfall (Gupta *et al.*, 2006).

Types of photosensitization

There are four types of photosensitization are commonly observed in animals as mentioned below:

Type- I (Primary form)

Type- II (Congenital form) Due to Aberrant Pigment Synthesis

Type-III (Hepatogenous form)

Type-IV (Photosensitivity) Unknown Etiology

Type-I (Primary Form)

Ingestion of exogenous agents like phenothiazine, Rose Bengal, Acridine dyes, plants containing photodynamic agents like hypericin, fagopyrin and furanocoumarins reaches stomach where active principle was formed. The toxic principle then gets absorbed into peripheral circulation through capillaries under the skin. On exposure to the harmful sun rays, sensitization due to photodynamic agents occurs resulting in photosensitivity (Robinson, 1989). Although primary photosensitization, by definition, does not result from hepatic failure, a number

of primary photosensitizing compounds are also known to cause liver damage, making the distinction between primary and secondary photosensitization less clear in practice (Gupta *et al.*, 2006).

Type -II (Congenital Form)-Due to Aberrant Pigment Synthesis

This type of photosensitization is usually hereditary in origin. In this syndrome, the photosensitizing porphyrin agents are endogenous pigments that arise from inherited or acquired defective function of enzymes involved in haem synthesis like Glucose-6-phosphate dehydrogenase, which on deficit in RBC leads to disruption of haem biosynthetic pathway. As a result porphyrins accumulates in body (Including skin) and when exposed to sunlight, oxygen free radicals formed due to interaction with cellular macromolecules, which ultimately damage the cell and get released into circulation (Barrington, 2017). Congenital erythropoietic porphyria (BCEP) and congenital erythropoietic protoporphyria (BCEPP) have both been reported in domestic cattle. Accumulation of uroporphyrin I and coproporphyrin I results in type-II photosensitization in BCEP. Bovine Congenital Erythropoietic Proto Porphyria (BCEPP), which is caused by a deficiency in the activity of ferrochelatase. This enzyme is involved in the final stage of the 8-step haem biosynthesis pathway, catalysing the chelation of ferrous iron to protoporphyrin in the production of haem. Accumulation of protoporphyrin is the cause of photosensitization in BCEPP (McAloon *et al.*, 2015).

Type-III (Hepatogenous Form)

Majority of photosensitization is of this type. The plant-derived toxins (excluding mycotoxins produced by parasitic or saprophytic fungi on plants) most often associated with hepatogenous photosensitization belongs to the following groups: steroidal saponins, terpenes and tannins. Plant or microbial products associated with hepatogenic photosensitization include lantadenes, steroidal or lithogenmic saponins, mycotoxins (sporidesmin and phomopsin) and certain tannins (Gupta, 2012).

Failure or partial failure of liver to excrete pigments which are normally present in bile leads to this condition. Majority of cattle breeders in developing or underdeveloped countries are landless and marginal farmers. They send their cows to grazing for more than 9 hours and sometimes 1 to 2 hours rest was provide to prevent heat stroke (Djohy e al 2013; Patel et al, 2016). So the animals are susceptible to the poisonous plants like *Lantana camara* which causes hepatotoxicity and photosensitivity. Toxic substances (plant/other origin like mycotoxin, chemicals, etc.) after ingestion reach liver and obstruct the bile duct leading to cholestasis, which in turn accumulates phylloerythrin. Phylloerythrin, the porphyrin pigment is a product of chlorophyll degradation produced in the digestive tract of herbivorous animals. Accumulated phylloerythrin then reaches the peripheral circulation through capillaries under skin. On exposure to sunlight, this photodynamic substance causes photosensitization (Sharma *et al.*, 2008). In one study, evidence of Dicrocoeliosis leading to hepatogenous photosensitization by accumulation of phylloerythrin has been, established (Sarigson *et al.*, 2012). In another study photosensitivity in cattle in Europe as a result of liver fluke (*Fasciola hepatica*) disease has been evidenced (Flock *et al.*, 2003). Thus parasitic damage to liver and bile duct may also leads to hepatogenous photosensitization.

Type-IV (Photosensitivity) - Unknown Etiology

Photosensitivity in which the pathogenesis is unknown or the photodynamic agent is not identified is classified as type 4. Outbreaks of photosensitization have been reported in cattle exposed to water-damaged alfalfa hay, moldy straw and foxtail-orchard grass hay. These cases were suspected to be hepatogenous in origin. Many of these plants are believed to be type I photosensitizers. Forages such as oats, wheat and red clover have been suspected in cases of photosensitization and may be associated with specific environmental conditions such as heavy rainfall (Barrington *et al.*, 2017).

Clinical Signs

Clinical signs of photosensitization include progressive weight loss and anorexia, oedema and necrotic tissue, crusting and sloughing of skin in non-pigmented and exposed areas such as ears, face, rump, flank and vulva regions in females as well as visible jaundice. Affected animals seek shade, grazing in the evening or early mornings or remaining under trees and shrubs rather than actively grazing (Low, 2015). The difficulty in identifying the specific cause of the syndrome along with simultaneous occurrence of secondary diseases usually complicates the prognosis of the disease.



Fig1 Photosensitization on cattle teat and skin



Fig 2 lantana camera plant

Fig 3: Lantana camera affected animals-skin lesions)

Most definitive sign observed in all affected animals is presence of necrosis and exfoliation of superficial layers of skin. In cattle, udder and teats are worst affected. In small ruminants-ears, nose, muzzle, eyes, inter-mandibular region (distended so called as "Big head disease" in sheep) and ear tip are affected showing oedema and blistering in non-pigmented areas. Severe irritation, restlessness, rubbing and shaking of head and ears can be noticed. Cloudiness in cornea and neurological signs like ataxia, dizziness and convulsions are also seen in affected sheep and goats. In birds erythema, blistering on beak, feet, legs and sloughing of comb and wattles are also seen in affected birds.

Pathological Changes

Generalized icterus in body tissues, extensive subcutaneous edema along with enlargement of local lymph nodes is usually noticed. Teeth and bones show pink-brownish discoloration. Enlarged and granular liver with thin margin and distended gall bladder are usually noticed in affected animals.

Liver

Gross Changes

Early stages of disease were characterized by slight thickening of the portal spaces and yellowish tinting of the parenchyma. As the disease progresses, intense yellowish discoloration reflecting a greater degree of bile retention was noticed in liver. Thickening of the portal tracts and proliferation of the interlobular connective tissue was also noticed in liver of affected animal (Glenn *et al.*, 1965). Hydropic degeneration of hepatocytes, necrotic cells and the presence of foamy macrophages were found in association with degenerated hepatocytes of affected animal (Flock *et al.*, 2003).

Microscopic Changes

Cholangitis and pericholangitis leading to occlusion of the lumen of affected bile ducts are usually noticed. The small and intermediate interlobular ducts were mainly affected. Distinct hypertrophy and hyperplasia of the biliary epithelium are most noticed in the ductules and small interlobular ducts. Infiltration of immediate periductal area by small numbers of lymphocytes, mononuclear phagocytes, a few eosinophils and occasional neutrophils are also noticed in affected animal.

Elevated liver enzymes like GGT, sorbitrate dehydrogenase and aspartate amino transferase along with increased serum phyloerythrin concentration can be observed. GGT is an enzyme located in the cell membranes in the bile ducts and hepatocytes. Serum levels of this enzyme increase with membrane damage due to accumulation of

bile salts resulting in oxidative stress and decreased antioxidant potential (Ritz *et al.*, 2008). Increased CPK due to increased activity of muscles due to restlessness of animals, produced by painful skin lesions are also noticed in the serum samples of affected animals (Araya and Ford, 1981).

Gall Bladder

Gross Changes

A diffuse, mild congestion and edema were grossly evident in the mucosa and submucosa of the gall bladder.

Microscopic Changes

Microscopic lesions were observed in the extrahepatic biliary system in severely affected animal in which gross lesions were noted in the gall bladder. In addition to a mild to moderate mucosal and submucosal congestion and edema, there was partial to complete denudation of the epithelial lining of the gall bladder of the affected animal (Glenn *et al.*, 1965).

Treatment

As far as now no specific antidote for the photo toxins are available. Treatment regimen follows symptomatic approach on removing the toxin from body. Animals should be kept in dark areas until the toxin is completely excreted (5 to 7 days) to avoid further complication. Topical application of demulcents, antibiotics and corticosteroid ointments can be used. Antihistamines and antibiotics can be administered intramuscularly. Keep fly and ectoparasites away from skin lesions. Laxatives or saline purgatives can be administered to remove the ingesta from stomach/rumen. Hepatoprotectants like liver tonics and stimulants can be administered to prevent further damage to liver (Robson, 2007).

Prevention

Ameliorative measures must be taken to minimize the direct exposure of sunlight to our valuable animals in the form of roof or shed shelters using kachcha, semi-pakka or pakka house depending on the economic condition. Once the animal is affected with photosensitization, immediate veterinary care is to be advocated. They should be preferably kept and maintained under a stall fed rearing system. The animals identified as a carrier of genes having defective enzyme production should be avoided for breeding purpose. Proper feeding management should be carried out to avoid ingestion of phytotoxic plants by animals during natural grazing. As the condition is most common in drought period where unmonitored consumption of available feed by animals takes place, proper measures should be carried out to provide adequate feed for animals in order to avoid plant induced photosensitization.

Conclusion

Photosensitization is a management disease condition causing heavy damage to hides and production value of the animals. Hence, extensive veterinary extension activities should be planned to create awareness among the stakeholders. Recent studies showed animals with pigmented skin are less likely to be affected with dermal photosensitization, while reverse is seen in young, sick, non-pigmented or hairless animals, however, further studies are necessary to better understand this condition and to quantify irradiation and draw proper line of treatment to explore the productive potential of our valuable livestock.

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