INTRODUCTION

Bovine erythropoietic protoporphyria (BCEPP) was first reported in the United States (1,2). It has been described in Limousin (3) and, infrequently, in Blonde Aquitaine (4). The reduction, or the absence, of mitochondrial enzyme activity called ferrochelatase, leads to the abnormal accumulation of protoporphyrin in blood and tissues (5). Subsequently, accumulated protoporphyrin becomes toxic when animals are continuously exposed to the sunlight, causing photosensitivity and seizure (1). Although the pathogenesis of neurological signs has not been fully understood, the direct epileptogenic role of d-aminolaevulinic acid (dALA) is the most plausible one. It has been hypothesised that dALA interferes with neurotransmitters such as gamma-aminobutyric acid and glutamate, causing seizure-like activity (6). The molecular basis of this disorder was first publicly disclosed by Jenkins and collaborators in 1998 (7). They cloned and sequenced a candidate gene (*FECH*; p.(*417Lext*27)), chosen for its similarity to the human disorder, and identified a base substitution in the stop codon of the bovine ferrochelatase gene (OMIA:000836-9913). This mutation eliminated the stop codon, adding 27 amino acids to the peptide.

CASE HISTORY

A four-month-old female Limousin cross calf was referred to the Scottish Centre for Production Animal Health and Food Production, University of Glasgow, in October 2020 with a one-month history of dermatological signs and an episode of seizure-like activity. The animal was born without assistance from a Limousin cow mated with a Limousin bull, leaving a healthy cow and a viable calf. Initially, the farmer noticed that the animal started showing an aversion to sunlight (photosensitivity) and attempted to find shade. Additionally, skin lesions on the ears and the muzzle were noted, so the farmer treated the calf with moxidectin 1.0 mg/kg body weight SC, SID (Cydectin 10 LA ®, moxidectin 1.0 mg/kg, Zoetis, UK) for possible ectoparasites. A veterinary practitioner was called to examine the calf two weeks after the onset of the clinical signs. At the clinical examination, ataxia and seizure without signs of blindness were reported.

The calf was referred from a 50 beef suckler herd of Limousin cross cows situated in the South-West of Scotland. The farm was closed (since 2014) and complied with the mandatory Bovine Viral Diarrhoea (BVD) testing, which had a negative status. Interestingly, a historical pattern emerged, with previous cases in the herd displaying similar neurological and dermatological signs. While the referred animal stood as the sole affected individual in 2020, an occurrence unfolded in 2019 when another calf was born from a distinct dam. Both affected calves were born from the same sire. Furthermore, the farmer recounted two additional cases involving young Limousin calves with the same presentation between 2010 and 2018.

CASE PRESENTATION AND ANCILLARY DIAGNOSTICS

On physical examination, the Limousin calf was bright, alert and responsive. She had a body condition score of 2/5 and weighed 116 Kg. The skin was covered with crusty lesions on the planum nasale and the ears' pinnae. On the planum nasale, two necrotic lesions measuring 1 x 3 cm were observed. The haired skin of the dorsal aspect of both ears' pinnae was alopecic with rough, reddened to crusty lesions irregularly extended for 2 x 5 cm (Figure 1). The periocular skin was less severely affected. In a craniocaudal order, the neck, thorax, limbs and the areas close to the base of the tail were carefully inspected and palpated and no signs of pruritus, alopecia or pathological modifications were noted. A moderate amount of mucoid bilateral nasal discharge was observed. The respiratory rate was 38 breaths per minute. No signs of coughing were noted. The palpation, percussion and auscultation of both upper and lower respiratory tracts were unremarkable. All explorable lymph nodes were normal on palpation. The rectal temperature was 38.7 °C. The capillary refill time was less than 2 seconds. The skin tent was one second. The heart rate was 68 beats per minute, and there were no abnormalities in the frequency and rhythm. On the oral cavity examination, no lesions of the oral mucosa or dentition issues (colour or structure) were observed. On the auscultation of the left paralumbar fossae, the rumination rate was normal, one every 40 seconds, and no abnormal sounds were auscultated. Equally, the examination of the right side of the abdomen was unremarkable. No

evidence of thoracic or abdominal pain was present on the withers test. Faecal consistency, quantity and colour were normal. Urine colour was normal, and there were no signs of umbilical pathologies. As part of the ancillary tests, haematology and biochemistry analyses were conducted. Haematology was unremarkable; on biochemistry, the only relevant finding was an increased GLDH level (73.8 U/L, range: 0-10). An ultrasonographic examination of the liver, performed as described by Braun (2009), did not reveal any lesions (8). Urinalysis and faecal analysis were carried out and did not reveal any significant abnormalities (Table 1).

Based on the neurological signs reported from the history, a full clinical neurological exam was performed. The mental status and behaviour, cranial nerves, gait and posture, spinal reflexes and nociception were assessed (9). Overall, the neurological examination was unremarkable.

The animal was eating and drinking normally. Seven days after admission, the skin lesions started to heal, with crusty lesions on the ears and the muzzle sloughing off and being replaced by healthy tissue. Moreover, the mucoid nasal discharge disappeared within three days after admission.

Approximately three weeks after admission, the patient experienced a cluster of two short, generalised tonic-clonic seizures in a short space of time, with loss of consciousness but with no autonomic signs such as urination or defecation, except for salivation. Subsequently, the patient developed neurological signs. On neurological examination performed immediately after the seizures, she was in a recumbent position and showed a star gazing posture and opisthotonos. She was then able to ambulate with a wide-based stance, head and body sway and demonstrated vestibular ataxia characterised by leaning to the side and accompanied by vertical nystagmus. Given the presence of seizures, the lesion was localised to the forebrain. The vestibulocerebellar signs were also suggestive of brainstem and cerebellar involvement. On the same day, within a few hours while she was displaying post-ictal signs, it was decided to euthanise the animal on welfare grounds, and the carcase was sent to post-mortem examination for further investigations.

On the post-mortem examination, the most relevant findings were the skin lesions affecting the ear pinna and the periocular region, and no other gross abnormalities were detected. A histopathological examination of the liver, skin, and brain was carried out using haematoxylin and eosin staining. The haired skin of the affected regions were examined microscopically. Within the superficial dermis, there was a multifocal, mild to moderate accumulation of lymphocytes around blood vessels and, to a lesser extent, around adnexal structures, along with fewer plasma cells and occasional eosinophils. In the deep dermis, low numbers of these same cell types were also present. The apocrine sweat glands appeared mildly to moderately dilated (ectatic) in multiple areas. The overlying epithelium showed mild orthokeratotic hyperkeratosis. Overall, the skin histopathological findings were compatible with chronic dermatitis. On the liver, large areas of the hepatic parenchyma were disrupted, and some degree of hepatocyte degeneration was observed. No histological abnormalities were noted in the brain in the following regions: midbrain, cerebellum, thalamus, and cerebrum.

Figure 1. The 4-month-old female Limousin calf presented two crusty lesions on the planum nasale (1 x 3 cm) and some mucoid nasal discharge. The skin of the dorsal aspect of both ear pinnae was

also alopecic, with rough, reddened, and crusty lesions irregularly extended for 4 x 5 cm. A topical treatment (white) was applied to the dorsal aspect of the ear pinnae.

Table 1. Other ancillary tests

Parameter	Result
Full Urine analysis	Specific gravity: 1.016 (ref:1.015.1.035) pH: 8.5 Sediment examination: no abnormalities
McMaster:	The worm egg count revealed 250 strongyles eggs per gram (reference range ≤250) and 2200 oocyst/gram of *Eimeria zuernii* (reference range <5000)
Boray (faecal sedimentation)	No liver and rumen eggs fluke were detected

INITIAL PROBLEM LIST

- Individual history of photosensitivity seizure-like activity and dermatological lesions
- Historical patterns of similar clinical cases on farm
- Clinical examination
  - Dermatological signs: lesions on the dorsal aspects of the ear pinna, muzzle and in the periocular region
  - Neurological signs: star gazing posture, opisthotonos, vestibular ataxia and vertical nystagmus
  - Poor body condition score (2/5)

DIFFERENTIAL DIAGNOSES

Based on the history and the clinical examination findings, the following differential diagnoses were considered:

- Photosensitivity
  - Primary (direct): ingestion of external photodynamic substances found in certain plants (i.e. *Hypericum perforatum, Lolium perenne, Secale Cereale*)
  - Secondary (indirect or hepatogenous): where phylloerythrin, a byproduct of chlorophyll metabolism, acts as the photodynamic agent (i.e. Pyrrolizidine alkaloid toxicosis caused by *Senecio jacobea*)
  - Endogenous: Bovine erythropoietic protoporphyria (BCEPP) and Congenital Erythropoietic Porphyria (CEP)
  - Idiopathic
- Inflammatory/infectious
  - Brain abscess, fasciolosis, coccidiosis, BVD
- Deficiency
  - Vitamin B1 (thiamine)
- Toxics
  - Inorganic poisons (i.e. lead), nutritional (salt toxicity), farm chemicals (i.e. metaldehyde, organophosphates)
- Metabolic
  - Portosystemic shunt

GENETIC DIAGNOSIS

Based on the breed, history, the dermatological and neurological signs, secondary photosensitivity by aberrant pigment was suspected. Genomic DNA was isolated from an EDTA blood sample using

standard methods and a GGP Bovine100K chip (NEOGEN The Dairy School, Auchincruive, Ayr, KA6 5HU). The animal was homozygous for the previously reported autosomal recessive mutation in the ferrochelatase gene (*FECH*; p.(*417Lext*27)), a mutation that causes the obliteration of the stop codon and consequent extension of the transcript, leading to loss of function (7). This confirmed the diagnosis of BCEPP.

FOLLOW-UP

From a herd management point of view, since the farmer wanted to change the phenotypic expression of his cattle for commercial reasons, it was decided to use a pure Aberdeen Angus bull to improve hybrid vigour and eliminate the probability of transmitting the mutation from the sire line (10).

DISCUSSION

According to Collett et al. (2019), photosensitisation diseases in animals have been classified as primary (or direct), secondary (indirect or hepatogenous), endogenous (aberrant porphyrin synthesis), and idiopathic (uncertain cause) (11).

Various causes of photosensitivity were thoroughly examined to identify the primary aetiology. Primary and secondary photosensitivity were deemed unlikely as there were no reports of toxic plants or chemicals on the farm, and the affected calf stood as the only case with skin lesions in the herd. Clinicopathological examination findings were not supportive of liver dysfunction. Other differentials, such as inflammatory/infectious, metabolic, deficiency and toxic causes, were ruled out due to the progression of clinical signs and negative ancillary test results.

The primary focus then shifted to endogenous photosensitivity, eliminating both primary and secondary causes. Two distinct inherited recessive diseases known for inducing seizure-like activity and photosensitivity reactions were considered: Congenital Erythropoietic Porphyria (CEP) and BCEPP. CEP is characterised by defective uroporphyrinogen III synthase (URO-synthase) and typically affects Shorthorn and Longhorn breeds (12). Recognisable by pink-coloured teeth, urine discolouration, and anaemia. CEP was excluded as the Limousin calf did not exhibit any of these characteristic signs.

BCEPP emerged as a more plausible diagnosis (13,14). BCEPP arises from insufficient ferrochelatase activity, an enzyme critical for the last step in the seven-step pathway of heme synthesis (5). Excess protoporphyrin is lipophilic and accumulates in cellular membranes (5). This compound can absorb light across various wavelengths, and the energy from this light can be transferred to oxygen, forming reactive oxygen species and triggering the clinical signs as described in the present case (15). The diagnosis was confirmed by analysing an EDTA blood sample, which showed the animal had two copies of the autosomal recessive mutation in the ferrochelatase gene.

Further considerations can be made about the prevention of inherited disease. Bull selection for pure breeds has seen an increasing trend (10). As in the case presented, this has created a vicious circle in some farms. The increment of frequency of recessive alleles in both the maternal and paternal sides has caused an increasing risk of animals displaying the disease. Control strategies are based on the correct diagnosis by genetic tests. The aim is to identify heterozygous animals to avoid the use of carrier animals as breeders (10). With this aim, several Limousin breeding societies have proposed testing and controlling programmes to help producers decrease the chance of having homozygous animals (15).

CONCLUSION

This case shows the diagnostic challenges and decisions involved in managing an inherited disease such as BCEPP (16). Thorough examinations ruled out primary and secondary photosensitivity causes, emphasising the importance of considering historical patterns. Similarly, the differentiation of BCEP and CEP was based on clinical signs and breed. Overall, the case underscores the significance of precise diagnostics, genetic testing, and informed breeding decisions, particularly in managing and preventing such disorders in cattle populations effectively.

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Conflict of Interest
The authors declare no conflict of interest.

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