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Technical note

Congenital malformations. Report of meromelia, amelia, and anury in calves

Medali Cueva-Rodríguez [a*]

Nevil Itamar Pomatanta-Escobal [a]

Jorge Portal-Torres [a]

Wigoberto Alvarado C. [b]

Carlos Quilcate-Pairazamán [c]

[a] Universidad Nacional de Cajamarca. Facultad de Ciencias Veterinarias. Laboratorio de Patología Veterinaria, Av. Atahualpa Nº 1050 - Carretera a Baños del Inca, Ciudad de Cajamarca, Perú.

[b] Universidad Nacional Toribio Rodríguez de Mendoza. Facultad de Ingeniería Zootecnista, Agronegocios y Biotecnología, (UNTRM). Ciudad de Chachapoyas (Amazonas), Perú.

[c] Instituto Nacional de Innovación Agraria. Dirección de Desarrollo Tecnológico Agrario. La Molina, Lima, Perú.

* Corresponding author: mcuevar@unc.edu.pe

Abstract:

Amelia is a malformation represented by the absence of one or more limbs. The causes of this anomaly are multifactorial, involving genetic, environmental, and epigenetic components. Mutations in critical genes, such as *Shh* (*Sonic Hedgehog*) and *Hox* genes, which are essential for limb formation and differentiation during embryonic development, and disruptions in *Shh*, *Hox*, or their signaling pathways can result in amelia. Mutations in these genes can also cause severe disruptions in limb development. Amelia is anatomically characterized by the complete absence of one or more forelimbs or hindlimbs. As for meromelia, this type of anomaly consists of the partial absence of one or more limbs. Three cases of cattle presented malformations of the forelimbs; the first and third cases showed anury. Macroscopic examination identified the first case with

meromelia and anury. In the second case, amelia of the right and left forelimbs was identified, and in the third case, anury was present. It is concluded that congenital anomalies were present in all three cases.

Keywords: Amelia, Brown Swiss, Bovine.

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Congenital malformations have been described in multiple animal species, including cattle; although seldom, they may be due to idiopathic, genetic, and non-genetic causes, as well as to the interaction between the last two[(1)]. These occur due to an interruption in the normal development of the fetus or embryo, resulting in a congenital defect present or evident at birth[(2)]. It should be noted that these not only group those evident to macroscopic observation, but also those defects that can occur at the microscopic level, such as cellular/molecular or metabolic/physiological abnormalities. It is reported that 10 % of malformations are usually related to environmental causes, 25 % to genetic causes, and 65 % respond to unknown factors, probably of multifactorial origin[(3)].

Their classification depends on the body system; they can occur individually or in combination with other malformations, with the musculoskeletal system being the most affected in cattle[(4)], in which malformations such as amelia, meromelia, and anury are reported. Amelia is a rare type of congenital defect characterized by the complete absence of one or more limbs at birth. In calves, this condition implies the total absence of forelimbs or hindlimbs, resulting in a severe disability that affects their mobility and ability to survive without intervention[(5)]. The first documented description of this anomaly in cattle dates back to 1914, reported by Schmaltz in Germany; amelia and other types of congenital malformations reported in calves are not considered endemic to any specific region, as they occur sporadically worldwide[(6,7)].

Regarding amelia and meromelia, as they are defects related to the limbs of animals, their causes can be chromosomal abnormalities, genetic disorders, and environmental and intrauterine exposures. With respect to meromelia, this anomaly is the partial absence of one or more limbs[(8)]. As for anury, it is described as a congenital defect in which the animal lacks the caudal vertebrae that form the tail and is usually associated with vertebral and spinal defects[(9)]. Therefore, they can have multifactorial causes, involving genetic and environmental factors[(10)].

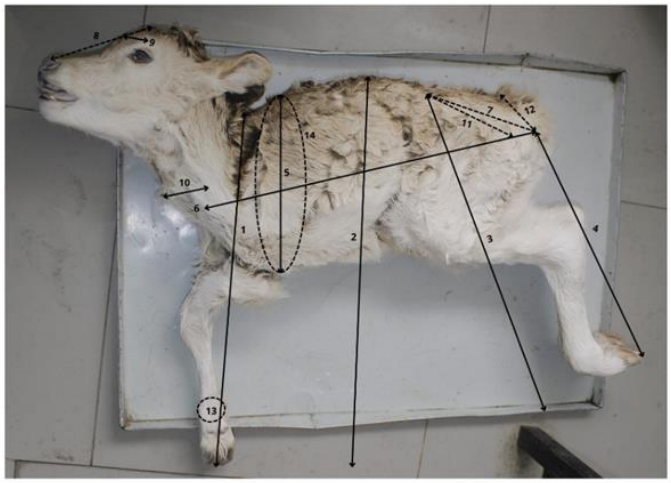
Among the genetic factors, mutations in key genes, such as *Shh* (*Sonic Hedgehog*) and *Hox* genes, have been identified as the primary causes; these genes are essential for the formation and differentiation of limbs during embryonic development, and any alteration in their functioning can result in severe malformations, such as amelia; the *Shh* gene is

crucial for the establishment of the anteroposterior axis and cell differentiation in limb buds[10,11]. Mutations in *Shh* or disruptions in its signaling pathway can lead to the complete absence of limbs. Besides genetic factors, various environmental factors can contribute to the development of congenital malformations in calves[12]. Likewise, exposure to teratogens, such as certain medications and environmental toxins, together with nutritional deficiencies, especially folic acid, during pregnancy, has been associated with an increased risk of congenital malformations[13]. In this regard, it has been described that when congenital defects occur in groups of unrelated animals, this is usually taken as a probable sign that the etiology is chemical or infectious[14]. Likewise, maternal infections during pregnancy can interact with genetic predispositions, increasing the risk of developmental defects. Amelia in calves has been reported in various breeds of cattle, including Dexter, Hereford, Holstein, Brown Swiss, and Angus, as well as in buffaloes. In some cattle breeds, it has been reported as a recessive hereditary trait[14,15]; heritability indicates the proportion of variation in a characteristic of genetic factors, which has been studied in relation to amelia in calves, implying that this disease may have a genetic predisposition[15,16].

Three cattle cases were presented to the Veterinary Pathology Laboratory of the National University of Cajamarca, Peru. These were three newborn calves, a female and a male of the Brown Swiss breed, and the third case was a cross between Brown Swiss and Holstein, with malformations consisting of the absence of the forelimbs; the first case also presented anury. The mothers have not manifested any pathological problems, and their fathers are unknown. The first case is from the town of Otuzco; the second, from the Huayrapongo Cooperative-Baños del Inca-Cajamarca; and the third, from the Baños del Inca district, Cajamarca, Peru.

Case 1. A male bovine of the Brown Swiss breed, named Harol, with a birth weight of 37 kg. Type of conception: natural mating, gestation time of 9 mo. The mother has no reports of pathologies, is 4 yr old, and weighs 400 kg; it was her second calving, the first calving did not present any alteration; the breeding system was semi-confinement, and the diet was based on rye grass and alfalfa. No vaccination history. Details of the father are unknown. At birth, the calf presented meromelia and absence of the sacral and coccygeal vertebrae (anury). Physical examination revealed incomplete development of the scapula and absence of the caudal vertebrae that form the tail. The case was reported in the town of Otuzco, northeast of the city of Cajamarca in Peru, at an altitude of 2,850 m asl (Figure 1).

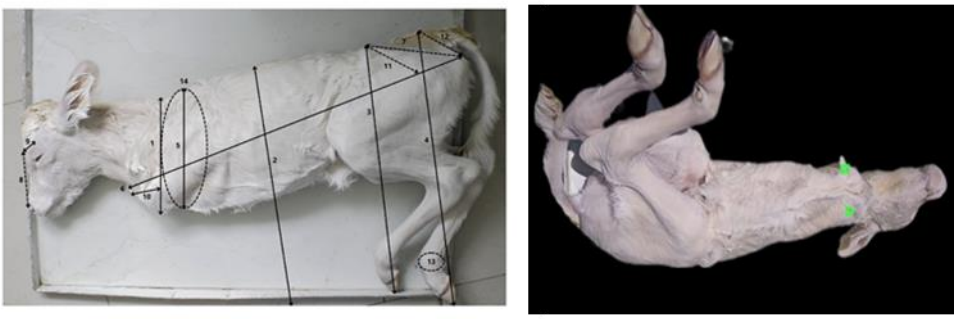
Figure 1: Case of meromelia and anury in a male calf



A male bovine in right lateral position, presence of meromelia of the left forelimb (M), anury (R). The main measurements of the specimen were (1) 66 cm, (2) 72 cm, (3) 73 cm, (4) 75 cm, (5) 34 cm, (6) 64 cm, (7) 18 cm, (8) 23 cm, (9) 15 cm, (10) 20 cm, (11) 16 cm, (12) 10 cm, (13) 11 cm, and (14) 68 cm.

Case 2. A female bovine of the Brown Swiss breed, 7 d old, weighing 38.5 kg. Type of conception: natural mating. She was bottle-fed, the animal tried to get up, and she sucked milk from the bottle normally. Mother of the same breed, with a weight of 420 kg, with no reports of pathologies. It was the third calving. Details of the father are unknown. The breeding system was semi-confinement, with a diet based on rye grass. At birth, delays were observed in the location of the scapula, presenting the congenital malformation called amelia, with the absence of both forelimbs. The case was reported in the Huayrapongo Cooperative-Baños del Inca, Cajamarca (Figure 2). The cattle are preserved in 10 % formaldehyde at the Veterinary Pathology Laboratory of the National University of Cajamarca.

Figure 2: Lateral and ventral views of a case of amelia in a male calf

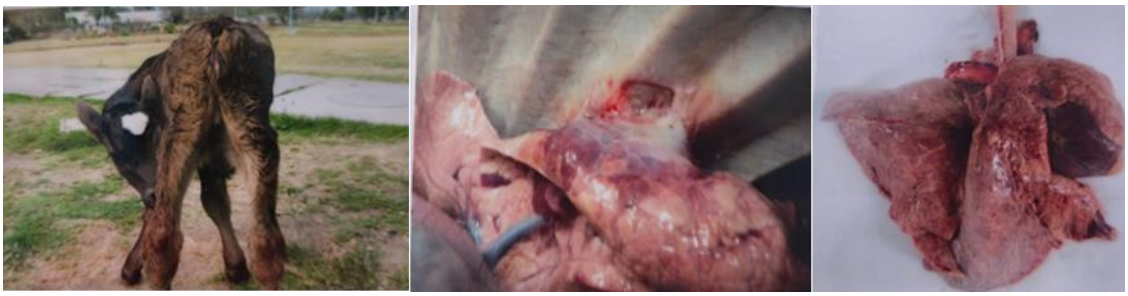


The main measurements of the specimen are as follows: (1) 25 cm, (2) 57 cm, (3) 60 cm, (4) 53 cm, (5) 23 cm, (6) 64 cm, (7) 21 cm, (8) 25 cm, (9) 14 cm, (10) 10 cm, (11) 16 cm, (12) 11 cm, (13) 10 cm, and (14) 62 cm.

Case 3. A female bovine, a cross between the Brown Swiss breed and Holstein, 10 d old. She was born at 0430 h, weighing 36 kg (Figure 3). She had breathed problems and a

deficiency in milk intake. She had dyspnea. Mother named Marianita, of Holstein breed, 4 and a half years old, weight of 415 kg, and second calving. Father named Jeferson, of the Swiss Brown breed, 5 yr old. The breeding system was semi-confinement, and the diet consisted of rye grass, alfalfa, and feed concentrate. The case was reported at the Huayrapongo Estate, Baños del Inca, Cajamarca, Peru. The necropsy was then performed according to protocols established by the teaching staff of the Veterinary Pathology Laboratory of the UNC.

Figure 3: Female calf with different physical and organic malformations



A. Presence of anury. B. Adhesion of the left lobe of the lung to the costal pleura at the level of the fourth and fifth ribs. C. Reddish to dark brown areas, especially in the right lobe, common in cases of pneumonia.

The most obvious findings on physical examination of the cases were meromelia of the right forelimb and another malformation (anury) in the first case. In the second case, amelia was observed in the forelimbs; in these cases, mutations in *Hox* genes disrupt this process, leading to one or more limbs not fully developing, and this may be related to environmental factors. Prevention of these malformations involves limiting exposure to teratogens in the environment of pregnant cows, which requires strict monitoring of the drugs administered, the handling of chemicals in the agricultural environment, and the provision of a contaminant-free environment. Continuous research to identify new teratogens and understand their mechanisms of action is essential to develop more effective preventive strategies[13,14,15]. On the other hand, amelia malformation is also influenced by *Hox* genes, which encode proteins that act as transcription factors, directing the differentiation and organization of cells in the limbs along the anteroposterior axis, alerting the signaling necessary for the correct development of the limb buds, leading to defects in the segmentation and arrangement of bone structures and soft tissues[15]. In some cattle breeds, amelia has not been reported as a recessive hereditary trait. Although in the cases observed (Figure 3), there is no genetic information from the parents to determine with certainty a hereditary component, it is possible to affirm that the absence of a similar clinical history in the parents could suggest a possible sporadic cause or one associated with environmental factors. However, in other breeds, such as the Dexter, a specific hereditary pattern has been documented that links amelia to certain genetic lines[15,16]. Studies have identified that amelia in this breed follows an autosomal recessive inheritance pattern, implying that two copies of the mutated gene must be present for the calf to be affected. This genetic knowledge is crucial, as it enables breeders to perform screening tests and properly select animals for breeding, thereby reducing the incidence

of this malformation. Genetic research continues to be essential for identifying the specific genes involved and for developing effective management and prevention strategies in affected cattle populations[16]. Genetic factors during the embryonic stage of development influence the *Shh* gene, which is essential for the correct segmentation and organization of limb structures, affecting cell proliferation and differentiation in the limb bud, a region essential for the development of bones and tissues[16,17]. Mutations or dysfunctions in *Shh* signaling can result in a variety of malformations, including amelia, in which one or more limbs do not fully develop. Understanding the implications of the *Shh* gene in limb development not only provides information on the genetic mechanisms underlying this malformation but can also guide strategies for early detection and possible intervention in cases of risk.

Among the most important environmental teratogens are toxic plants: *Lupinus* spp, *Astragalus* spp, *Conium maculatum*, *Nicotiana* spp[17]. Among these plants, *Lupinus mutabilis* is known to be endemic to Peru and grows in high Andean areas such as Cajamarca. Like other species of its genus, it is characterized by the presence of toxic alkaloid compounds. Nevertheless, to date, there are no reports of its effect on congenital malformations in cattle; it is worth noting that the animals feed on the pastures found near *Lupinus mutabilis* plantations. Congenital malformations in calves are usually the result of a combination of genetic and environmental factors due to the mechanisms through which teratogens cause malformations, including interference with molecular signaling, disruption of the cell cycle, and alteration of gene expression.

Cases of cleft palate have also been reported in cattle in the Cajamarca region, Peru[18]. It is concluded that the pathological cases in calves were meromelia, amelia, and anury.

Conflict of interest

The authors had no conflict of interest.

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