

ORIGINAL ARTICLE

Body stalk anomalies in pig—Definition and classification

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Abstract

The presence of body wall closing defects (abdominoschisis and thoracoabdominoschisis) in combination with other congenital malformations was studied in the pig (*Sus scrofa domesticus*). After clinical examination and literature review, body wall defects with multiple congenital anomalies in eight pigs were described, and classified using anatomical and embryological criteria. Several BSA presentations were identified and classified as follows: (a) BSA Type I: fetus with spinal and UC defects, thoracoabdominoschisis, anal atresia and/or other internal organs structural defects, and structural limb defects; (b) BSA Type II: fetus with spinal and UC defects, thoracoabdominoschisis, anal atresia and/or other internal organs structural defects, and nonstructural limb defects; (c) BSA Type III: fetus with spinal and UC defects, abdominoschisis, anal atresia and/or other internal organs structural defects, and structural limb defects; and (d) BSA Type IV: fetus with spinal and UC defects, abdominoschisis, anal atresia and/or other internal organs structural defects, and nonstructural limb defects. Two types of LBWC were differentiated: LBWC Type I: characterized by thoracoabdominoschisis and structural limb defects, and LBWC Type II: characterized by abdominoschisis and structural limb defects, corresponding to BSA type I and type III. This is the first report on BSA and LBWC in the pig.

KEYWORDS

BSA, CBW, LBWC, pig

1 | INTRODUCTION

Definition and classification of complex body wall defects (CBWD) is a matter of continuous debate in human medical literature (Luebke, Reiser, & Pauli, 1990; Martínez-Frías, 1997, 2000a; Patten et al., 1986; Rittler et al., 2019; Russo, d'Armiento, Angrisani, & Vecchione, 1993; Sahinoglu et al., 2007). One definition used for CBWD is body stalk anomaly (BSA), which it is characterized by a large abdominal wall closing defect, a short umbilical cord (UC), and other defects, such as sharp angulation of

the spine (Goldstein, Winn, & Hobbins, 1989). For some authors BSA is not associated with craniofacial or limb defects (Goldstein et al., 1989; Lockwood, Scioscia, & Hobbins, 1986), for some others BSA is associated with cranial malformations and limb defects (Paul, Zosmer, Jurkovic, & Nicolaidis, 2001; Zeidler et al., 2014). Patten et al. (1986) and Van Allen et al. (1987) proposed limb body wall complex (LBWC) to be named BSA (Bijok et al., 2017), and LBWC was included in the body stalk complex or Cyllosomas group (Saritha & Sumangala, 2013). The term LBWC has been most commonly used when two of

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FIGURE 1 (a) Left lateral view of piglet 184, showing lateral right abdominoschisis. Abdominal organs are eviscerated and partially covered by the amniotic membrane. Pelvic limbs were rotated and displaying ankylosis and arthrogriposis. (b) Caudal view of piglet 160, showing lateral right abdominoschisis. Abdominal organs are exposed. Left thoracic limb is absent (amelia). (c) Left lateral view of piglet 168, showing thoracoabdominoschisis. Reflected body wall is observed. Thoracic and abdominal organs are exposed. Pelvic limbs were rotated and displaying ankylosis and arthrogriposis. (d) Left lateral view of piglet 208, showing thoracoabdominoschisis. Reflected body wall is observed. Thoracic and abdominal organs are exposed. Pelvic limbs showed ankylosis and arthrogriposis. (e) Right lateral view of piglet 240, showing thoracoabdominoschisis. Thoracic and abdominal organs are exposed. Pelvic limbs were showed ankylosis and arthrogriposis, and amelia was observed in left thoracic limb. (f) Right lateral view of piglet 17, showing thoracoabdominoschisis. Thoracic and abdominal organs are exposed. Focomelia was observed in left pelvic limb. (g) Left lateral view of piglet 79, showing thoracoabdominoschisis. Thoracic and abdominal organs are exposed. Amelia was observed in right thoracic limb. (h) Right lateral view of piglet 278, showing thoracoabdominoschisis. Thoracic and abdominal organs are exposed. Arthrogriposis in right thoracic limb, focomelia in left thoracic limb, and focomelia in pelvic limbs were observed

three of the following defects are present: thoraco and/or abdominoschisis, cranial defects/encephalocele with facial clefts, and limb anomalies (Patten et al., 1986; Van Allen

et al., 1987). The fact that there is phenotypic overlap between BSA and LBWC (Chen et al., 2007) might explain why LBWC was considered equivalent to BSA. The use of

TABLE 1 Summary of the internal and external anomalies of the studied piglets

	P184	P160	P168	P208	P240	P17	P79	P278
Defects	Female 0.800 Kg	Female 0.900 Kg	Female 0.950 Kg	Male 0.850 Kg	Female 1.150 Kg	Female 1.020 Kg	Female 1.650 Kg	Female 1.100 Kg
Body wall	LAB (right)	LAB (right)	THO/AB	THO/AB	THO/AB	THO/AB	THO/AB	THO/AB
Eviscerated organs	AO	AO	AO	AO	AO	AO	AO	AO
UC	Disperse umbilical vessels	Disperse umbilical vessels	Disperse umbilical vessels	Disperse umbilical vessels	Disperse umbilical vessels	Disperse umbilical vessels	Disperse umbilical vessels	Disperse umbilical vessels
Limbs	Anomalous rotation and arthrogryposis and ankyloses in pelvic limbs	Left thoracic limb amelia	Anomalous rotation and arthrogryposis and ankyloses in pelvic limbs	Arthrogryposis and ankyloses in pelvic limbs	Amelia left thoracic limb	Left pelvic limb phocomelia	Right thoracic limb amelia	Left thoracic limb phocomelia in pelvic limbs
Spine	Extreme scoliosis	Extreme scoliosis	Extreme right lateral retroflexion	Extreme retroflexion (lordosis)	Extreme right lateral retroflexion	Extreme retroflexion (lordosis)	Extreme retroflexion (lordosis)	Extreme retroflexion (lordosis)
Thorax		Cleft sternum No ribs articulating Costal defect	Cleft sternum No ribs articulating Costal defect	Cleft sternum No ribs articulating Costal defect	Cleft sternum (bifid) Two first pair of ribs articulating Costal defect	Cleft sternum (bifid) Two first pair of ribs articulating Costal defect	Cleft sternum No ribs articulating Costal defect	Cleft sternum (bifid) Three first pair of ribs articulating Costal defect
Heart		Ectopic Dorsoventrally compressed	Ectopic Dorsoventrally compressed	Ectopic Dorsoventrally compressed	Ectopic Dorsoventrally compressed	Ectopic Dorsoventrally compressed	90° rotated Dorsoventrally compressed	90° rotated Dorsoventrally compressed
Respiratory system		Collapsed trachea Hypoplastic lungs	Collapsed trachea Hypoplastic lungs	Collapsed trachea Hypoplastic lungs	Collapsed trachea Hypoplastic lungs	Collapsed trachea Hypoplastic lungs	Collapsed trachea Hypoplastic lungs	Collapsed trachea Hypoplastic lungs abnormal lobation Accessory lobule absent
Diaphragm		Rudimental	Rudimental	Rudimental	Absent	Absent	Absent	Absent
Digestive system	Anomalous liver Atypical colon morphology Anal atresia	Anal atresia	Collapsed esophagus Anomalous liver lobation Polycystic liver Atypical colon morphology Anal atresia	Collapsed esophagus Anomalous liver lobation Polycystic liver Anal atresia	Atresic colon Anomalous liver lobation Anal atresia	Collapsed esophagus Anomalous liver lobation Atypical colon morphology Anal atresia	Collapsed esophagus Anomalous liver lobation Absent gallbladder Atypical colon morphology Anal atresia	Colon atresia Anomalous liver lobation Absent gallbladder Anomalous pancreas Polysplenia Anal atresia
Urinary tract	Hypoplastic kidneys Persistent urogenital sinus	Unilateral left kidney agenesis	Unilateral right kidney agenesis	Persistent urogenital sinus Hydro ureters Absent urinary bladder	Persistent urogenital sinus Hydro ureters Absent urinary bladder	Persistent urogenital sinus Hydro ureters Absent urinary bladder	Persistent urogenital sinus Hydro ureters Right kidney hydronephros Left kidney hypoplastic Absent urinary bladder	Hydroreters Hypoplastic urinary bladder Left kidney absent Right kidney anomalous

(Continues)

TABLE 1 (Continued)

	P184	P160	P168	P208	P240	P17	P79	P278
Defects	Female 0.800 Kg Hypoplastic genitalia	Female 0.900 Kg	Female 0.950 Kg	Male 0.850 Kg Absent scrota Bilateral cryptorchidism Hypoplastic penis	Female 1.150 Kg Hypoplastic genitalia	Female 1.020 Kg Uterus connected to urogenital sinus	Female 1.650 Kg Uterus connected to urogenital sinus Hypoplastic genitalia	Female 1.100 Kg Hypoplastic genitalia
Genitalia								
Other defects		Palatoschisis						
Diagnosis	BSA Type 4	BSA Type 3 LBWC Type 2	BSA Type 2	BSA Type 2	BSA Type 1 LBWC Type 1	BSA Type 1 LBWC Type 1	BSA Type 1 LBWC Type 1	BSA Type 1 LBWC Type 1

Abbreviations: AB, abdominoschisis; AO, abdominal organs; BSA, body stalk anomaly; LAB, lateral abdominoschisis; LBWC, limb body wall complex; SR, schistosomus reflexus; SUA, single umbilical artery; THO/AB, thoracoabdominoschisis; TO, thoracic organs.

these terms is still under debate, moreover some authors state that BSA and LBWC are distinct conditions on the same spectrum, and some others have presented criteria on how to differentiate the two (Bijok et al., 2017; Murphy & Platt, 2011; Rittler et al., 2019).

There is a congenital disorder described in veterinary medicine that it might be included in the CBWD group, the *Schistosomus reflexus* (SR) which its defining features include spinal inversion, exposure of the abdominal viscera because of a fissure of the ventral abdominal wall, pelvic limb ankyloses, positioning of the thoracic limbs adjacent to the skull, and lung and diaphragm hypoplasia (Laughton, Fisher, Halina, & Partlow, 2005; Martín-Alguacil & Avedillo, 2020; Mateo & Camón, 2008). Notter described SR in pig in 1927, to date there is not a description of SR in man. Martín-Alguacil and Avedillo (2020) in a recent study proposed a general classification for body wall defects, including SR and BSA in the pig. The aim of this study is to go over a group of malformative syndromes with compound anomaly pattern in body wall closing defects in pigs. To present a comparative anatomical description of CBWD in pigs and men, showing both similarities as well as different anomalies presentation. And to establish a unified criterion for classification and diagnosis.

2 | MATERIALS AND METHODS

All malformations included in this study were found sporadically during 2002–2018. Animals were obtained from a swine farming association from Toledo (Spain), grouping 15 pig production facilities, with an annual average census of 6,500 breeding sows in close production cycle. A total of eight piglets presenting extreme curved spine with large abdominal organs evisceration were selected for the study. All animals were legally procured in accordance with the regulations and laws of the European Union (86/609/EEC) and Spain (RD 223/1998) for the care, use, and housing of animals in research. The study was conducted in the Laboratory for the study of Congenital Malformations (Anatomy and Embryology Department), School of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain. Detailed gross evaluation of the eight specimens was carried out using conventional anatomical methods. To evaluate the morphology of the umbilical arteries, a section of the arteries was stained with hematoxylin and eosin and microscopically evaluated. The study was completed by X-ray examination.

3 | RESULTS

Eight crossbred (*Landrace—Large White—Pietrain*) still-born piglets, and the only abnormal members of their litter,

seven females and 1 male, were selected for the study and presented in Figure 1. A summary of all the anomalies identified in the eight pigs is showed in Table 1. After careful inspection no craniofacial abnormalities were observed, except for piglet 160 that showed cleft palate (secondary palatoschisis). Two piglets (P160 and P184) presented right lateral abdominoschisis with evisceration of all the abdominal organs and extreme scoliosis (Figure 1a,b). The large closing abdominal wall defect extends from the intact thorax until the pelvis ending just cranial to the genital tubercle. Nonunion of the pelvic symphysis was present. Abdominal organs were completely exposed into a big extraembryonic coelom cavity only covered by chorion. A thoracoabdominoschisis was observed in the other six pigs with evisceration of all the thoracic and the abdominal organs (Figure 1c–h). The sterna were cleft and the large closing ventral wall defect extend until the pelvis ending just cranial to the genital tubercle and nonunion of the pelvic symphysis was present in the six pigs. There was not UC in the studied piglets and the umbilical vessels were found dispersed. Single umbilical artery (SUA) was identified in P208 and P240. Left umbilical artery was hypoplastic in all the other cases. The amniotic membrane was attached to the skin margin of the thoracoabdominal or abdominal fissure. No amniotic bands were identified. Abdominal wall was reduced to a narrow band of skin reflected dorsally in all the piglets.

Limbs and internal organs anomalies were considered structural on the basis of embryological failures. And were considered nonstructural anomalies when they were thought to be caused by amniotic bands actions, and/or fetal movement restrictions, including arthrogryposis. Amelia and/or pelvic limbs phocomelia were considered as structural anomalies, and thoracic limbs phocomelia, arthrogryposis, ankyloses, and/or anomalous rotation as nonstructural. A classification for the studied CBWD in the pig is proposed and presented in Figure 2.

4 | DISCUSSION

BSA is considered when there is a body wall defect, skeletal abnormalities, and the umbilical cord is absent or rudimentary. Russo et al., (1993) described two phenotypes for LBWC: a placentocranial adhesion phenotype and placentoabdominal adhesion phenotype. They reported eight placentoabdominal adhesion phenotype cases without craniofacial defects, with urogenital anomalies, anal atresia, and abdominal placental attachment, together with a persistence of the extraembryonic coelom and lower limbs anomalies, in which seven were females and one was a male. Some authors mentioned that LBWC did not show any sex predilection (Saritha & Sumangala, 2013) in current studied group there were seven females and only one male affected. All the studied piglets presented the BSA features and five of them LBWC placentoabdominal adhesion phenotype features, with multiple congenital malformations such as curved and deformed appearance of the spine associated with UC abnormalities, abdominal placental attachment, anal atresia, visceral evisceration, genital and/or urinary defects, and different limb defects. The UC was absent in all the piglets, with umbilical vessels dispersed on the amniotic membrane. Two piglets showed SUA and one umbilical vein, and unilateral hypoplasia of an umbilical artery was observed in all the other piglets. The presence of only two umbilical vessels was also described by Russo et al. (1993) in the eight placentoabdominal adhesion phenotype cases.

Rittler et al. (2019) after evaluating 450 cases concluded that amniotic bands are responsible of limb partial amputation especially in upper limbs, observing that phocomelia in hind limbs predominated in cases without amniotic bands, although they only considered amelia as structural defect. Arthrogryposis is characterized by multiple congenital contractures in at least two different parts of the body (Hall & Vincent, 2003). Congenital contractures generally

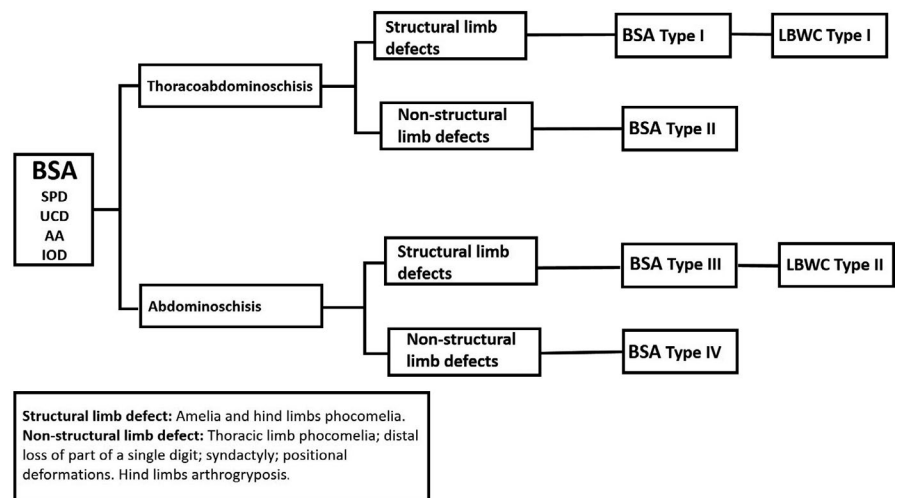


FIGURE 2 Schematic classification for CBWD studied in the pig. AA, anal atresia; BSA, body stalk anomalies; IOD, internal organs defects; LBWC, limb body wall complex; SPD, spinal defect; UCD, umbilical cord defect

occur because of decrease in fetal movement (Haliloglu & Topaloglu, 2013; Hall & Vincent, 2003).

The eight piglets showed anal atresia, it was confirmed by Martínez-Frías (1997) that the presence of anal atresia is very frequent in body stalk anomalies. Furthermore they confirmed that the association of anal atresia, spine defects, renal/urinary tract defects, and genital defects constitutes a group of defects that tended to be present together in the same child because they are pathogenically related, and since they are of blastogenetic origin they constitute a primary polytopic developmental field (Martínez-Frías, Bermejo, & Rodríguez-Pinilla, 2000b). All the studied piglets presented either renal or urinary anomalies and/or genital anomalies confirming the association of defects in BSA as a primary polytopic developmental field. The presence of midline cleft palate in P160 can be explained by amniotic bands action during early embryo development (Gupta, Venkatesan, Chandra, Rajeswari, & Devi, 2015; Muraskas, McDonnell, Chudik, Salyer, & Glyn, 2003). However, the presence of amniotic bands was not observed. Palatoschisis can also occur as a result of failure of structures to migrate or converge in the midline since the more usual clefts represent a failure of structures to merge at the midline (Light & Ogden, 1993).

A classification for BSA, attending to the type of wall defect and limb defects is proposed (Figure 2). All cases presented herein were considered BSA, all fetus displayed a large ventral wall defect with spinal and UC defects, and anal atresia and/or genitourinary defects. We propose the following classification: four different types for BSA: BSA Type I: piglets with spinal and UC defects, anal atresia, thoracoabdominoschisis, thoracic defects, (cleft sternum, costal defects, respiratory and cardiac defects), structural limb defects, digestive system, and genitourinary tract defects (P17, P79, P240, and P278); BSA Type II: cases with spinal and UC defects, anal atresia, thoracoabdominoschisis, thoracic defects (cleft sternum, costal defects, respiratory and cardiac defects), nonstructural limb defects, digestive system, and genital and/or urinary tract defects (P168 and P208); BSA Type III: cases with spinal and UC defects, anal atresia, abdominoschisis, structural limb defects, digestive system, and genital and/or urinary tract defects (P160); and BSA Type IV: cases with spinal and UC defects, anal atresia, abdominoschisis, nonstructural limb defects, digestive system, and genital and/or urinary tract defects (P184). After reviewing the medical literature and studying the current cases, we consider true LBWC only the BSA that additionally presented structural limb defects. Thus, we differentiate two types of LBWC; LBWC Type I: characterized by structural limb defect and thoracoabdominoschisis, and LBWC Type II: characterized by structural limb defect and abdominoschisis. SR syndrome described in veterinary medicine presenting thoracoabdominoschisis

and nonstructural limb defect was classified as BSA Type II. The final classification and diagnosis for all cases is presented in Figure 2, and in Table 1.

The proposed classification is based on anatomical features and on the presumptive etiology of the limb defects as unifying criterion for a precise diagnosis of CBWD when limbs are affected as in BSA, LBWC, and SR.

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CONFLICT OF INTEREST

The authors have no potential conflict of interests.


AUTHOR'S CONTRIBUTION

Nieves Martín-Alguacil has made substantial contributions to conception and design, analysis, and interpretation of data. And also has been involved in drafting and revising the manuscript for intellectual content. Luis Avedillo has made substantial contributions to acquisition and interpretation of data. And also has contributed to the revision of the manuscript content. Both authors gave the final approval of the version to be published. And agreed to be accountable for all aspects of the work. And if necessary, they ensure that questions related to the accuracy or integrity of any part of the work will be appropriately investigated and resolved.

ETHICAL STATEMENT

All animals were legally procured in accordance with the regulations and laws of the European Union (Directive 86/609/EEC) and Spain (RD 223/1998) for the care, use, and housing of animals in research. The study was approved by the Complutense University of Madrid Bioethics Committee.

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