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Clinical Diagnosis of the Cryptorchid Stallion

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Cryptorchidism, or failure of testicular descent, can be a challenging clinical diagnosis, particularly in horses with an unknown castration history. Etiology of cryptorchidism is multifactorial and includes a genetic component. Diagnosis is centered on a detailed physical examination. Transrectal ultrasonography and endocrinologic assays including baseline testosterone, estrone sulfate, and human chorionic gonadotrophin stimulation are diagnostic aids. Treatment of cryptorchidism in horses is surgical removal of testicular tissue. A review of testicular descent, proposed etiologic mechanisms of cryptorchidism, as well as diagnosis and treatment options are presented.
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Testicular Descent

In the normal foal, both testicles typically descend into the scrotum between 30 days prior and 2 weeks after birth. This is the final resting place after a relatively long journey. The fetal gonad is initially located in the dorsal abdomen near the fetal kidney. Testicular migration is a complex, multifactorial event that is guided by the caudal ligament of the testis, or the gubernaculum, and regression of the cranial suspensory ligament of the testis. The gubernaculum extends from the posterior gonadal ligament to the posterior vaginal process. The cranial suspensory ligament of the testis attaches the testicle to the ventral surface of the mesonephros.[1] These structures exist in the female as well: the cranial ligament remains prominent to maintain the ovary in the abdomen, whereas the caudal ligament becomes the round ligament and the ligament of the ovary. Equine fetal testes are uniquely large: at 55 days gestation, the equine fetal testicular volume is double that of a fetal pig or calf of the same gestational age.

In order for transabdominal migration to occur, the gubernaculum enlarges due to increased cell division and increases in glycosaminoglycans and hyaluronic acid.[2] During descent, the gubernaculum shortens to draw the testicle near the inguinal region, while the cranial suspensory ligament that initially held the testicle near the dorsal abdomen regresses. Abdominal pressure may contribute to propelling the testicle through the inguinal canal and into the scrotum, while it is anchored and directed by the gubernaculum. By 150 days gestation, the epididymis and vas deferens connection to the gubernaculum is drawn to or is within the inguinal canal. The testes are thus 10 to 15 mm from the canal. At this stage, on average, the inguinal canal is approximately 3 mm in diameter, whereas the testis is 30 mm in diameter and weighs 20 g on average. By 250 days gestation, the testis has enlarged to 5 cm in diameter and weighs 50 g on average. The epididymal tail mass expands the inguinal canal to 1.5 cm in diameter, which is critical for eventual passage of the testicle through the inguinal canal. At 270 days gestation, the caudal pole of the right testicle is typically at the internal inguinal ring. The left testicle is either at the same level or slightly further from the inguinal ring. Inguinal passage is completed between 270 and 300 days gestation.[1]

Etiology/Pathogenesis

The word "cryptorchid" originates from Greek, meaning "hidden testicle," and is the term used to describe failure of testicular descent. Because of the complex nature of testicular descent, the etiology of cryptorchidism is likely multifactorial and involves a disturbance in steroid hormone metabolism, androgen deficiency, or insensitivity and neurological anomalies. Factors that may be involved in testicular descent include Müllerian inhibiting substance (MIS), androgens, the genitofemoral nerve, and a calcitonin gene-related peptide.[3] MIS is produced by Sertoli cells and is responsible for regression of the Müllerian (paramesonephric) ducts. In addition to this function, there are suggestions requiring further research that MIS contributes to normal testicular descent, specifically the swelling reaction of the gubernaculums;[3] however, a MIS-receptor knockout mouse model did not demonstrate any effect on gubernaculum size or development.[4] Androgens are necessary for testicular descent from the inguinal canal into the scrotum, although the exact site of action on the gubernaculum remains to be resolved. Androgens are also thought

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to be involved in regression of the cranial suspensory ligament. The genitofemoral nerve and the neurotransmitter calcitonin gene related peptide may also play a role in normal testicular descent. Malfunction or severance of this nerve appears to lead to cryptorchidism and can subsequently be partially alleviated by treatment with calcitonin gene related peptide.[3,5]

Recently, insulin-like factor-3 (INSL3) has been investigated as a component cause of cryptorchidism in mice and men. INSL3 is produced by Leydig cells and acts on gubernaculum development to maintain the testis in the inguinal region from where it subsequently passes into the scrotum. INSL3 knockout mice demonstrate cryptorchidism with no other obvious defects in the other reproductive organs.

The INSL3 receptor is LGR8 (*GREAT* gene). Mutations in this receptor have been associated with cryptorchidism in both mice and humans.[5] In horses, a transcriptional difference has been observed in INSL3 and LGR8 in unilateral cryptorchid versus descended testes.[6]

Mechanical abnormalities may also contribute to cryptorchidism. Evaluation of the locations of distal gubernacular attachments in cryptorchid testes in humans revealed a high rate (93%) of abnormal attachments in cryptorchid testes.[7]

Incidence, Heritability, Consequences

Cryptorchidism is heritable in many mammalian species, including pigs, dogs, sheep, goats, and horses.[8] The genetic basis for heritability in horses requires clearer determination; however, some references suggest a dominant inheritance.[9] The prospect of heritability is strong incentive to discourage breeding of affected animals.

Cryptorchid testes may be located intraabdominally or inguinally. Intraabdominal testicles are either completely or incompletely retained. As the description implies, with completely retained testicles, both the testicle and epididymis are in an intraabdominal location. With incompletely retained testes, the epididymal tail is located within a well developed vaginal process that may extend into or through the inguinal canal and into the scrotum. Inguinally located testicles can be categorized into temporary or permanent retention. Similar to humans, temporary retention may eventually resolve with testicular descent once puberty has been reached.[10,11]

An undescended testis is one of the most common urogenital disorders of human infants. The incidence ranges from 1% to 4% in full-term infants to as high as 30% in premature infants.[5,11] In an epidemiological evaluation of 5009 cases of equine cryptorchidism, several breeds were found to have a higher risk of cryptorchidism: Percheron, American Saddle horse, American Quarterhorse, as well as ponies and crossbred horses. Five breeds had decreased relative risks: Thoroughbred, Standardbred, Morgan, Tennessee Walking horse, and Arabian.[8]

Testicular retention is not symmetrical. In horses, the right retained testicle is more likely to be inguinal, whereas the left retained testicle is more likely to be abdominal.[12] This finding is in accordance with observations of testicular descent in the equine fetus where the right testicle engages the inguinal canal earlier than the left testicle.[1] Ponies, on the other hand, demonstrate the reverse asymmetry.[13] In a review of reported cases, 14% of cryptorchid cases were bilateral.[8] Inguinal retention is more common than abdominal retention; however, interestingly, the incidence of inguinal retention decreases with age, suggesting that some inguinal testicles experience delayed descent.[13]

Cryptorchidism may lead to abnormal testicular function. The increased temperature of the retained testis leads to disruption of spermatogenesis[14,15]; however, hormone production by the Leydig cells continues in cryptorchid testicles. Androgen production has been reported to be similar to the descended testicle or slightly decreased.[16,17] Additionally, estrogen production appears to be reduced in retained testes.[18]

An increased risk of neoplasia is associated with retained testicles, presumably due to the hyperthermic environment. The most common testicular tumor type in the adult horse is the seminoma, which can occur in both retained and descended testes, may cause testicular enlargement, and may metastasize.[19] Another tumor type is a teratoma, which contains tissues derived from multiple germ layers. Teratomas are the most common testicular tumor type in young horses. Teratomas are most frequently associated with retained testes and may be the cause rather than the result of testicular retention.[19,20] Other tumor types include interstitial or Leydig cell tumors and Sertoli cell tumors.

Diagnosis

Cryptorchid animals may be presented because of known failure of testicular descent; however, alternative presentations frequently include persistent stallion-like behavior in an animal that does not externally appear to have testicular tissue. Although rare, monorchidism should be considered in an animal in which only one testicle is identified.[21,22]

Behavior evaluation is an important diagnostic component. Behavior associated with stallions may include sexual excitement, erection, mounting, genital investigation, and sexually aggressive behavior. Continuous monitoring of the animal, such as with videotaping, may provide valuable information. Stallion-like sexual and aggressive behavior needs to be interpreted with caution, since geldings may also occasionally exhibit this type of behavior. Whether castration occurred pre- or postpubertally does not appear to have an effect on the rate of stallion-like sexual behavior. Twenty to 30% of geldings may exhibit stallion-like sexual behavior and aggression toward horses, and 5% may exhibit stallion-like aggressive behavior toward people without significant differences between animals castrated before or after puberty.[23,24] Stallion-like behavior in geldings has been documented to occur in the absence of residual testosterone or production of testosterone by nongonadal tissue.[25] Although castration eliminates sexual behavior in the majority of individuals, persistence of copulatory behavior after castration has been documented in many species, including the horse, bull, rats, hamsters, rabbits, guinea pigs, cats, goats, and primates.[26]

Careful physical examination can be very rewarding and includes external and internal palpation and ultrasonography. The general physique, or secondary sex characteristics, should be observed with stallions often having a thicker, more muscular neck and body. Attentive palpation of the inguinal region, scrotum, and base of the penis should be