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Ectopic ureters-pathophysiology and genetics

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Definition
Congenital malformation of the uretero-vesical junction (UVJ) with termination of the ureter at a site other than the bladder trigone area.

Embryology
Formation of the nephric duct is one of the earliest events in urinary tract formation, establishing a primary connection between the upper and lower urinary tract. The ureteric bud sprouts from the caudal nephric duct. While the proximal part of the ureteric bud differentiates into the collecting system, the distal part elongates and differentiates into the non-branched ureter. The ureter is brought into contact with the bladder epithelium by ureter maturation, a process which is depending on apoptotic elimination of the most caudal segment of the nephric duct. The caudal ureter undergoes apoptosis forming a new ureteral orifice in the bladder primordium. Subsequent expansion of the bladder moves the ureter orifice which is now fused with epithelium to its final position in the bladder (Literature review in Chia et al., 2011; Paces-Fessy et al., 2012). It is thought that a failure in ureteric sprouting and/or ureter maturation results in the most common ureteral abnormality in dogs, when the ureters terminate into the bladder neck or proximal urethra (Owen 1973).

Epidemiology
In 1984 data was published by Howard Hayes about 228 case records collected from 15 North American veterinary teaching hospitals over a 17 year period. Of these 228 cases of ectopic ureters diagnosed and treated only 11 were males. Among more than 32 affected breeds 6 breeds were represented significantly higher than expected by chance, these were Siberian Husky, Newfoundland, bulldog, West Highland white terrier, fox terrier and toy poodles. A study from the UK published in 2000 (Holt, Thrusfield and Moore) reported an increased prevalence also in Border terriers, Briards, Golden and Labrador Retrievers, Griffons and Skye terriers. It was also noted that many oft he affected cases were closely related to each other (Holt, Gibbs and Peason 1982).

The highest prevalence of 67% was found in Entlebucher mountain dogs (Fritsche et al., 2012). Of all affected dogs, 30 Entlebucher mountain dogs and 1 Appenzeller mountain dog with extravesical ureteral ectopia and 10 Entlebucher mountain dogs with intravesical ureteral ectopia, had urinary incontinence. In the recent study including more than 500 Entlebucher mountain dogs males were affected more often than females and in Briard dogs the male to female ratio is almost even (Fritsche et al. 2012; Nickel et al. 2010 and unpublished data). The female /male ratio of cases, on which surgery was performed in Switzerland was 1,1:1 (Reichler et al. 2012), whereas the retrospective analysis from cases treated in Germany between 2007 and 2011 (n=34) revealed a female/male ratio of 1,4:1 with Golden Retrievers counting for 50% of the females (unpublished data).

Pathophysiology
Most commonly the ureter is approaching the bladder trigone but does not express the usual horse shoe or half moon like orifice inside the bladder. Instead a tubular structure is continuing in the wall of the bladder neck and urethra and terminates somewhere between the bladder neck and the vaginal vestibule. This is called an intramural ectopic ureter and seen in the vast majority of cases (Wiegand, Nickel, van den Brom 1996; Smith, Radlinsky and Rawlings 2010). In male dogs the termination occurs most often in the prostatic urethra (Bitterli et al 2010). In cats, in which the disease is very rare, extramural course of the ureter is observed more often than in dogs (Holt and Gibbs 1992). The shape of the orifice can be altered, look like a trough or there can be branches or multiple perforations in the membrane separating the ureter from the urethra.

Urinary incontinence occurs, but not in all affected animals and not only as a result of the abnormal termination. Persistence of urinary incontinence after surgical correction is common in female dogs and several criteria were identified, which suggest urethral sphincter mechanism incompetence (USMI) to be a concurrent problem in many females (McLoughlin and Miller 1991; Lane, Lappin and Seim 1995; Holt and Moore 1995; Wiegand, Nickel and van den Brom 1996). Response to phenylpropanolamine administration, intra-pelvic bladder neck position and low urethral closure pressure during urodynamic studies were found. Based on the study of prognostic factors published in 1996 (Wiegand, Nickel and van den Brom) selection criteria for female dogs with ectopic ureter were applied. In a retrospective analysis of 20 cases (2007-2011) the success rate was increased with 65% of female dogs being completely continent, 15% with
only intermittent mild incontinence not requiring further treatment and only 4 of 20 requiring medication, urethral bulking or additional surgery (Nickel, unpublished data). In female dogs with ectopic ureters suspected to have USMI as a cause of urinary incontinence treatment for USMI is recommended. As prognosis of surgical or laser-assisted endoscopic treatment in male dogs is excellent it can be concluded that concurrent USMI is not a problem in male dogs (Wiegand, Nickel and van den Brom 1996; Berent, Mayhew and Porat-Mosenco 2008).

Ectopic ureters can be asymptomatic, (North et al. 2010), males may develop clinical signs during adulthood (Bitterli et al. 2010) and even female dogs are found to become incontinent after spaying (Thomas and Yool 2010). However, most often female puppies already show signs of incontinence with concurrent problems such as scalding of the skin in the perivulvar region and urinary tract infection (UTI). UTI is found in up to 75% of cases (Ho et al. 2003; Troy and Waldron 2011; Wiegand, Nickel und van den Brom 1996) with E.Coli being the predominant isolate. Another consequence of an abnormal terminating ureter may be the dilatation of the ureters and renal pelvis, which is significantly related to an intramural course and termination in the distal urethra or vaginal vestibule in females or in those rare cases with ureterocoele (Canizzo et al. 2003; Wiegand, Nickel and van den Brom 1996). However, sometimes the wall of the ureter becomes thickened as a result of lymphocellular inflammation which may contribute to obstruction and secondary formation of megaureter and hydronephrosis. Hydronephrosis and/or megaureter were found in 18 Entlebucher mountain dogs with ectopic ureters, eight of which were clinically inapparent (Fritsche et al. 2012).

Genetic studies

The phenotype has been studied intensely in Entlebucher mountain dogs in Switzerland and North America (Bitterli et al. 2010; North et al. 2010; Fritsche et al. 2012). For characterization of the phenotype in the Entlebucher mountain dogs and Briard dogs ultrasonography was used with enhancement of the ureteral jet by administration of furosemide (Hischer, Hungerbühler and Nickel 2010; Hungerbühler, Reichler and Nolte 2012 subm.). Colour Doppler or colour B-Flow technology were used to improve the detection of abnormal position and shape of the ureterovesical junction. Of 552 Entlebucher mountain dogs with known phenotype status, 33% had normal termination of both ureters in the trigone, 47% had at least one ureteral orifice in the bladder neck and 20% had at least one ureteral orifice at the vesicourethral junction or urethra (Fritsche et al. 2012). In contrast only 16% of the screened Appenzeller mountain dogs, which are of same size and share a common ancestry with the Entlebucher mountain dogs, had ureteral openings not in the area of the trigone (Bitterli et al. 2010). The prevalence of abnormal anatomy of the uretero-vesical junction in 439 examined Briard dogs was 25 %, with 8 % having the same phenotype as dogs which are presented with clinical signs. Sex distribution is almost even in the Briard dog, while 1.4 times more males than females are affected in the Swiss Entlebucher mountain dog population (Fritsche et al. 2012). It becomes apparent from the anatomic diversity that there must be a variable expression, if a candidate gene is suspected. Pedigree analysis in the study of Entlebucher mountain dogs from North America (North et al. 2010) was not able to identify a mode of inheritance because of incomplete penetrance. In Switzerland complex segregation analysis using PAP (Hasstedt 2005) was performed on a data set of 283 individuals with a diagnosis, including 18 complete litters and 36 litters with 50% of their puppies examined. To connect these litters within the pedigrees 274 individuals, like sibling, grand-parents and so forth, without a diagnosis were added. Different parameters such as frequency of alleles, transmission probability, dominance, displacement, heritability for one environmental and four genetic models were tested. Major gene with further polygenous components was the most likely model to explain the dataset. The variation approach method bayz using a data set of 307 Entlebucher mountain dogs concluded in a recessive major gene, being responsible for 50% of segregation. The hypothesis of a major gene was furthermore supported by the decline of the incidence after breeding restrictions were applied in 2008 (Fritsche et al. 2012). Genome chip analysis in the Entlebucher is suspicious for 2 gene loci involved in the complex malformation (Besold, unpublished data). A recessive gene with variable expression is also the most likely mechanism concluded from pedigree analysis in Briard dogs (Hischer, Nickel and Distl, unpublished data). Selection based on phenotype has already reduced the prevalence in the Entlebucher mountain dog population in the last 2 years (Fritsche et al. 2012).

Conclusion

Breeding may be improved in high risk breeds by ultrasonicographic identification of the phenotype. Genetic testing may be available in a rather distant future. Identification of female dogs with USMI prior to surgery or endoscopic laser ablation of the ectopic ureters should receive more attention.
References

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