Hereditary Kidney Disease

A look at Renal Dysplasia and other heritable renal diseases:
Possible relation to disease in Cairn terriers.

Dr. Anne M Traas
Matthew J Ryan Veterinary Hospital of the University of Pennsylvania
Anne M. Traas, DVM
contact information

- Phone: 215-898-8078
- Email: atraas@vet.upenn.edu
- Address:
  Room 4037
  MJR-VHUP
  3900 Delancey St
  Philadelphia, PA 19118

- Please send pedigrees, biopsy and ultrasound or necropsy reports to the above address.
Renal anatomy

- Renal = of the kidney
- Renal Cortex
- Renal Medulla
- Renal Pelvis

http://www.ic.sunysb.edu/Stu/sumusso/webquest.htm
Renal anatomy

- Nephron = functional unit
- Composed of glomerulus, blood vessels, tubule and empties in to collecting duct
- 300,000 nephrons in 2 normal kidneys
- Only 1/3 of nephrons needed for normal function

http://bioweb.wku.edu/courses/Biol131/stokes/131f96chap26.html
Renal Disease

- Congenital or Acquired
- Clinical Signs are the almost all the same for all diseases – Chronic Renal Failure
Signs of Trouble

Clinical Signs of CRF

- Anorexia
- Weight loss or poor growth
- Lethargy
- Excessive drinking and urination
- Vomiting (occasionally diarrhea)
- Bad breath, oral ulceration
Physical exam findings CRF

- Poor body condition, hair coat
- Oral ulceration, uremic breath
- Kidney palpation may be abnormal
  - large or small
  - Only one??
- “Rubber jaw”
- Pale gums
Lab Tests - CRF

- **Urinalysis**
  - Decreased concentration
  - Signs of Infection?
  - Protein?

- **CBC**
  - Nonregenerative anemia
  - Low protein in some cases
Lab Tests - CRF

Chemistry
- Azotemia = inc. BUN and creatinine
- High phosphorus
- High or low calcium
- Low protein in some cases
- Low or high Potassium
Causes of CRF in Young Dogs

- Pyelonephritis
- Systemic infection - Leptospirosis
- Congenital — herpes, hereditary, toxins
- Hereditary
- Nephrotoxins — Antifreeze
- Lymphoma and other cancer
- Urolithiasis — Stones
Hereditary Kidney Diseases

Basic types

- Anatomical
  - Our topics for today
- Functional
  - Cystinuria
  - Fanconi’s Syndrome
  - Amyloidosis
  - Protein Losing Nephropathy
  - Immune mediated
  - Etc.
Select Hereditary Kidney Diseases

- **Hereditary nephritis / Glomerulonephropathy**
  - Bull Terrier, Dalmation, mix, Samoyed, Cocker spaniel, Bull Mastiff, Doberman Pinscher
- **Familial Renal Disease / Tubulointerstitial nephropathy**
  - Norwegian Elkhound
- **Renal Dysplasia**
  - Border Terrier, Golden Retriever, Kooikerhondje, Lhasa Apso, Rhodesian Ridgeback, Shih Tzu, Soft Coated Wheaton Terrier
- **Juvenile Nephropathy**
  - Schnauzer (miniature)
- **Polycystic kidney and liver disease**
  - Cairn Terrier, Westie, Bull Terrier
- **Glomerulocystic Kidney Disease**
  - Belgian Shepherd
- **Protein Losing Nephropathy**
  - Soft Coated Wheaton Terrier
Progressive Nephropathy

- Renal disease that continues to worsen
- Often familial
- Inclusive term for many diseases
- Also: Juvenile Nephropathy, Hereditary Nephropathy
Renal Dysplasia

- **Dys** = abnormal; **Plasia** = growth
- Incomplete or disorganized growth of kidney
- Congenital disease
  - May be acquired or hereditary
- Onset of disease depends on severity of pathology
  - Some dogs may be affected yet never develop disease
- Dogs often present before 1 year of age
- Clinical signs of chronic renal failure
- Wedge biopsy is the ONLY definitive diagnostic technique in the live dog.
  - True cut biopsy may miss areas of dysplasia
Renal Dysplasia

This is a histological (microscopic tissue) definition of renal dysplasia:

1. fetal or immature glomeruli,
2. persistent metanephric ducts surrounded by primitive mesenchyme,
3. fetal or immature tubules
4. anomalous presence of interstitial fibrous tissue

http://www.lhasa-apso.org/health/kidney.htm
Renal Dysplasia

- Embryonic arrest in late gestation or newborn period
- Some areas stop growing too soon
- Areas of the kidney develop unevenly
- Development of some sections is unorganized
- Abnormality may leave the kidney more susceptible to infection, mineralization and abnormal compensation for lost tissue.
- Clinical signs do not occur until 2/3 of the normal number of nephrons are diseased or missing
  - age at CRF diagnosis 4 wks to 5 years; most <2 yrs
- Protein is not usually found in urine
Renal Dysplasia

- Can occur sporadically in any breed
- Can be induced in puppies by in utero infection with canine herpes virus
- Autosomal recessive in:
  - Shih Tzu, Lhasa Apso, Standard Poodle, Soft Coated Wheaton
- Unknown inheritance in:
  - Kooikerhondje, Lhasa Apso, Keeshonds, Golden retriever, Alaskan Malamute, Miniature schnauzer, Chow Chow, Cocker Spaniel
- Sporadic Reports in:
  - Border Terrier, Rhodesian Ridgeback, Beagle, Great Dane, Bedlington terrier, Briard
Ultrasound of Kidneys

Normal

Cortex

Medulla

End Stage – Fibrotic

Group 1 type

Group 2 type
Study of Cocker Spaniels with Renal Dysplasia biopsy confirmed with CRF


- kidneys significantly reduced in size
- Group 1: corticomedullary demarcation was distinct and the renal cortex was remarkably thin
- Group 2: poor corticomedullary demarcation
- Based on ultrasound findings alone, renal dysplasia (renal familial disease) can be suspected when small kidneys with thin echogenic cortex are present in young dogs.
- An ultrasound image, similar to that of fibrotic kidneys cannot be differentiated from chronic inflammatory disease and from end-stage kidneys.

- Biopsy or necropsy is needed for diagnosis
### Renal Aplasia

- **Aplasia** = No Growth
- **Renal Aplasia** = One or both kidneys do not develop
- **Also**: Renal unilateral agenesis
- **Often associated** with congenital malformations in other portions of the urinary and genital tract.
- **Can be acquired in utero**
  - Chlorambucil and sodium arsenate
Renal Aplasia

- Often are asymptomatic with normal life span
- Only one report involving both dysplasia and aplasia
- Ultrasound is wonderful for diagnosis of aplasia but does not rule out concurrent dysplasia
- Seen in many breeds as a sporadic event
Renal Hypoplasia

- Hypo = low, plasia = growth
- Small kidney or kidneys composed of reduced numbers of normal adult nephrons
- Considered sporadic and not hereditary
- May be clinically silent if total number of nephrons is sufficient
- Difficult to separate from dysplasia
Polycystic Kidney and Liver Disease

- Affects liver and kidneys
- Hereditary – found in cairn terriers, west highland white terriers, bull terriers, beagles
- Common in humans
- Progressive
- Autosomal Recessive in Cairns and Westies, Autosomal Dominant in other breeds and cats, humans have both forms
Polycystic Kidney and Liver Disease

- Small cysts form early in life and get larger and more numerous as the animal ages.
- Clinical signs of CRF:
  - May also have abdominal enlargement.
  - Large kidneys or liver may be felt on physical exam.
- Can be diagnosed by ultrasound:
  - Greater than 3 cysts in both kidneys with family history of disease.
  - Sensitivity of ultrasound increases with age.
  - Should be performed prior to breeding.
- DNA test available in cats but not yet in dogs.
Glomerulopathies

- Renal disease affecting primarily the glomerulus
- Hereditary Nephritis
  - Bull terriers and Dalmations
  - Autosomal dominant
  - can be very late onset 8 mo to 8 yrs
- X-linked Alport syndrome
  - Samoyed
  - X-linked dominant
- English Cocker spaniel glomerulopathy
  - Autosomal recessive
- Other Breeds affected but unknown inheritance
  - Doberman pinscher, Bullmastiff, Newfoundland, Rottweiler, Pembroke Welsh Corgi, Beagle
- Persistent proteinuria is often the first sign
**Where are we now**

- Pedigree collection of affected animals
  - Must have a necropsy or biopsy diagnosis
- Ultrasound of affected dogs and possibly affected puppies
  - We can detect renal aplasia
  - We may possibly be able to detect renal dysplasia but we are unsure
- This process will help us to determine if a large scale study is possible and how much funding will be required
Where are we now

- There appear to be two clinical signs in the current pedigrees
  - Only one kidney - Renal aplasia
  - Two kidneys that did not form correctly – Renal dysplasia

- These are typically two diseases
  - One report of a Cavalier King Charles Spaniel having both aplasia and dysplasia
Are they the same disease?

- Biopsy the present kidney of aplastic dogs
- Test matings
  - Help explain how the disease(s) is inherited
    - Ethical considerations
  - Breed aplastic dogs to dysplastic dogs
What we can do right now

- Biopsy all dogs over 6 months from lines with known issues that will be kept for breeding
- Breed only dogs that biopsy as normal
- Consider removing dogs from the breeding program that have produced affected dogs
  - Remember these things may be sporadic or have other causes so more than one affected offspring may be needed before eliminating the parents
- Ultrasounds can be used as a screening test and abnormal dogs not used for breeding but the normal dogs by ultrasound will still need biopsies before they can be cleared
Dysplasia Studies

- **Difficulties**
  - No way to tell if a particular dog truly has the hereditary form or has an other cause for dysplasia
  - Truly clear dogs are needed for studies
    - Must biopsy older dogs to be sure they are truly unaffected – Both kidneys?
  - Must have 100-150 affected dogs to do whole breed linkage analysis
  - Several 3 generation pedigrees each with affected dogs are needed familial linkage studies
  - Several forms of dysplasia may exist in the breed – how to tell them apart
  - Biopsies should all be reviewed by the same pathologist
  - Genes involved in normal renal development are largely unknown making a candidate gene approach unavailable
Steps in Investigating Genetic Diseases

- Evaluate the disease
  - ACCURATE DIAGNOSIS on all affected dogs
  - Confirm all affected have the same disease
  - Look at the age of onset
  - Determine if parents of affected dogs have any changes
  - Find an easy and repeatable way to diagnose the disease
Steps in Investigating Genetic Diseases

- Accurate diagnosis
- Determine the mode of inheritance
- Determine the incidence in the breed
- Obtain funding
- Collect diagnosis, pedigree and DNA samples of affected and normal dogs
- Look for the same disease in another species where the genetics basis is known for a candidate gene
- When affected animal numbers are high enough begin linkage study