Meningoencephalitides of unknown etiology (MUE) in dogs

Andrea Tipold
TiHo Hannover

Meningoencephalitides of unknown etiology/origin

- Granulomatous meningoencephalomyelitis (GME)
- Necrotizing encephalitis (NE)
- Hydrocephalus with periventricular encephalitis
- Nonsuppurative Meningoencephalitis in Greyhounds
- Steroid-responsive Meningitis-Arteritis (SRMA)
- Little White Shaker/Cerebellitis/tremor syndrome
- Eosinophilic encephalitis
- Encephalitis of unknown origin (histopathology not defined) (MUE)

Mixed breed dog, m, 4 years

- Since several days gait abnormalities
- Clinical examination normal
- Neuro- exam
- Localisation
- VETAMIN D (differentials)
Mixed breed dog, m, 4 years

- Blood, urin normal
- Thorax rx and ultrasound abdomen normal
- MRI – multifocal lesions, hyperintense T2, contrast enhancing
- CSF: pleocytosis (320 cells/ul)
- Mixed cell population
- Protein 250 mg/dl
- Histopathology: GME

Granulomatous meningoencephalomyelitis

GME - clinics

- localisation – focal, multifocal, brain, spinal cord, n.opticus
- blood work: leukocytosis possible
- MRI, hyperintense T2, contrast enhancing T1
- CSF:pleocytosis – mixed or mononuclear, protein elevated

GME - DIAGNOSIS

- Imaging techniques: CT, MRI
- Biopsy
CT - Biopsy - GME

Brain biopsy

Further examinations without biopsy
- AB and PCR neospora/toxoplasma
- response to immunosuppressive drugs
- DIAGNOSIS: granulomatous encephalomyelitis
- DD: protozoal, GME, mycotic
- suspected diagnosis: GME, encephalomyelitis of unknown origin
Granulomatous Meningoencephalomyelitis (GME)

etiology and pathogenesis mostly unknown – potential infectious triggers? delayed-type hypersensitivity reaction, genetic factors?

- dogs of all breeds, age and sex
- mostly adult dogs; purebred, small dogs; female (sex steroid-associated alterations in T-helper cytokines?)

Talarico, Schatzberg 2010

Granulomatous Meningoencephalomyelitis (GME)

- disseminated
- focal
- ocular

- acute progressive
- chronic progressive
- central vestibular, forebrain, spinal, multifocal

- extraneural: rare, hyperthermia, eye

GME

- worldwide
- white substance - brain, spinal cord; meninges
- perivascular cuffs with macrophages, lymphocytes, plasma cells and some neutrophiles
GME - treatment
- no etiological therapy
- response to steroids and/or azathioprin (individual dosis regimen)
- Cytosine arabinoside (100 mg/m² i.v. or s.c. for 4 days) Lowrie et al 2013
- Procarbazine (25 – 50 mg/m² p.o. daily)
- Leflunomide, cyclosporine, lomustine, radiation therapy
- selflimiting cases?

Inflammatory CNS diseases of unknown origin- Treatment in general
- ?
- influence on the disease per se?
- regular clinical and CSF controls - cell count
- Blood examination (leucopenia)

GME - prognosis
- Generally guarded
- More focal signs – forebrain longest lifespan
- selflimiting cases? Exact survival not known
- Studies – mixed quality, not all histopathology
- Median survival – 14 – 930 days (range steroids alone 2 – 1200 days) (Granger et al 2009)
Necrotizing encephalitis (NE)
- Necrotizing meningoencephalitis (NME) and necrotizing leukoencephalitis (NLE) > overlap in clinical signs and neuropathology > NE
- Former „breed specific meningoencephalitis“
  - Yorkshire Terrier
  - Pug Dog
  - Maltese dogs
  - Chihuahua, Pekingese, WHWTerrier etc..

Necrotizing encephalitis (NE)
- Etiopathogenesis poorly understood
- Pug dogs: familial inheritance pattern, MHCII
- Multifactorial
- Genetic and infectious triggers (virus) – immune dysregulation?

Necrotising encephalitis (NE)
- Genetics + Trigger (infectious?) – immune dysregulation?
- Broadly reactive PCR assays for viruses negative for NE and GME (Schatzberg 2005, 2012)
- Mycoplasma? Bartonella?

Hit and run......
Concurrent GME and NE
3 Yorkshire Terriers

Genetic modification of the immune system – different phenotype, similar disease?
Hoffmann et al, 2011, ECVN

EVALUATION OF BLOOD AND CEREBROSPINAL FLUID OF DOGS WITH MENINGITIS AND MENINGOENCEPHALITIS OF UNKNOWN ETIOLOGY FOR VECTOR-TRANSMITTED MICROORGANISMS


<table>
<thead>
<tr>
<th>Group</th>
<th>pathogen</th>
<th>CSF/blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUE (22)</td>
<td>A. phagocytophilum</td>
<td>4x SRMA</td>
</tr>
<tr>
<td></td>
<td>Bartonella spp. 1x MUE</td>
<td>1x MUE</td>
</tr>
<tr>
<td>SRMA (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCR: Anaplasma phagocytophilum, Ehrlichia canis and Bartonella spp.
Serum antibodies against E. canis, Bartonella spp., Tick-borne encephalitis virus (TBEV) and Borrelia burgdorferi sensu lato
qualitative eubacterial PCR

Pug Dog, 5 years, f

- Since 3 weeks seizures, focal onset, generalised
- Neuro-exam: localisation, forebrain left sided
- VETAMIN D
- MRI
- CSF
mononuclear pleocytosis, protein 40 mg/dl
Clinical findings NE
- Onset of neuro signs: 6 months to 7 years (mostly young dogs)
- Inflammatory disease: multifocal (pugs and maltese – forebrain, yorkshire brainstem)
- Rapidly progressive signs: seizures, depression, circling, vestibulo-cerebellar…..
- Diagnosis: breed, clinical signs, CSF mononuclear pleocytosis, biopsy, MRI

Treatment NE
- prognosis guarded
- as described with GME, treatment of seizures

Eosinophils in CSF
Idiopathic eosinophilic encephalitis – rare, cause unknown, rule out other causes for eosinophilia
**Case dog ws**
- WHW Terrier, 4 years, f
- history: tremor, gait abnormalities

- clinics
- neuro-exam

**Case dog ws**
- Localisation
- VITAMIN D

- special examinations:
- blood work: normal
- CSF cells 12/3 /ul; protein 30 mg/dl
- MRI

**Little White Shaker**
- „Shaker dog disease“
- „idiopathic tremor of adult dogs“
- „sporadic acquired tremor of adult dogs“
- (cerebellitis)

- Young adult dogs
- Maltese, WHW Terrier
- Yorkshire, Beagle....
Little White Shaker

**Pathogenesis**
- unclear, immune reaction against tyrosine-producing cells
- tyrosine metabolised to melanin
- tyrosine: important for neurotransmitter-production: dopamin, epinephrine, norepinephrine

**Histology:** mild diffuse, non-suppurative encephalomyelitis

**Diagnosis:** breed, clinical signs, slight mononuclear pleocytosis in the CSF

**Treatment:** prednisolon 3-4 months, 80% of the dogs respond well (Study including 24 dogs, Wagner et al 1997)
- Prednisolone decreasing dosage (start 1-2 mg/kg)
- Ev. Diazepam 0.5 – 1 mg/kg 3x daily
- anticonvulsant therapy ineffective
- prognosis: usually favorable
Periventricular Encephalitis

- Hydrocephalus
- Young dogs (normal at birth, 2-3 months of age neuro-signs with skull enlargement)
- Severe periventricular inflammation
- CSF: pleocytosis – mononuclear cells, macrophages, xanthochromia
- imaging

Periventricular encephalitis

- Prognosis guarded, better if signs occur in older dogs
- Attention – surgery (shunting) hydrocephalus
- Some dogs remain stable
- Therapy: with mild clinical signs, ?, Dexamethason: 0,05 mg/kg/day, reduce to 0,01 mg/kg every 2nd day, shunting?

Steroid responsive Meningitis-Arteriitis (SRMA)
• Most frequent meningitis in dogs (Muñana, 1996)
• 15% of inflammatory diseases of CNS (Tipold, 1995)
• most common cause of fever of unknown origin (Battersby, 2006)
• Naturally occurring animal model for human vasculitides of unknown origin
• aetiology unknown
• pathogenesis not well understood

White Boxer, f, 8 months
Apathic, weight loss
Body temperature: 40.1° C
Rest: normal

Neurological exam
• apathic
• Stiff neck, reluctant to move, stiff gait
• Cranial nerves: normal
• Normal proprioception
• Spinale Reflexes: normal
• Painful neck palpation
Localisation – Structures, which might be affected with neck pain

- Meninges
- Facette joints
- Vertebral body
- Disc
- Muscles

Results CSF

Cerebrospinal fluid: protein 45 mg %; 3200 cells/ul, mostly neutrophils (90 %), some monocytes (6 %) and lymphocytes (4 %)

SRMA – MRT pre/post contrast T1 weighted images
SRMA

- Systemic inflammatory disease with most pronounced manifestation within the cervical meninges
- Relapsing course
- Juvenile to young adult dogs
- Breed predisposition

Diagnosis of SRMA

- Laboratory findings
  - Marked neutrophilic leukocytosis
  - Marked neutrophilic pleocytosis
  - Increased acute phase proteins

Clinical diagnosis

- "Steroid responsive meningitis-arteriitis" (SRMA)
  - IgA values elevated in CSF and Serum – supports diagnosis of SRMA.
  - Other confirmation: response to steroids > control examinations, good contact with the owner.
SRMA

- acute chronic
- neck pain, fever additional neuro deficits
- steroid treatment
- uncomplicated complicated, relapses

SRMA

- chronic, protracted form – looks like a spinal cord disease
- Cerebrospinal fluid mononuclear pleocytosis. IgA elevated in CSF and Serum.
SRMA
- CSF
- neutrophils (acute)
- mononuclear pleocytosis (chronic)
- meningitis
- arteritis
- IgA, immune complexes (chronic)

Treatment SRMA
- „Steroid responsive meningitis-arteritis“
- „Beagle Pain Syndrome“
- „Canine juvenile polyarteritis syndrome“
- „Steril purulent Meningitis-Ateritis“
Treatment SRMA

- Prednisolone for about 6 months
- CSF re-exams to receive an individual treatment regimen and a useful reduction of the prednisolone dosis – cell count, CRP
- No response, recurrent signs: immunosuppressiva
- Treatment = no therapy of the disease, prevention of tissue damage

Treatment

- Pain medication – one episode, few leukocytes in the CSF
- Glucocorticosteroids
- Immunosuppressive drugs
- "Immune modulatory" drugs (mofetil mycophenolate)

Therapy with Prednisolone

- Recurrent signs, high cell count in CSF: Prednisolone – start 4 mg/kg BW (1-2 days), reduce to 2mg/kg BW (2 days - 1-2 weeks).
- > for a longer period 1mg/kg BW Prednisolone orally until first control examination of the CSF (4-6 weeks).
Prognosis SRMA

- **good** – treatment at an early stage under control of a vet
- **Guarded** - older dogs, frequent recurrences, bleeding in the meninges – arteritis, chronic form

Side effects Prednisolone - SRMA

- Rare, longterm study reversible
- Polyuria, Polydipsia, Polyphagia and increase of the body weight
- Find the lowest effective dosage of prednisolone to increase the compliance of the owner
  - Control exams!

Therapy with Prednisolone in SRMA

- Only symptomatic!
- Prevention of cell influx in the nervous system
- Prevention of tissue damage – development of the chronic form
- Studies: cell count in CSF decreased, other parameters for an inflammation remain elevated
  - **Spontaneous recovery!** - pathogenesis
IgA

CSF and serum elevated

IgA values

IgA determination in serum and CSF:
- Statistical analysis of a large population
- Establishing sensitivity and specificity
- 1050 samples of CSF and serum collected from 441 dogs (1999 - 2008)
- IgA determination (ELISA)
- Statistical analysis (SAS)
Conclusion: highly sensitive, not specific. Useful for studies on the pathogenesis.

### IgA Diagnostic Performance Results

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRMA compared to all other diseases</td>
<td>91</td>
<td>78</td>
</tr>
<tr>
<td>Inflammation</td>
<td>91</td>
<td>74</td>
</tr>
<tr>
<td>IVDD</td>
<td>91</td>
<td>72</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>91</td>
<td>65</td>
</tr>
<tr>
<td>IE</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>Other</td>
<td>91</td>
<td>85</td>
</tr>
</tbody>
</table>

- after therapy stop / no clinical signs

- maximal normal value: 0.2 μg/ml
- maximal normal value: 100 μg/ml

**CSF IgA**

- At presentation
- under therapy during relapses
- under therapy no clinical signs
- other therapies no clinical signs

**Serum IgA**

**results serum C reactive protein CRP**

CRP of Dogs with SRMA activity significantly higher than in other neurological diseases and healthy controls

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
<th>VII</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (µg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Bathen-Nöthen, JVIM, 2008
Albumin in dogs with SRMA significantly lower than in other groups with neurological diseases and healthy controls.
C-reactive protein (CRP) in dogs with steroid responsive meningitis-arteritis

- serum CRP most probably helpful to support the diagnosis and to monitor treatment control of SRMA

- serum CRP is not specific for SRMA, so rule out other systemic inflammatory diseases

Etiology

- unknown
- epidemiological studies: environmental factor - infectious?
- different approaches:
  - virus isolation attempts
  - bacterial examinations
  - indirect examinations (T-cell stimulation - superantigen)

Etiology of SRMA

- no infectious agent identified to date

- presumably overshooting immune reaction
  - unknown trigger
BREEDS

- Beagles
- Bernese Mountain dogs
- Boxers (family)
- Petit Basset Griffon de Vandeene (family)
- every breed
- in Germany
- Weimaraners?
- GENETICS????

Steroid-responsive meningitis-arteritis in Nova Scotia duck tolling retrievers

Genome-wide association mapping identifies multiple loci for a canine SLE-related disease complex

Pathomechanism meningitis

CSF – differential cell count

acute  chronic

CSF enhanced chemotactic activity, high IL 8 levels and C5a (Burgener et al)
**Pathomechanism**

Upregulation of CD11a, MMP-2, MMP-9

![Diagram](Source: www.nature.com (modified)

Schwartz et al, 2009

**Results (Schwartz et al., 2008)**

Might explain high IgA levels

**IL-6 and TGF-β1 - Results**

Interleukin 6 in cerebrospinal fluid and serum

Increased concentrations of bioactive IL-6 in SRMA might be the key leading to fever, acute phase protein and IgA production
IL-6 and TGF-β₁ - Results
Transforming Growth Factor Beta 1 in cerebrospinal fluid and serum

- TGF-β₁ increased intrathecally during CNS inflammation
- Not the only responsible signalling protein for IgA production

Maiolini, 2012

Signalling Proteins – IL-6 and TGF-β₁

Hypothesis II

CD4⁺ progenitors

IL-6 + TGF-β₁

Th1

Th2

Th17

Treg

Immunosuppression

Maiolini, 2012

Toll-like Receptors - Conclusions

Only few similarities between SRMA and pyogenic infections:

→ infectious agent can only trigger the disease

→ A relatively high expression of TLR4 and TLR9 in acute SRMA:

→ possible involvement in the inflammatory process in SRMA

Maiolini et al, J Neuroinflammation, 2012
Conclusion

- Infectious agents –
  inducing dysregulation of the immune system
  hit and run...
- Ongoing and recurrent disease