ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

MYLAV
Laboratorio La Vallonea

"Meningoencephalomyelitis of Unknown Etiology (MUE)"

Gualtiero Gandini

1

GOAL:

provide updated information on the approach to "sterile" inflammatory disorders of the Central Nervous System (CNS)

Index:

1. Clinical approach to CNS inflammatory/infectious disorders
2. Meningoencephalomyelitis of Unknown Etiology (Origin) – (MUE/MUO)
3. *Granulomatous Meningoencephalomyelitis (GME)*
4. *Necrotising Encephalitides (NE)*
5. Treatment and outcome

2

1.

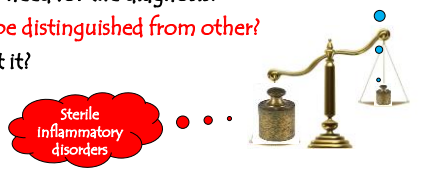
Clinical approach to CNS inflammatory/infectious disorders

3

Clinical approach to a CNS inflammatory sterile disorder

THE MAIN QUESTIONS:

1) Clinical presentation?
2) What do I need for the diagnosis?
3) How can be distinguished from other?
4) Can I treat it?



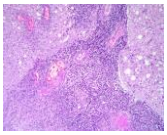
4

Meningoencepha(lomye)litis

1) Clinical presentation?

CNS INFLAMMATORY LESION:

- Leucocytes infiltration in the nervous tissue
- Altered permeability of the blood-brain barrier (BBB)
- Diffusion through contiguity /blood stream
- Multifocal/diffuse lesions



CLINICAL SIGNS:
Reflect the pathogenesis of the CNS inflammatory lesions

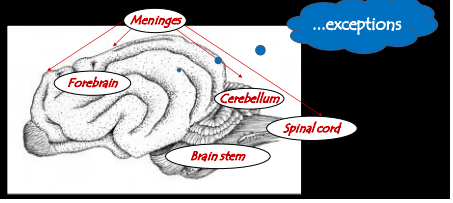
→ Acute/subacute ONSET; PROGRESSION of the signs MULTIFOCAL signs

5

Clinical presentation

NEUROANATOMIC LOCALIZATION OF THE LESION: MULTIFOCAL

Progressive signs affecting more than one region →
± contemporary presence of signs affecting:



6

Meningoencepha(lomye)litis

2) What do I need for the diagnosis?

BLOOD WORK
- Cell Blood Count?
- Biochemical profile?

SEROLOGY and PCR
- Serology or PCR?
- From which material?
- When?

CSF EXAM
- Cells
- Proteins
- Other?

DIAGNOSTIC IMAGING
- XRays?
- Computed Tomography?
- Magnetic Resonance Imaging?

7

Cerebrospinal fluid examination

1. PHYSICAL ANALYSIS — Colour, Turbidity
2. BIOCHEMICAL ANALYSIS — Proteins
3. CYTOLOGICAL ANALYSIS — Cells: Number, Cells: Type

<30mg/dL (Occipital); <45mg/dL (Lumbosacral)

↕

INCREASED due to BBB damage

NORMAL: < 5 cells/µL

↕

PLEOCYTOSIS > 5 cells/µL

8

Cerebrospinal fluid examination

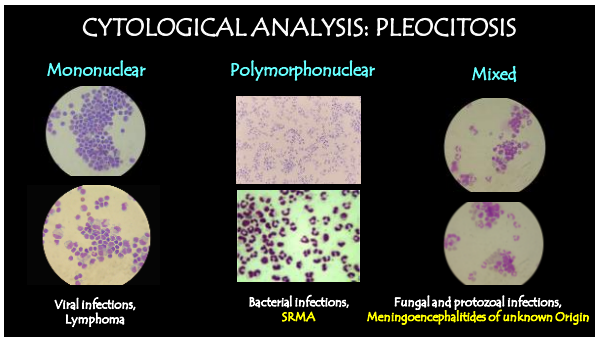
NORMAL: < 5 cells/µL ←→ PLEOCYTOSIS > 5 cells/µL

Cytological analysis

QUANTITATIVE:
- MILD <=50 cells/µL
- MODERATE <=200 cells/µL
- SEVERE >200 cells/µL

QUALITATIVE:
- MONONUCLEAR
- POLIMORPHONUCLEAR
  neutrofilic / eosinophilic
- MIXED

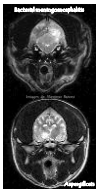
9

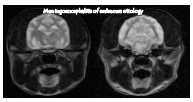


10

Magnetic Resonance Imaging

- Much more sensitive than CT!!!
- Multifocal hyperintense lesions in T2W sequences
- Less frequently, focal or diffuse lesions
- Variable (from marked to none) contrast enhancement
- Sometimes negative MRI
- ASPECIFIC RESULTS!!!
- → Always associate CSF exam





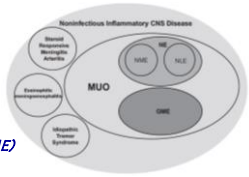
11

12

Noninfectious Inflammatory CNS disease

"MUE (MUO)"

- ✓ *NECROTIZING ENCEPHALITIDES*
  - ✓ *NME (Necrotizing Meningoencephalitis)*
  - ✓ *LNE (Necrotizing Leucoencephalitis)*
- ✓ *Granulomatous Meningoencephalomyelitis (GME)*



- ✓ *Eosinophilic Meningoencephalitis*
- ✓ *SRMA (Steroid-responsive Meningitis Arteritis)*

Perspectives on Meningoencephalomyelitis of Unknown Origin

13

MUE: general concepts

"MENINGOENCEPHALITIS OF UNKNOWN ETIOLOGY (MUE)":
Umbrella term encompassing most of the "sterile" inflammatory disorders without neuropatologic confirmation

ONSET: tipically acute
COURSE: progressive, sometimes very aggressive
LOCALIZATION: usually multifocal
CLINICAL PRESENTATION:
highly variable in term of severity
sometimes "focal" signs
RESPONSE TO TREATMENT:
highly variable

14

MUE – Etiopathogenetic hypotheses (2014)

Perspectives on Meningoencephalomyelitis of Unknown Origin
Joan R. Coates, DVM, MS
Nicholas D. Jeffery, BVSc, PhD, MSc, FRCVS
Vet Clin Small Anim 44 (2014) 1157–1185

MUO has long been assumed to have an **autoimmune** and **genetic pathogenesis**.
In general, major factors that contribute to the development of autoimmunity are **genetic susceptibility** and **environmental factors** (eg, infections, tissue injury).

Nevertheless, a **trigger factor** is assumed to initiate signs of disease in each specific dog at a specific time.

Suspected agents include **environmental or infectious antigenic triggers** that might activate autoreactive cells in the CNS, although **no such agent has yet been incriminated in the development of MUO**.

15

"Benny", Mixbreed, F, 4y

- Since one month obtundation, disappetence, gait abnormalities on 4 limbs, episodes of neck rigidity with yelping and tremors
- treated with NSAIDs without improvement
- suspected cervical disk herniation

16

"Chicco"
Mixbreed M,3y, 4,5 kg - NRN 2984

17

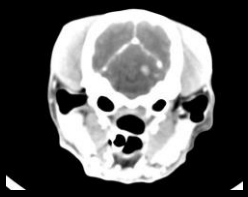
MUE: diagnostic work-up

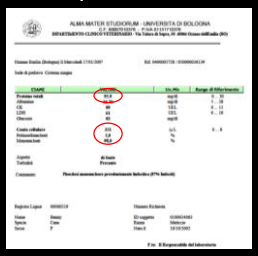
CLINICAL PRESENTATION:
"Specific" Signalment *(breed and age ←→ not always!)*,
Acute onset and progressive course,
Multifocal signs

- ✓ CBC and biochemical profile (incl. C-reactive protein)
- ✓ Advanced Diagnostic imaging
  MRI > CT
- ✓ Cerebrospinal fluid examination
- ✓ PCR and/or serology for infectious diseases

18

"Benny", Mixbreed, F, 4y





ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA

ESAME	VALORE	Un.Mis	Range di Riferimento
Proteine totali	81.6	mg/dl	5 - 10
Albumine	36.36	mg/dl	5 - 28
CK	60	U/L	0 - 15
LDH	68	U/L	0 - 10
Glucosio	89	mg/dl	
Conta cellulare	455	/µ L	0 - 8
Polimorfonucleati	5.0	%	
Mononucleati	95.0	%	
Aspetto	di fonte		
Torbidità	Presente		

Commento: Pleocitosi neutrofilica predominante Infettiva (97% Infetti)

Registro Liquor 0000319 Numero Richiesta

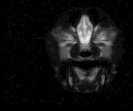
Nome	Benny	ID soggetto	0100034081
Specie	Cane	Razza	Mixbreed
Sesso	F	Nato il	10/10/2005

Il/la Responsabile del laboratorio

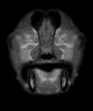
Diagnosis: Meningoencephalomyelitis of Unknown Etiology
(suspected GME)

19

"Chicco"
Mixbreed M,3y, 4,5 kg – NRN 2984



T2w



T1W+ mdc

20

"Chicco"
Mixbreed M,3y, 4,5 kg – NRN 2984

- Ozzano Emilia (BO) li Mercoledì 31/03/2010 Rif. 0400009758 / 050000074197

Sede di prelievo Cisterna magna

ESAME	VALORE	Un.Mis	Range di Riferimento
Proteine totali	139.2	mg/dl	0 - 30
Albumine	139.35	mg/dl	5 - 28
CK	363	U/L	0 - 15
LDH	265	U/L	0 - 10
Glucosio	107	mg/dl	
Conta cellulare	126	/µ L	0 - 8
Polimorfonucleati	8.0	%	
Mononucleati	92.0	%	
Aspetto	di fonte		
Torbidità	Presente		

Commento: 40% linfociti
40% citotecnidi macrofagiche

Registro Liquor 00000345 Numero Richiesta

Nome	Spillo	ID soggetto	0400013E07
Specie	Cane	Razza	Pinscher
Sesso	M	Nato il	18/06/2007

21

3.

GME: Granulomatous Meningoencephalomyelitis

22

GME – history

- 1962: described for the first time as "*reticulosis*"
- 1972: new classification of the "reticuloses":
  - *neoplastic (monomorphicleukocytes)*
  - *inflammatory (mixed istiocytes, leucocytes and plasmacells)*
  - *microgliomatosis*
- ~ 1980: further (and definitive) re-classification:
  - *neoplastic* → *B-cell lymphoma or istiocytoma*
  - *inflammatory* → *GME*

23

GME: Clinical Presentation

ONSET: acute
COURSE: progressive
LOCALIZATION: multifocal (forebrain, brain stem, spinal cord)

SIGNALMENT

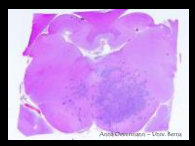
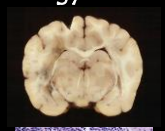
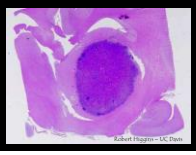
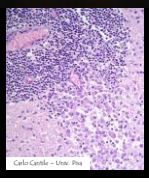
- ✓ female
- ✓ toy e terrier breeds
- ✓ onset (median age): 4.5 y (6 -144m; peak 4-8y)

CLINICAL and NEUROPATHOLOGIC FORMS

- *Disseminated*
- *Focal*
- *Ocular*

24

GME - neuropathology

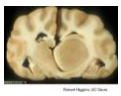
25

GME: Clinical Presentation

DISSEMINATED FORM
- ✓ mainly vestibulo/cerebellar/spinal cord signs *(Ataxia and paresis)*
- ✓ caudal brain stem involvement
- ✓ epileptic seizures
- ✓ cervical/spinal pain

FOCAL FORM
- ✓ focal subacute/chronic signs
- ✓ → dependent upon the localization
- ✓ similar to neoplasia!!!

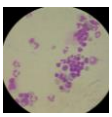
OCULAR FORM
- ✓ Acute visual and pupillary signs ←→ Diff: ocular disorders
- ✓ Oedema of the optic disc
- ✓ may evolve in the disseminated form



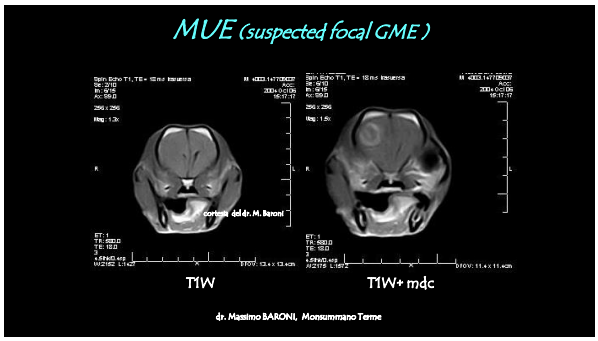
26

GME: Diagnosis

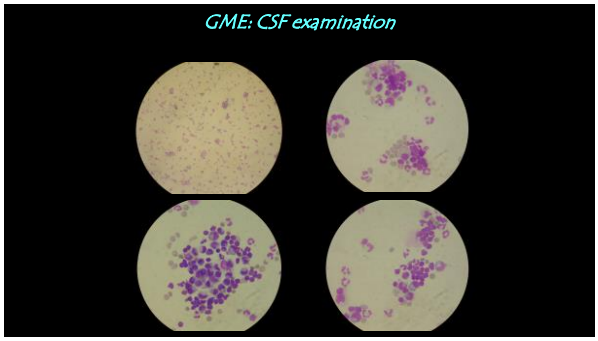
- Signalement
  - *toy and terrier, female,*
  - *mean age: 55 months*
- Clinical Signs
  - *variable according to affected area and severity → mainly BRAIN STEM/ SPINAL CORD*
  - *possible forebrain and ocular localization*
- Advanced Diagnostic Imaging
  - *MRI: hyperintensity multiple in T2W and FLAIR → mainly White Matter variable contrast enhancement (+++)*
  - *TC: focal or disseminated post-contrast lesions (- - -)*
- Cerebrospinal fluid examination
  - *mixed pleocytosis (1mononuclear) and increased proteins)*
  - *marked pleocytosis compared to NE*
- Neuropathology



27


MUE (suspected focal GME)
T1W
T1W+ mdc
dr. Massimo BARONI, Monsummano Terme

28


GME: CSF examination

29


4.
NME, NLE: Necrotizing (Meningo)Encephalitides (NE)

30

Necrotizing Meningoencephalitis (NME)/ Necrotizing leukoencephalitis (NLE)

- "PUG Encephalitis";
- "Yorkshire Encephalitis"

Described with overlapping clinical and patholo… …ds including :
Pug, Maltese, Chihuahua, Yorkshire Terrier, Pek… …errier,
Miniature Pinscher (PUG encephalit… …itis (NME)
Yorkshire Terrier, Jap. Spitz, …nitis) → Necrotizing
Leukoencephalitis (NM…

NE: same etiopathogenetic hypotheses as GME

antemortem:
"NECROTIZING ENCEPHALITIDES" (NE)

31

NE: Clinical Presentation – 1

ONSET: acute / peracute
COURSE: progressive, sometimes very aggressive and devastating
LOCALIZATION: multifocal intracranial

MEAN AGE AT THE ONSET

NME: 29 months (6 –84)

NLE: 54 months (4 –120)

CLINICAL FORMS *(normally more severe compared GME)*

NME: mainly forebrain signs

NLE: forebrain and caudal brain stem signs

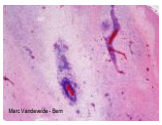
32

NE: Clinical Presentation – 2

Mainly FOREBRAIN SIGNS

severe progressive signs:
- Seizures (often as cluster)
- Obtundation; disorientation
- Compulsive circling
- Proprioceptive deficits
- Visual deficits

→ Possible DEATH



mainly NLE:
- vestibulo-cerebellar signs
- ataxia and paresis
- cranial nerves deficits

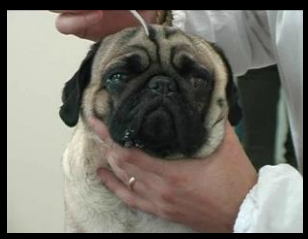
→ Possible permanent neurologic dysfunction

33

"Oliver", PUG M, 18m; NME

34

"Oliver", PUG M, 18m; NME



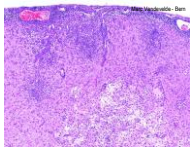
35

"Baby" Yorkshire M, 5y; MUE *(suspected NLE)*

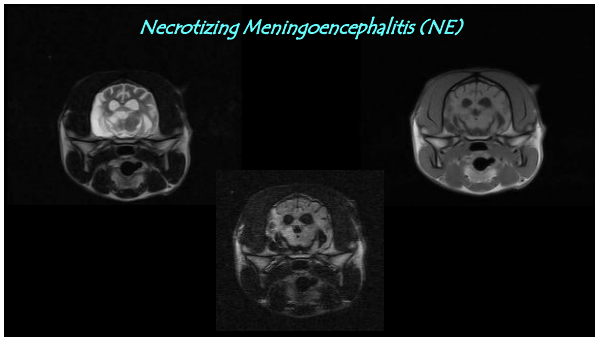
36

NME/NLE: Diagnosis

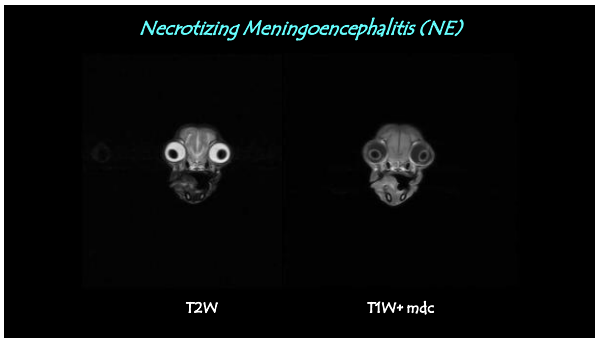
- Signalement
  - *breed :* Pug, Maltese, WHWT, Yorkshire, Pekingese, Boston Terrier, Japanese Spitz and Miniature Pinscher
  - *age:* NME : younger dogs compared to NLE
- Clinical signs.
  - severe and progressive, maily affetcting the *forebrain*
- Magnetic Resonance Imaging (MRI)
  - distribution pattern; *hyperintensity T2* e *FLAIR*
  - variable contrast enhancement
  - *chronic NLE* : cistic areas
- Cerebrospinal fluid examination
  - *pleocytosis* – less marked than in GME
- Neuropathology



37



38



39

5.

Treatment and prognosis

40

MUE: Prognosis

- GME: in the past poor prognosis:
  - focal form: median 114 days
  - disseminated form: median 8 days!!!

Old Study (1998) limited to post-mortem confirmed cases
(selection of most severe cases)

- NME/NLE: no studies → empirically considered worst than GME
- MUE: most of dogs that die, dies within 1-3 months
  - 2010 metanalysis data study – median survival time:
    - → combined therapy 240-590 days
    - → prednisone alone 28-357 days

→ the new treatment protocols have significantly increased the survival time

41

Protocols

Keyword: IMMUNOSUPPRESSION!!!

- ✓ high variability of the response to treatment
- ✓ often persistency of neurologic signs
- ✓ relapses are quite common and sometimes aggressive!

Glucocorticoids:
Avoid most powerful corticosteroids
~~(beta e dexamethason)~~
→ USE Predniso(lo)n!

Preventive and symptomatic treatment:
Gastroprotective and antiepileptic drugs

42

MUE: associated treatment

Cytosine Arabinoside:
50 mg/m2 SC every 12 hours for 2consecutive days,
repeated every 3 weeks for 4 cycles;
then 4 cycles every 4 weeks → till interval is increased to 6 weeks, indefinitely.

Cyclosporine
3-15 mg/KG PO BID , achieve serum levels between 200 and 400 ng/mL and continue indefinitely.

Procarbazine
25-50 mg/m2 PO SID indefinitely.

Lomustine
6mg/m2 every 6 weeks.

Mofetil mycophenolate
20mg/KG PO BID; after one month 10mg/kg BID.

43

Treatment plan

(Coates e Jeffery, 2014; De Risio e Platt, 2014)

Prednis(o)one:
1 mg kg/SID → till the results of infectious diseases tests ←→ immediately!!!

2 mg/kg BID for 2-4 days
1 mg/kg BID for 4 weeks
0,5 mg/kg BID for 4/8 weeks
0,5 mg/kg SID for 4/8 weeks
0,5 mg/kg every other day for 8/16 settimane
0,25 mg/kg every other day indefinitely

Cytosin Arabinoside:
50 mg/m² SC every 12 h for 2 days, every 3 weeks(3/4 volte)
THEN : every 4 weeks for 3 times
every 5 weeks for 3 times
every 6 weeks indefinitely

44

MUE:

*Take home message

- ✓ Inflammatory non-infectious CNS diseases in the dog are frequent and potentially life-threating
- ✓ Distinguished on neuropathologic basis as GME; NME; NLE
- ✓ Due to immune-mediated mechanisms
- ✓ Highly variable in terms of SEVERITY of the clinical signs
- ✓ Possible genetic predisposition and role of environmental and pathogen triggers
- ✓ Signalement : breed and age
- ✓ NE clinical presentation: mainly forebrain (more severe)
- ✓ GME clinical presentation : brain stem and spinal cord
- ✓ Diagnostic Work-up: CSF exam and brain/SC MRI

45

MUE: treatment

*Take home message

- ✓ Treatment : immunesuppressive – long period
  - glucocorticoids
  - immunesuppressive drugs
- •Usually there is very good initial response to glucocorticoids
- • it's very important to start soon immunosuppressive dosages and … is meaningless to decrease dosages too early: RELAPSES!!!
- • RELAPSES usually appear when prednisone is tapered under the dosage of 1 mg/kg per day
- • It's important to propose very early a combined immunosuppressive treatment
- • Cytarabin is the most commonly used «second-line» drug
- •Relapses have to be treated soon, usually restarting from the beginning the treatment PROTOCOL

46

47