SYLLABUS

TC28: Neuroimmunological Diseases

Tuesday, November 15, 2011 14:30-18:00 Hall I

Marrakesh, Morocco, November 12-17, 2011

XXth WORLD CONGRESS OF NEUROLOGY

XXth WCN 2011 MARRAKESH World Congress of Neurology

WFN

SMN SOCIETE MAROCAINE DE NEUROLOGIE

NEUROIMMUNOLOGICAL DISEASES

Chairperson: **Marc de Baets**, *The Netherlands*

AUTOIMMUNE ANTI-RECEPTOR DISEASES: MYASTHENIA GRAVIS
Marc de Baets, *The Netherlands*

AUTOIMMUNE NEUROLOGY OF THE CENTRAL NERVOUS SYSTEM
Sean Pittock, *USA*

NEUROMYELITIS OPTICA SPECTRUM DISORDERS
Brigitte Wildemann, *Germany*

16:00-16:30 *Coffee Break*

AUTOIMME ANTI-RECEPTOR DISEASES/ MYASTHENIA GRAVIS

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Autoimmune diseases with antibodies against membrane receptor are associated with many neurological diseases including myasthenia gravis(MG), Epilepsy, Lambert- Eaton myasthenic syndrome etc.The clinical presentation of MG start with ocular (ptosis plus diplopia) or bulbar symptoms. The fluctuating fatigable weakness is typical for myasthenia.

There are several clinical subtypes:

1. The typical early onset MG patient is a young women (<40 yrs), with antibodies against the acetylcholine receptor (AChR) and a hyperplastic thymus.
2. Late onset MG patients are older than 40 and have a normal or atrophic thymus and antibodies against AChR and other cytoplasmic muscle antigens (titin etc)
3. About 30 % of thymoma patients have MG as a paraneoplastic disease (15 % of the MG patients have a thymoma).All MG thymoma patients have antibodies against AChR and other muscle proteins.
4. MuSK MG is a severe form of MG with mainly bulbar and respiratory symptoms occurring in young patients? and associated with muscle atrophy of bulbar muscles.
5. Seronegative MG patients have either low affinity anti AChR antibodies or antibodies against LRP4 or other yet unidentified proteins.
6. A minority of MG patients have pure ocular disease. The disease does not generalize after more than 2 years. Only half of the patients have detectable antibodies.

Pathogenesis: Antibodies against membrane proteins of the postsynaptic membrane interfere with the neuromuscular transmission. The main targets are AChR and MuSK. Anti AChR antibodies destroy, in combination with complement proteins, the postsynaptic membrane and in addition they accelerate? the degradation of AChR by crosslinking.

Anti MUSK antibodies do not fix complement because they are of the IgG4 isotype and because of their monovalency they are not able to cross link MuSK. They interfere with agrin-MuSK signaling and therefore destroy the postsynaptic scaffolding.

These scaffolding proteins including rapsyn, utrophine and DOK7 are essential for the integrity if the synapse.

Diagnosis:

1. Clinical evidence of fluctuating muscle fatigability of ocular or bulbar muscle generalizing to many other striated muscle
2. Beside test: ICE test. Apply ice-pack for 2 minutes on a ptotic eye. The ptosis will temporally improve because of an improved neuromuscular transmission as seen during the pyridostigmine test.
3. A typical decremental response is found after repetitive nerve stimulation. (RNS). A single fiber EMG (SFEMG) of the ocular muscles is a more sensitive test (95%) than RNS, but has more false positive testing's.
4. Anti- AChR or MuSK antibodies are positive in 90 % of the patients with MG.

Treatment:

Symptomatic: mild cases can be controlled with Mestinon in doses up to 300-500 mg sometimes adding one sustained release table of 180 mg.

The standard immunosuppressive treatment is a combination of prednisolone (in escalating doses with a max of 0.75 mg/kg) with azathioprine. If after one year no tapering of prednisolone is achieved

cyclosporine A is added (3-5 mg/kg) or alternatively the aza is replaced by mycophenylate 25 mg/kg).

Thymectomy is performed in all cases of thymoma and in patients younger than 50 yrs preferable by minimal invasive procedures because.

Future treatments are aimed at blocking the pathogenic effects of anti AChR antibodies by genetically modified human anti-AChR antibodies that are not able to crosslink AChR nor activate complement. The proteasome inhibitor bortozemib, used for the treatment of multiple myeloma, is much more efficient in rapidly reducing anti-AChrR titers in experimental MG or in vitro with human MG plasmacells.

Take home messages:

1. Ptosis and diplopia is the presenting symptom in 85 % of the MG patients. Weakness improves after resting or cold.
2. If ocular MG stays ocular for 2 years no generalization of the weakness will occur.
3. Check for associated autoimmune diseases (thyroid, rheumatoid arthritis or SLE) Hyper or hypothyroidism increases muscle weakness.
4. Removal of a thymoma does not improve the clinical signs of MG. Thymectomy for follicular hyperplasia does improve the prognosis and is restricted to patients younger than 50 and positive for anti AChR antibodies.
5. MG is seen more frequently in the elderly population.

References:

De Baets, M. H. (2010). GUEST EDITOR Insights in the autoimmunity of myasthenia gravis. Autoimmunity, 43(5-6),

M Farrugia and A Vincent

Autoimmune mediated neuromuscular junction defects.

Curr Opin Neurol 2010;23:489-495.

Gomez AM, Vrolix K, Martínez-Martínez P, Molenaar PC, Phernambucq M, van der Esch E, Duimel H, Verheyen F, Voll RE, Manz RA, De Baets MH, Losen M..

Proteasome inhibition with bortezomib depletes plasma cells and autoantibodies in experimental autoimmune myasthenia gravis.J Immunol 2011;186:2503-13

Guptill JT, Sanders DB, Evoli A.

Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts.

Muscle Nerve. 2011 ;44:36-40.

M .Meriggioli and D Sanders

Autoimmune Myasthenia Gravis: emerging clinical and biological heterogeneity

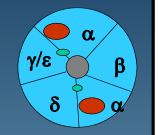
Lancet neurol 2009;8:475-490

Autoimmune anti Receptor Diseases

- **The concept**
- Disease examples
- Diagnosis of myasthenia gravis
- Pathogenesis of myasthenia gravis
- Competitor antibodies as a treatment
- The role of rapsyn
- How to treat MG?

Autoimmune anti Receptor Diseases in Neurology

Disease	*Receptor*	*Main Symptom*
Myasthenia Gravis	muscle nicotinic αAChR	Muscular weakness
Arthrogriposis multiplex congenita	muscle nicotinic γAChR	Arthrogryposis
Acquired slow channel syndrome	muscle nicotinic εAChR	Muscular weakness
Autonomic neuropathy	neuronal nicotinicAChr	Autonomic ganglionopathy
Guillain Barre Syndrome	muscle nicotinic AChR presynaptic channel	Muscle weakness



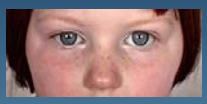
Signs and symptoms

Presenting symptoms

muscular weakness

fatigable

distribution is variable



- ocular: ptosis plus diplopia (85%)
- bulbar weakness (15%)

respiratory failure: rare

progression: generally slowly over weeks to months

Diagnosis Myasthenia gravis

- History
- Bedside test: ice test
- Antibodies (AChR/MUSK)
- EMG/SFEMG
- Mestinon test

Diagnostic usage of anti-AChR antibodies

Anti-AChR antibodies are measurable in up to 85 % of patients with generalized MG

Titers are highly variable among MG patients and roughly correlate with disease severity

Titers correlate well the clinical score in an individual patient.(effect of treatment/relapse)

ocular MG	50%
early onset MG	80%
late onset MG	90%
thymoma MG	100%

Plasmapheresis

thymectomy

immunosuppresive treatment

relapse

Proof of principle

1.MG patients have circulating antibodies against AChR.(Lindstrom)

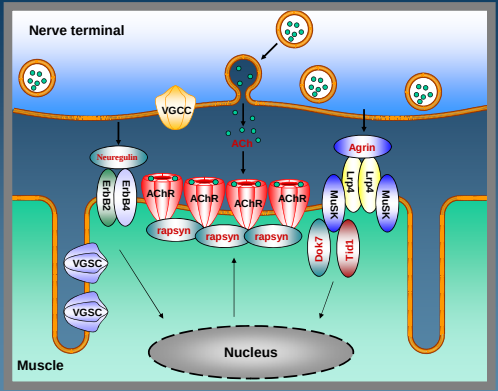
2.Myasthenic mothers may transfer the disease to their babies.(Nastuk)

3.Plasmapheresis is beneficial for MG patients.(Newsom Davis, Dau)

4.IgG and complement is present at the neuromuscular junction.(Engel)

5.The IgG fraction of sera from myasthenic patients induces EAMG in mice. (Toyka)

6.Immunizations of animals with AChR induces EAMG .(Lindstrom, Patrick, Lennon)

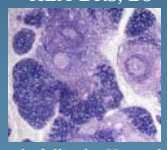


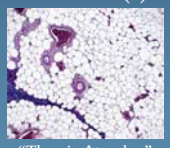
Pathogenesis of AChR-MG

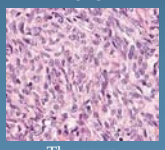
- ***Antigenic modulation***
  Cross-linking of Ab to acetylcholine receptor (AChR) increases AChR internalization
- ***Complement-mediated lysis***
  Binding of Ab to AChR triggers complement cascade
- ***Inactivation of AChR***
  Binding of Ab to AChR blocks AChR from binding of acetylcholine (ACh) or inhibits ion channel function

Heterogeneity of Anti-AChR pos Generalized MG

Early Onset MG	Late Onset MG	Thymoma-associated MG
< 40 y	40+ y	all ages
70%	20%	10%
80% female	~50% female	~50% female
HLA-DR3, B8	HLA-DR2 (?)	none


Lymphofollicular Hyperplasia


"Thymic Atrophy "

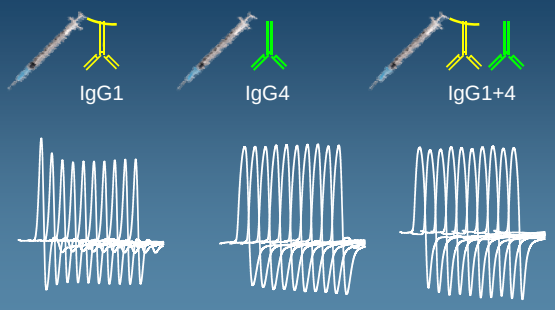

Thymoma

Characteristics of MG with anti-MUSK antibodies

1. Predominant oculo bulbar weakness (80%)
2. Frequent appearance of oromandibular atrophy
3. Intolerance to Mestinon
4. Repetitive nerve stimulation test has a low sensititivity (50%) SFEMG is positive in all cases
5. Low incidence of thymus pathology, no thymoma
6. High prevalence in females (8/1)
7. Linkage to HLA DR 14-DQ5

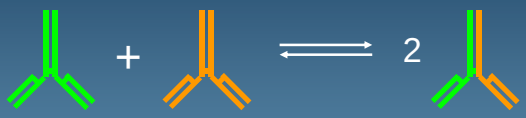
Are we able to transform pathogenic into therapeutic antibodies?

Immunotherapy



IgG4 immunotherapy prevents impairment of neuromuscular transmission in EAMG

IgG4 Fab arm exchange



Aalberse R.C and Schuurman J. Immunology 2002

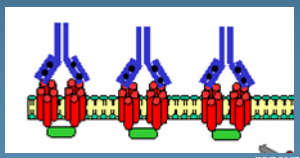
Introduction

Rapsyn:

- Postsynaptic peripheral membrane protein
- Anchor protein of AChR
- 1:1 ratio → AChR versus Rapsyn

Opposite effects of anti-AChR antibodies and rapsyn on AChR degradation

- Crosslinking of AChR by antibodies and activation of complement increases the degradation rate of AChR
- Crosslinking of AChR by rapsyn protects against antibody mediated antigenic modulation (Losen Martinez Brain 2005; Martinez Losen Am J Path 2007)



Possible applications of EAMG resistance against anti-AChR antibody attack in MG

1. A category of late onset myasthenia needs only little immunosuppresion to induce remission.
2. Explains the absence of correlation between anti-AChR antibody titer and disease severity
3. Gene transfer of rapsyn to increase muscle strength.

Therapy of MG

- Symptomatic: Mestinon
- Immunosuppression:
  - Thymectomy
  - Prednisolon
  - Imuran
  - Neoral
  - Cellcept
  - Plasmapherese
  - Intravenous gammaglobulines

Therapy of MG

- Symptomatic: Mestinon
- Immunosuppression:
  - Thymectomy
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  - Neoral
  - Cellcept
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  - Intravenous gammaglobulines

Immunosuppressive Therapy of MG my Recipe

- Prednisolon (0.75 mg/kg) and Azathioprin (2,5 mg/kg)
- Add Cyclosporin A (4 mg/kg)
- Replace Azathioprin by Mycophenylate (25 mg/kg)
- Add on IVIg 0.4 g/kg once every 3 weeks

UniversitätsKlinikum Heidelberg

Neuromyelitis Optica Spectrum Disorders

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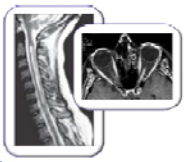
Department of Neurology, University Hospital Heidelberg

neuromyelitis optica (nmo)

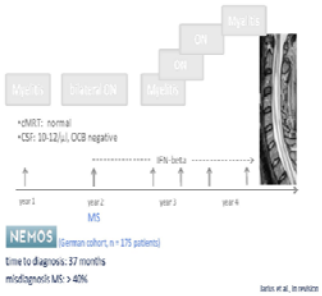
Optic neuritis
Transverse myelitis
- longitudinal
- ≥ 3 spinal segments



relapsing > monophasic
rare

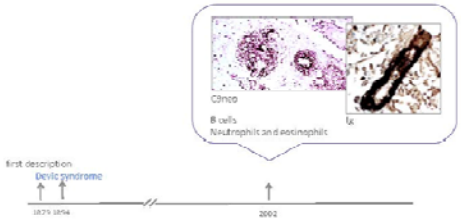
DD: multiple sclerosis

multiple sclerosis? nmo



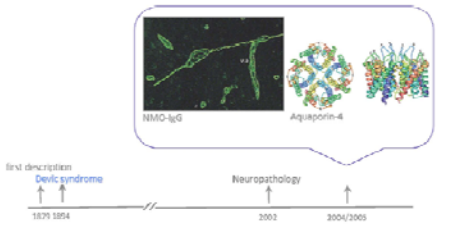
NEMOS (German cohort, n = 175 patients)
time to diagnosis: 37 months
misdiagnosis MS: > 40%

nmo



Lucchinetti et al., Brain 2002

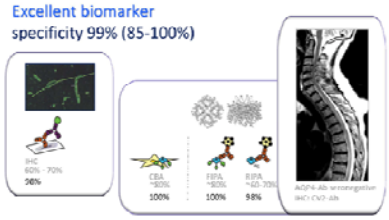
nmo



Lennon et al., Lancet 2004, Lennon et al., J Exp Med 2005

nmo-igg/aqp4-antibody

Excellent biomarker
specificity 99% (85-100%)



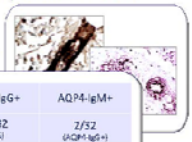
Jarius and Wildemann, Nat Rev Neurol 2010

aqp4-igm

20% of patients with NMO remain seronegative

AQP4-IgM diagnostically relevant? -> no

- 32 NMO sera
- 10 LETM sera
- IgG_{total} eliminated (IP)



	AQP4-IgG+	AQP4-IgM+
NMO	22/32 (67%)	2/32 (AQP4-IgG+)
LETM	8/10 (80%)	2/10 (AQP4-IgG+)

Jarius et al., Clin Chem Lab Med 2010

diagnostic criteria

Since 2006

absolutely required

- optic neuritis
- transverse Myelitis

supportive (2 von 3)

- NMO-IgG /AQP4-Ab seropositive
- longitudinal spinal cord lesion (≥ 3 segments)
- cMRT not diagnostic for MS

Wingerchuk et al., Neurology 2006

nmo-igg/aqp4-antibody

NMO

NMOSD

- NMO
- LETM/rLETM
- rON/bON
- brainstem encephalitis, diencephalitis
- brain abnormalities
- PRES
- opticospinal MS (Asia)
- opticospinal symptoms Sjögren syndrome, SLE

limited forms

extending phenotype

overlap syndromes

autoimmune AQP4 channelopathies

nmo-igg/aqp4-antibody

NMO

NMOSD

- NMO

- LETM/rLETM 60%
- rON/bON 5-25%

NMO within 12 months

consider testing for AQP4-Ab

- opticospinal MS (Asia)
- opticospinal symptoms Sjögren syndrome, SLE

autoimmune AQP4 channelopathies

Jarius et al., JNS 2010; Pittock et al., JNNP 2010; Mandler et al., Neurology 2004

nmo-igg/aqp4-antibody

NMO

NMOSD

- NMO
- LETM/rLETM
- rON/bON
- brainstem encephalitis
- brain abnormalities
- PRES

- opticospinal symptoms

AQP4-Ab seropositive
- ON + Myelitis
- LETM
- rON

-> 49/68, 72%

AQP4-Ab seronegative
- NMO -> 0/107
- ON -> 0/124

- CTD and NMO coexistent?

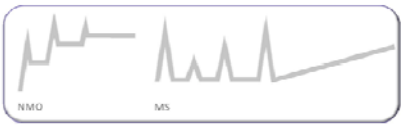
consider testing for AQP4-Ab

thies

Pittock et al., Arch Neurol 2008; Wandinger et al., Arth Rheum 2010; Jarius et al.,2011

distinct entity?

Aggressive course

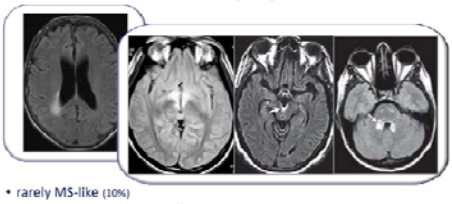


- further attacks within first 5 years
- within 7-8 years: blind (60%), para(tetra)plegic (52%)

Wingerchuk et al., Neurology 1999

distinct entity?

Cranial MRI -> abnormal in 60% (course)



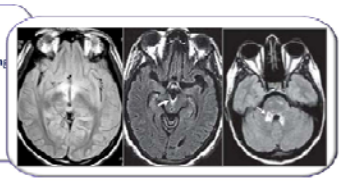
- rarely MS-like (10%)
- when periventricular -> diffuse shape
- osmosensitive regions

Pittock et al., Arch Neurol 2006

distinct entity?

Clinical spectrum

- narcolepsy
- SIADH
- refractory vomiting
- refractory hiccup

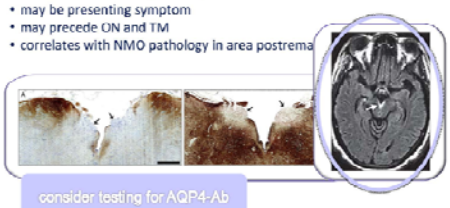


Pittock et al., Arch Neurol; Apiwattanakul et al. 2010

distinct entity?

Intractable vomiting/hiccups

- may be presenting symptom
- may precede ON and TM
- correlates with NMO pathology in area postrema

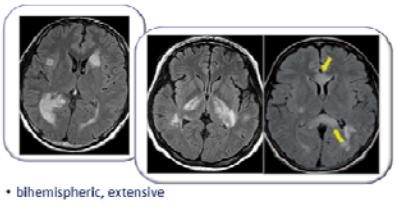


consider testing for AQP4-Ab

Apiwattanakul et al. 2010, Popescu et al. 2011

distinct entity?

other brain abnormalities



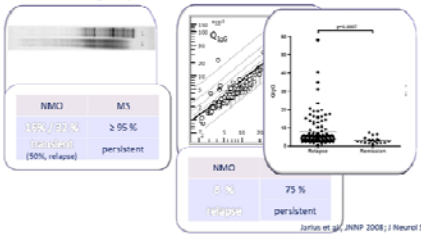
- bihemispheric, extensive
- internal capsule
- lateral ventricles, periependymal

Kim et al 2010, Kim et al. 2011

distinct entity?

CSF findings (n = 211, n = 89 patients with NMOSD)

intrathecal IgG synthesis



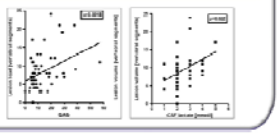
Jarius et al., JNNP 2008; J Neurol Sci 2011

distinct entity?

CSF findings

Cells / blood-CSF-barrier dysfunction, lactate

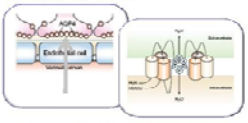
Parameter	NMO	acute attacks
Pleocytosis (50%)	11/µl (6 -380)	up to > 100/µl
Cytology	Neutrophils Eosinophils	



Jarius et al., JNNP 2008; J Neurol Sci 2011

aquaporin-4

Astrocytic protein



- component of the blood/brain-barrier

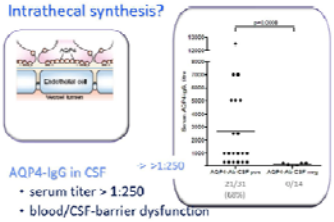
Intrathecal synthesis?

- $31_{AQP4\text{-}Ak+}$ und $14_{AQP4\text{-}Ak-}$ patients with NMOSD
- 23 parallel CSF/serum samples -> calculation of AI_{AQP4}
- 55 CSF samples from patients with OND

Jarius et al., JNI 2010; Kalluri et al, Arch Neurol 2010

aqp4-antibody

Intrathecal synthesis?



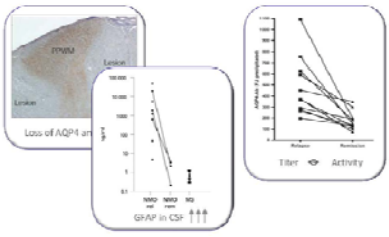
AQP4-IgG in CSF

- serum titer > 1:250
- blood/CSF-barrier dysfunction
- AI_{AQP4} >4: 1/23 cases (AI_{AQP4} = 7.7)
- AQP4-IgG from serum -> CSF via passive diffusion

Jarius et al., JNI 2010; Kalluri et al., Arch Neurol 2010

aqp4-antibody, effects

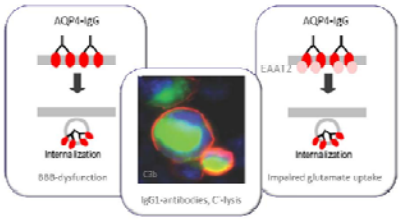
Indirect effects



Roemer et al., Brain 2007; Misu et al. JNNP 2009; Jarius et al., Brain 2008

aqp4-antibody, effectse

Indirect effects



Hinson et al., Neurology 2007; J Exp Med 2008; Waters et al. Arch Neurol. 2008

aqp4-ab⊕ vs aqp4-ab⊖

NEMOS (n = 175 patients with NMOSD)

- seropositive (n = 137, 78,3%)
- seronegative (n - 38; 21,7%)

Differences

AQP4-seropositive	AQP4-seronegative
Predominance of	Predominance of
•females (10,4 : 1 vs 1,9 : 1)	•bilateral ON at onset
•severe ly (ON, motor symptoms)	•simultaneous ON and myelitis
•higher spinal cord lesion load	•monophasic course
•co-existing autoimmunity	•shorter time to diagnosis

Jarius et al, in revision

treatment

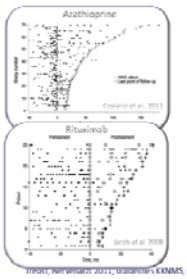
Acute attacks

- Methylprednisolone i.v.
- Plasma exchange

Long-term prevention

- Rituximab
- Azathioprine + prednisolone

GA ?
Natalizumab ?
~~IFN-β~~



Trebst, Neurology 2011; Guidelines EANMS, submitted

conclusion

AQP4
- first defined autoantigen in human MS-spectrum disorder

AQP4-antibodies
- highly specific diagnostic marker in NMO and NMOSD
- AQP4-IgM without additional diagnostic relevance
- AQP4-IgG producing B-cell clones reside in systemic compartment
- pathogenic
- other antibodies?

NMO
- primary astrocytic disease
- antibody-mediated channelopathy
- often aggressive
- treatment -> target humoral immune response