SYLLABUS

TC07: Antibodies In Neuroimmune Diseases

Sunday, November 13, 2011 14:30-18:00 Hall K

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

WCN Education Program

Sunday, 13 November, 2011

14:30-18:00

ANTIBODIES IN NEUROIMMUNE DISEASES

Chairperson: **Angela Vincent**, *UK*

14:30 **PART I: HISTORICAL - ANTIBODIES TO NEURONAL AND MUSCLE ANTIGENS IN NEUROLOGICAL DISEASES**

ANTIBODIES IN MG AND LEMS, MENTION NEUROMYOTONIA
Angela Vincent, *UK*

MOVING CENTRALLY - VGKC AND GAD
Sean Pittock, *USA*

PARANEOPLASTIC STORY
Josep Dalmau, *USA*

16:00 *Coffee Break*

16:30 **PART II: CURRENT - ANTIBODIES INVOLVED IN DIFFERENT FORMS OF ENCEPHALITIS AND INFLAMMATORY CNS DISEASE**

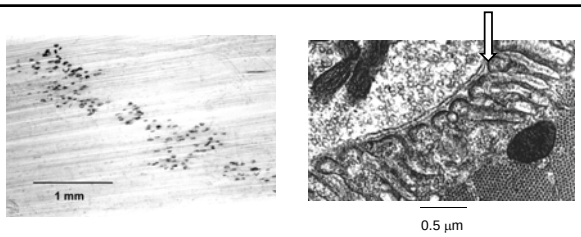
NMDAR ENCEPHALITIS
Josep Dalmau, *USA*

VGKC-COMPLEX ANTIGENS AND GLYR IN ENCEPHALITIS
Angela Vincent, *UK*

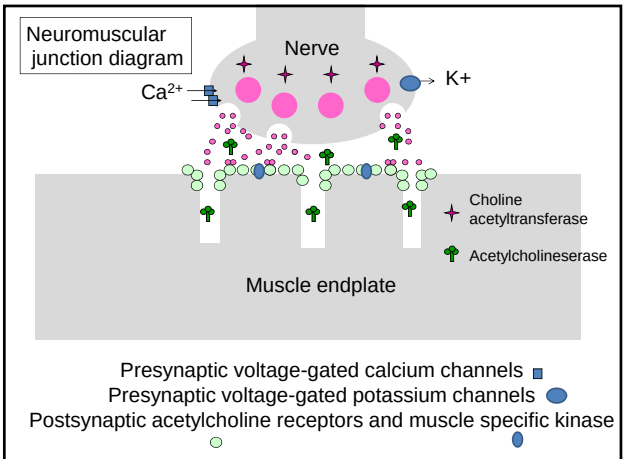
NMO AND OTHER DEMYELINATING DISEASES
Sean Pittock, *USA*

Autoantibodies, myasthenia, tumours and encephalitis – how it all started and where its going

Angela Vincent
Nuffield Department of Clinical Neurosciences
University of Oxford
John Radcliffe Hospital
Oxford



Neuromuscular junction
Very small synapse on a very long muscle fibre!
Very narrow gap between nerve and muscle (arrow)
But accessible to circulating antibodies



Presynaptic voltage-gated calcium channels
Presynaptic voltage-gated potassium channels
Postsynaptic acetylcholine receptors and muscle specific kinase

Plan of talk

A sense of the history of antibodies in neurological diseases

Subtypes of MG, thymus and tumour

Other neuromuscular junction diseases

Paraneoplastic or non-paraneoplastic

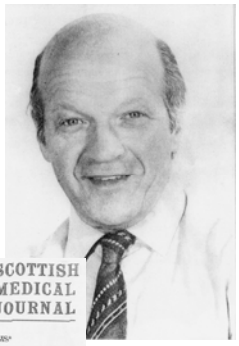
Some are associated with CNS involvement

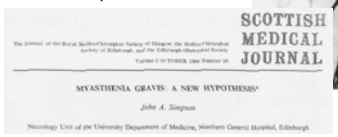
MG was thought to be autoimmune before 1970s

Buzzard 1903
"Autotoxic" substance

Strauss, Nastuk and colleagues 1959
Complement activating antibodies

Simpson 1960
Antibodies to an 'endplate protein'




SCOTTISH MEDICAL JOURNAL

MYASTHENIA GRAVIS: A NEW HYPOTHESIS*

John A. Simpson

Neurology Unit of the University Department of Medicine, Northern General Hospital, Edinburgh

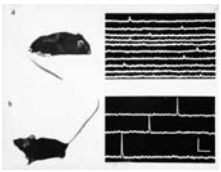
Subsequent key events in the history of MG

1973	Patrick, Lindström. Immunisation of rabbits with purified AChR leads to animal model of MG Fambrough, Drachman, Satyamurti. Reduced AChRs at endplates of MG
1975/6	Lindström, Seybold Circulating antibody to AChR found in 80%-90% of MG patients
1975/6	Passive transfer of MG from man to mouse
1976-8	Engel; Lennon; Heinemann; Drachman Mechanisms of AChR loss; role of complement
1977	Kao, Drachman Cultured myoid cells in thymus have AChRs
1977	Newsom-Davis, Pinching, Peters. Plasma exchange temporarily improves MG
1978	Vincent, Scadding. Cultured thymic lymphocytes make AChR antibody
1980	Compston, Batchelor. HLA and age of onset defines different MG subgroups
1990s	Hohlfeld, Willcox, Conti-Fine. AChR-specific T cells identified.
2001	Hoch, Vincent. Antibodies to muscle specific kinase in subgroup of MG

Patients with myasthenia gravis get better when their plasma is exchanged

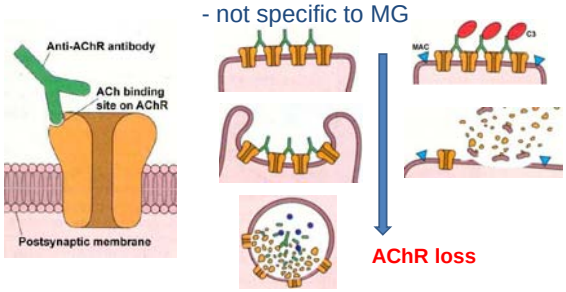
Newsom-Davis et al 1978

Mice injected with myasthenia gravis IgG developed myasthenia (top) compared with control IgG (bottom)



Toyka et al 1975

Mechanisms of antibody-mediated AChR loss - not specific to MG



Direct block of Ach binding or channel is not important in most patients

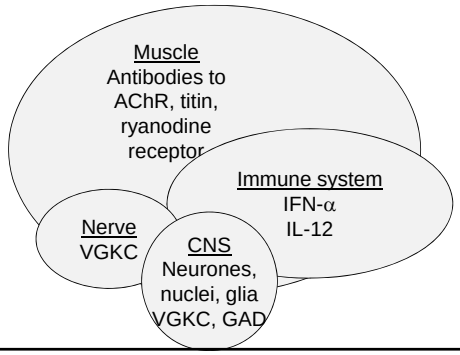
Divalent binding and increased internalisation of AChRs is common

Complement activation and lysis of postsynaptic membrane important

Four main types of MG patients – thymus and thymoma

Type	Thymus	HLA	AChR Ab
Early onset (<40 years)	Hyperplastic	B8DR3	+++
Late onset (>40 years)	Atrophic	B7DR2	++
Thymoma	Tumour	None	++
Seronegative	Atrophic Hyperplastic	None ?	MuSK Ab Clustered AChR Ab

Patients with thymomas can have many different antibodies – including to CNS proteins



Lambert Eaton myasthenic syndrome

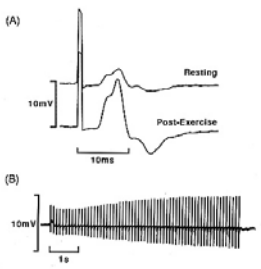
Muscle weakness

Autonomic signs

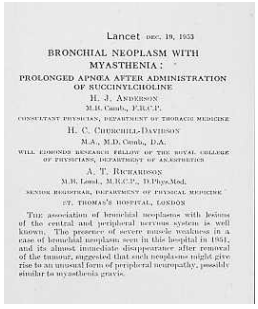
Improves after repetitive stimulation or sustained contraction

Associated with small cell lung cancer (paraneoplastic)

Antibodies to presynaptic voltage-gated calcium channels



A form of neuromuscular junction disorder associated with small cell lung cancer



Lancet DEC. 19, 1953

BRONCHIAL NEOPLASM WITH MYASTHENIA;

PROLONGED APNŒA AFTER ADMINISTRATION OF SUCCINYLCHOLINE

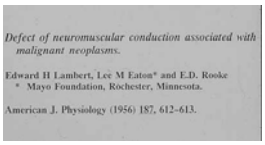
H. J. ANDERSON
M.B. Camb., F.R.C.P.
CONSULTANT PHYSICIAN, DEPARTMENT OF THORACIC MEDICINE

H. C. CHURCHILL-DAVIDSON
M.A., M.D. Camb., D.A.
WILL EDMONDS RESEARCH FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, DEPARTMENT OF ANÆSTHETICS

A. T. RICHARDSON
M.B. Lond., M.R.C.P., D.Phys.Med.
SENIOR REGISTRAR, DEPARTMENT OF PHYSICAL MEDICINE

ST. THOMAS'S HOSPITAL, LONDON

THE association of bronchial neoplasms with lesions of the central and peripheral nervous system is well known. The presence of severe muscle weakness in a case of bronchial neoplasm seen in this hospital in 1951, and its almost immediate disappearance after removal of the tumour, suggested that such neoplasms might give rise to an unusual form of peripheral neuropathy, possibly similar to myasthenia gravis.



Defect of neuromuscular conduction associated with malignant neoplasms.

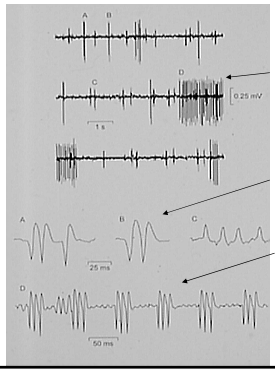
Edward H Lambert, Lee M Eaton* and E.D. Rooke
* Mayo Foundation, Rochester, Minnesota.

American J. Physiology (1956) 187, 612-613.

Eaton

Lambert

Acquired neuromyotonia often associated with thymoma and MG, and antibodies to voltage-gated potassium channels



spontaneous neuromyotonic discharge

doublet motor unit 'myokymic' discharge

triplet discharge

Courtesy of KR Mills

Antibody-mediated diseases of the NMJ are sometimes associated **with *CNS disease***

Myasthenia gravis	Lambert-Eaton syndrome	Neuromyotonia Cramp-fasciculation
AChR antibody Clustered AChR antibody MuSK antibody	Ca^{++} channel antibody +/-	K^{+} channel antibody +/-
	Cerebellar ataxia	***Maladie de Morvan*** ***Limbic encephalitis***

Summary relevant observations

Antibody mediated diseases are immunotherapy responsive

Antibodies to extracellular regions of important membrane proteins

Clinical feature eg. neuromuscular junction failure can be associated with different antibodies (AChR, MuSK, VGCC)

Other antibodies can cause hyperexcitability (VGKC)

The diseases can be paraneoplastic or non-paraneoplastic

Some are associated with CNS involvement

Part 1: The historical evolution of Autoimmune Neurology: Changing concepts

Sean J. Pittock, MD

Professor of Neurology
Department of Neurology and
Laboratory Medicine and Pathology
Mayo Clinic

Neurologic Autoimmunity

Idiopathic, Paraneoplastic

CNS PNS ANS ENS

IgG markers

Plasma membrane*
channels, receptors, other

IgG effectors

* e.g., VGKC complex, ganglionic or muscle AChR, AQP4

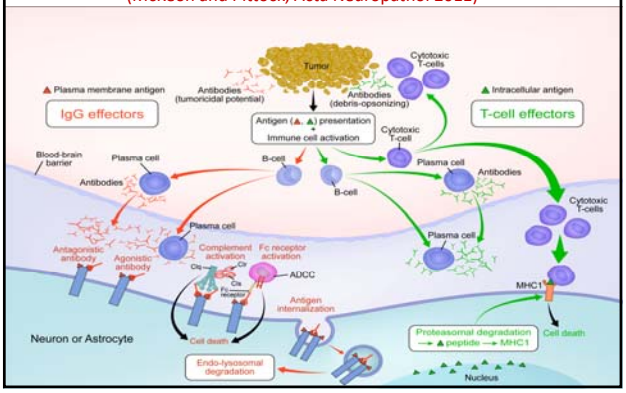
Nuclear & cytoplasmic peptides*

T-cell effectors

* surface MHC-I-complexes
e.g., ANNA-1 (Hu), CRMP-5, ANNA-2 (Ri) GAD65

Paraneoplastic neural autoantibodies and immunopathogenic mechanisms

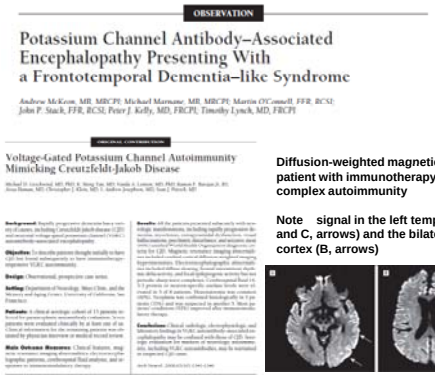
(McKeon and Pittock, Acta Neuropathol 2011)



Neural Autoantibody Associations
Historical (BLACK) →Current (BLUE)

- *ANNA-2 (anti-Ri)*
  - Historical: Opsoclonus Myoclonus
  - Current: Multifocal neurological disorder in most
    - opsoclonus/myoclonus < 50% cases
    - Jaw dystonia or laryngospasm in 25%
- *Amphiphysin-IgG*
  - Historical: Stiff man syndrome/PERM
  - Current: Multifocal neurological disorder in most
    - Neuropathy; Encephalopathy; Myelopathy; Cerebellar syndrome; Myoclonus
- *Gad 65-IgG*
  - Historical :Stiff-man; cerebellar ataxia; temporal lobe seizures
  - Current: *Above +* Brainstem syndrome; Myelopathy; Extrapyramidal
- *VGKC Complex-IgG*
  - Historical : Morvan syndrome; Isaac syndrome; Limbic Encephalitis
  - Current: Broader spectrum of neurological manifestations
    - Dysautonomia; cognitive impairment; peripheral neuropathy; Seizures; Brainstem; Cerebellum; Dysomnia

Autoimmune Encephalopathy and Dementia
Evolving Spectrum of VGKC complex autoimunity


OBSERVATION

Potassium Channel Antibody–Associated Encephalopathy Presenting With a Frontotemporal Dementia–like Syndrome

Andrew McKeon, MB, MRCPI; Michael Maraganore, MB, MRCPI; Martin O'Connell, FFR, RCSI; John P. Stack, FFR, RCSI; Peter J. Kelly, MD, FRCPI; Timothy Lynch, MD, FRCPI

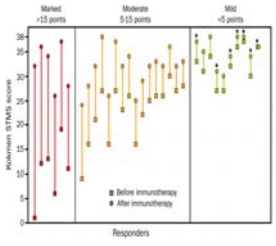
Voltage-Gated Potassium Channel Autoimmunity Mimicking Creutzfeldt-Jakob Disease

Diffusion-weighted magnetic resonance images in a patient with immunotherapy-responsive VGKC complex autoimmunity

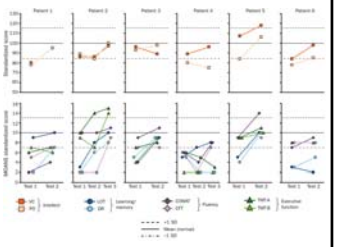
Note signal in the left temporo-occipital cortex (A and C, arrows) and the bilateral mesial frontal cortex (B, arrows)

Evaluations before and after treatment in patients positive for VGKC complex antibody with dementia.

MMTS



Neuropsychological tests



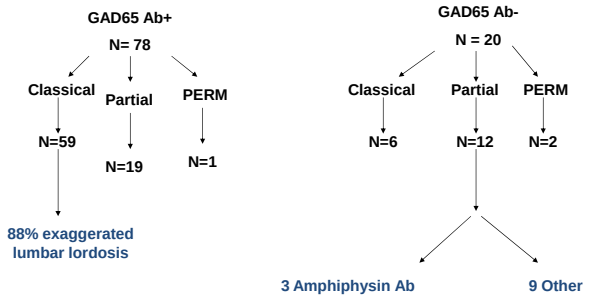
Flanagan E P et al. Mayo Clin Proc. 2010;85:881-897

Predictors of Immunotherapy Response in Autoimmune Dementia

	Responders	Non-responders	P value	Odds Ratio
Subacute onset	93%	35%	<0.001	27.1
Fluctuating course	91%	19%	<0.001	44.1
Headache	24%	4%	0.06	7.9
Tremor	43%	8%	0.0013	8.4
CSF protein (>100 mg/dL) or pleocytosis	35%	9%	0.036	6.9
Neuronal ion channel Ab	41%	10%	0.009	8.1
Mean time to treatment (months)	11	25	<0.001	0.95

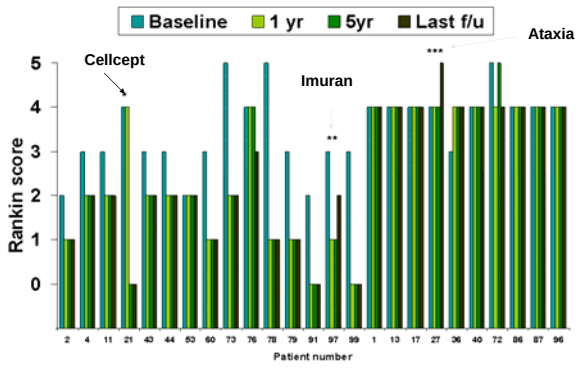
What happens to patients with SMS?

A longitudinal study of 98 SMS patients.

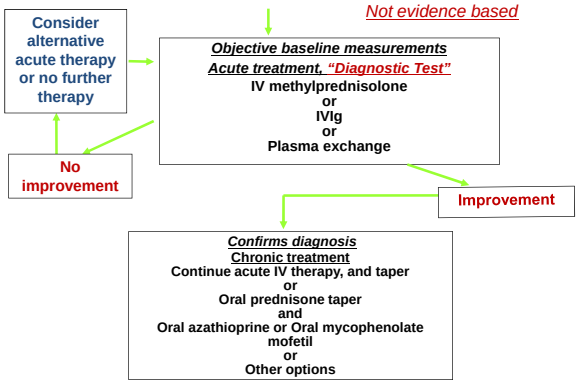


Outcome in 25 SMS patients with ≥ 5 years follow-up

McKeon et al, Archives Neurol 2011(in press)



Diagnosis of Possible Autoimmune Neurological Disorder

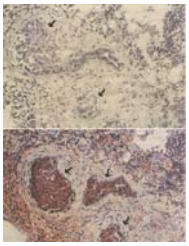


History and General Concepts on Paraneoplastic Neurologic Disorders

Josep Dalmau, MD, PhD
ICREA Research Professor at IDIBAPS/Hospital Clinic, University of Barcelona
Adjunct Professor of Neurology, University of Pennsylvania.
Josep.dalmau@uphs.upenn.edu

Professor Armand Trousseau (1801-1867)

Phlegmasia Alba Dolens, migratory thrombophlebitis, "Trousseau's syndrome"



On January 1, 1867, Dr. Trousseau noticed phlebitis in his own upper left extremity, reportedly telling his student, Peter: "I am lost: the phlebitis that has just appeared tonight leaves me no doubt about the nature of my illness".

Paraneoplastic syndromes: mechanisms and target organs

- Coagulopathy
- Secretion of hormones, cytokines:
  - (ACTH, SIADH, IL6, VEGF)
- Competition for substrate:
  - Tryptophan (carcinoid)
  - Glucose (sarcomas)
- Immune-mediated
- Nervous system
- Body as a whole (fever, anorexia)
- Bone marrow (anemia)
- Skin (pemphigus, acanthosis nigricans, tylosis, Bazex's syndrome
- Joints (clubbing, rheumatoid arthropathies)
- Kidney (nephrotic syndrome)

Neurologic Complications in Patients with Cancer

Metastatic

Non-metastatic

- Iatrogenic
- Metabolic, nutritional
- Infectious
- Vascular, coagulopathy
- Paraneoplastic

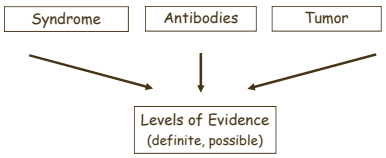
Paraneoplastic

- Prior to tumor diagnosis
- Difficult to diagnose
- More debilitating than cancer
- Immunologic mechanisms

Paraneoplastic Syndromes

- Brain and Cranial nerves
- Retina
- Spinal cord
- DRG
- Peripheral nerves
- Neuromuscular junction
- Muscle

Diagnosis



Graus et al. J Neurol Neurosurg Psychiatry 2004;75:1135-1140

Paraneoplastic Syndromes

Area Involved	Classical Syndromes	Non-classical Syndromes
CNS	Encephalomyelitis Limbic encephalitis Cerebellar degeneration Opsoclonus-myoclonus	Brainstem encephalitis Stiff-person syndrome Myelitis Necrotizing myelopathy Motor neuron disease
Dorsal root ganglia or peripheral nerves	Subacute sensory neuronopathy Gastrointestinal paresis or pseudo-obstruction	Acute sensorimotor neuropathy (Guillain-Barré syndrome, plexitis) Subacute and chronic sensorimotor neuropathies Neuropathy of plasma cell dyscrasias and lymphoma Vasculitis of the nerve and muscle Pure autonomic neuropathy Acquired neuromyotonia
Muscle	Dermatomyositis	Acute necrotizing myopathy Polymyositis
Neuromuscular junction	LEMS	Myasthenia gravis
Eye and retina	Cancer-associated retinopathy Melanoma-associated retinopathy	Optic neuritis

Adapted from Dalmau and Rosenfeld, Lancet Neurol 2008;7: 327-340

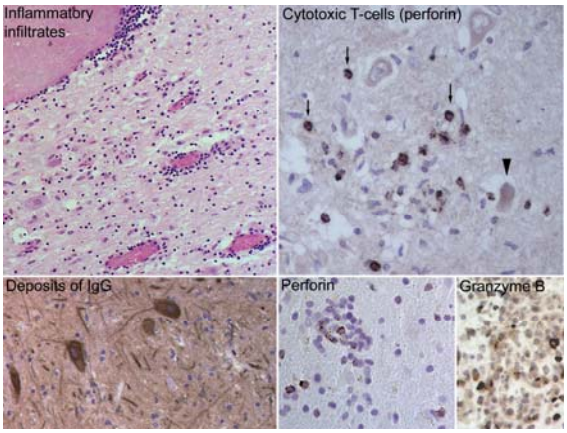
General Clinical Features

- Symptom presentation is subacute (days, weeks)
- Usually precede tumor diagnosis
- CSF inflammatory findings (pleocytosis, increased proteins, oligoclonal bands)
- MRI, EMG/NCV, biopsy, tumor markers often of limited help

Antibodies that are paraneoplastic markers

Antibody	Associated cancer	Syndrome
Hu	SCLC, other	Encephalomyelitis, sensory neuronopathy
Yo	Gynecological, breast	Cerebellar degeneration
Ri	Breast, gynecological	Cerebellar ataxia, opsoclonus
Tr	Hodgkin's lymphoma	Cerebellar degeneration
CV2/ CRMP5	SCLC, thymoma, other	Encephalomyelitis, uveitis, neuropathy
Ma proteins	Testicular germ-cell tumors, other	Limbic, diencephalic, brainstem encephalitis
amphiphysin	Breast, SCLC	Stiff-man syndrome, encephalomyelitis

Adapted from Dalmau and Rosenfeld, Lancet Neurol 2008;7: 327-340



Treatment Considerations

- Type of paraneoplastic syndrome
- Tumor:
  - Known, unknown
- Stage of the neurologic disease:
  - Progressing or stabilized?
- Immune mechanism:
  - T- or B-cell mediated?

Immune Mechanism

T-cell mediated
- Vasculitis of the nerve
- Poly/ Dermatomyositis
- Stiff-person syndrome
- Sensory neuronopathy
- Sensorimotor neuropathies
- Cerebellar degeneration
- Encephalomyelitis
  - (Hu, CRMP5, Ma2)
- Necrotizing myopathy

Antibody mediated (responsive)
- LEMS
- Myasthenia gravis
- Neuromyotonia
- Autonomic neuropathy
- Encephalitis
  - NMDAR, AMPAR, GABAB, VGKC

Corticosteroids, IVIg, plasma exchange
Rituximab, cyclophosphamide
Tacrolimus, Cyclosporine

Encephalitis related to antibodies against NMDA and other synaptic receptors

Josep Dalmau, MD, PhD
ICREA Research Professor at IDIBAPS/Hospital Clinic,
University of Barcelona
Adjunct Professor of Neurology, University of Pennsylvania.
Josep.dalmau@uphs.upenn.edu

The importance of encephalitis with antibodies to cell surface or synaptic antigens

- May affect young individuals and children
- May occur with or without cancer association
- Some autoantigens define new syndromes
- Disorders of memory, behavior, cognition, psychosis
- They are curable

Paraneoplastic Encephalitis, Psychiatric Symptoms, and Hypoventilation in Ovarian Teratoma

Roberta Vitaliani, MD,[1] Warren Mason, MD,[2] Beau Ances, MD, PhD,[3] Theodore Zwerdling, MD,[3] Zhilong Jiang, PhD,[1] and Josep Dalmau, MD, PhD[1]

Ann Neurol 2003;53:594–604

Paraneoplastic Anti–*N*-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma

Josep Dalmau, MD, PhD,[1] Erdem Tüzün, MD,[1] Hui-yan Wu, PhD,[1] Jaime Masjuan, MD,[1] Jeffrey E. Rossi, BA,[1] Alfredo Voloschin, MD,[2] Joachim M. Baehring, MD,[4] Haruo Shimazaki, MD, PhD,[5] Reiji Koide, MD,[6] Dale King, MD,[7] Warren Mason, MD,[8] Lauren H. Sansing, MD,[4] Marc A. Dichter, MD, PhD,[1] Myrna R. Rosenfeld, MD, PhD,[1] and David R. Lynch, MD, PhD[1]

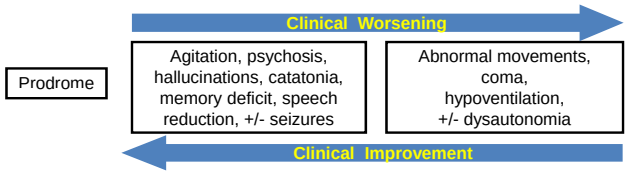
Ann Neurol 2007;61:25–36

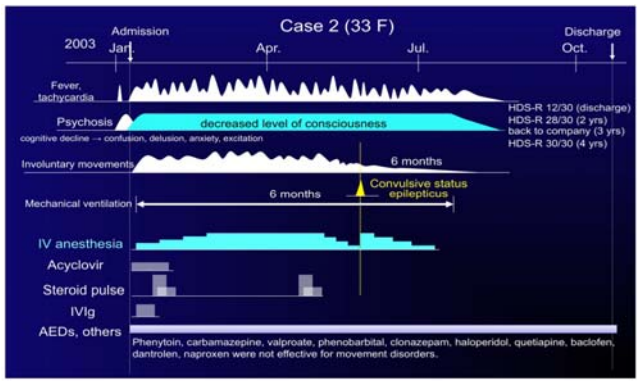
Frequency of anti-NMDAR encephalitis

- 1% of patients (aged 18-35 years) admitted to ICU
- 4% of all cases of encephalitis in a multicentre population-based prospective study in UK
  - (2^{nd} most common immune-mediated cause after ADEM, and before all antibody-associated encephalitis)
- It took 13 years to accrue 200 patients with anti-Hu encephalitis; it took 3 years to accrue 400 with anti-NMDAR encephalitis.

Dalmau et al., Lancet Neurol 2011;10:63-74.

Sequential Stages of Progression/ Resolution of symptoms correlate with levels of NMDAR blockade





Iizuka et al, Neurology 2008;70:504-511

Implications

- Defines a new syndrome
- Provides a model to study how antibodies affect memory, learning, and behavior
- Strengthens theories (NMDAR hypofunction and psychosis)
- Reclassifies syndromes known only by descriptive terms
- Identification of other disorders of synaptic autoimmunity
- Change of concepts related to treatment and outcome

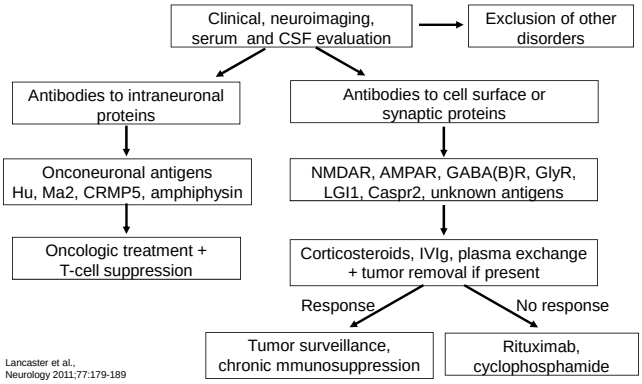
Antibodies to cell surface and synaptic antigens

Antibody	Syndrome	Tumor
NMDAR (NR1)	"Anti-NMDAR encephalitis"	8-55%: teratoma
AMPAR (GluR1/2)	Limbic encephalitis; relapses	70%: thymus, breast, lung
$GABA_{B1}$ R	Limbic encephalitis; prominent seizures	60% SCLC
mGluR1	Cerebellar degeneration	Hodgkin's, or no tumor
mGluR5	Limbic encephalitis, "Ophelia syndrome"	Hodgkin's
LGI1	Limbic encephalitis, RPD	20%: thymoma, SCLC
Caspr2	Morvan's, neuromyotonia	Tumor frequency?
Glycine R	PERM, hyperekplexia, stiff-person syndrome	Low tumor frequency

Common Features of Disorders of Synaptic Autoimmunity

- The epitopes are extracellular
- The antibody binding is visible in cells transfected to express the target cell surface protein or receptor
- The antibodies alter the structure/ function of the antigen
- The antibody effects are often reversible
- The disorder resembles pharmacologic or genetic models in which the antigen is disrupted

Autoimmune Encephalitis: Diagnosis and Treatment



Lancaster et al.,
Neurology 2011;77:179-189

Antibodies to voltage-gated potassium channel complex proteins and glycine receptors in different clinical syndromes

Angela Vincent
Nuffield Department of Clinical Neurosciences
University of Oxford
John Radcliffe Hospital
Oxford

Autoantibodies in CNS diseases 2000 onwards

New concepts of treatment-responsive diseases of the CNS with specific antibodies in adults and children

VGKC-complex Ab limbic encephalitis and related diseases

GlyR-Ab encephalomyelitis

NMDAR-Ab encephalitis and others (J Dalmau)

Neuromyelitis optica (S Pittock)

New concepts of antibody-mediated central nervous system diseases

Usually acute or subacute onset

May be postinfectious or tumour associated, but *many* non-paraneoplastic

Associated with autoantibodies to *extracellular domains* of ion channels or receptors or associated proteins

Often monophasic and respond substantially to immunotherapies

Neuromyotonia with CNS involvement
Morvan's syndrome

Peripheral Muscle twitching, pain

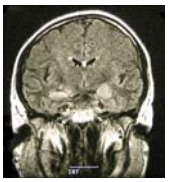
Autonomic Sweating, cardiac arrhythymias, constipation, urinary problems

Central Insomnia, hallucinations, confusion, sometimes seizures, disturbed circadian rhythms

VGKC-complex Abs moderate to high

40% association with thymomas

VGKC-complex Ab limbic encephalitis



Personality change or psychiatric features, memory loss, seizures

Amnesia or seizures can predominate

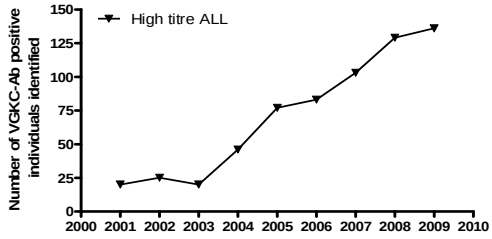
High signal on MRI

Low plasma sodium (SIADH) common at onset

Usually non-paraneoplastic and responds to immunotherapies

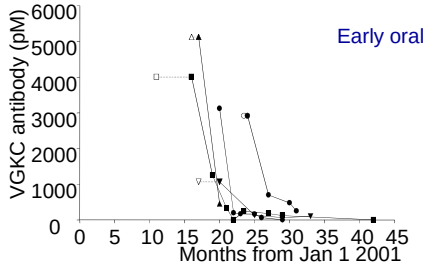
Vincent et al 2004
Irani et al 2010

All VGKC-complex Ab positives >400 pM detected by Oxford 2001-2009 in the UK
Males>females Adults>children



Around 2/million per year
The majority >400 pM had limbic encephalitis without tumours

VGKC-complex antibodies can fall markedly after treatment. Usually includes iv steroids, plasma exchange, IvIg – longer-term oral steroids important



Vincent et al Brain 2004

A new seizure type

Very frequent brief facio-brachial dystonic seizures with with very high VGKC-complex antibodies

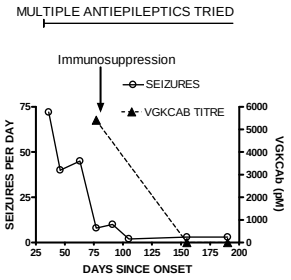
Subacute onset of frequent, unprovoked "seizures", up to 70 times per day.

No temporal lobe seizures

No apparent cognitive involvement

Poor response to AEDs

Very good respond to immunotherapies

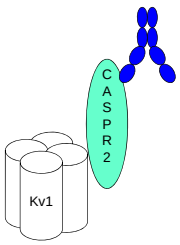


Irani et al Neurology 2008; Irani et al Ann Neurol 2011

VGKC-complex Abs are not mainly directed at VGKCs! Some VGKC-complex antibodies bind to CASPR2

CASPR2 has important role in clustering VGKCs at juxtaparanodes of PNS and CNS

Also widely expressed in the brain



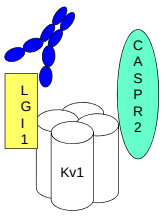
CASPR2 antibodies mostly neuromyotonia, thymomas/MG common

Irani, Alexander, Waters, Kleopa et al Brain 2010
Lancaster et al 2011; Irani et al submitted 2011

More frequently VGKC-complex antibodies bind to LGI1

LGI1 is mainly expressed in the CNS particularly the hippocampus

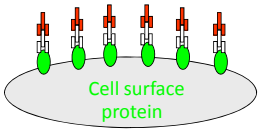
Mutated in dominant lateral temporal lobe epilepsy

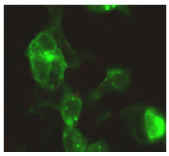


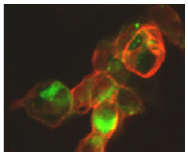
LGI1 antibodies mostly in FBDS and limbic encephalitis

Irani, Alexander, Waters, Kleopa et al Brain 2010
Lai et al Lancet Neurology 2010

How does one measure disease-relevant antibodies? The cell-based assays are the way forward

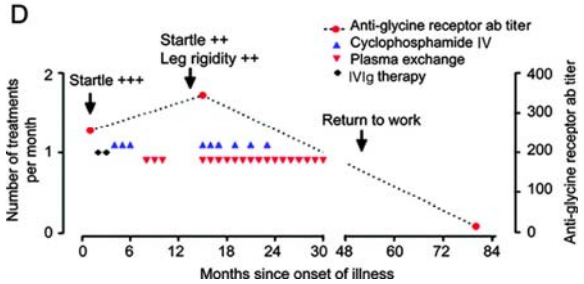






Negative for antibody Positive for antibody

First patient with glycine receptor antibodies Eventually but improved and returned to work. These patients can need extensive immunotherapies



Hutchinson et al Neurology 2008

Patients with glycine receptor antibodies

2 – 69 years

Rigidity
Spasms, often very painful
Sweating
Startle
Stiffness
Autonomic - urinary retention, tachycardia, other
Ataxia
Seizures
CSF OCBs rare

Leite, Meinck H-M et al in preparation

Summary

CNS diseases associated with highly specific antibodies

Antibody assays can be very helpful in confirming a suspected diagnosis

VGKC-complex (LGI1, CASPR2) and GlyR are all related to immunotherapy-responsive diseases

These diseases are proving to me more common than expected

They can be in both children and adults

Part 2: The Evolving Spectrum of Neuromyelitis Optica and Other Autoimmune Mimics of Multiple Sclerosis

Sean J Pittock, MB, MRCPI, MMed Sci, MD,

Professor of Neurology
Department of Neurology
Mayo Clinic
Rochester, MN

Diagnostic criteria for NMO

Category	*NMSS Criteria*	*Wingerchuk 2006 Criteria*
Required	Optic neuritis	Optic neuritis
	Myelitis	Myelitis
	MRI T2 hyperintense >3 vertebral segments and T1 hypointense during myelitis	
	Sarcoidosis, vasculitis or lupus erythematosus (clinically manifest) exclude diagnosis of NMO	
Additional specificity criteria	1 of 2	2 of 3
	Initial brain MRI normal (doesn't satisfy McDonald DIS criteria)*	Initial brain MRI normal (doesn't satisfy McDonald DIS criteria)
		MRI T2 lesion >3 vertebral segments during myelitis
	Positive serology for NMO-IgG (aquaporin-4 autoantibodies)	Positive serology for NMO-IgG (aquaporin-4 autoantibodies)

NMO: Evolving Concept

1999 Relapsing; *MRI* cord lesions extend 3+ segments; female bias (2.6:1)

2002 Distinctive neuropathology: perivascular IgG, IgM & complement

2004 NMO-IgG, a specific biomarker- defines NMO spectrum disorders

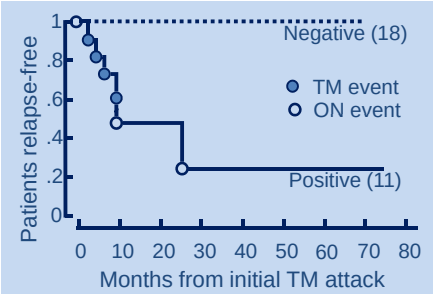
2005 NMO-IgG targets Aquaporin-4

2006-present Evolving spectrum of NMO
Brain lesions-common
Area postrema-intractable vomiting
Circumventricular organs-SIAD
PRES like lesions-encephalopathy

Immunopathology of NMO

	NMO		MS	ADEM
	OS	ST		
N	10	6	98	5
Eosinophils	+++	+++	+/-	++
C9neo Rosettes	+++	+++	-	-
AQP-4	-	-	⇈	⇈
NMO-IgG+	NA	3/4	0/85	0/5

NMO-IgG at first transverse myelitis (TM) or optic neuritis (ON) attack predicts TM relapse or future ON



Weinshenker et al, Ann Neurol,2006

AQP4-rich Area Postrema First Point of Attack in NMO

(Annals Neurology, 2010)

- Intractable vomiting: initial presenting symptom in 12% of all Mayo Clinic NMO patients
- Initial evaluation in 75% was gastroenterologic.
- Vomiting lasted a median of 4 weeks (range, 2 days – 80 weeks).
- 11 of 12 developed ON or TM after vomiting onset (median interval, 11 weeks; range, 1-156).
- At last follow-up (median, 48 months) 7 fulfilled NMO criteria.

Syndrome of Inappropriate Antidiuresis may Herald or Accompany Neuromyelitis Optica
(Iorio et al, Neurology, in press)

Pt	Sex/ Age at Onset	Hyponatremia features				Timing of SIAD occurrence in disease course
		Serum Sodium concentration (mmol/L)	Blood osmolality (mOsm)	Urine osmolality (mOsm)	Neurologic accompaniment	
1	F/72	118	270	314	LETM, area postrema lesion	Initial attack
2	M/60	130	270	965	LETM with brainstem lesions	Initial attack
3	F/40	127	271	285	LETM, PRES	4th relapse
4	F/71	126	269	734	LETM, brain lesions	Initial attack
5	F/15	111	265	538	LETM	Initial attack
6	F/62	129	269	482	LETM	Initial attack
7	F/65	128	273	211	**	4th relapse

Pathogenic potential of NMO-IgG:

1. Water channel downregulation
2. Glutamate transport downregulation (new Rx option – gluR antagonists)
3. Promotion of inflammation (new Rx option – anti-C5)
4. Lysis of membranes expressing AQP4
5. Demyelination initiation at paranodal AQP4; glutamate toxicity on oligodendrocytes
6. Animal models

Current Treatment Data

Drug	Ref	N	Median ARR pre	ARR post Median	% pred-nisone	% drug naïve	% relapse-free post	Follow-up duration, months (range)
Rituximab	Cree et al, 2005	8	2.6	0	0	50	75	12 (6-18)
Rituximab	Jacob et al, 2008	25	1.7	0	12	32	48	19 (6-40)
Cellcept	Jacob et al, 2009	24	1.28	0.09	33	40	60	28 (18-89)
AZA	Costanzi et al, 2010	99	2.18	0.52	73	88	39	21 (6-180)
AZA (MCV < 5)	Costanzi et al, 2010	8	0.99	0.93	88	0	25	21 (1-28)
AZA (MCV >5)	Costanzi et al, 2010	19	3	0.46	74	80	33	23 (0-103)

We need 100%!!

Brain Advance Access published July 17, 2010

BRAIN

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)

Sean J. Pittock,[1,2] Jan Debruyne,[3] Karl N. Krecke,[4] Caterina Giannini,[2] Jelle van den Ameele,[3] Veerle De Herdt,[3] Andrew McKeon,[1,2] Robert D. Fealey,[1] Brian G. Weinshenker,[1] Allen J. Aksamit,[1] Bruce R. Krueger,[1] Elizabeth A. Shuster[5] and B. Mark Keegan[1]

Summary

Definable, treatable, inflammatory CNS brainstem-predominant syndrome

Similar clinical, radiological, pathological syndrome responsive to immunosuppression especially steroids

Symptoms

- Brainstem symptoms: Gait ataxia, diplopia, facial paresthesias, dysarthria (ataxic ± spastic)
- Myelopathic symptoms: paraparesis, sensory level, spasticity

Neuroimaging

- Punctate, curvilinear Gd enhancement predominantly but not restricted to pons (~1-3 mm)

Investigations

- No other diseases found despite extensive and prolonged follow-up
- Biopsy-immunopathology