SYLLABUS

TC04: Neuropathies

Saturday, November 12, 2011 14:30-18:00 Hall L

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

NEUROPATHIES

Chairperson: **Jean-Marc Léger**, *France*

GBS AND CIDP
Richard A.C. Hughes, *UK*

INHERITED NEUROPATHIES
Michael Shy, *USA*

PARAPROTEINEMIC NEUROPATHIES
Jean-Marc Léger, *France*

16:00-16:30 *Coffee Break*

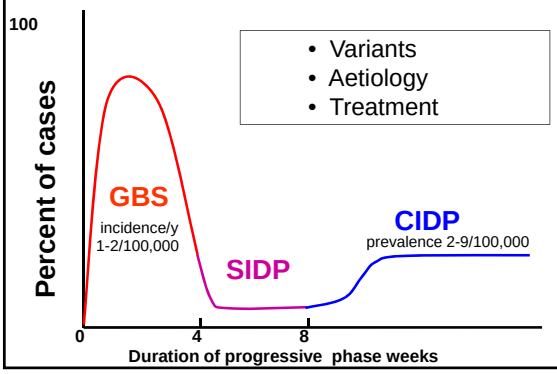
GBS and CIDP

Richard Hughes
Teaching course
WCN Marrakesh 2011

History

- 1916 Guillain, Barré and Strohl
- 1956 (Miller)Fisher syndrome
- 1958 Austin: steroid responsive neuropathy
- 1975 Dyck; Prineas: CIDP
- 1985 Plasma exchange
- 1988 Antibodies to gangliosides
- 1991 Acute motor axonal neuropathy
- 1992 Intravenous immunoglobulin

Spectrum GBS to CIDP



GBS subtypes

- Acute inflammatory demyelinating polyradiculoneuropathy
- Acute motor axonal neuropathy
- Acute motor and sensory axonal neuropathy

- Fisher syndrome
- Formes frustes

Differential diagnosis 1

- Brain stem stroke or encephalitis
- Poliomyelitis
- Acute myelopathy
- Myasthenia, botulism or toxins
- Muscle disease and hypokalaemia

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Differential diagnosis 2

- Peripheral neuropathy
  - Toxic
    - Drugs
    - Organophosphates, heavy metals
  - Diphtheritic neuropathy
  - Porphyria
  - Alcohol
  - Vasculitis
  - Critical illness
  - Lymphoma
  - GBS

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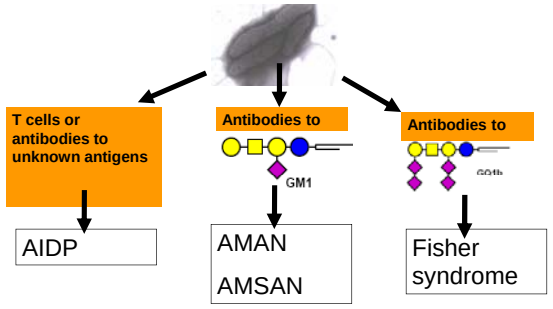
GBS pathogenesis



GBS supportive treatment

Hughes et al 2005 Arch Neurol 62 1192

- Heparin; support stockings
- Monitoring vital capacity; ventilation
- Percutaneous tracheostomy
- Nutrition and hydration
- Percutaneous endoscopic gastrostomy
- Bladder and bowel care
- Pain control
- Physiotherapy
- Psychological support
- Rehabilitation

Practice parameter: immunotherapy for GBS
Report of Quality Standards Subcommittee of AAN

Hughes et al 2003 Neurology 61 736

1) PE recommended for non-ambulant adult patients within 4 weeks and considered for ambulant patients within 2 weeks
2) IVIg recommended for non-ambulant adult patients within 2 or possibly 4 weeks. PE and IVIg equivalent.
3) Corticosteroids not recommended
4) Sequential treatment with PE followed by IVIg, or immunoabsorption followed by IVIg not recommended
5) PE and IVIg are options for children with severe GBS

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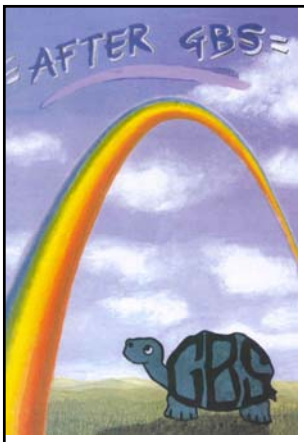

5% die

15% dead or disabled after a year

80% persistent fatigue

www.gbs.org.uk

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GBS rehabilitation

Hughes et al 2005 Arch Neurol 62 1192

- Pain control
- Physiotherapy
- Psychological support
- Fatigue
- Immunisations: care

Note: improvement will continue for at least 3 years

Subacute inflammatory demyelinating polyradiculoneuropathy (SIDP)

Nadir 4 – 8 weeks

Frequent preceding infection

Demyelinating neurophysiology

No other cause

CSF protein raised in 19/21

Macrophage associated demyelination

Complete recovery in 18/23 with no treatment or steroids

Hughes R et al. Arch Neurol 1992 49 612-16 7 cases

Oh SJ et al. Neurology 2003 61 1507-12 16 cases

CIDP definition

European Journal of Neurology 2010, 17: 356–363
EFNS TASK FORCE/CME ARTICLE

Viala et al 2010 JPNS 15 50

- **Typical** 51%

  Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and absent or reduced tendon reflexes in all extremities

- **Atypical**
  - Distal (DADS)
  - Pure motor 10%
  - Pure sensory 35%
  - Multifocal (Lewis-Sumner syndrome) 15%
  - Focal
  - CNS involvement

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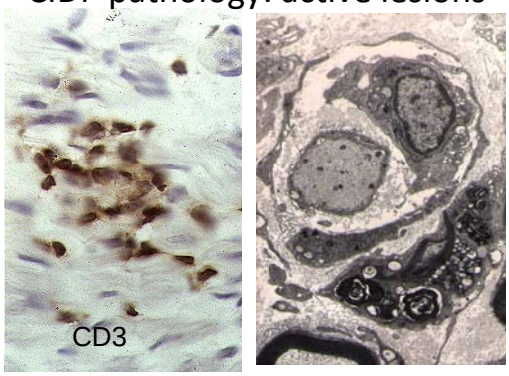
CIDP pathology: active lesions



Pathogenesis

- Inflammatory (T cell) pathology
- Response to immunotherapy
- Defects of
  - T cell regulatory function
  - FcγRIIB (inhibitory) expression on B cells
- Animal models caused by T cell autoimmunity
- But
  - Antibodies to P0 or gangliosides in only a minority
  - Little evidence of T cell response to myelin proteins

Differential diagnosis

- Chronic idiopathic axonal neuropathy
- Paraproteinaemic demyelinating neuropathy
- Multifocal motor neuropathy
- Lyme disease
- Vasculitic neuropathy
- Lymphoma
- Amyloid neuropathy
- Hereditary sensory and motor neuropathy

EFNS/PNS Guideline on CIDP Recommendations

van den Bergh 2010 EJN 17 356 or www.efns.org

- sensory and motor CIDP: IVIg* or steroids

  * 2 courses needed to assess response
  *regular trials of withdrawal of treatment

- pure motor CIDP: IVIg
- if IVIg and steroids ineffective: PE
- if response inadequate consider
  - combination treatments
  - immunosuppressant

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Lewis-Sumner syndrome

or Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)

Treatment

11 patients Saperstein et al 1999 Muscle and Nerve 22 560

- 5/9 responded to IVIg
- 3/6 responded to corticosteroids

23 patients Viola et al 2004 Brain 127 2010

- 71% chronic progressive 29% rel-remitting
- 54% responded to IVIg
- 33% to steroids
- 73% to one or other

Multifocal motor neuropathy

Diagnostic criteria

van Schaik et al. 2006 JPNS

Core criteria (both must be present)

- Slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement of => 2 nerves, for > 1 month
- No objective sensory abnormality except minor VS in legs

Supportive clinical criteria

- Predominant upper limb involvement
- Decreased or absent tendon reflexes in affected limb
- Absence of cranial nerve involvement
- Cramps and fasciculations in affected limb

Neurophysiological criteria

Electrophysiological criteria for conduction block

Definite*

CMAP prox/dist area reduction > 50% but dist CMAP must be >20% LLN and increase of prox CMAP duration < 30%

Probable*

CMAP prox/dist area reduction > 30% with increase of prox CMAP duration < 30%
or
CMAP area reduction > 50% with prox CMAP duration >30%

Normal sensory nerve conduction in upper limb segments

*Evidence for CB must be found at sites distinct from common entrapment or compression syndromes

Multifocal motor neuropathy

Treatment

- IVIg effective in 80%
- Short-term
- High doses for sustained response
  - 2.0 g/kg per month Vucic et al 2004 Neurology
- Steroids can worsen

References

- Cochrane reviews (GBS, CIDP and MMN) www.thecochranelibrary.com
- EFNS/PNS guidelines (CIDP and MMN) www.efns.org
- Hughes et al 2005 Supportive Care for GBS Arch Neurol 62: 1194
- Vallat et al 2010 CIDP Lancet Neurology 9:402
- van Doorn et al 2008 Clinical features, pathogenesis, and treatment of GBS. Lancet Neurol 7: 939

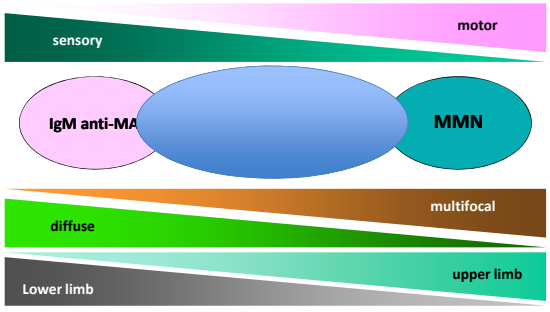
An update on the management of paraproteinaemic neuropathies

Jean-Marc Léger
Referal Center for Neuromuscular Diseases
Hôpital de la Salpêtrière. Paris.

Dysimmune neuropathies

- Acute: Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)
- Polyneuropathy associated with IgM anti-MAG monoclonal gammopathy
- Polyneuropathy associated with IgG/IgA MG ?
- Chronic idiopathic axonal polyneuropathy ?

Clinical spectrum of chronic immune-mediated neuropathies



Lymphoproliferative diseases associated with neuropathy

- Myelomas — IgG/IgA
- Solitary Plasmocytoma — IgG/IgA
- POEMS syndrome — IgG/IgA
- Waldenström's disease — IgM
- Malignant Lymphoma — IgM/IgG
- Cryoglobulinemia
- Primary Amyloidosis — IgG

Journal of the Peripheral Nervous System 11:9–19 (2006)

EFNS/PNS PDN GUIDELINES

European Federation of Neurological Societies/Peripheral Nerve Society Guideline* on management of paraproteinemic demyelinating neuropathies. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society

Joint Task Force of the EFNS and the PNS†

Prevalence of MGUS

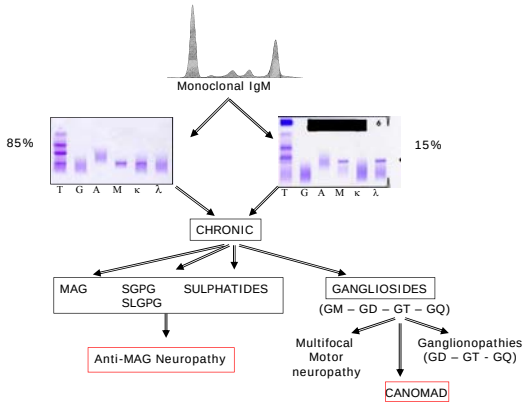
- 3.4% in individuals > 50 years
- Increasing prevalence matched to age
- 6.6% in individuals > 80 years
- Respectively higher prevalence: IgM, IgG, then IgA (Kyle et al. 1978)

Natural history of MGUS
(Kyle et al. 2004: n = 1384)

- Diagnostic between 1960 et 1994
- Mean age at inclusion: 72 y
- Mean follow-up: 15.4 y (0-35)
- Overall risk for developing LD: 1% per year
- 10% at 10 y, 21% at 20 y, 26% at 25 y
- Higher relative risk for WD (46), then myeloma (25), amyloidosis (8.4), lymphoma (2.4)

Predictive factors for evolution to malignant LD

- Isotypes IgA and IgM vs IgG
- Monoclonal component > 15g/L
- Degree of plasmocytosis at bone biopsy
- Light chain λ vs κ



Polyneuropathy associated with IgM anti-MAG MGUS: DADS (distal acquired demyelinating symmetric) neuropathy

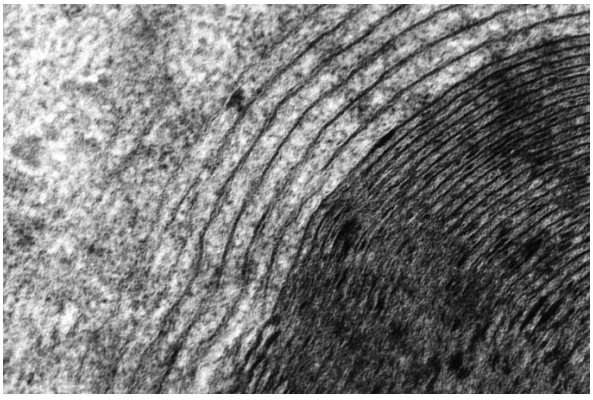
- Chronic, symmetric, predominantly sensory, ataxic polyneuropathy
- Generalized areflexia
- Slowly progressive course
- Reduced MNCV with disproportionately raised distal latencies

Demyelinating neuropathy associated with IgM MGUS: auto-antibodies

- The paraprotein has an activity directed to myelin-associated-glycoprotein (MAG) at significant titres in 50-60% of cases
- It has also an activity directed to glycolipids sharing a common oligosaccharidic epitope with MAG:

SGPG : sulfate glucuronyl paragloboside

SGLPG : sulfate glucuronyl lactosaminyl paragloboside



CANOMAD
(Willison et al, Brain, 2001)

- Chronic Ataxic Neuropathy, Ophthalmoplegia, monoclonal M protein, cold agglutinins and Anti-Diasalosyl antibodies
- Relapsing predominantly sensory neuropathy
- Ophthalmoplegia and bulbar signs
- IgM directed to specific ganglosides: GD1b, GT1b, GQ1b, GD3….with presence of cold agglutinins in 50% of cases


Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies (Review)

Lunn MPT, Nobile-Orazio E

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DADS neuropathy associated with anti-MAG IgM MGUS: therapy

- Chlorambucil (Oksenhendler et al. 1995)(class III)
- High-dose IVIg (Comi et al. 2002) (class II)
- Rituximab (Pestronk et al. 2003) (class III) (Renaud et al. 2003) (class IV)
- Oral fludarabine for monthly 6 cycles of 5 days (Niermeijer et al. 2006) (Class III)
- Monthly oral CTx:500mg/d x 4 + oral prednisone: 60mg/d x 5 (Niermeijer et al. 2007) (class II)

Placebo-controlled trial of rituximab in anti-MAG neuropathy. Dalakas et al. 2009

- 26 included patients with anti-MAG neuropathy: 13 receiving 4 weekly infusions of 375 mg/m2 and 13 placebo
- At 8 months, by intention to treat, 4 of 13 treated patients improved by ≥ 1 INCAT score compared with 0 of 13 patients taking placebo ($p = 0.096$).
- The most improved patients were those with high anti-MAG titers and most severe sensory deficits at baseline

RIMAG trial : design

- Double-blind randomised controlled trial
- Parallel group
- 54 participants
- Eight French and one Swiss centres
- Patients randomised to receive 4 weekly infusions of 375mg/m² rituximab or placebo

Primary outcome: Protocol Definition

- The main analysis will use the delta change in INCAT sensory sumscore (ISS)
- ISS measured at baseline will be compared to ISS at month 12

Final Analysis
Primary outcome (1)

	Variables	Placebo (n=27)	Rituximab (n=20)	p-value
Between day 0 and month 12	Mean Variation of ISS ± sd	1.0 ± 2.8	1.3 ± 3.0	0.68
	ISS improvement ≥4, n (%)	6 (22.2)	4 (20.0)	1.00
	Mean Variation of ISS leg ± sd	0.2 ± 1.3	1.0 ± 2.0	0.15
Between day 0 and month 9	Mean Variation of ISS score ± sd	1.1 ± 3.3	1.6 ± 2.8	0.60
	ISS improvement ≥4, n (%)	5 (18.5)	4 (22.2)*	1.00

* total n=18 due to missing value

INCAT score. Self-evaluation scale
Descriptive statistics

	Variables	Placebo (n=27)	Rituximab (n=20)	p-value
Between day 0 and month 12	Mean Variation of Hugues score ± sd	- 0.2 ± 0.7	0.2 ± 1.3	0.22
	Hugues score improvement ≥2, n (%)	0 (0.0)	4 (20.0)	0.03

Variables	Placebo	Rituximab	p value
Mean Self Evaluation Score at M12 ± sd	14.8 ± 4.3 (n=25)	12.0 ± 5.5 (n=17)	0.07
Self Evaluation Scale at M12	(n=25)	(n=19)	
Improvement	1 (4.0)	5 (26.3)	0.02
Stabilization	9 (36.0)	10 (52.6)	
No effect	15 (60.0)	4 (21.0)	