L'algoritmo diagnostico e le ricadute terapeutiche

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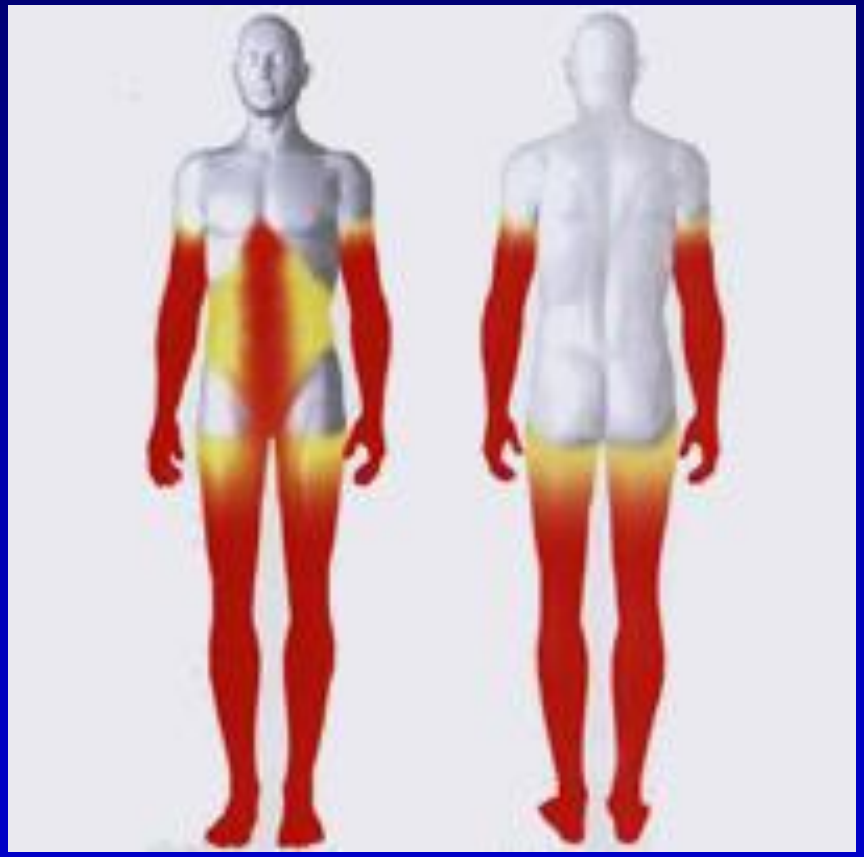
Algoritmo diagnostico

- Anamnesi!
- Esame obbiettivo!
- Esami laboratorio
- Esami strumentali



♦ Anamnesi

- Albanese, abita in Italia?
- Viaggi recenti?
- Intossicazioni recenti? (botulino)
- Infezioni recenti? (↑ PCR), vaccini?

♦ Quadro clinico

Vertigini, disfagia, poi deficit di forza acuto prevalentemente prossimale ai 4 arti

Areflessia (ma storia di diabete)

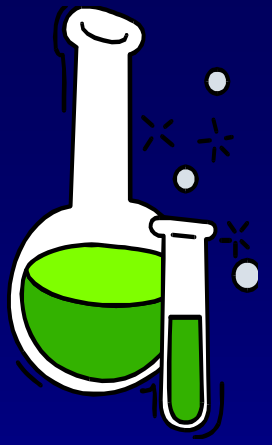
Disartria, deficit linguale, tetraplegia, diplegia facciale, oftalmoparesi, insufficienza respiratoria acuta

Algoritmo diagnostico - Laboratorio

- Routine ematochimica
  - escludere ipokaliemia
  - CPK (escludere miopatia/miosite)
  - VES/PCR
  - enzimi epatici (epatite E?)
  - vasculiti

Da considerare
- HIV (GBS alla sieroconversione)
- Lyme
- ACE
- Sierologia agenti infettivi
- Ab anti-gangliosidi

Laboratorio



- ↑PCR (infezione asintomatica?)
- Negativa ricerca di CJ, EBV, Borrelia, Lue, epatite B,C, HIV, porfiria

  West Nile? Epatite E? Enterovirus 72?
- Negativa autoimmunità (escluse vasculiti?)
- Liquor: negativo il giorno successivo all'ingresso

  Liquor 10 giorni dopo: non «franca» dissociazione
- RMN encefalo negativa

Algoritmo diagnostico

Liquor

Neurofisiologia

Rx/TC torace

ECG/capacità vitale

MRI → to esclude cerical spine or brainstem pathology

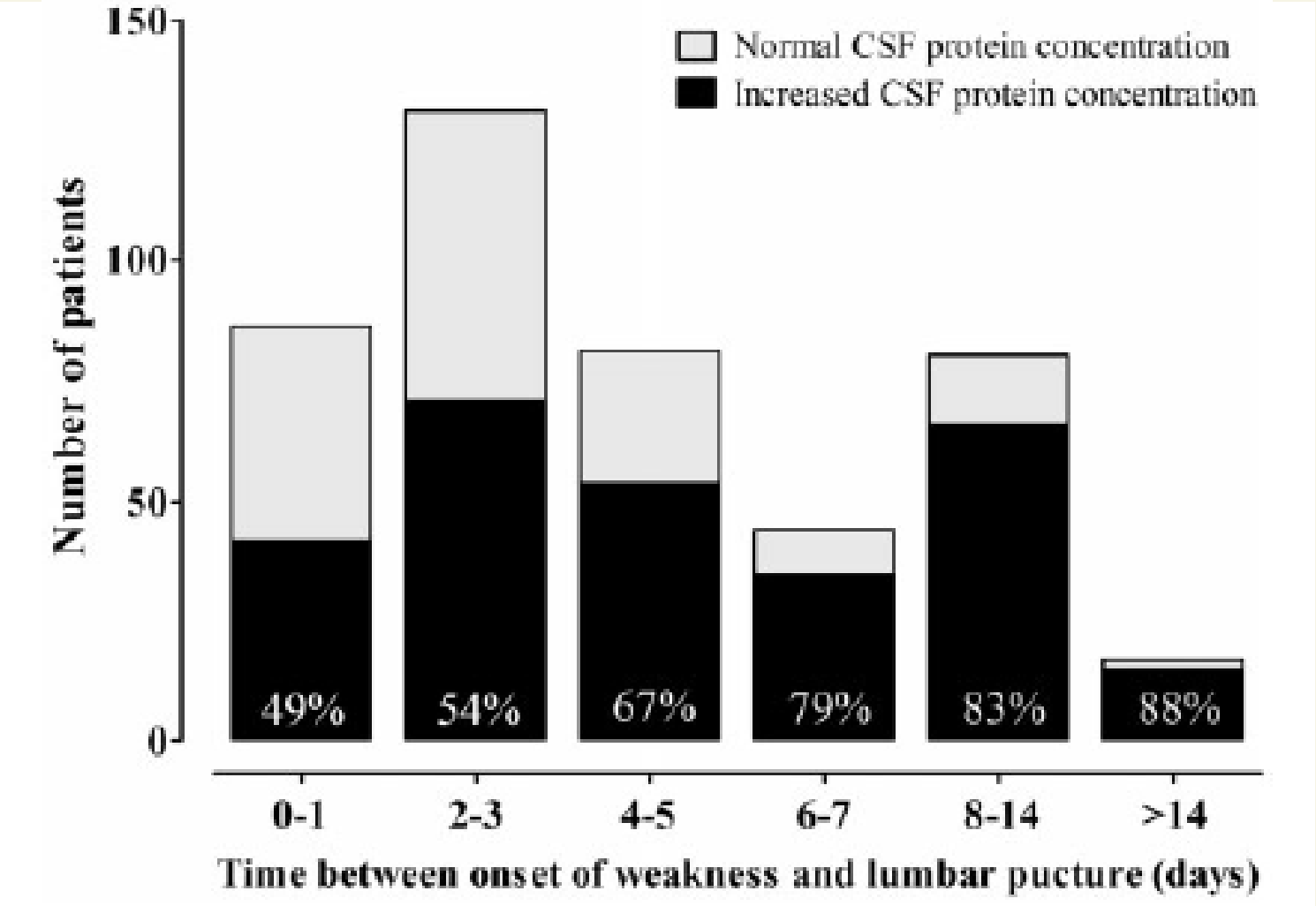
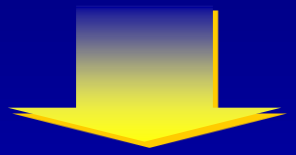


Figure 3 Number of patients and percentages with elevated protein concentration in CSF in relation to the timing of the

Studio neurofisiologico il 4.4 (giorno successivo all'ingresso)

♦ Blocchi di conduzione all'ulnare di sinistra (il blocco è prossimale all'Erb o distale?) e al peroneo di sinistra

♦ Allungamento latenze delle onde F (tutte le F sono alterate? da median e ulnare, peroneo e tibiale)?

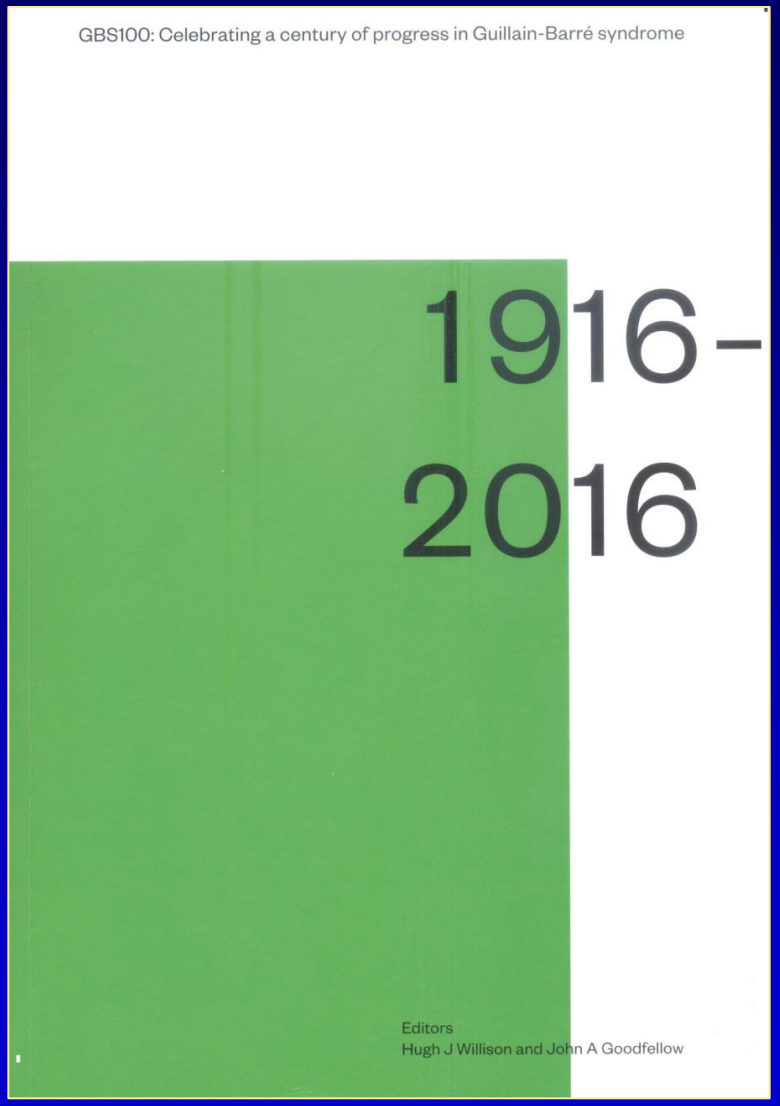


danno mielina

♦ Però i potenziali d'azione sensitivi sono ipovoltati (= danno assonale)
(ricordiamoci che pz è diabetico)

♦ ENG/EMG eseguiti alla seconda e alla terza settimana
Danno assonale ai 4 arti, prevalentemente motorio, denervazione diffusa ai muscoli degli arti

Sindrome di Guillain-Barré-Strohl



EPIDEMIOLOGIA

Incidence
1-2:100.000/years
M/F 1.25:1
age : young adults or > 55 y

Infections

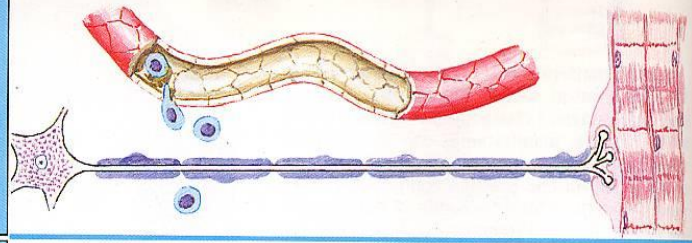
Positive history of antecedent infection disease (2/3pts)
a) Viral infections

- CMV:15%pz
- EBV:10% pz
- Hemophilus influenza
- Hepatitis E (↑ AST)
- b) Bacterial infections
- Campylobacter jejuni 32% pz
- Mycoplasma pneumoniae 5%

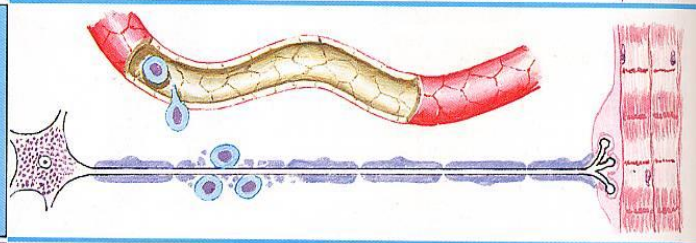
1976 - Vaccines : swine flu vaccines increased incidence
1980's- "Cronassial" i.m. in Italy

patogenesi

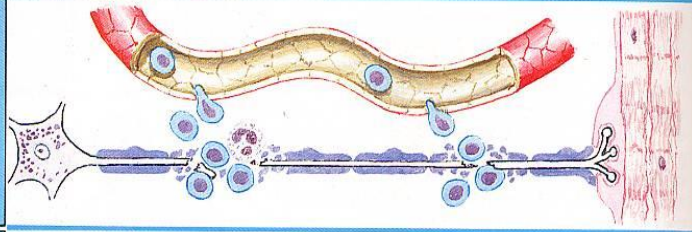
stadio I. Linfociti migrano attraverso i vasi endoneurali e circondano la fibra nervosa; la guaina mielinica e l'assone non sono ancora danneggiati



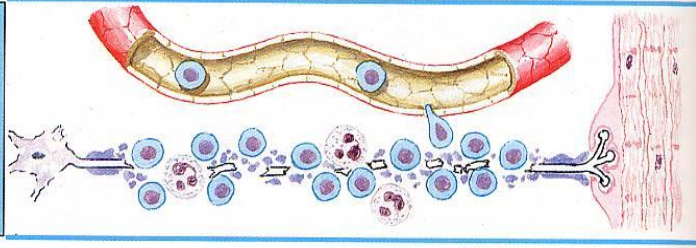
stadio II. I linfociti fuoriescono in maggior numero e compaiono i macrofagi. Inizia una demielinizzazione segmentale, tuttavia l'assone non è ancora colpito



stadio III. Danno multifocale della guaina mielinica e dell'assone. Si verifica una cromatolisi centrale del corpo neuronale e il muscolo inizia a presentare un'atrofia da denervazione

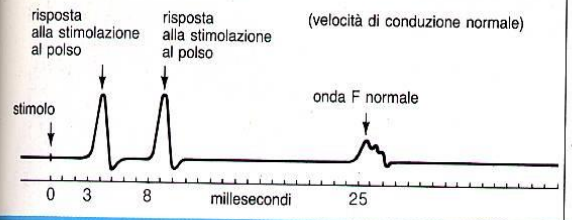


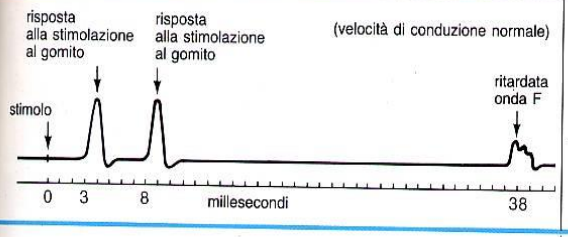
stadio IV. Estesa distruzione assonica. Alcuni corpi neuronali irreversibilmente danneggiati, ma la funzione può essere conservata grazie alle fibre nervose adiacenti meno danneggiate

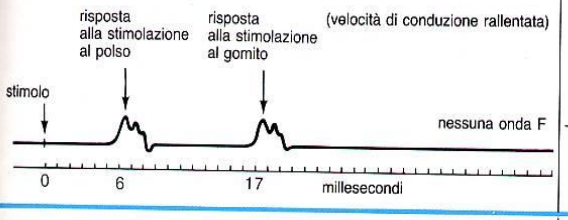


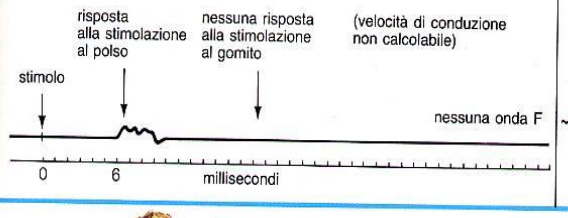
velocità di conduzione nervosa

risposta dei muscoli ipotenari alla stimolazione del nervo ulnare

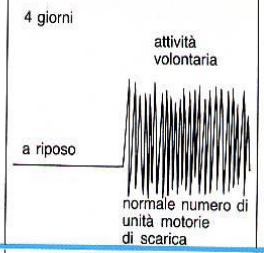


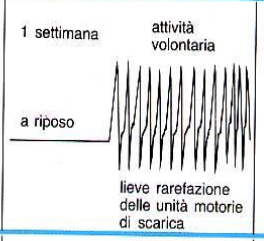


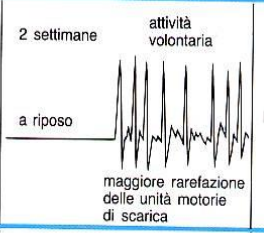


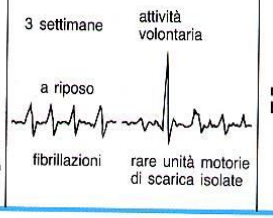


elettromiografia









prognosi

eccellente

eccellente

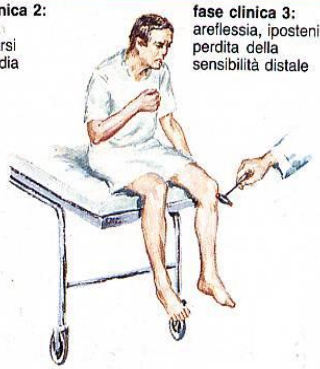
buona

relativamente buona

fase clinica 1: parestesie formicolanti alle mani e ai piedi

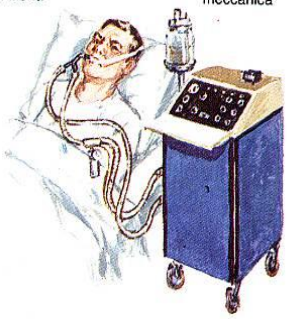
fase clinica 2: difficoltà nell'alzarsi dalla sedia

fase clinica 3: areflessia, ipostenia, perdita della sensibilità distale

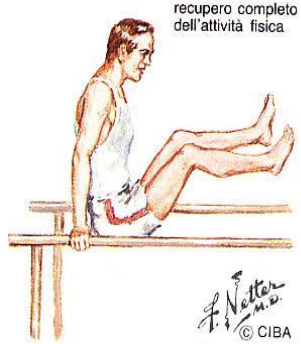


fase clinica 4 monitoraggio della funzione respiratoria

fase clinica 5 ventilazione meccanica



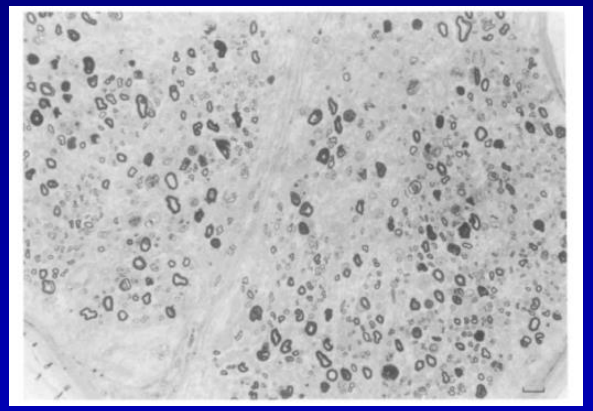
fase clinica 6 recupero completo dell'attività fisica



Brain (1986), **109**, 1115–1126

AN ACUTE AXONAL FORM OF GUILLAIN-BARRÉ POLYNEUROPATHY

by T. E. FEASBY,[1] J. J. GILBERT,[1,2] W. F. BROWN,[1] C. F. BOLTON,[1] A. F. HAHN,[1,2] W. F. KOOPMAN[1] *and* D. W. ZOCHODNE[1]

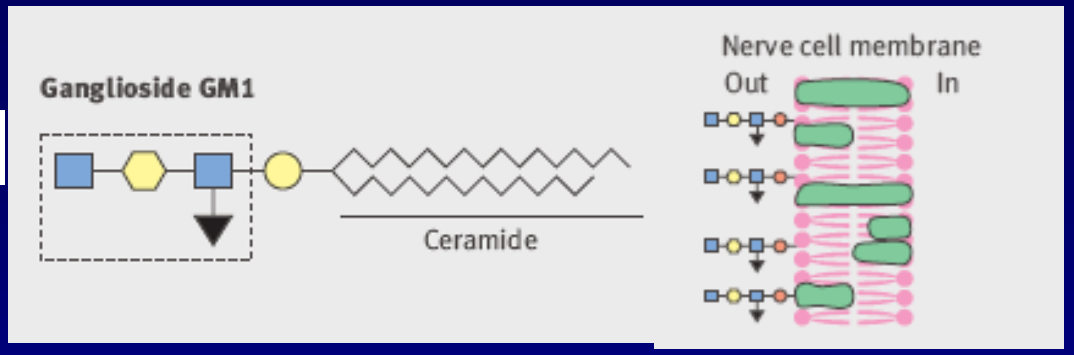


- 5 severe quadriplegic pts
- inexcitable motor nerves
- EMG: abundant widespread fibrillation
- Poor prognosis
- 1 autopsy: severe axonal degeneration without demyelination or inflammation

Nobuhiro Yuki, MD; Hiide Yoshino, MD;
Shuzo Sato, MD; and Tadashi Miyatake, MD

Acute axonal polyneuropathy associated with anti-GM_1 antibodies following *Campylobacter* enteritis

NEUROLOGY 1990;40:1900-1902



MUSCLE & NERVE 15:899–903 1992

SEVERE ACUTE AXONAL FORM OF GUILLAIN–BARRÉ SYNDROME ASSOCIATED WITH IgG ANTI-GD_{1a} ANTIBODIES

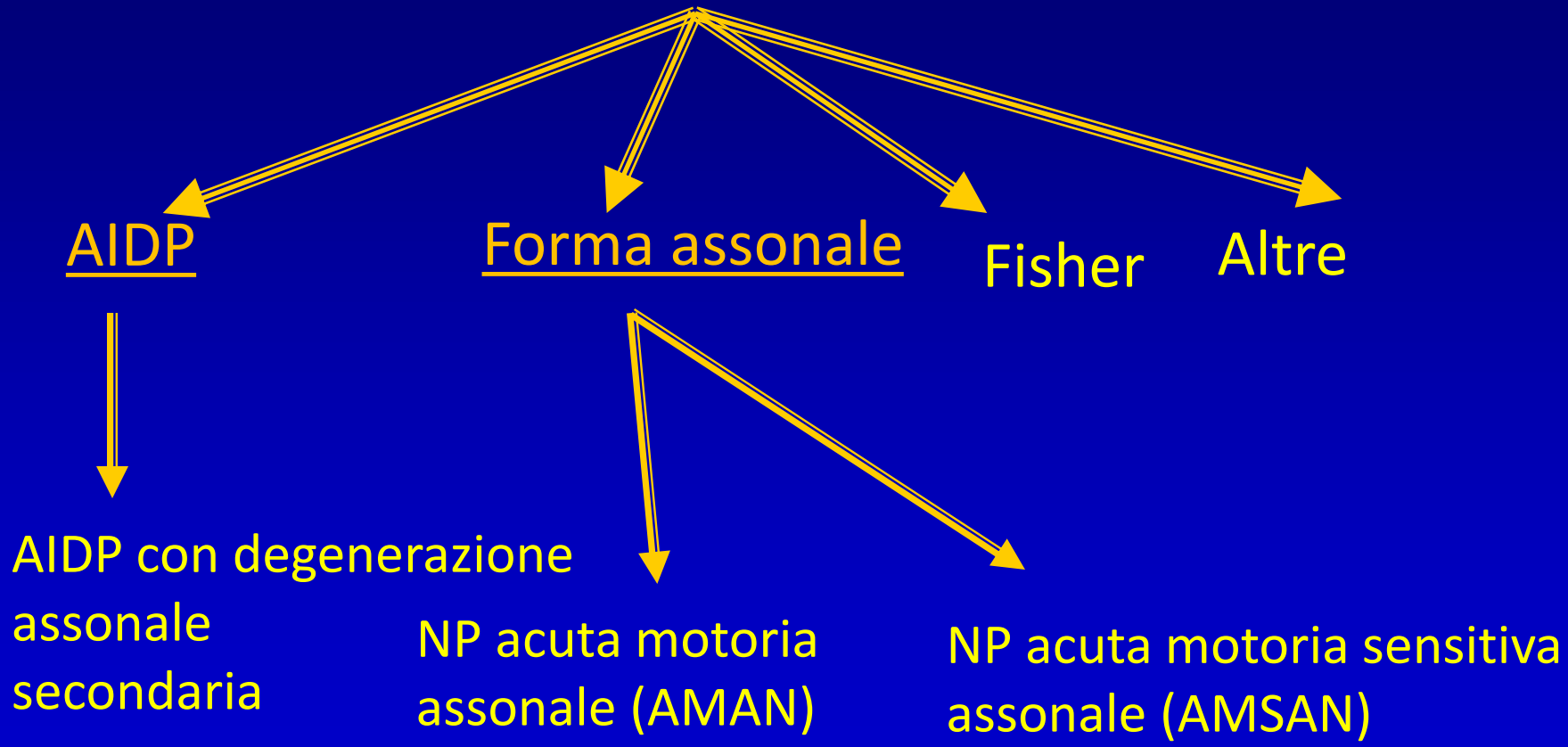
NOBUHIRO YUKI, MD, HIIDE YOSHINO, MD, SHUZO SATO, MD,
KAZUKI SHINOZAWA, MD, and TADASHI MIYATAKE, MD

BRITISH MEDICAL JOURNAL VOLUME 285 17 JULY 1982

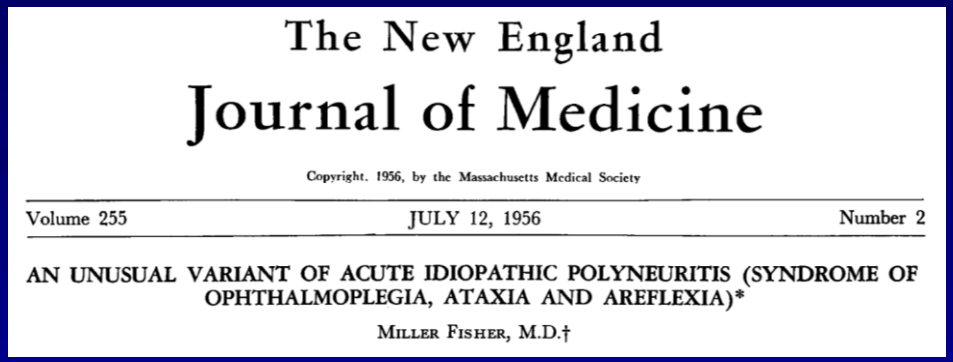
Guillain-Barre syndrome associated with Campylobacter infection

K M RHODES, MB, MRCP, medical registrar
A E TATTERSFIELD, MD, FRCP, reader in medicine

Sindrome di Guillain-Barré-Strohl



Fisher syndrome



The New England

Journal of Medicine

Volume 255 JULY 12, 1956 Number 2

AN UNUSUAL VARIANT OF ACUTE IDIOPATHIC POLYNEURITIS (SYNDROME OF OPHTHALMOPLEGIA, ATAXIA AND AREFLEXIA)*

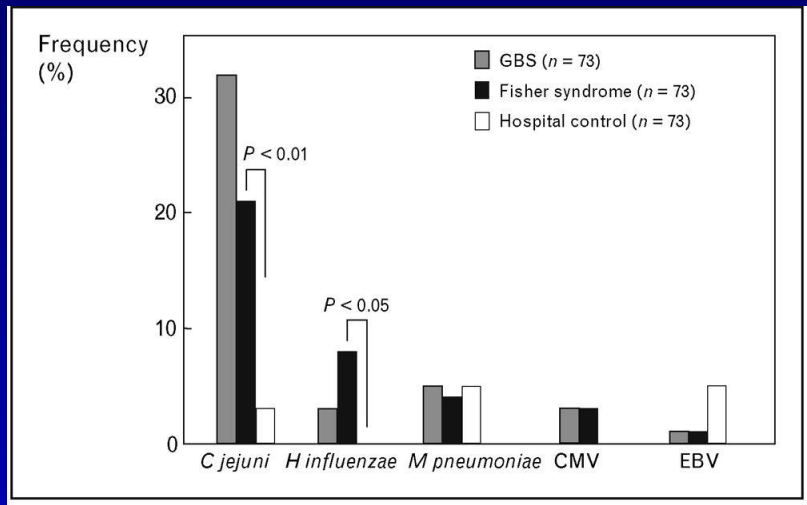
MILLER FISHER, M.D.†

3 pts:

- infective antecedent 3/3
- ophthalmoplegia 3/3
- ataxia (no dysarthria or nystagmus) 3/3
- areflexia 3/3
- mild proximal weakness in 1/3
- mild drowsiness and headache 1/3
- CSF albuminocytological dissociation in 1/3
- Complete or good recovery 3/3

Fisher syndrome

- Più frequente delle varianti
  5% West, 19-25% East
- Atassia, areflessia, oftalmoplegia
- Di 5 precedenti infettivi
  (CJ, CMV, EBV, HI, Mycopl pn):
  - CJ 21%
  - H. influenzae 8%
- Ac anti-GQ1b/GT1a (> 90%) *(Chiba A, '92)*



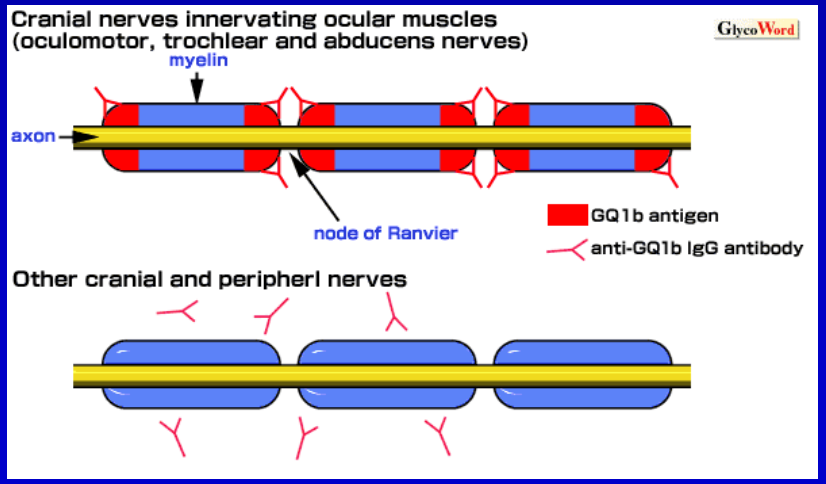
Hospital controls were sex and age-matched (±5 years) with each patient with Fisher syndrome. CMV, cytomegalovirus; EBV, Epstein-Barr virus.

(Koga M, 05)

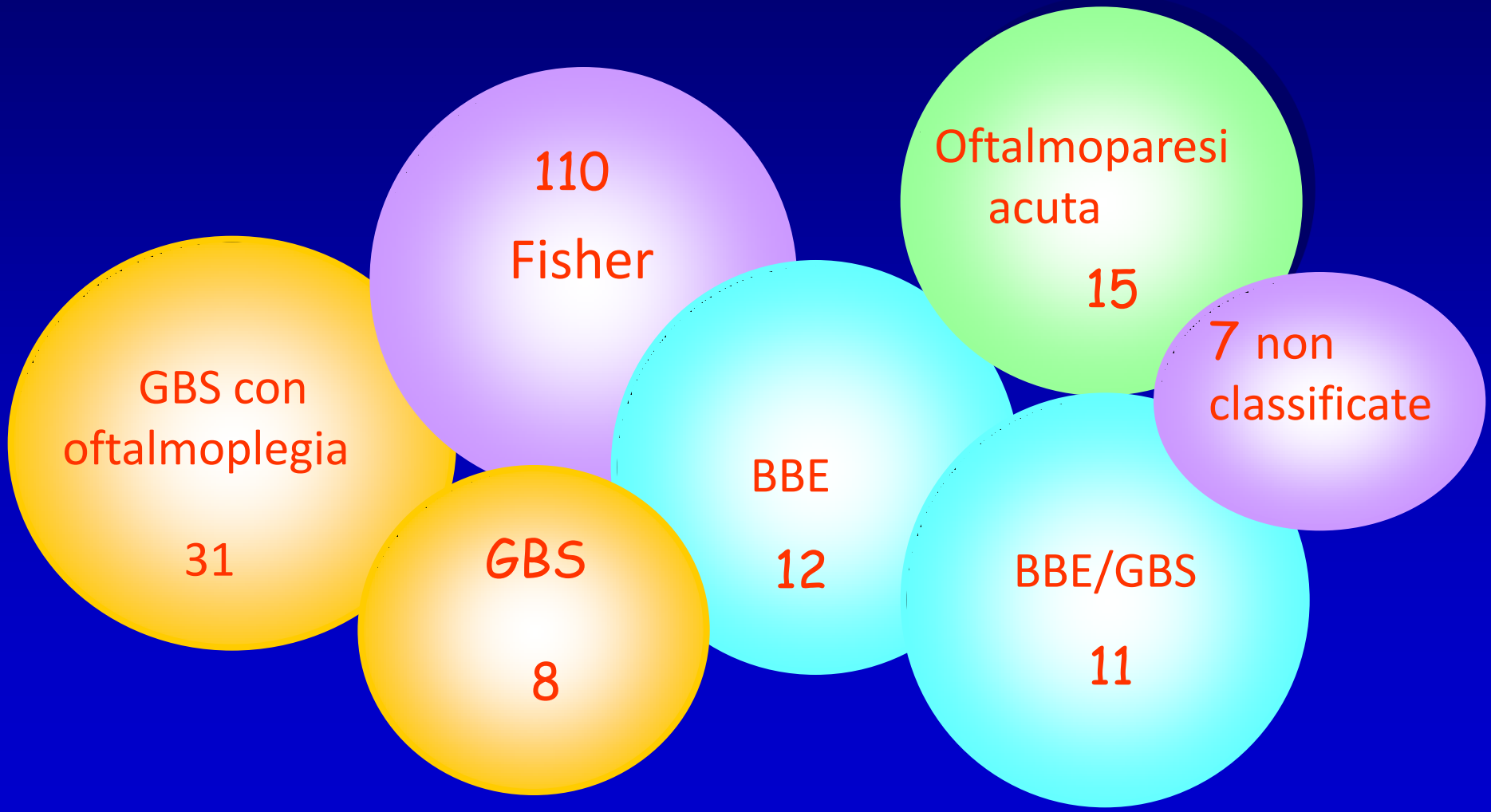
GQ1b

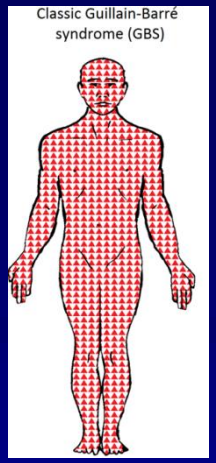
- GQ1b: tetra-sialoganglioside

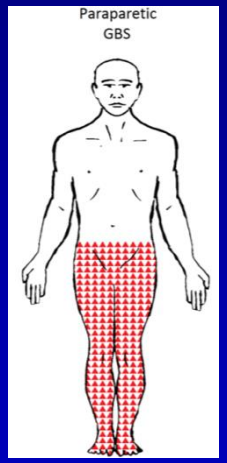
- I nervi oculomotore, trocleare e abducente esprimono ↑↑ GQ1b *(Chiba, '97)*

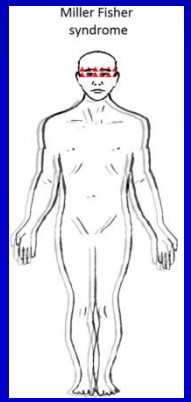


Anti-GQ1b antibody syndrome *(Odaka M, '07)*



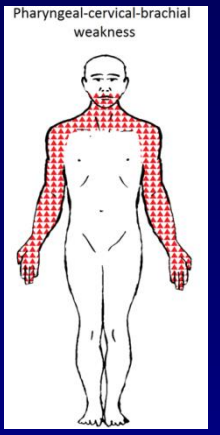


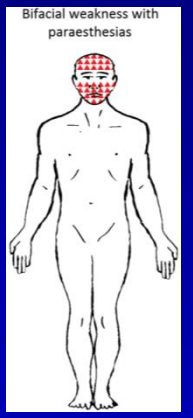


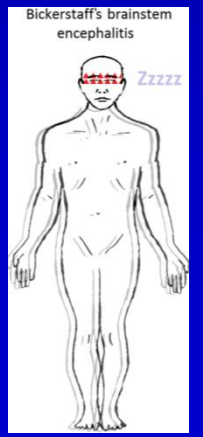


GBS, MFS and their subtypes

Category	Clinical features		
	Pattern of weakness	Ataxia	Hypersomnolence
GBS			
Classic GBS	Four limbs	No or minimal	No
Pharyngeal–cervical–brachial weakness*	Bulbar, cervical and upper limbs	No	No
Acute pharyngeal weakness‡	Bulbar	No	No
Paraparetic GBS*	Lower limbs	No	No
Bifacial weakness with paraesthesias*	Facial	No	No
MFS			
Classic MFS	Ophthalmoplegia	Yes	No
Acute ophthalmoparesis§	Ophthalmoplegia	No	No
Acute ataxic neuropathy§	No weakness	Yes	No
Acute ptosis§	Ptosis	No	No
Acute mydriasis§	Paralytic mydriasis	No	No
BBE‖	Ophthalmoplegia	Yes	Yes
Acute ataxic hypersomnolence¶	No weakness	Yes	Yes







Patients may present with overlapping syndromes

Benjamin R Wakerley, and Nobuhiro Yuki Pract Neurol 2015;15:90-99

Differential diagnoses for classic Guillain–Barré syndrome

♦ *Viruses targeting anterior horn cells or motor neurones*
Poliomyelitis, non-polio enterovirus (enterovirus 71), West Nile virus
Herpes simplex virus, cytomegalovirus, EBV, varicella zoster virus
Rabies virus, HIV

♦ *Transverse myelitis*
Mycoplasma pneumoniae
Herpes simplex virus, cytomegalovirus, EBV, varicella zoster virus

♦ *Spinal cord injury*
Acute spinal stenosis (eg, disc prolapse, epidural abscess or haematoma)
Anterior spinal artery occlusion

♦ *Acute peripheral neuropathies*
Infections (eg, herpes simplex virus, HIV)
Consumption of toxins or poisons (eg, puffer fish poisoning -tetrodotoxin), lead, thallium, arsenic)
Tick paralysis, Lyme disease (painful, asymmetric, CSF lymphocytes)
Porphyria (abdominal pain, psychiatric symptoms)

Differential diagnoses for classic Guillain–Barré syndrome

♦ *Neuromuscular junction disorders*
Myasthenia gravis
Lambert–Eaton myasthenic syndrome
Botulism

♦ *Neuromuscular weakness related to critical illness*
Critical illness neuropathy and myopathy

♦ *Muscle disorders*
Acute myositis
Periodic paralysis
Functional

Differential diagnoses for Miller Fisher syndrome, Bickerstaff's brainstem encephalitis and pharyngeal-cervical-brachial weakness

- Myasthenia gravis
- Brainstem stroke (eg, basilar artery occlusion)
- Diphtheritic neuropathy
- Botulism
- Brainstem encephalitis

– Infective (eg, listeriosis, tuberculosis, brucellosis, Lyme disease, herpes simplex virus, EBV, JC virus, toxoplasmosis, cryptococcosis)
– Autoimmune (eg multiple sclerosis, sarcoidosis, Behçet's disease, systemic lupus erythematosus
– Malignancy (eg lymphoma, paraneoplastic syndrome)

- Basal meningitis (Inflammatory, infective, carcinomatous and lymphomatous)

Algoritmo diagnostico e ricadute terapeutiche

- Quadro clinico
  (paralisi flaccida, simmetrica, ai muscoli degli arti tronco, nervi cranici, insufficienza respiratoria)

- Laboratorio

- RNM cerebrale → ha escluso problemi SNC
  Neuroimaging SNP? Ecografia e Risonanza neurografia

- CSF → non di supporto?

- Neurofisiologia → demielinizzaione → danno assonale

- Ab anti-gangliosidi?

Mimics and chameleons in Guillain–Barré and Miller Fisher syndromes

Wakerley BR, *et al*. *Pract Neurol* 2015;**15**:90–99. doi:10.1136/practneurol-2014-000937

Key points

- GBS and MFS subtypes form a continuous spectrum of overlapping syndromes.

- GBS spectrum disorders should always be considered if relatively symmetric limb or cranial nerve weakness and ataxia, follow antecedent upper respiratory infectious symptoms or diarrhoea. This is supported by the presence of distal paraethesias, CSF albuminocytological dissociation, abnormal nerve conduction studies, or anti-ganglioside antibodies.

- GBS is very likely in acute flaccid paralysis with facial weakness

- MFS and the pharyngeal-cervical-brachial variant of GBS are frequently mistaken for myasthenia gravis, botulism or brainstem stroke.

- 10% of patients with GBS have normal or exaggerated deep tendon reflexes.

Brighton Collaboration GBS Group

Vaccine 2011

2. Clinical case definitions: Guillain–Barré syndrome (GBS)[3,4,5]

Level 1 of diagnostic certainty

- Bilateral AND flaccid weakness of the limbs[6,7,8]

  AND
- Decreased or absent deep tendon reflexes in weak limbs[9]

  AND
- Monophasic illness pattern[10] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[11]

  AND
- Electrophysiologic findings consistent with GBS[12]

  AND
- Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μl)[13]

  AND
- Absence of an identified alternative diagnosis for weakness (see Appendix A.3)[3].

Level 2 of diagnostic certainty

- Bilateral AND flaccid weakness of the limbs[6,7,8]

  AND
- Decreased or absent deep tendon reflexes in weak limbs[9]

  AND
- Monophasic illness pattern[10] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[11]

  AND
- CSF total white cell count <50 cells/μl (with or without CSF protein elevation above laboratory normal value)[13]

  OR
- IF CSF not collected or results not available, electrophysiologic studies consistent with GBS[12]

  AND
- Absence of identified alternative diagnosis for weakness (see Appendix A.3)[3].

Level 3 of diagnostic certainty

- Bilateral AND flaccid weakness of the limbs[6,7,8]

  AND
- Decreased or absent deep tendon reflexes in weak limbs[9]

  AND
- Monophasic illness pattern[10] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[11]

  AND
- Absence of identified alternative diagnosis for weakness (see Appendix A.3)[3].

Plasma exchange for Guillain-Barré syndrome (Review)

Chevret S, Hughes RAC, Annane D

Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD001798.

THE COCHRANE COLLABORATION®

- PE è il primo trattamento dimostrato superiore alla sola terapia di supporto nella GBS
- PE è pertanto la terapia nei confronti della quale nuovi trattamenti devono essere confrontati
- PE è più efficace quando iniziata entro 7 giorni dall'esordio, ma è a utile fino a 30 giorni dall'esordio

Ann Neurol 1997;41:298–306 ORIGINAL ARTICLES

Appropriate Number of Plasma Exchanges in Guillain-Barré Syndrome

The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome*

- 556 GBS pz
- 91 lieve (> 5 m senza aiuto, ma no corsa)
  - randomizzati a no PE (ctl) o 2 PE
- 304 moderata (impossib stazione eretta)
  - randomizzati a 2 o 4 PE
- 161 grave (ventilazione meccanica)
  - randomizzati a 4 o 6 PE

- GBS lieve: 2 PE meglio di 0
- GBS moderata: 4 PE meglio di 2
- GBS grave: 6 PE non meglio di 4

A RANDOMIZED TRIAL COMPARING INTRAVENOUS IMMUNE GLOBULIN AND PLASMA EXCHANGE IN GUILLAIN–BARRÉ SYNDROME

F.G.A. VAN DER MECHÉ, M.D., PH.D., P.I.M. SCHMITZ, PH.D., AND THE DUTCH GUILLAIN–BARRÉ STUDY GROUP*

N Engl J Med 1992;326:1123-9

- 150 pz
  - < 14 gg dall'esordio
  - perdita deambulazione
- Randomizzati: 5 PE (in 7-14 gg) o Ig ev (2g/Kg in 5 gg)

Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome

Vol 349 • January 25, 1997

THE LANCET

*Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group**

- 379 pz
  - < 14 gg dall'esordio
  - perdita deambulazione
- Randomizzati
  - 121 pz PE (5 in 8-13 gg)
  - 130 Ig ev (2g/Kg in 5 gg)
  - 128 PE + Ig ev

Risultati

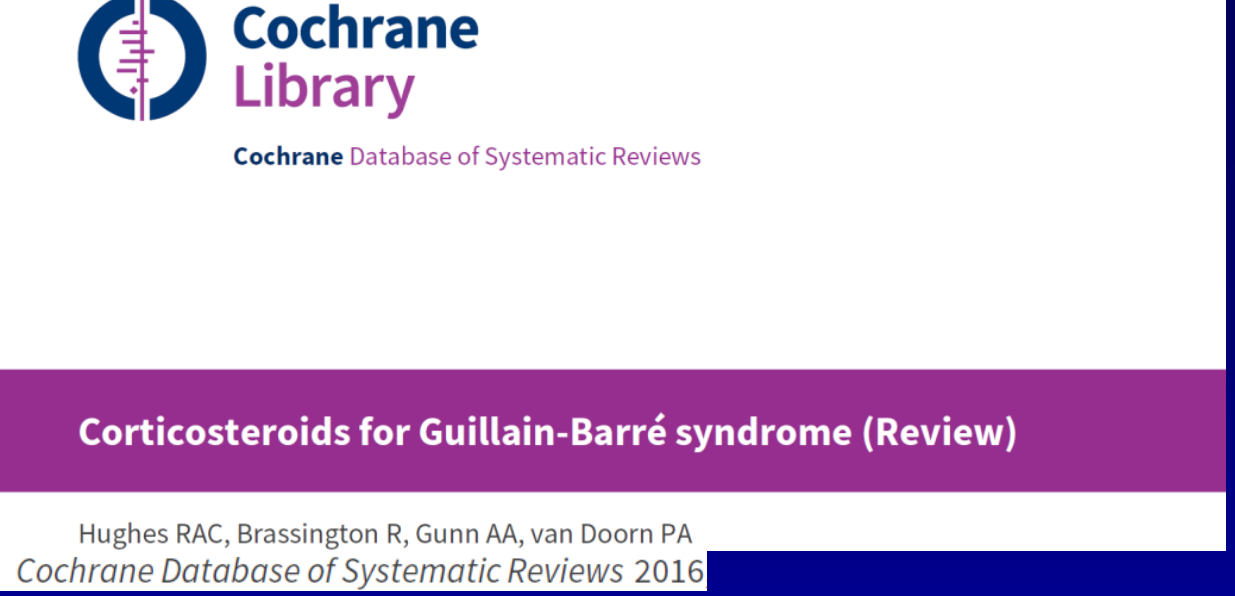
- Miglioramento disabilità a 4 settimane (outcome primario)
- Tempo alla deambulazione autonoma
- Tempo alla sospensione ventilazione
- Recupero disabilità a 48 settimane

PE e Ig ev sono ugualmente efficaci

(NEJ, 1992; Lancet, 1997)

PE + Ig ev non > PE o Ig ev

(*Lancet, 1997)*



- I corticosteroidi da soli non velocizzano la guarigione della GBS nè migliorano la prognosi a lungo termine

- I corticosteroidi per os possono ritardare la guarigione

PROGNOSI

The prognosis and main prognostic indicators of Guillain–Barré syndrome

A multicentre prospective study of 297 patients

The Italian Guillain–Barré Study Group*

Brain 1996

Correspondence to: Dr Ettore Beghi, Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea, 62–20157-Milano, Italy

Summary

To assess the prognosis of the Guillain–Barré syndrome and identify the main prognostic indicators, 297 patients with Guillain–Barré syndrome recruited through a network of Italian centres were followed up for 24 months or until clinical recovery, whichever was earliest. For each patient the time to plateau, improvement, clinical recovery, or death was calculated, and prognostic indicators (age, sex, antecedent events, disability at admission and nadir, electrophysiological patterns) and treatments were noted. The mean duration of follow-up was 309 days. During this period, 212 patients (71%) recovered, 48 (16%) had residua and 33 (11%) died. The mean times to nadir, improvement and clinical recovery were 12, 28 and 200 days. Using life-tables and survival curves, the cumulative probability of achieving the plateau of symptoms was 73% by 1 week and 98% by 4 weeks. Improvement started during the first week in 36% of cases and within 4 weeks in 85%. The rates of clinical recovery at 1 and 4 weeks, 6, 12 and 24 months were 4, 24, 57, 70 and 82%, respectively. The chance of recovery was significantly affected by age, antecedent gastroenteritis, disability, electrophysiological signs of axonopathy, latency to nadir and duration of active disease. The main treatments did not seem to affect the chance of recovery.

Long-term disability and social status after GBS

(Bersano A, '06)

Studio caso-controllo su 70 pz con GBS:

Recupero completo 64%

Limitazioni lievi 27%

Necessità di aiuto 9%

30% modifiche daily life

*Take home message

- GBS and MFS subtypes form a continuous spectrum of overlapping syndromes.
- GBS is very likely in acute flaccid paralysis with facial weakness
- MFS and the pharyngeal-cervical-brachial variant of GBS are frequently mistaken for myasthenia gravis, or brainstem stroke.

Grazie per l’attenzione