CONVEGNO REGIONALE SIN /SNO
Liguria - Piemonte e Valle d'Aosta
Ivrea, 6-7 dicembre 2019
Università infermieristica di Ivrea

Neuropatie Immunomediate

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Disclosure: Akcea, Alnylam, Pharmanext, CSL Behring, Kedrion

Neuropatie Immunomediate

- Classificazione e clinica
- Varianti di malattia e criteri diagnostici
- Forme «atipiche»
- Trattamento
- Forme «refrattarie»

Classification

- Acute

✓ Guillain Barrè syndrome (GBS) & variants

- Chronic

✓ Chronic inflammatory demyelinating polyneuropathy (CIDP) & variants

✓ Multifocal Motor Neuropathy (MMN)

✓ Neuropathies associated with monoclonal gammopathies

✓ Paraneoplastic neuropathies

✓ Vasculitic neuropathies & neuropathies associated with systemic autoimmune disorders (AR, LES, Sjogren etc.)

Guillain-Barrè Syndrome (GBS)

" In 1916, Guillain, Barrè and Strohl described a previously unrecognized type of polyneuritis characterized by definite changes in the cerebrospinal fluid. The essential of the disease were *widespread flaccid paralysis*, *loss of tendon reflexes*, preservation of cutaneous reflexes, conservation of idiomuscular contraction on percussion, *minimal changes in the electrical reactions of the muscle and nerves*, muscle tenderness, paresthesias with little disturbances of objective sensibility and, most specifically, *increase in the protein content of the CSF* which was not accompanied by a proportionate degree of pleocytosis ".

Dr. Guillain, G.

From:

The Guillain-Barrè syndrome: polyradiculoneuritis with albuminocytologic dissociation

De Jong R.N.

Archives of Neurology and Psychiatry, 44: 1044-1068, 1940

Preceding Infection (1-2 weeks)

Progression: less then 4 weeks

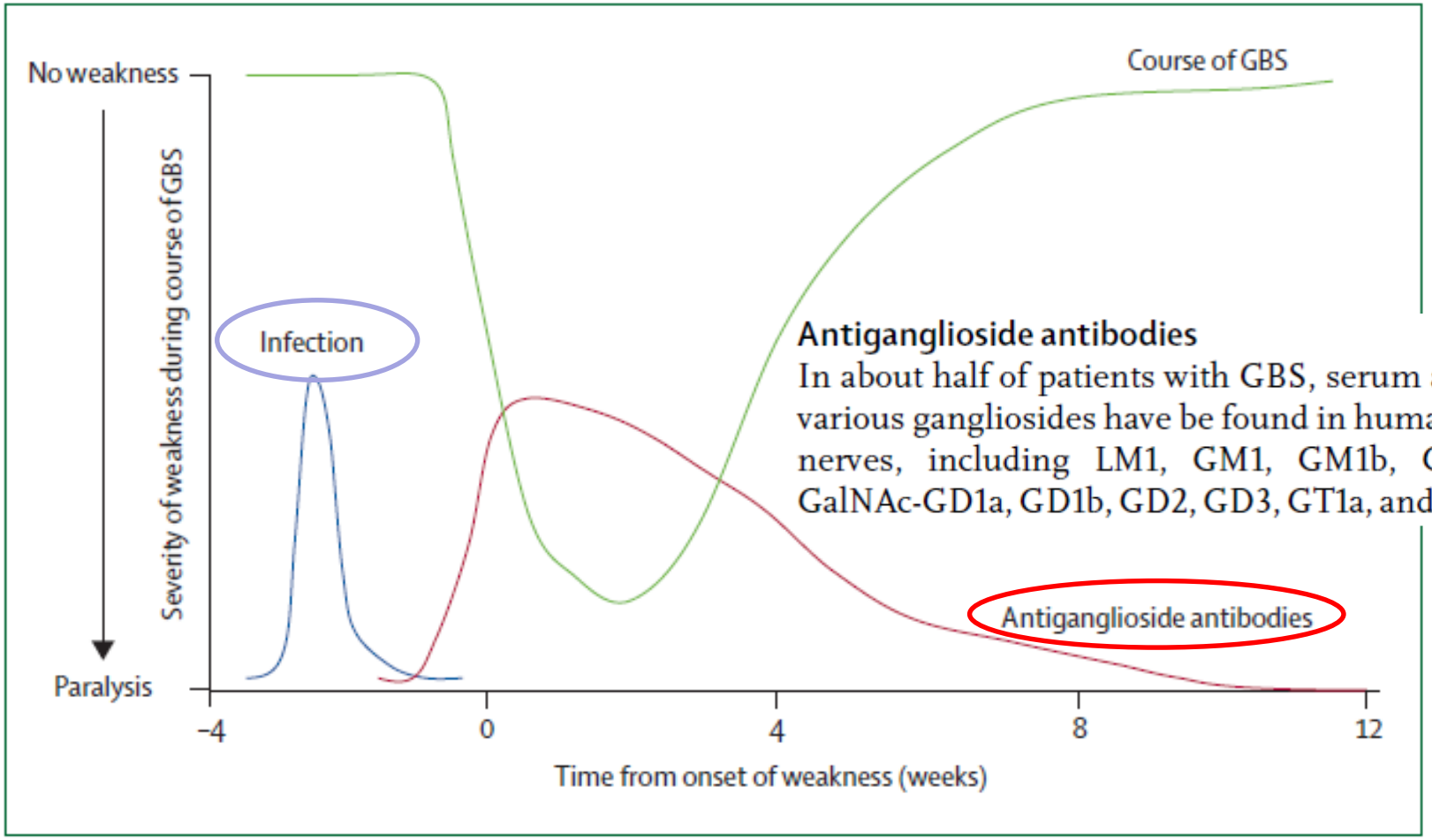


Figure 1: **Relation between infections, antiganglioside antibodies, and clinical course of GBS**

van Doorn PA et al., Lancet Neurol 2008;7: 939-950

Table 1. Clinical spectrum of the anti-GQ1b antibody syndrome.

Disorder	Clinical features	Anti-GQ1b antibody frequency
MFS	Ataxia, areflexia, ophthalmoplegia[40]	Up to 95%[76]
GBS	Weakness, sensory loss, areflexia, cranial neuropathy[164]	Up to 26%[22]
BBE	Ophthalmoplegia, ataxia, hypereflexia or disturbed consciousness[120]	Up to 66%[120]

Variants

- Acute Inflammatory Demyelinating Polyneuropathy (AIDP)
- Acute Motor Axonal Neuropathy (AMAN)
- Acute Motor Sensory Axonal Neuropathy (AMSAN)
- Miller Fisher syndrome (ataxia, areflexia, ophthalmoplegia)
- Acute pandysautonomia
- Subacute Inflammatory Demyelinating Polyneuropathy
  - ➢ Progression continues for 4-10 weeks → CIDP with acute onset

L. Ruts, MD
J. Drenthen, MD
B.C. Jacobs, MD, PhD
P.A. van Doorn, MD, PhD
On behalf of the Dutch GBS Study Group

Distinguishing acute-onset CIDP from fluctuating Guillain-Barré syndrome

A prospective study

Neurology® 2010;74:1680-1686

Background: The distinction between Guillain-Barré syndrome (GBS) with fluctuations shortly after start of treatment (treatment-related fluctuations, or GBS-TRF) and chronic inflammatory demyelinating polyneuropathy with acute onset (A-CIDP) is difficult but important because prognosis and treatment strategy largely differ.

Results: The first TRF in the GBS-T
range 10–54 days) from onset of
second TRF and none had more TR
severely affected than patients wit
nial nerve dysfunction, and tended t
GBS-TRF patients were severely a
compared to the GBS group without

Although for most individual electrophysiologic variables there was no statistical significance, the A-CIDP group displayed a trend toward a more CIDP-like electrophysiologic investigation.[26] Signs of axonal damage (denervation potentials) are rare in the A-CIDP group, while more than half of the patients with GBS-TRF showed signs of axonal damage in the acute phase. Probably the numbers of patients per group were too small to reach statistical significance.

Treatment-related fluctuation

Circa il 10% dei pazienti affetti da GBS che sono stati trattati con IVIg o con plasmaferesi peggiorano dopo un iniziale miglioramento o stabilizzazione clinica

A-CIDP

Se pazienti precedentemente diagnosticati come GBS hanno tre o più ricadute cliniche entro otto settimane dall'esordio della malattia.

GBS «classica» e forme «localizzate»

Classic GBS	Weakness* and areflexia/ hyporeflexia in all four limbs	Weakness usually starts in the legs and ascends but may start in the arms Weakness may be mild, moderate or complete paralysis Cranial-nerve-innervated muscles or respiratory muscles may be involved Muscle stretch reflexes may be normal or exaggerated in 10% of cases
Pharyngeal–cervical–brachial weakness	Oropharyngeal, neck and arm weakness*‡ and arm areflexia/ hyporeflexia Absence of leg weakness	Absence of certain features indicates incomplete pharyngeal–cervical–brachial weakness: patients without arm and neck weakness have 'acute oropharyngeal palsy'; patients without pharyngeal palsy have 'acute cervicobrachial weakness' Some leg weakness may be present, but oropharyngeal, neck and arm weakness should be more prominent Presence of additional features indicates overlap with other GBS variants: ataxia with ophthalmoplegia suggests overlap with MFS; ataxia without ophthalmoplegia suggests overlap with acute ataxic neuropathy; ataxia, ophthalmoplegia and disturbed consciousness suggests overlap with BBE
Paraparetic GBS	Leg weakness* and leg areflexia/ hyporeflexia Absence of arm weakness	Typically, bladder function is normal and there is no well-defined sensory level
Bifacial weakness with paraesthesias	Facial weakness* and limb areflexia/hyporeflexia Absence of ophthalmoplegia, ataxia and limb weakness	In some patients, limb paraesthesias may be absent and muscle stretch reflexes may be normal

Wakerley R, Uncini A. *Nat Rev. Neurol.* 2014

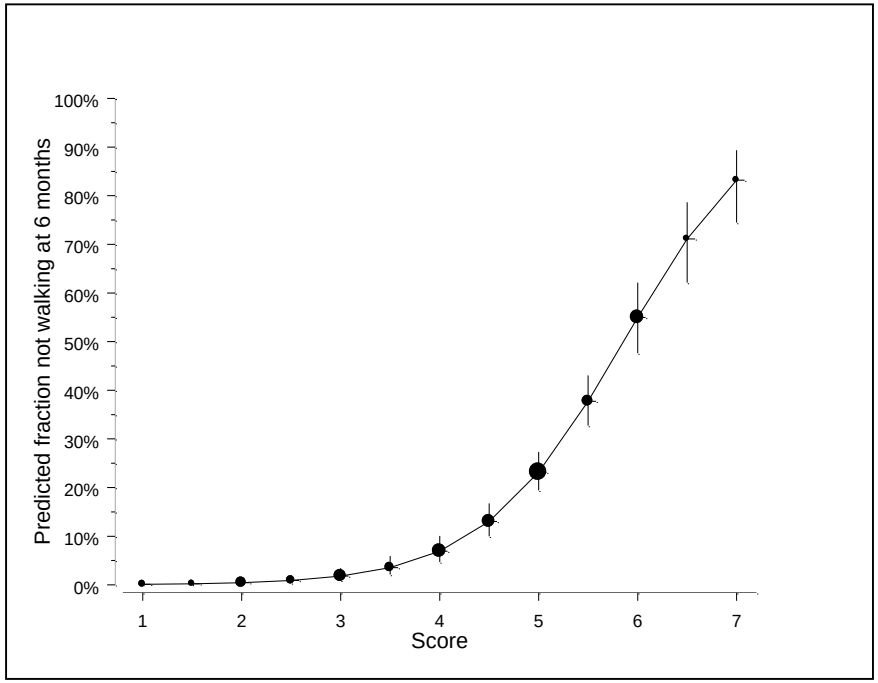
International GBS Outcome Study (IGOS)

A prospective INC study on clinical and biological predictors of disease course and outcome in GBS

Erasmus GBS Outcome Scale (EGOS), sum of scores of 3 clinical features:

- **Age**
  - 0 if <40 years
  - 0.5 if 40-60 years
  - 1 if >60 years
- **Preceding diarrhoea**
  - 0 if absent
  - 1 if present
- **GBS dis. score at 2 weeks**
  - 1 if GBS score is 0 or 1
  - 2 if GBS score is 2
  - 3 if GBS score is 3
  - 4 if GBS score is 4
  - 5 if GBS score is 5

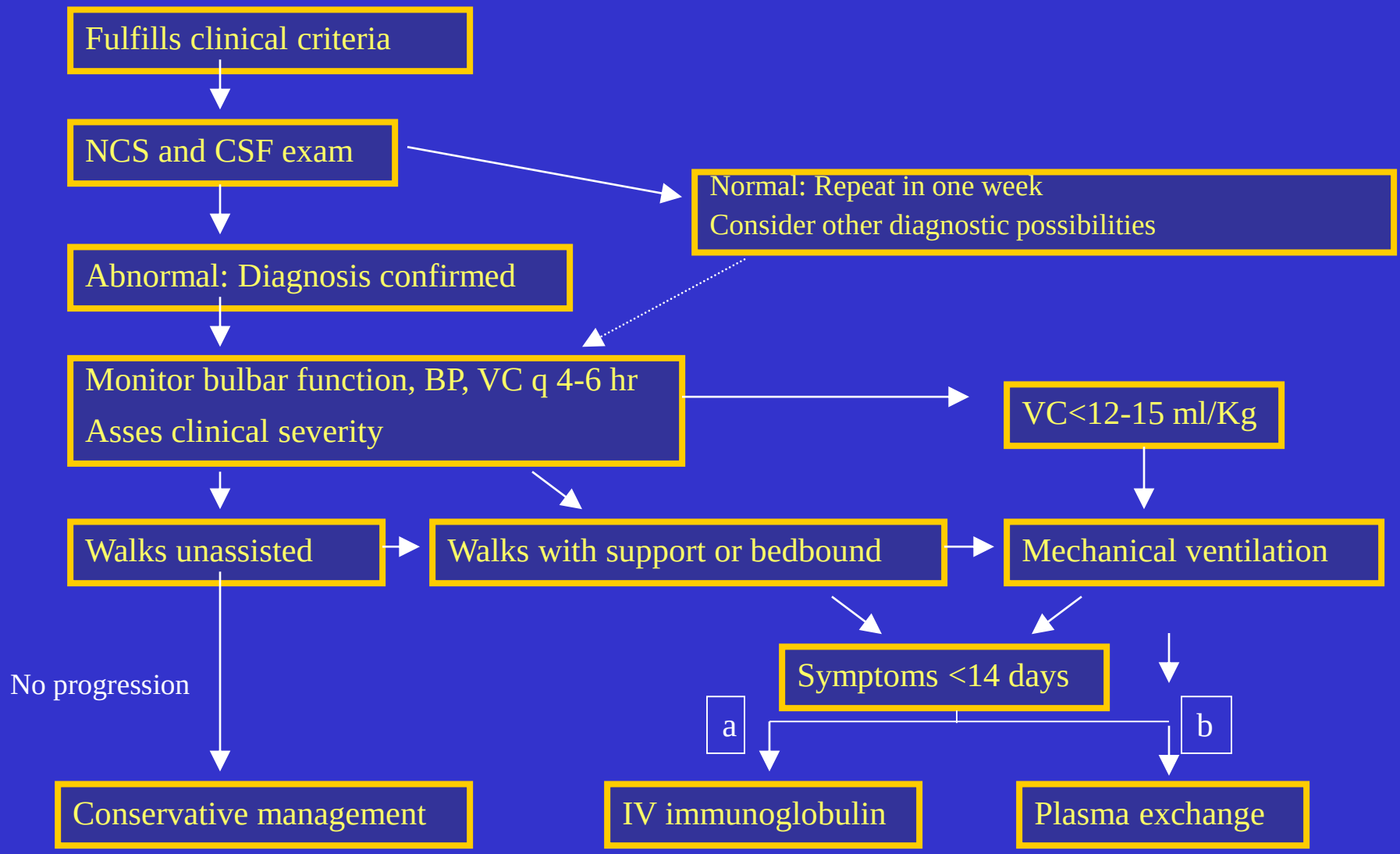
Guillain-Barré Syndrome Disability Scale (Hughes)	
0	Healthy
1	Minor symptoms or signs of neuropathy but capable of manual work/capable of running
2	Able to walk without support of a stick (5m across an open space) but incapable of manual work/running
3	Able to walk with a stick, appliance or support (5m across an open space)
4	Confined to bed or chair bound
5	Requiring assisted ventilation (for any part of the day or night)
6	Death



van Koningsveld R et al, Lancet Neurol 2007

Slide: courtesy of Prof. E. Nobile Orazio

Decision-making pathway in the management of GBS. Bosh E.P. and Smith B.E., Disorders of Peripheral Nerves, in Neurology in Clinical Practice, eds Bradley W.G. et al, 2000



ECULIZUMAB and GBS

doi:10.1093/brain/awm316 *Brain* (2008), **131**, 1197–1208

Eculizumab prevents anti-ganglioside antibody-mediated neuropathy in a murine model

Susan K. Halstead,[1,*] Femke M. P. Zitman,[2,3,*] Peter D. Humphreys,[1] Kay Greenshields,[1] Jan J. Verschuuren,[2] Bart C. Jacobs,[4] Russell P. Rother,[5] Jaap J. Plomp[2,3] and Hugh J. Willison[1]

body pre-incubated NMJs *in vitro* when using normal human serum (NHS) as a complement source. In a novel *in vivo* mouse model of MFS generated through intraperitoneal injection of anti-GQ1b antibody and NHS, mice developed respiratory paralysis due to transmission block at diaphragm NMJs, resulting from anti-GQ1b antibody binding and complement activation. Intravenous injection of eculizumab effectively prevented respiratory paralysis and associated functional and morphological hallmarks of terminal motor neuropathy. We show that eculizumab protects against complement-mediated damage in murine MFS, providing the rationale for undertaking clinical trials in this disease and other antibody-mediated neuropathies in which complement activation is believed to be involved.

ECULIZUMAB and GBS

2 Trials (Inglese/Giapponese)

Inhibition of Complement in Guillain–Barrè Syndrome: The ICA-GBS Study
Davidson AI et al. J Peripher Nerv Syst. 2016

Safety and efficacy of eculizumab in Guillain-Barré syndrome: a multicentre, double-blind, randomised phase 2 trial

*Sonoko Misawa, Satoshi Kuwabara, Yasunori Sato, Nobuko Yamaguchi, Kengo Nagashima, Kanako Katayama, Yukari Sekiguchi, Yuta Iwai, Hiroshi Amino, Tomoki Suichi, Takanori Yokota, Yoichiro Nishida, Tadashi Kanouchi, Nobuo Kohara, Michi Kawamoto, Junko Ishii, Motoi Kuwahara, Hidekazu Suzuki, Koichi Hirata, Norito Kokubun, Ray Masuda, Juntaro Kaneko, Ichiro Yabe, Hidenao Sasaki, Ken-ichi Kaida, Hiroshi Takazaki, Norihiro Suzuki, Shigeaki Suzuki, Hiroyuki Nodera, Naoko Matsui, Shoji Tsuji, Haruki Koike, Ryo Yamasaki, Susumu Kusunoki, for the Japanese Eculizumab Trial for GBS (JET-GBS) Study Group****

Lancet Neurol 2018; 17: 519–29

ECULIZUMAB and GBS

Pazienti e metodi

- Entro 2 settimane da esordio dei sintomi
- GBS disability scale ≥ 3

IVIg 2g/Kg + Eculizumab 900 mg (week 1,2,3,4)

vs

IVIg 2g/Kg + Placebo

(1° somministrazione almeno 1h dopo inizio IVIg)

Endpoint: miglioramento > 1 GBS disability scale a 4 sett

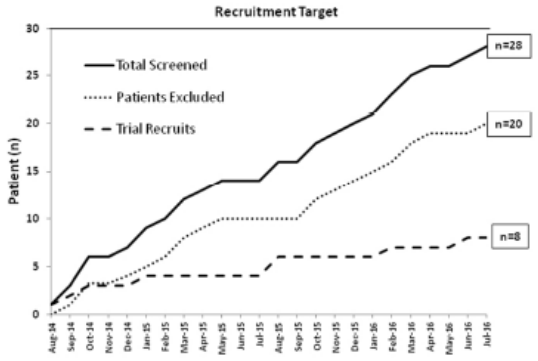
tollerabilità

Davidson et al. JPNS 2016

ECULIZUMAB and GBS

Trial Inglese

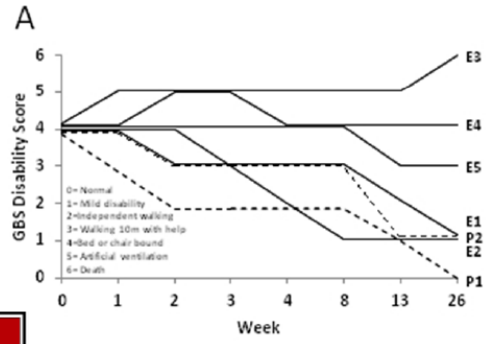
Risultati



28 pz pre-screening
20 non arruolati
8 esclusi per scarsa compliance o precedenti infezioni
12: non hanno firmato consenso

5 ricevuto Eculizumab

2/5 <u>non</u> hanno completato lo schema terapeutico,
uno per sepsi/decesso e l'altro per infez. vie respiratorie



2 pz placebo
2 pz Eculizumab

→ Migliorati ≥ 1 GBS-DS

Davidson et al. JPNS 2016

ECULIZUMAB and GBS

Pazienti

23 Eculizumab
11 placebo

Risultati

Pz in grado di deambulare autonomamente a 4 settimane
- 61% in Eculizumab
- 45% in placebo

No analisi statistica

Effetti collaterali

in tutti i pz in Eculizumab

	Eculizumab (n=23)	Placebo (n=11)
Any event	23 (100%)	11 (100%)
Adverse events affecting ≥10% patients in either group		
Insomnia	6 (26%)	1 (9%)
Headache	4 (17%)	2 (18%)
Nasopharyngitis	4 (17%)	0
Constipation	4 (17%)	2 (18%)
Rash	4 (17%)	0
Myalgia	3 (13%)	1 (9%)
Nausea	3 (13%)	1 (9%)
Dyshidrotic eczema	3 (13%)	0
Oral mucositis	3 (13%)	0
Hepatic function abnormal	4 (17%)	2 (18%)
Neutrophil count decrease	3 (13%)	1 (9%)
Hyponatraemia	3 (13%)	0
Haematuria	2 (9%)	2 (18%)
Serious adverse events	2 (9%)	1 (9%)
Anaphylaxis	1 (4%)	0
Intracranial haemorrhage	1 (4%)*	0
Brain abscess	1 (4%)*	0
Depression	0	1 (9%)

Misawa et al. Lancet Neurol 2018

ECULIZUMAB and GBS

Perplessità

- Ciprofloxacina 400 mg x os/500 mg ev /sett x 8-10 sett

  (profilassi x meningococco)

- Mancato consenso da parte del pz

- Eventi avversi infettivi importanti
- Risultati insoddisfacenti (placebo = Eculizumab nel primo studio no significatività nel secondo)

- Eculizumab attivo solo AMAN (gangliosidi ++)?

- 3% Giapponesi hanno mutazione C5, resistenti all'Eculizumab

Classification

- Acute

✓ Guillain Barrè syndrome (GBS) & variants

- Chronic

✓ Chronic inflammatory demyelinating polyneuropathy (CIDP) & variants

✓ Multifocal Motor Neuropathy (MMN)

✓ Neuropathies associated with monoclonal gammopathies

✓ Paraneoplastic neuropathies

✓ Vasculitic neuropathies & neuropathies associated with systemic autoimmune disorders (AR, LES, Sjogren etc.)

Chronic Inflammatory Demyelinating Neuropathy: Typical

Table 1 Electrodiagnostic criteria

(1) Definite: at least one of the following
(a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
(b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or
(c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP < 80% of LLN values), or
(d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
(e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve, or
(f) Abnormal temporal dispersion (> 30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or
(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms)[b] + ≥1 other demyelinating parameter[a] in ≥1 other nerve

(2) Probable
≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter[a] in ≥1 other nerve

(3) Possible
As in (1) but in only one nerve

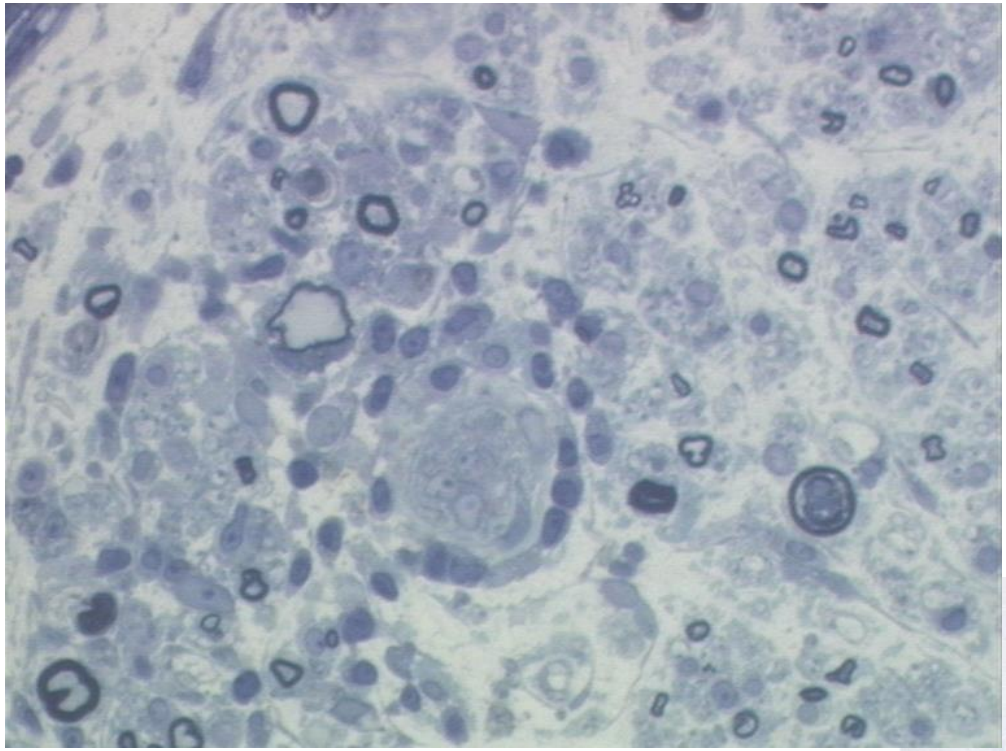
European Journal of Neurology 2010, **17:** 356–363
EFNS TASK FORCE/CME ARTICLE

Chronic Inflammatory Demyelinating Neuropathy: Typical

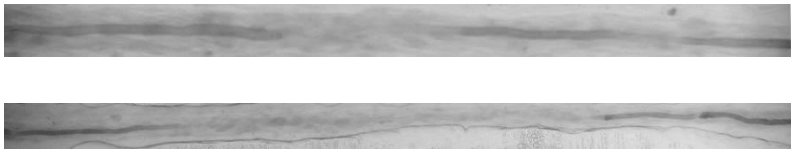
- Elevated CSF protein with leukocyte count <10/mm3 (level A recommendation)
- MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
- Abnormal sensory electrophysiology in at least one nerve (good practice points):
- Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or Conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal); or Delayed somatosensory evoked potentials without central nervous system disease
- Objective clinical improvement following immunomodulatory treatment (level A recommendation)
- Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (good practice point)

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

CIDP: TYPICAL

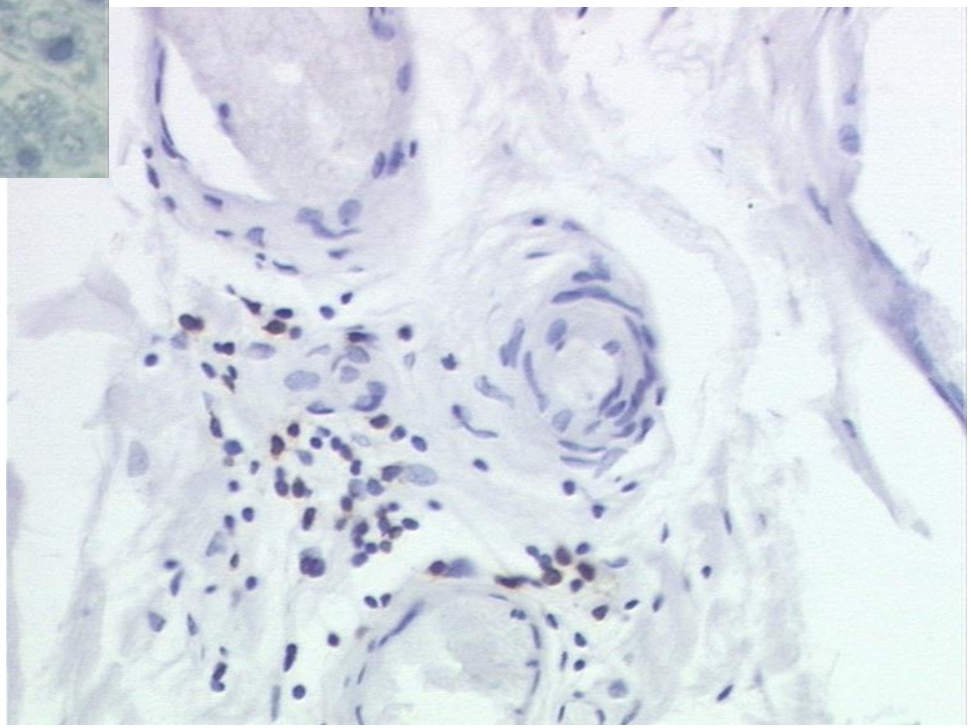


Toluidine blue



Teased fibers

Immunohistochemistry

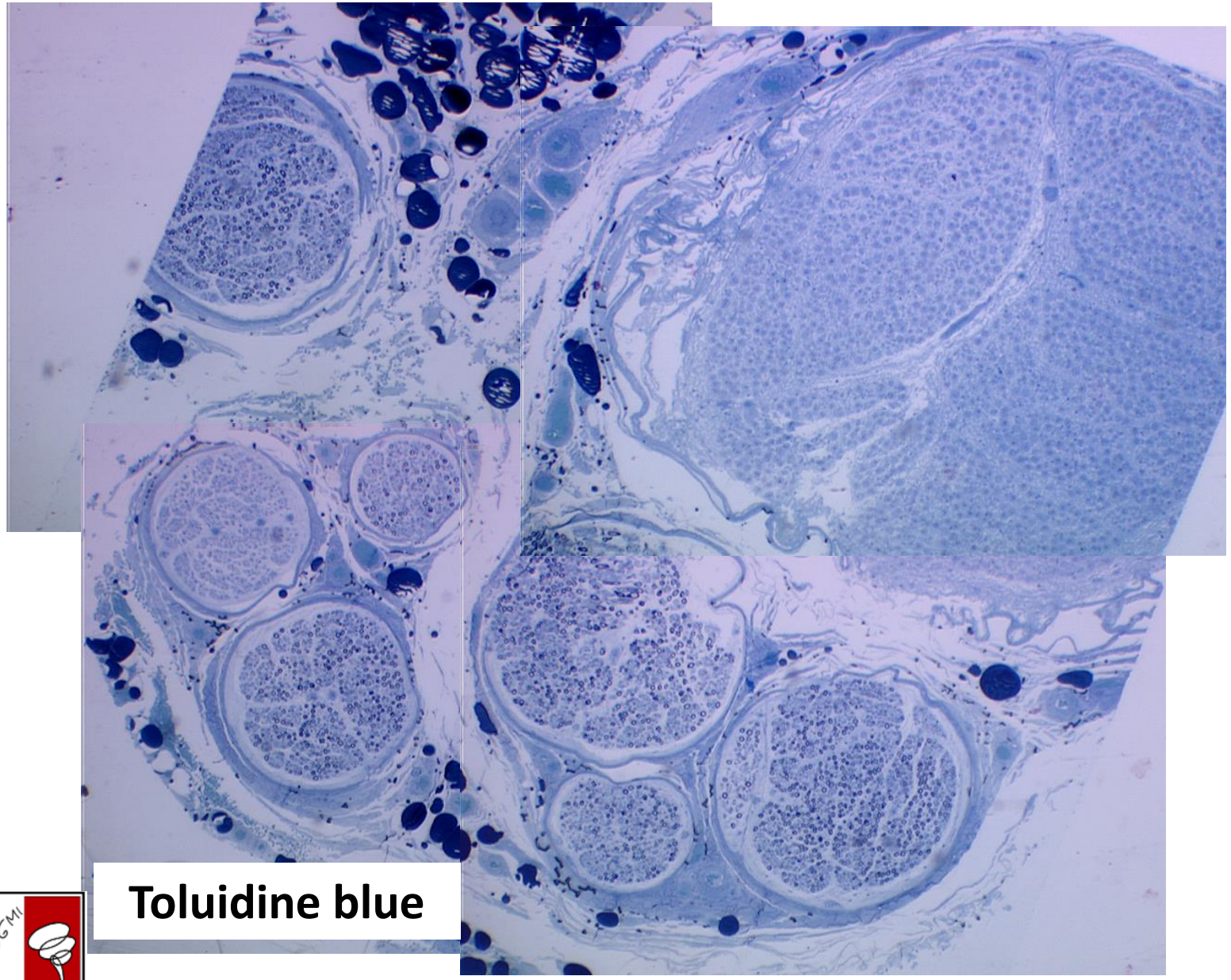


Chronic Inflammatory Demyelinating Neuropathy: atypical

- Predominantly distal (distal acquired demyelinating symmetric, DADS)
- Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis Sumner syndrome]
- Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
- Pure motor (Sabatelli et al., J Neurol 2001)
- Pure sensory (Oh et al., JNNP 1992) (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

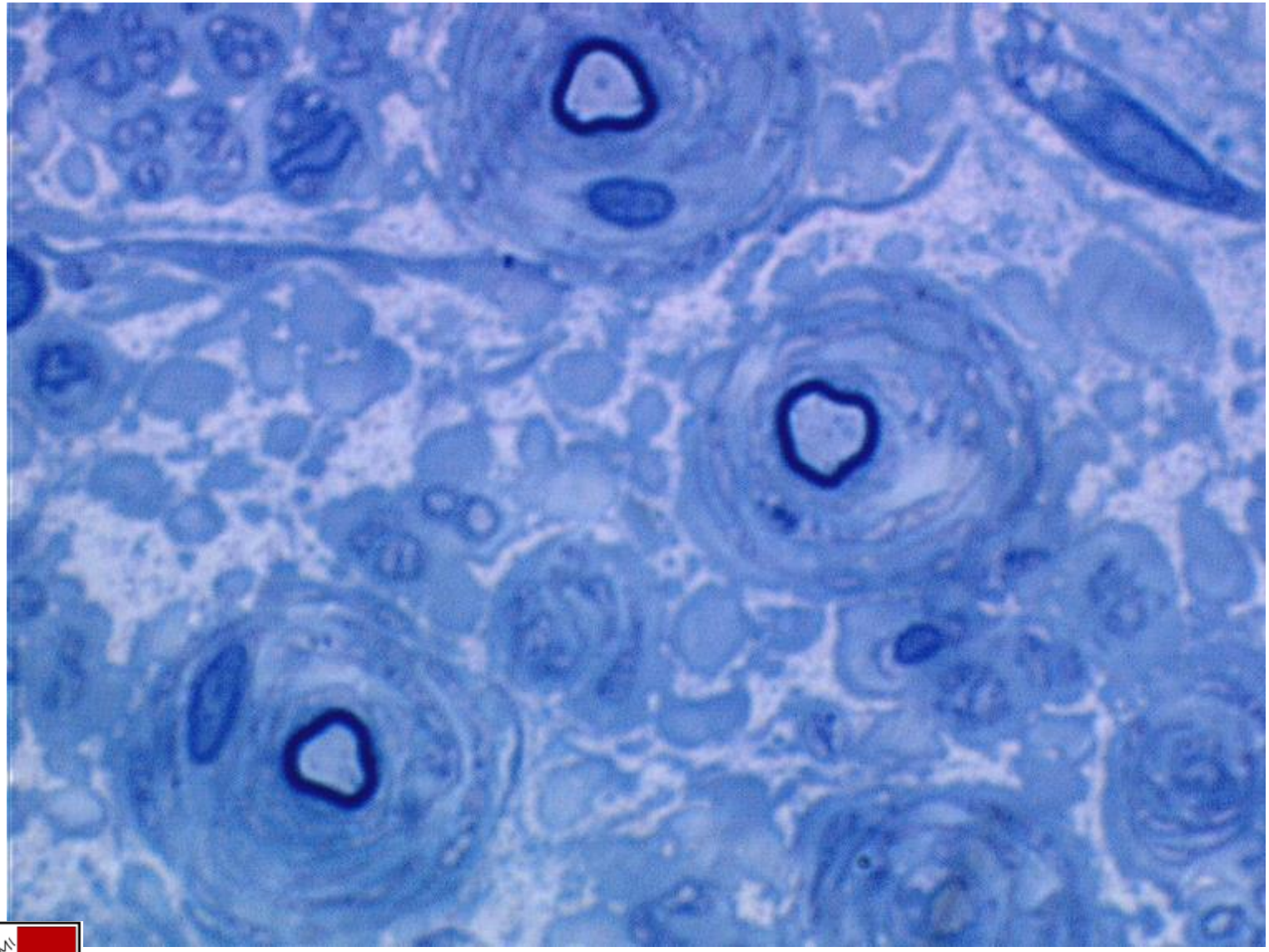
European Journal of Neurology 2010, **17:** 356–363
EFNS TASK FORCE/CME ARTICLE

CIDP: LEWIS SUMNER VARIANT



Toluidine blue

CIDP: LEWIS SUMNER VARIANT



Neuromuscular
Research paper

Atypical CIDP: diagnostic criteria, progression and treatment response. Data from the Italian CIDP Database

Pietro Emiliano Doneddu[1], Dario Cocito[2], Fiore Manganelli[3], Raffaella Fazio[4], Chiara Briani[5], Massimiliano Filosto[6], Luana Benedetti[7], Anna Mazzeo[8], Girolama Alessandra Marfia[9], Andrea Cortese[10], Brigida Fierro[11], Stefano Jann[12], Ettore Beghi[13], Angelo Maurizio Clerici[14], Marinella Carpo[15], Angelo Schenone[16], Marco Luigetti[17], Giuseppe Lauria[18, 19], Giovanni Antonini[20], Tiziana Rosso[21], Gabriele Siciliano[22], Guido Cavaletti[23], Giuseppe Liberatore[1], Lucio Santoro[3], Erdita Peci[2], Stefano Tronci[4], Marta Ruiz[5], Stefano Cotti Piccinelli[6], Antonio Toscano[8], Giorgia Mataluni[9], Laura Piccolo[10], Giuseppe Cosentino[11], Mario Sabatelli[17, 24], Eduardo Nobile-Orazio[1, 25] on behalf of the Italian CIDP Database study group

JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY, 2018

- 460 patients included in a database of Italian CIDP patients

Conclusions

The proportion of patients with atypical CIDP varies during the disease course. DADS and LSS have a less frequent response to intravenous immunoglobulin compared to typical CIDP, raising the possibility of a different underlying pathogenetic mechanism.

CIDP,

- Purely motor and sensory CIDP: a similar treatment response.

Donedddu et al, 2018

CONVEGNO REGIONALE SIN /SNO
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Ivrea, 6-7 dicembre 2019
Università infermieristica di Ivrea

La terapia

delle neuropatie disimmuni

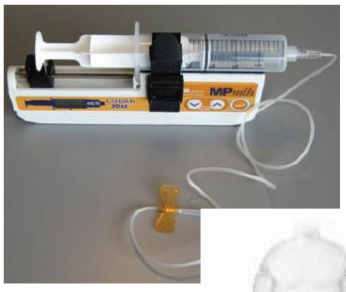
oltre gli steroidi, IVIg, PEX

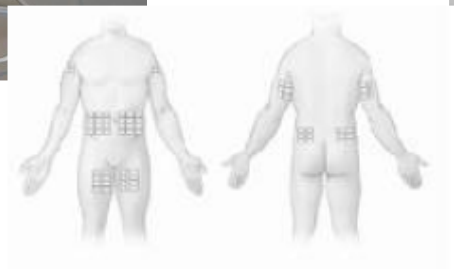
Donedddu et al, 2018

ScIg (Immunoglobuline s.c)

1 Flacone 10 ml = 1.6 gr

Non più di 20 ml x sito





Vantaggi rispetto IVIg

- **Trattamento di dimostrata eguale efficacia** *Koller H, J neurol 2006*
- **Evita le ricadute cliniche** *Lee DH, Muscle Nerve 2008*
- **Riduce ospedalizzazione con riduzione costi** *Lee DH, Muscle Nerve 2008*
- **Riduzione rischio di eventi avversi maggiori** *Eftimov F, JPNS 2009*
- **Migliora qualità della vita del paziente** *Lee DH, Muscle Nerve 2008*

Si ringrazia: Dr.ssa Benedetti

Immunomodulanti di nuova generazione (Ab monoclonali)

mAb	Meccanismo D'azione	Indicazioni	Tipo PN	Razionale	Dosaggio
Rituximab	Anti-CD20	NHL AR	Anti-MAG MMN CIDP	Ab mediata Ab mediata ?	375 mg/m^2/sett x 4 sett 1000mg/sett x 2 sett
Alemtuzumab	Anti-CD52	B-LLC	CIDP	+++ T attivati	30 mg/die x 5 gg e.v
Eculizumab	Anti-C5		MMN GBS	Ab anti-GM1 Azione complemento mediata	600mg/sett x 4 sett

RITUXIMAB e PN anti-MAG

Studi prospettici non controllati

	Steck Muscle&Nerve 2003	Benedetti JPNS 2007	Benedetti PNS Utah 2007	Delmont J Neurol 2011
N° pz	9	13	26	6
Scale cliniche	NDS, NSS	INCAT, MRC, ISS	INCAT, MRC, ISS	ISS, ONLS
% pz migliorati	66%	62%	62%	66%
Diminuz IgM	58%	39%	33%	44%
Diminuz Ab anti-MAG	52%	87%	81%	87%
sAE	no	no	no	no

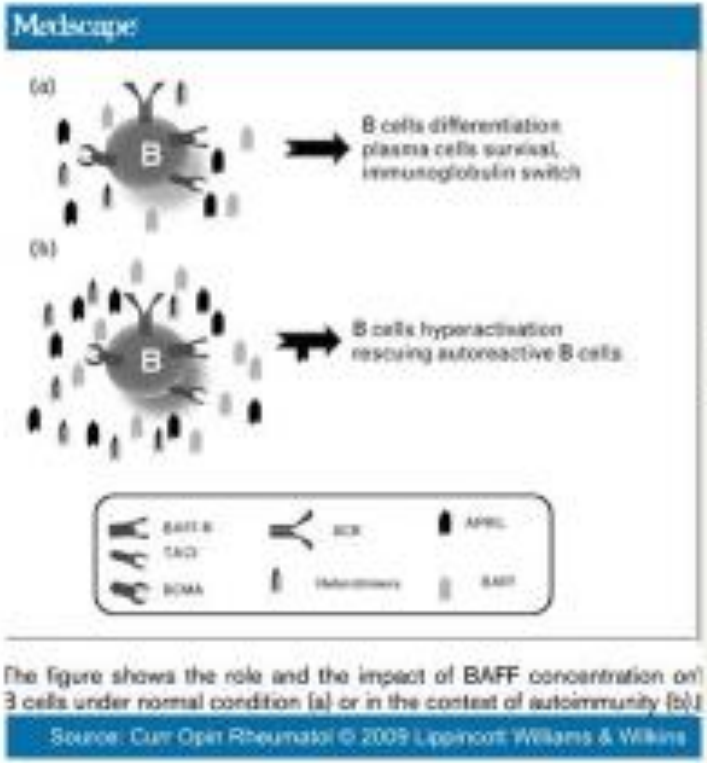
Follow-up 9-12; Deplezione linf B CD19+ fino al 9° mese;
Tempo risposta anticorpale 3 mesi, clinica 6-8 mesi

RECENTI CONFERME

Dalakas M et al. Ann Neurol 2009

Gazzola et al. J neurol Scie 2017

Si ringrazia: Dr.ssa Benedetti



The figure shows the role and the impact of BAFF concentration on
B cells under normal condition (a) or in the context of autoimmunity (b).

Source: Curr Opin Rheumatol © 2009 Lippincott Williams & Wilkins

Rituximab

↓

Deplezione linfociti B

↓

Aumento BAFF

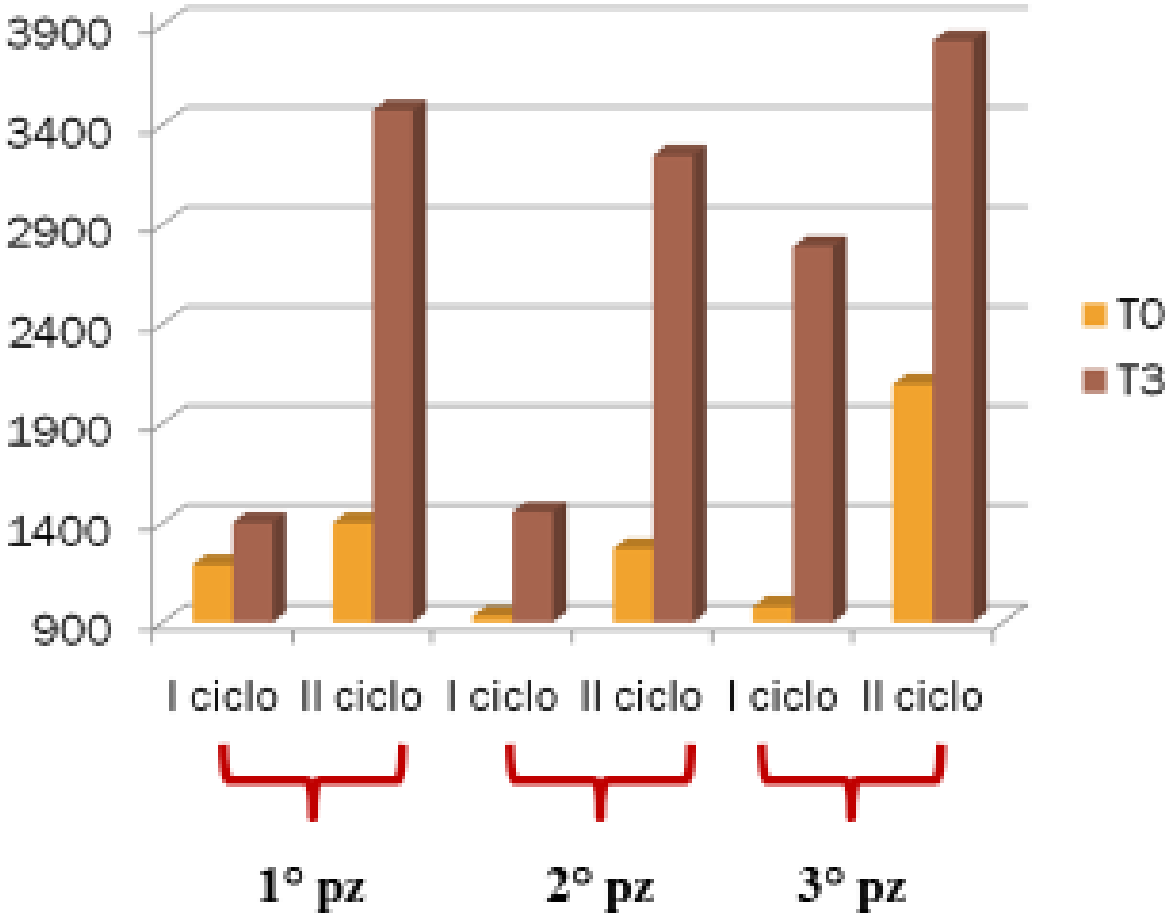
↓

Promuove differenziazione di

Short-lived plasmacells → Long-lived plasmacells

Si ringrazia: Dr.ssa Benedetti

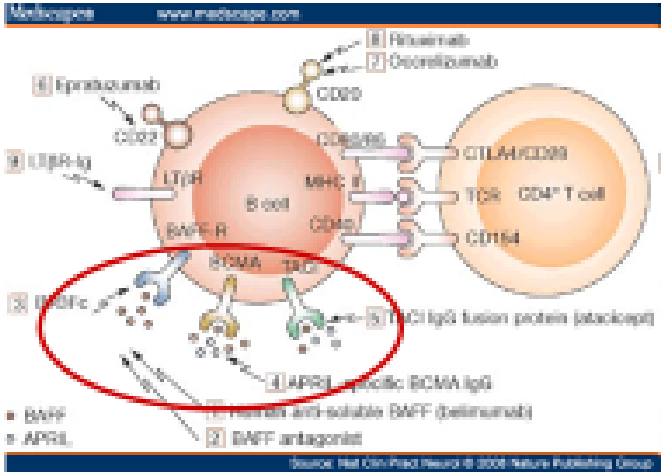
BAFF dopo I e II ciclo



Si ringrazia: Dr.ssa Benedetti

SPUNTI PER STUDI FUTURI.....

"Therapies targeting BAFF are attractive because they have the potential to halt the clonal expansion of B cells and suppress the autoimmune process"



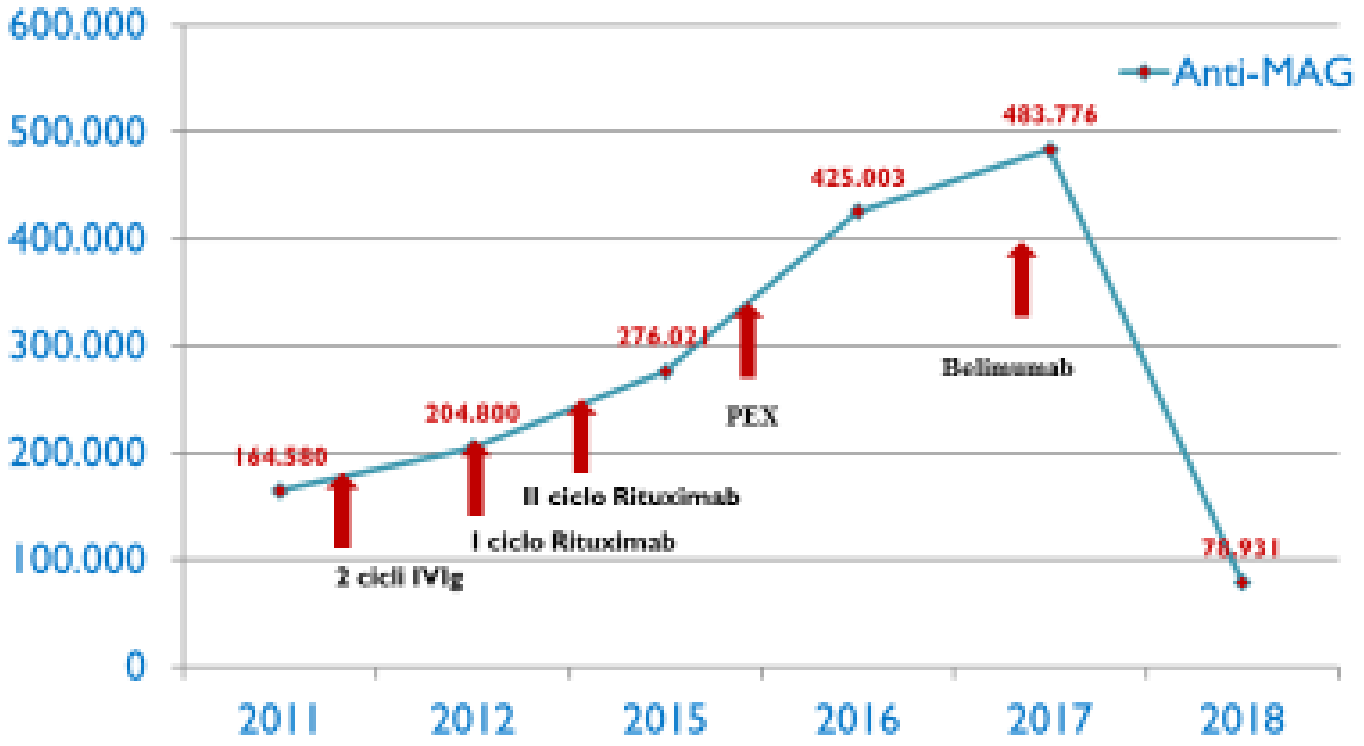
"Theoretically, a more prolonged effect on B cell functions and autoantibodies may be achieved by combining rituximab with anti-BAFF agents, which reduce the survival of BAFF-dependent, Ig- producing, long-lived plasma cells"

Inhibition of B cell functions. Implications for neurology

Dalakas M. Neurology 2008;70:2252-2260

Si ringrazia: Dr.ssa Benedetti

Belimumab



Dati preliminari

Si ringrazia: Dr.ssa Benedetti

RITUXIMAB e CIDP

	Nostri dati (13pz) (Benedetti et al. 2011	Letteratura (6pz)
% risposta	NR 25% R 75%	R 66%
Mal. Ematol. associata	NR 1/3 R 7/9	NR 0/2 R 3/4
Durata PN (media)	NR 10 aa R 3 aa	NR 5 aa R 1aa
Tempi di risposta (media)	2,6 mesi	2,7 mesi
Follow-up (senza ricadute)	≥ 1 aa	≥ 1 aa

Si ringrazia: Dr.ssa Benedetti

Neurology®

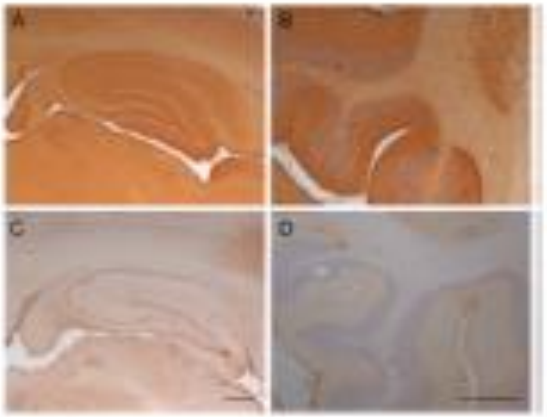
Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg

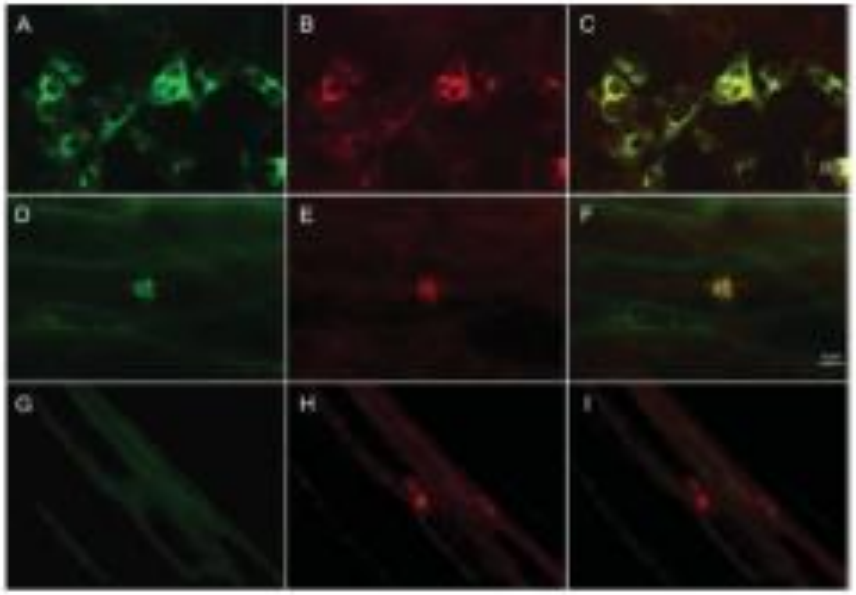
Luis Querol, Gisela Nogales-Gadea, Ricardo Rojas-Garcia, et al.

Neurology 2014;82;879-886 Published Online before print February 12, 2014

CIDP con Ab antiNF155 (4/53)

- Fenotipo severo
- Non rispondono IVIg
- Tremore disabilitante





Si ringrazia: Dr.ssa Benedetti

Movement Disorders
CLINICAL PRACTICE

LETTERS: NEW OBSERVATIONS

Remarkable Rituximab Response on Tremor Related to Acute-Onset Chronic Inflammatory Demyelinating Polyradiculoneuropathy in an Antineurofascin155 Immunoglobulin G4–Seropositive Patient

Chiara Demichelis, MD,[1,] Diego Franciotta, MD,[2] Andrea Cortese, MD, PhD,[2] Ilaria Callegari, MD,[2] Carlo Serrati, MD,[3] Gian Luigi Mancardi, MD,[1] Angelo Schenone, MD,[1] Alessandro Leonardi, MD,[4] Luana Benedetti, MD, PhD[1]*

MOVEMENT DISORDERS CLINICAL PRACTICE 2018; 5(5): 559–560. ‹

EVALUATION OF PATIENTS WITH REFRACTORY CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

ARTEM KAPLAN, MD, PhD, and THOMAS H. BRANNAGAN, III, MD *Muscle Nerve* **55**: 476–482, 2017

Table 3. Alternate diagnoses

	Alt dx
ALS	20%
Idiopathic neuropathy	15%
Small fiber neuropathy	10%
MMN	10%
CANOMAD	5%
HNPP	5%
POEMS	5%
Anti-MAG neuropathy	5%
TTR amyloid neuropathy	5%
Inclusion body myositis	5%
Fibromyalgia/CTS	5%
Small fiber neuropathy/CTS	5%
Spinocerebellar atrophy	5%

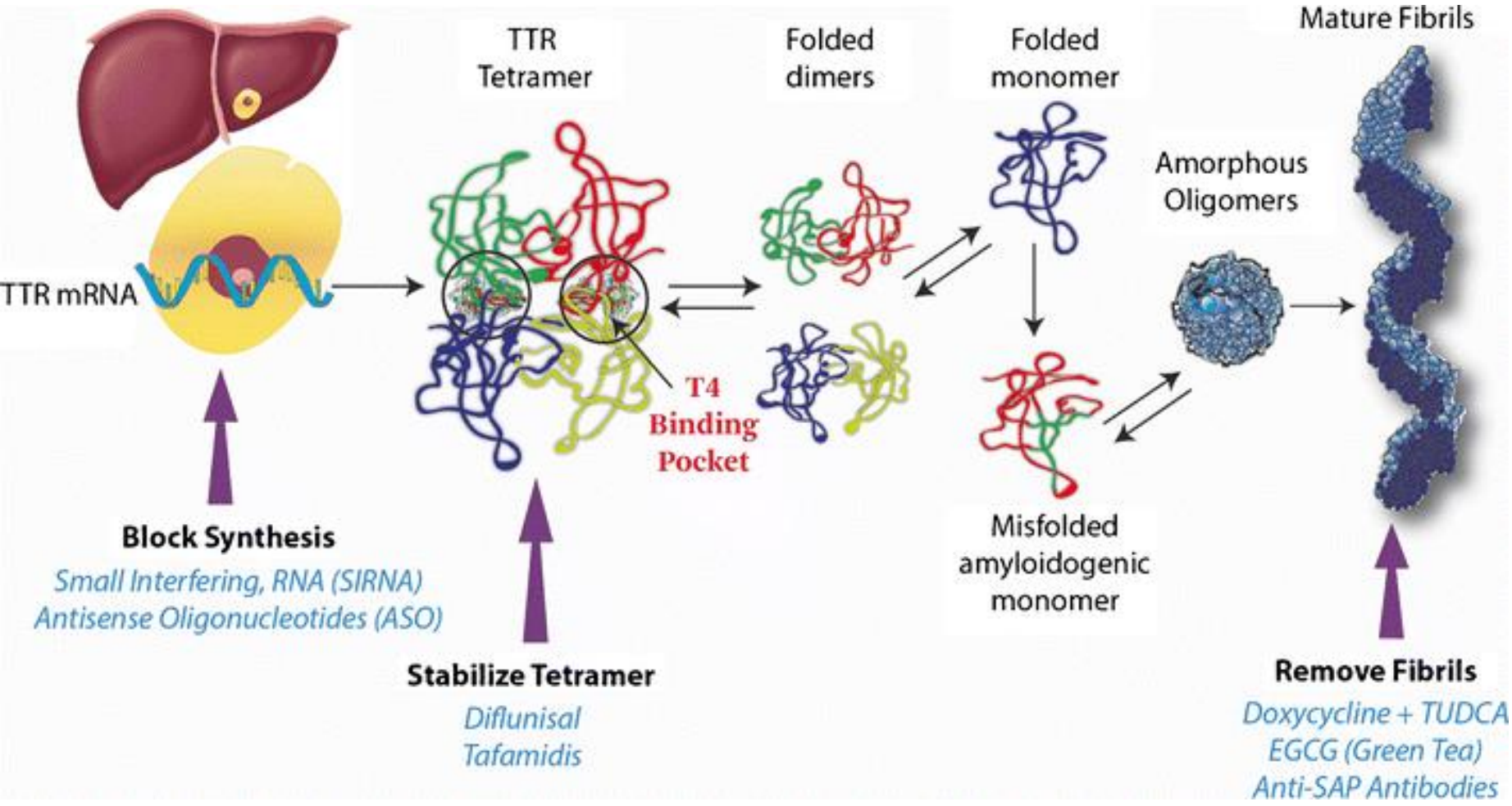
Alt dx, patients with alternate diagnosis; TTR, transthyretin.

Variable presentations of TTR-related familial amyloid polyneuropathy in seventeen patients

Manuel Cappellari[1], Tiziana Cavallaro[1], Moreno Ferrarini[1], Ilaria Cabrini[1], Federica Taioli[1], Sergio Ferrari[1], Giampaolo Merlini[2], Laura Obici[2], Chiara Briani[3], and Gian Maria Fabrizi[1]

Journal of the Peripheral Nervous System 16:119–129 (2011)

Abstract Autosomal-dominant transthyretin (TTR)-related amyloidosis usually manifests in the second to fourth decade with a length-dependent axonal neuropathy with prominent involvement of the small fibers and multi-organ systemic failure. We retrospectively analyzed seventeen probands, including thirteen apparently isolated cases, carrying eight mutations of *TTR* gene (age of onset = 60.4 ± 13.5 years). Thirteen patients were initially un/misdiagnosed; interval from onset to definite diagnosis was 3.3 ± 2.3 years. Inaugural syndromes were a length-dependent motor-sensory neuropathy in seven cases, a sensory neuropathy in four, an isolated carpal tunnel syndrome in three, a pure dysautonomia in two, and a painful neuropathy in one. Atypical presentations included demyelinating nerve conduction changes with increased cerebrospinal fluid proteins resembling chronic inflammatory demyelinating polyradiculoneuropathy and a predominantly motor involvement resembling a motor neuron disorder. Misleading findings also included amyloid-negative abdominal fat aspirate/biopsy, biclonal gammopathy, and hepatitis C virus (HCV) seropositivity. Sural nerve biopsy detected amyloid deposits in thirteen of fifteen patients, including one case with a previous negative biopsy. TTR-immunohistochemistry was necessary to complete the diagnosis of primary amyloidosis light chain in a patient with biclonal gammopathy. A recurrent p.Phe64Leu mutation manifested in the seventh decade with painful motor-sensory polyneuropathy, dysautonomia, bulbar palsies, and fasciculations. *TTR* should be tested in a wide clinical spectrum of cryptogenetic, progressive, and motor-sensory neuropathies even manifesting with a very late onset.


TTR mRNA
TTR Tetramer
Folded dimers
Folded monomer
Amorphous Oligomers
Mature Fibrils
T4 Binding Pocket
Misfolded amyloidogenic monomer
Block Synthesis
Small Interfering, RNA (SIRNA)
Antisense Oligonucleotides (ASO)
Stabilize Tetramer
Diflunisal
Tafamidis
Remove Fibrils
Doxycycline + TUDCA
EGCG (Green Tea)
Anti-SAP Antibodies

Neuropatie Immunomediate

Conclusioni

- Classificazione e clinica
- Varianti di malattia e criteri diagnostici
- Forme «atipiche»
- Trattamento
- Forme «refrattarie»

GRAZIE PER L'ATTENZIONE

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