09
GIUGNO
2017

CREMONA
AUDITORIUM
Museo del Violino
Piazza Marconi

DIAGNOSI DIFFERENZIALE DELLE
MALATTIE DEL SISTEMA NERVOSO CENTRALE

DIAGNOSI DIFFERENZIALE DELLE
MALATTIE DEL SISTEMA NERVOSO PERIFERICO

LE PATOLOGIE
DELLA MIELINA:
GLI STRUMENTI
PER LA DIAGNOSI
DIFFERENZIALE

E se sono coinvolti entrambi?

Enrico Marchioni
Istituto Neurologico Nazionale
IRCCS "C. Mondino", Pavia

indice

- Background
- Criteri classificativi
- Descrizione di un caso

Combined central and peripheral demyelination

Brain (1987), 110, 53–76

6 casi di SM associata a CIDP

CHRONIC DEMYELINATING PERIPHERAL NEUROPATHY ASSOCIATED WITH MULTIFOCAL CENTRAL NERVOUS SYSTEM DEMYELINATION

by P. K. THOMAS, R. W. H. WALKER, P. RUDGE, J. A. MORGAN-HUGHES, R. H. M. KING, J. M. JACOBS, K. R. MILLS, I. E. C. ORMEROD, N. M. F. MURRAY *and* W. I. McDONALD

(*From the National Hospital for Nervous Diseases and Institute of Neurology, Queen Square, and the Royal Free Hospital School of Medicine, London*)

DOI: 10.1093/brain/awg233 Advanced Access publication July 7, 2003 *Brain* (2003), **126,** 2279–2290

Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain–Barré syndrome

Masaaki Odaka,[1] Nobuhiro Yuki,[1] Mitsunori Yamada,[2] Michiaki Koga,[1] Toshihiko Takemi,[3] Koichi Hirata[1] and Satoshi Kuwabara[4]

Combined syndrome: 60%
MRI brain abnormalities: 30%
Anti GQ1b: 66%

Combined central and peripheral demyelination

Research paper

Relapsing demyelinating disease affecting both the central and peripheral nervous systems

H Zéphir,[1] T Stojkovic,[1] P Latour,[2] A Lacour,[1] J de Seze,[1] O Outteryck,[1] C-A Maurage,[3] C Monpeurt,[1] P Chatelet,[4] E Ovelacq,[1] P Vermersch[1]

Table 1 Clinical history of five patients with relapsing demyelinating CNS and PNS disease

	Patient No 1	Patient No 2	Patient No 3	Patient No 4	Patient No 5
Age at onset of neurological symptoms (y)	21	38	29	65	26
Initial symptoms	CNS	CNS	CNS	CNS	CNS
Initial CNS signs	1989	2002	1997	1995	1982
Initial PNS signs	2001 (areflexia)	2005 (ataxia)	2002 (pain and paraesthesia in lower limbs)	1997 (areflexia)	2005 (areflexia)
MS diagnosis	1989	2002	2005	1995	1984
PRN diagnosis	2003	2005	2002	1996	
Brain MRI lesions	+	+	+	+	+
Spinal cord MRI	+	+ (gadolinium enhanced roots on MRI and myelitis)	ND	+	ND
Nerve biopsy	ND	Inflammation and demyelination	ND	Inflammation and demyelination	ND
Treatment before PNS involvement	No	IFNβ1a	No	Corticosteroids	IFNβ1a
Deep tendon reflexes before testing for PNS involvement	?	Still present in 2005	Still present in 2002	?	Present in 1999

CNS, central nervous system; IFN, interferon; MS, multiple sclerosis; ND, not determined; PNS, peripheral nervous system; PRN, polyradiculoneuropathy.

J Neurol Neurosurg Psychiatry 2008;**79**:1032–1039.

Autoimmunity Reviews 11 (2012) 196–202

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Autoimmune disorders affecting both the central and peripheral nervous system

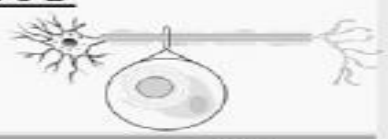
Christoph Kamm, Uwe K. Zettl *

CNS

Axon
Myelin
(Oligodendrocytes)

Lipids (%)	**60**
Cholesterol	30
Glycolipids	25
Cerebrosides	20
Sulfatides	5
Gangliosides	<1
Phospholipids (PL)	45
Ethanolamine PL	15
Choline PL	10
Serine PL	10
Inositol PL	<1
Sphingomyelin	10
Proteins (%)	**40**
PLP *Proteolipidprotein*	>50
MBP *Myelin basic protein*	15
MAG *Myelin-associated glycoprotein*	5
MOG *Myelin oligodendroglia glycoprotein*	<1

PNS



Axon
Myelin
(Schwann cells)

Lipids (%)	**60**
Cholesterol	30
Glycolipids	25
Cerebrosides	20
Sulfatides	5
Gangliosides	<1
Phospholipids (PL)	45
Ethanolamine PL	15
Choline PL	10
Serine PL	10
Inositol PL	<1
Sphingomyelin	10
Proteins (%)	**40**
P0	55
P1 (MBP)	20
P2	0.01
PMP-22 *Peripheral myelin protein-22*	2-10
MAG *Myelin-associated glycoprotein*	0.1

JNNP Online First, published on February 11, 2015 as 10.1136/jnnp-2014-309831

RESEARCH PAPER

A nationwide survey of combined central and peripheral demyelination in Japan

Hidenori Ogata,[1] Dai Matsuse,[1] Ryo Yamasaki,[2] Nobutoshi Kawamura,[1,3] Takuya Matsushita,[2] Tomomi Yonekawa,[1] Makoto Hirotani,[4] Hiroyuki Murai,[1] Jun-ichi Kira[1]

Table 6 Comparison of clinical features between patients with CCPD with simultaneous or temporarily separated onset of CNS and PNS involvement*

	Temporarily separated onset group	Simultaneous onset group	p Value†
Clinical course	n/N (%)	n/N (%)	
Monophasic	3/29 (10.3)	6/8 (75.0)	0.0008
Relapsing–remitting	19/29 (65.5)	1/8 (12.5)	0.0140
Chronic progressive	7/29 (24.1)	1/8 (12.5)	NS
Hughes functional scale score	N=30	N=8	
At the peak of illness	2.73±1.14	3.75±1.39	0.0457
Treatment efficacy	n/N (%)	n/N (%)	
Corticosteroid pulse therapy	25/27 (92.6)	6/8 (75.0)	NS
Oral corticosteroids	17/20 (85.0)	4/6 (66.7)	NS
IVIg	13/20 (65.0)	4/5 (80.0)	NS
Plasmapheresis	5/6 (83.3)	2/2 (100.0)	NS

Combined inflammatory damage of the CNS and PNS: syndromes

Post/parainfectiuos (MRN,EMRN)

MS+ CIDP

Bickerstaff/ Miller-Fisher, (anti-GQ1b spectrum)

GBS+ spinal cord lesions

CIDP+ CNS demyelination

Systemic inflammatory diseases with CNS and PNS involvement

Infectious diseases: HIV, HCV, LYME

Paraneoplastic EMRN (anti-Hu spectrum)

Combined inflammatory damage of the CNS and PNS: trend

Simultaneous (80%)

ADEM, PINS, Bickerstaff/M-F	
post vaccinal:	96%
paraneopl (anti-HU)	2%
Uncertain	2%

Monofasic:	65%
Relapsing:	20%
Progressive	15%

Demyelinating	55%
Axonal:	30%
Mixed	15%

Dissociated (20%)

Sjogren, LES, vasc.:	89%
HIV	4%
HCV	1%
CIDP+SM	4%
SM+CIDP	1%
GVHD	1%

Relapsing:	85%
Progressive	14%
Monophasic:	1 %

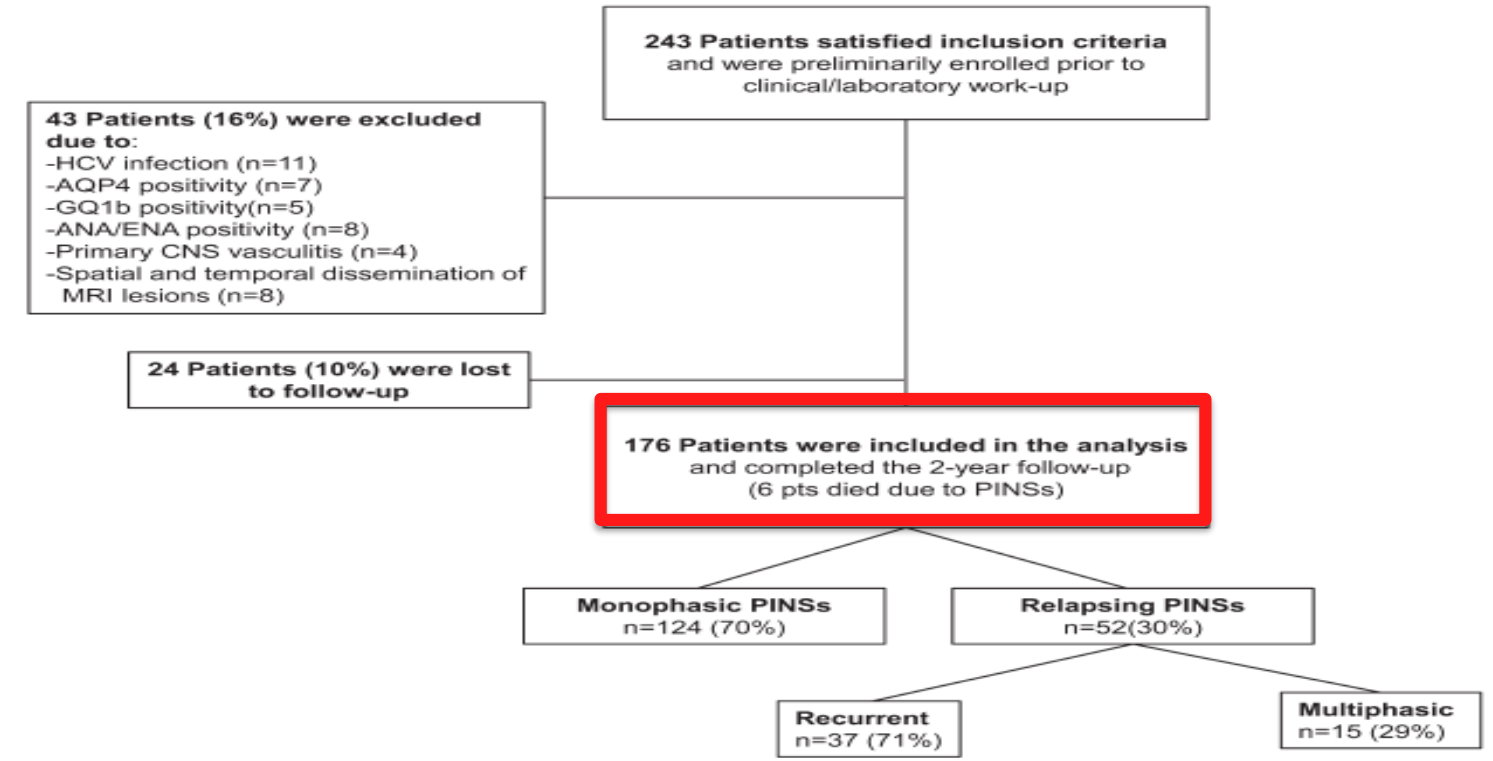
Axonal:	80%
Demyelinating	15%
Mixed	5%

Postinfectious neurologic syndromes

A prospective cohort study

Marchioni et al, Neurology 2013

Figure 1 Flow chart of enrolled and recruited patients



ANA = antinuclear antibody; AQP4 = aquaporin-4; ENA = extractable nuclear antigen; HCV = hepatitis C virus; PINS = postinfectious neurologic syndrome.

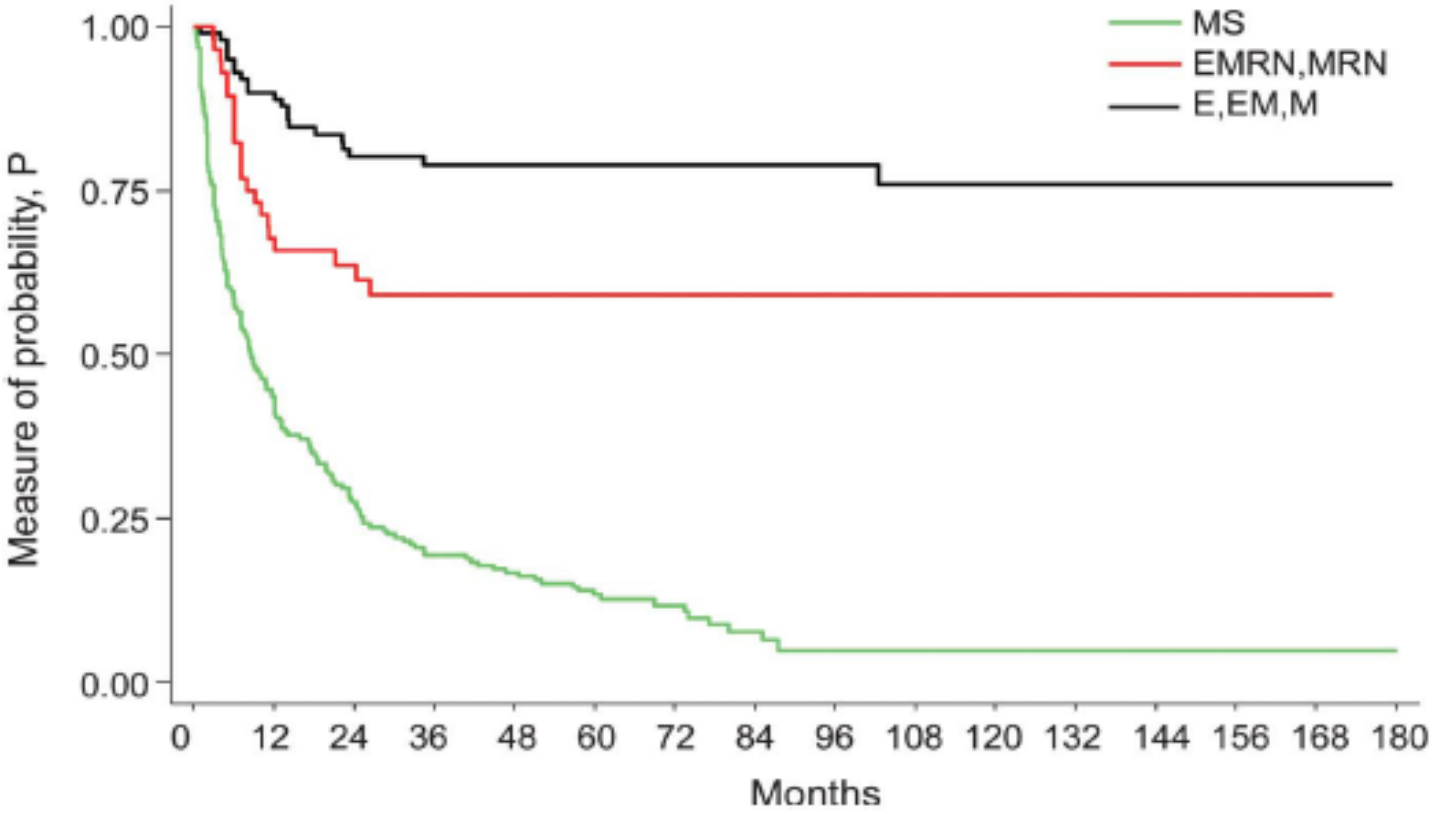
Table 1 Demographic features and disease course of the different PINSs

	Central PINSs (n = 112, 64%)			Mixed PINSs (n = 64, 36%)		
	E	EM	M	MRN	EMRN	Total
No. (%)	30 (17)	35 (19.9)	47 (26.7)	30 (17)	34 (19.3)	176
No. postvaccine[a]	2	4	2	5	1	14 (8%)
Sex, M:F	17:13	16:19	22:25	16:14	16:18	87:89
Age, y, min-max	18-74	18-77	18-78	39-80	21-78	18-80
Mean age, y, (SD)	46.4 (18.9)	46.7 (16.3)	54.9 (16.5)	64.6 (12.4)	57.3 (15.7)	59.9 (17.2)
Relapses,[b] n (%)	2/27 (7)	8/35 (23)	17/47 (36)	13/29 (45)	12/32 (37)	52/170 (30.6)
CSF albumin, mg/dL, mean ± SD	69.6 ± 42	147.2 ± 178.8	75.1 ± 86.7	75.5 ± 44.9	130.9 ± 78.9	98.9 ± 102.7
CSF albumin percentage transfer, mean ± SD	1.4 ± 0.6	1.9 ± 1.3	1.3 ± 0.9	1.8 ± 0.9	2.9 ± 2.2	1.8 ± 1.3
CSF, cells/mm^3, mean ± SD (range)	40.7 ± 60.1	43.9 ± 39.4	27.4 ± 56	16.9 ± 24.5	72.2 ± 92.9	39.6 ± 62 (4-120)
CSF IgG index, mean ± SD	0.6 ± 0.28	0.6 ± 0.1	0.5 ± 0.7	0.6 ± 0.1	0.6 ± 0.2	0.58 ± 0.16
Serum indices of systemic inflammation, n	8	7	6	7	7	35
PNS involvement,[c] n (%)	—			30	34	64/176 (36)
Demyelinating				14	17	31/64 (48.4)
Axonal				14	15	29/64 (45.3)
Undetermined				2	2	4/64 (6.2)

Table 2 Comparison of central PINSs (E, EM, M) with mixed (CNS + PNS) PINSs (EMRN, MRN)

	Central PINSs (n = 112, 64%)	Mixed PINSs (n = 64, 36%)	p Value
Age at onset, y, mean (SD)	50.1 (17.5)	60.8 (14.7)	0.0001[a]
Onset SNRS score, mean (SD)	64.8 (15.9)	51.9 (18.2)	<0.0001[a]
CSF albumin, % transfer, mean (SD)	1.5 (1)	2.3 (1.6)	0.0001[a]
Steroid effectiveness, n (%)	97/112 (86.6)	23/59 (39)	<0.0001[b]
IVIg effectiveness n (%)	3/8 (37.5)	17/36 (47.2)	NS[b]
Need for physical therapy support n (%)	45 (41)	43 (68)	0.038[b]
Poor final outcome, SNRS score <90 n (%)	30 (28.5)	44 (69)	0.001[b]
Wheelchair bound after the first event n (%)	7 (6)	19 (29)	0.0001[b]
Relapsing cases, n (%)[c]	27/109 (24.7)	25/60 (41.6)	0.011[b]

Figure 2 Kaplan-Meier estimates of relapse-free survival of 3 groups



Marchioni et al, Neurology 2013

Journal of the Neurological Sciences 363 (2016) 182–187

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Combined central and peripheral demyelination: Clinical features, diagnostic findings, and treatment

A. Cortese [a,*], D. Franciotta [a], E. Alfonsi [a], N. Visigalli [a], E. Zardini [a,b], L. Diamanti [a,c], P. Prunetti [a,c], C. Osera [a], M. Gastaldi [c,d], G. Berzero [a,c], A. Pichiecchio [a], G. Piccolo [a], A. Lozza [a], G. Piscosquito [e], E. Salsano [e], M. Ceroni [a,b], A. Moglia [a,b], G. Bono [d,f], D. Pareyson [e], F. Marchioni [a]

	Disease onset	Follow-up[a]
Previous infection	20 (65%)	1 (5%)
Clinical features		
Lower limb sensory-motor impairment	29 (94%)	19 (90%)
Urinary incontinence/retention	26 (84%)	2 (9%)
Distal paresthesia	11 (35%)	4 (19%)
Altered mental status	5 (16%)	–
Upper limb sensory-motor impairment	8 (26%)	7 (33%)
Headache	2 (6%)	–
Ascending four limb sensory-motor impairment	4 (13%)	–
Other	7 (23%)	4 (19%)
Response to treatments		
Steroids	17/23 (74%)	4/16 (25%)
IVIg	4/8 (50%)	4/11 (36%)
Other	1/1 (100%)	1/4 (25%)
Overall response	19 (73%)	6 (19%)
Disability (mRS)	N = 25[c]	N = 31
0	1 (4%)	2 (7%)
1	1 (4%)	2 (7%)
2	1 (4%)	1 (3%)
3	6 (24%)	4 (13%)
4	12 (48%)	4 (13%)
5	4 (16%)	18 (58%)

Combined variants in children:

- **CCP/Whole sample:** **14%**
- **Post infectious:** **85 %**
- **Relapsing:** **15,4%**
- **First event:** **CNS 69% vs PNS 31%**
- **Response to treatments:**
  - **Steroids** **40%**
  - **IVIg** **69%**
  - **PE** **15%**
- **Bad outcome:** **53%**

Maschio di 15 anni
APR: negativa

Marzo 2010

APP: comparsa acuta di cefalea, confusione, parestesie, dapprima limitate al piede sx e in pochi giorni estese a tutto l'arto inf sx fino alla regione glutea, con coinvolgimento del piede dx

↓

21 giorni prima: episodio simil-influenzale (febbre, rinite, malessere generalizzato)

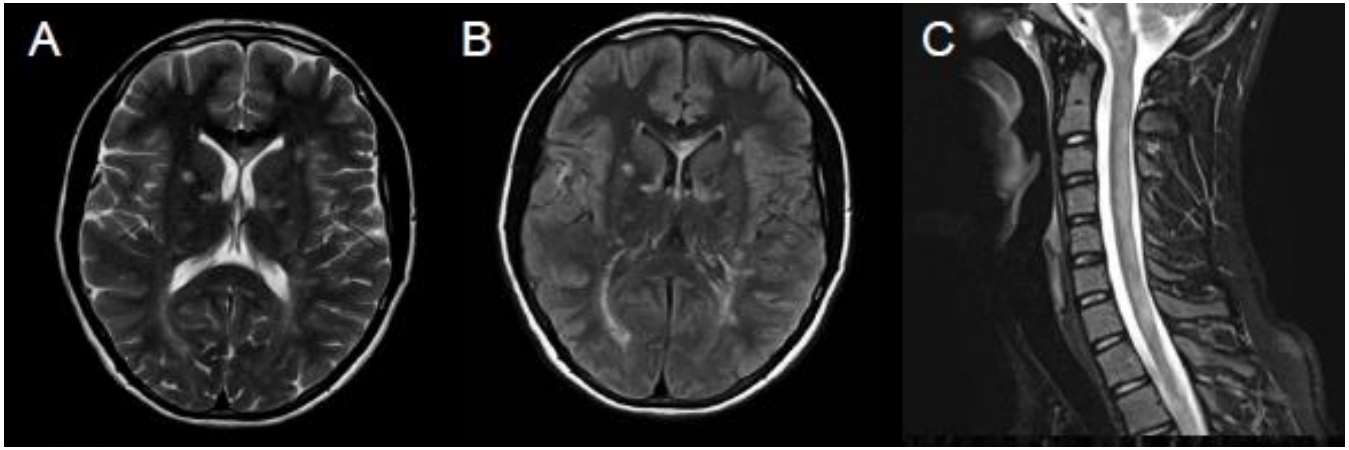
↓

Aggravamento della sintomatologia, con comparsa di instabilità posturale

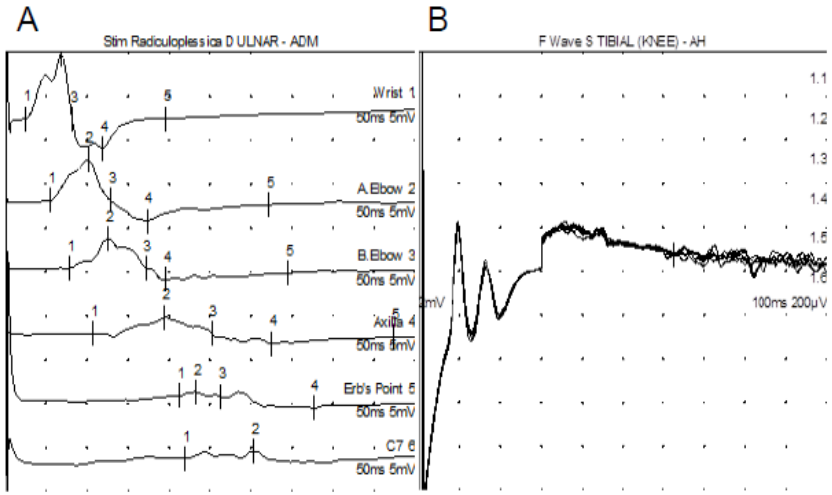
→ **RICOVERO (10 gg dopo l'esordio)**

Foiadelli et al, Neurology Clinical Practice, in press

esordio



CSF: alb transf: 1,3; cells: 11; IEF: normal

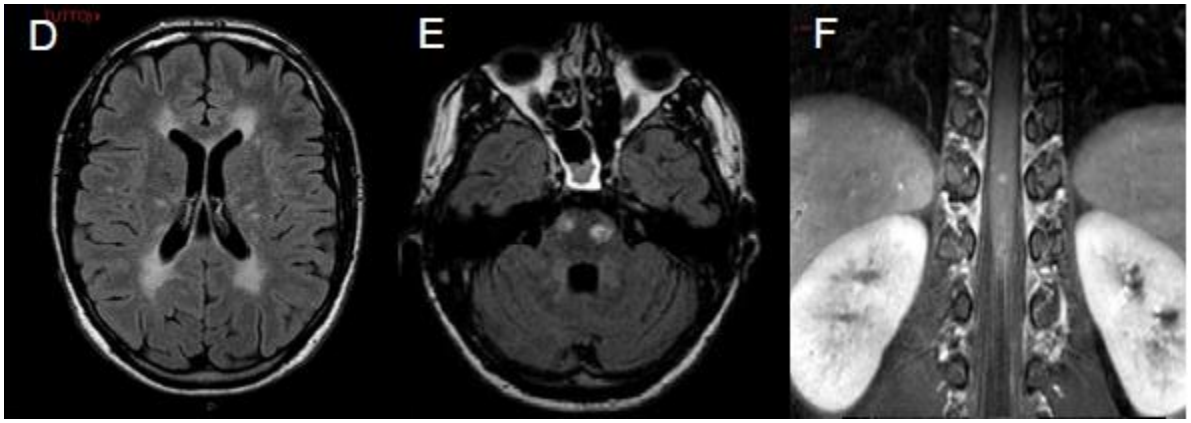


Supplementary Fig. e-2

Nerve conduction study (NCS) at baseline

Partial motor conduction block (from 7,3 mV to 4,6 mV) and temporal dispersion of Compound Motor Action Potential (CMAP) at right ulnar nerve stimulating at axilla and recording from muscle abductor digiti minimi (A); F-wave latency prolongation (63 ms) at left tibial nerve stimulating at knee and recording from muscle tibialis anterior (B). CMAP amplitudes were almost completely preserved, while sensory conduction velocities were reduced. Together with the clinical course, these findings fulfilled the 2010 EFNS/PNS electrodiagnostic criteria for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

Dopo natalizumab

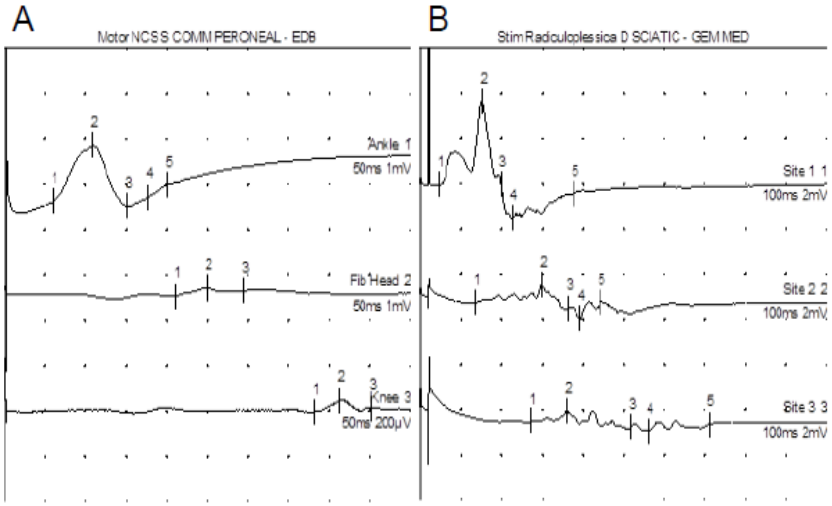


CSF: alb transf: 1,8; cells: 15; IEF: normal

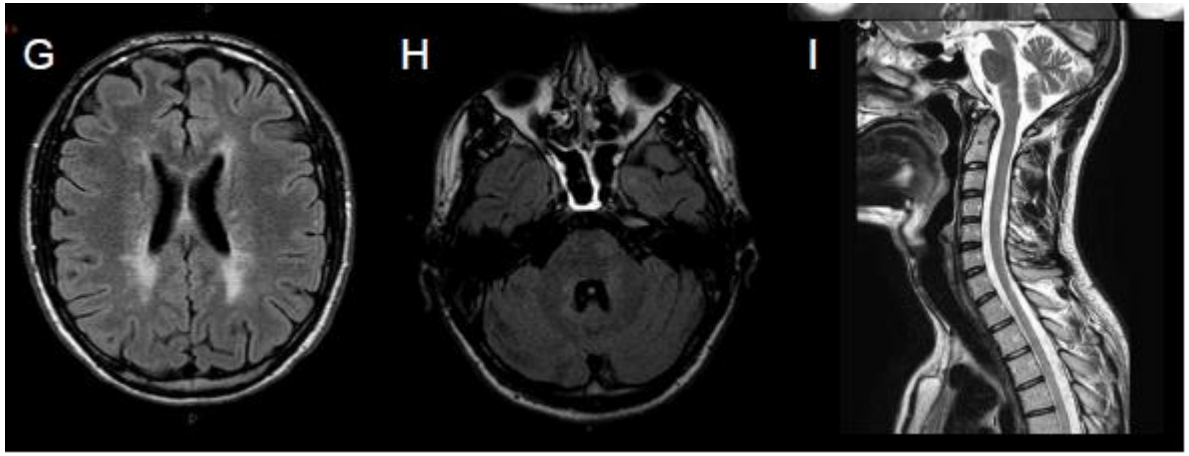
Supplementary Fig. e-3

Worsening of NCS during treatment with Natalizumab

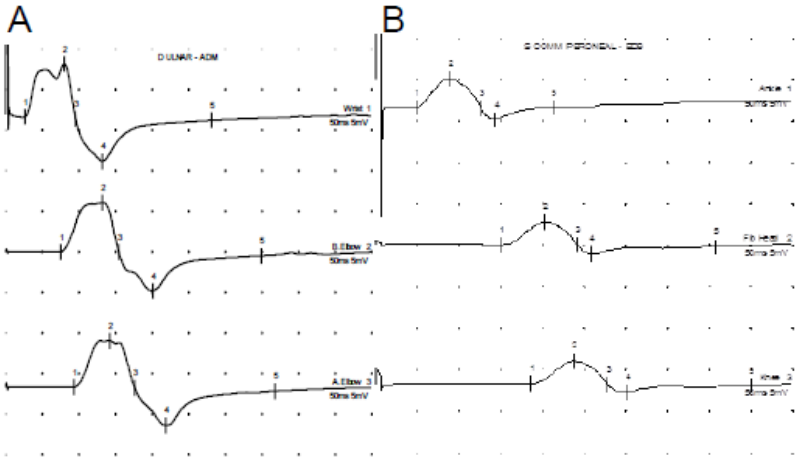
Reduction of motor conduction velocity (MCV 22 m/s) and partial conduction block (from 1,2 mV to 0,2 mV) at left peroneal nerve, stimulating at fibular head and recording from muscle extensor digitorum brevis (A); partial motor conduction block (from 3,7 mV to 0,5 mV) and temporal dispersion of CMAP at right sciatic nerve, recording from muscle gastrocnemius medialis (B).



Dopo rituximab



CSF: alb transf: 0,9; cells: 8; IEF: normal



NCS after 12 months of Rituximab

Resolution of the partial conduction block at right ulnar nerve (from 6,6 mV to 5,7 mV), recording from muscle abductor digiti minimi (A) NCSs at left common peroneal nerve (MCV 34 m/s) stimulating at fibular head and recording from muscle extensor digitorum brevis (B).

conclusioni

le sindromi «combinate» sono condizioni rare, ma sicuramente sottostimate

le modalità di insorgenza «simultanea o dissociata»» dipendono da eziopatogenesi diverse

le forme «simultanee» sono spesso post infettive, di cui rappresentano circa 1/3 e recidivano nei 2/3

i trattamenti sono poco efficaci, soprattutto nelle recidive

Grazie per l’attenzione