SINDROME POST POLIO : PROFILO DIAGNOSTICO e TERAPEUTICO

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The March of Dimes Criteria

1. **Prior paralytic poliomyelitis**

   with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness, and atrophy of muscles on neurological examination, and signs of denervation on electromyography (EMG).

2. **A period of partial or complete functional recovery**

   after acute paralytic poliomyelitis, followed by an interval (usually 15 years or more) of stable neurologic functions.

3. **Gradual or sudden onset of progressive and persistent muscle weakness or abnormal muscle fatigability**

   (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain. (Sudden onset may follow a period of inactivity, or trauma, or surgery). Less commonly, symptoms attributed to PPS include new problems with swallowing or breathing

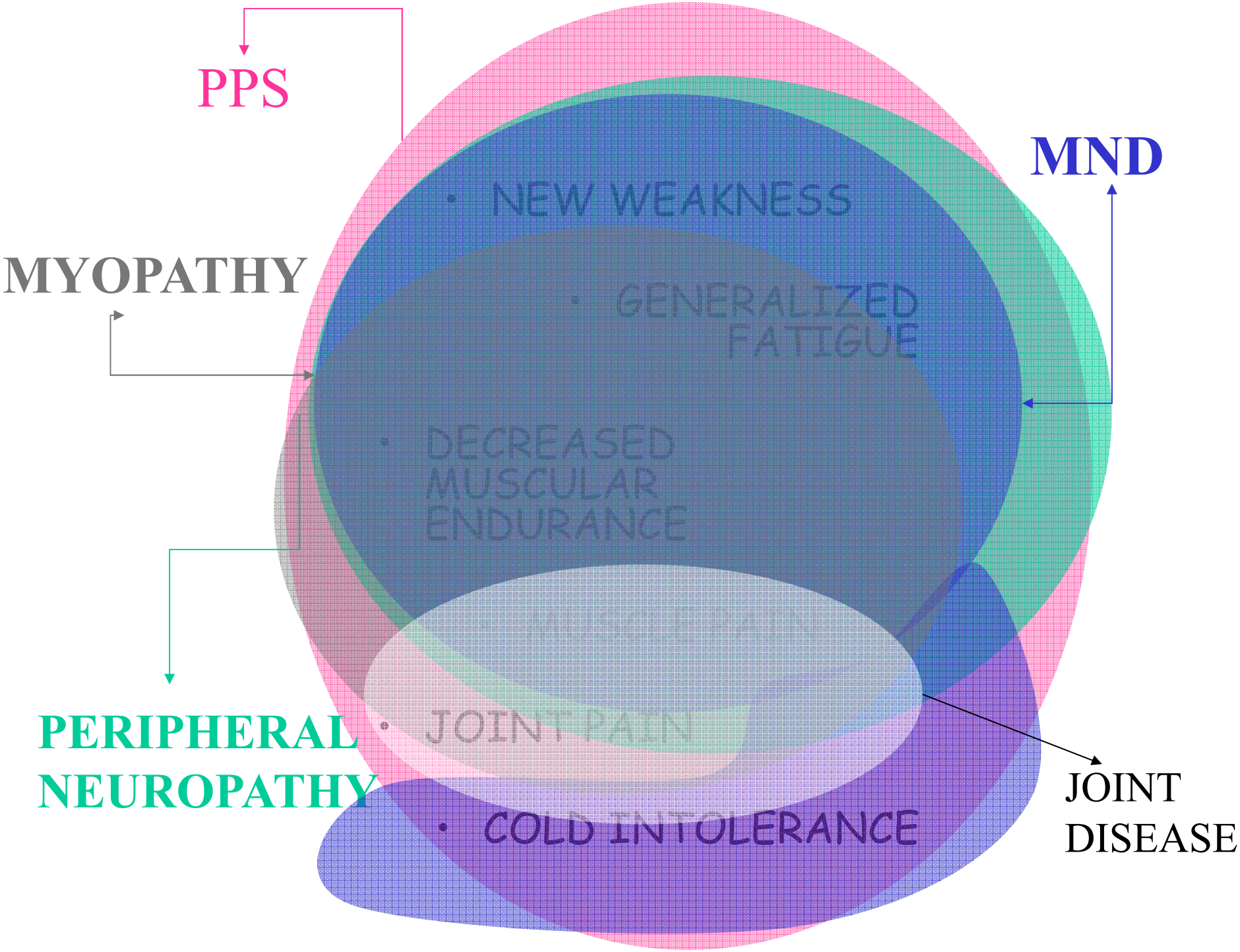
4. **Symptoms persist for at least a year**

5. **Exclusion of other neurologic, medical, and orthopaedic problems as causes of symptoms**

PPS

- NEW WEAKNESS
- GENERALIZED FATIGUE
- DECREASED MUSCULAR ENDURANCE
- MUSCLE PAIN
- JOINT PAIN
- COLD INTOLERANCE

Halstead 1985


PPS
MND
MYOPATHY
• NEW WEAKNESS
• GENERALIZED FATIGUE
• DECREASED MUSCULAR ENDURANCE
PERIPHERAL NEUROPATHY
• JOINT PAIN
• COLD INTOLERANCE
JOINT DISEASE

The March of Dimes Criteria

1. **Prior paralytic poliomyelitis**
   with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness and atrophy of muscles on neurological examination, and signs of denervation on electromyography (EMG).

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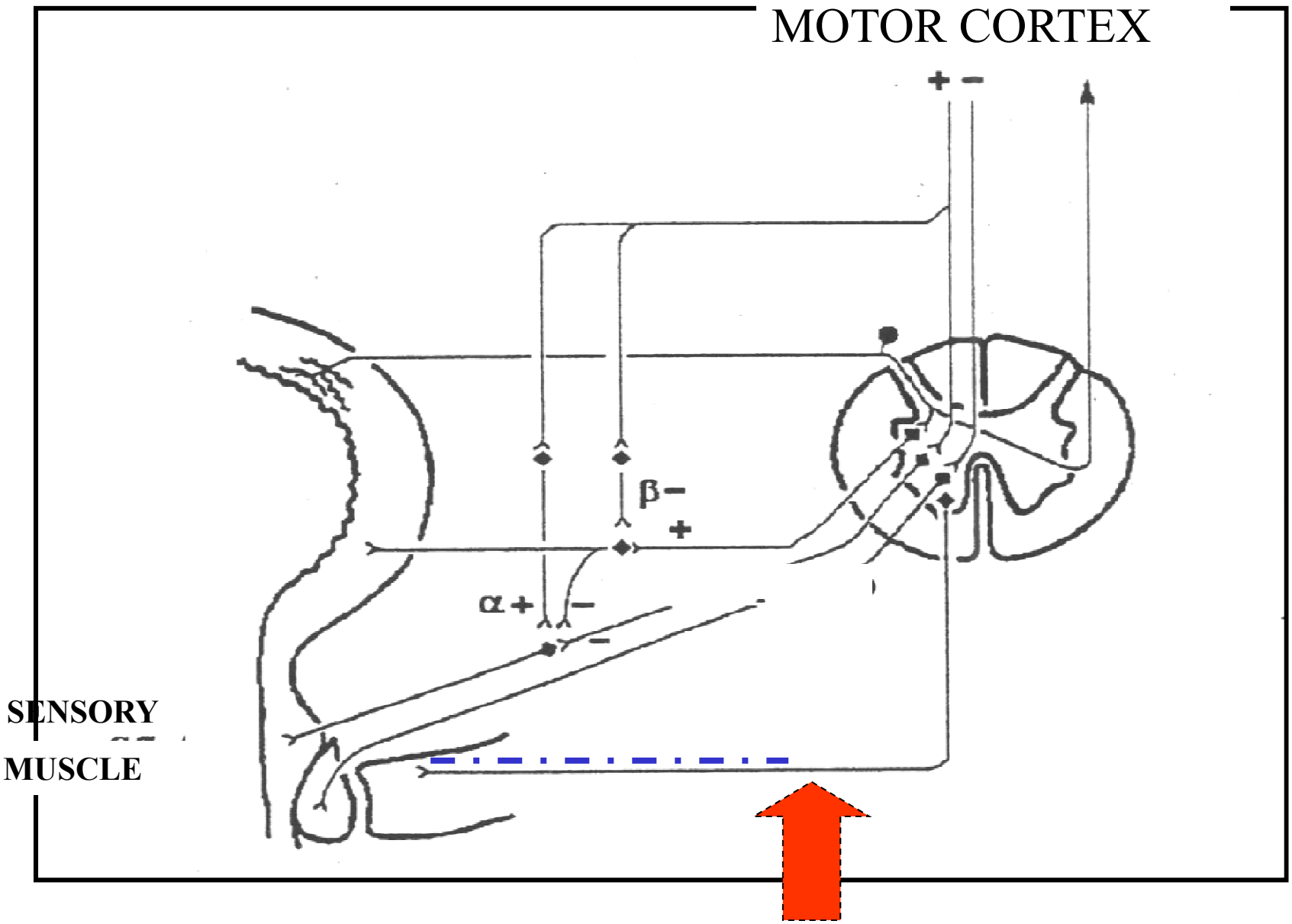
4. **Symptoms persist for at least a year**

5. Exclusion of other neurologic, medical, and orthopaedic problems as causes of symptoms

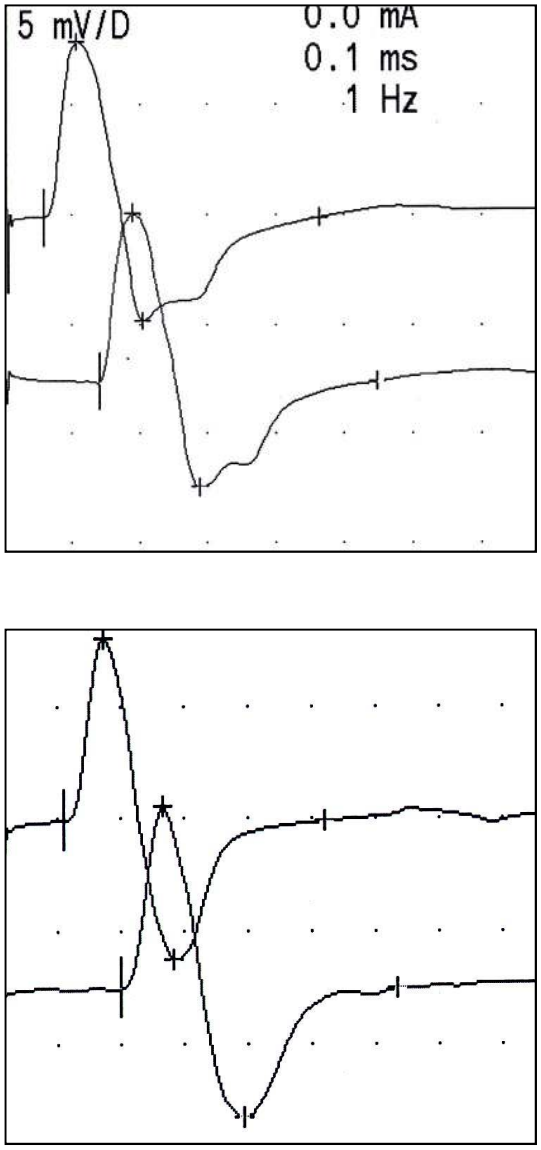
Common symptoms in the general ageing population and could be caused by a considerably amount of other conditions and illnesses.

Primary goal → rule out other possible contributing factors.

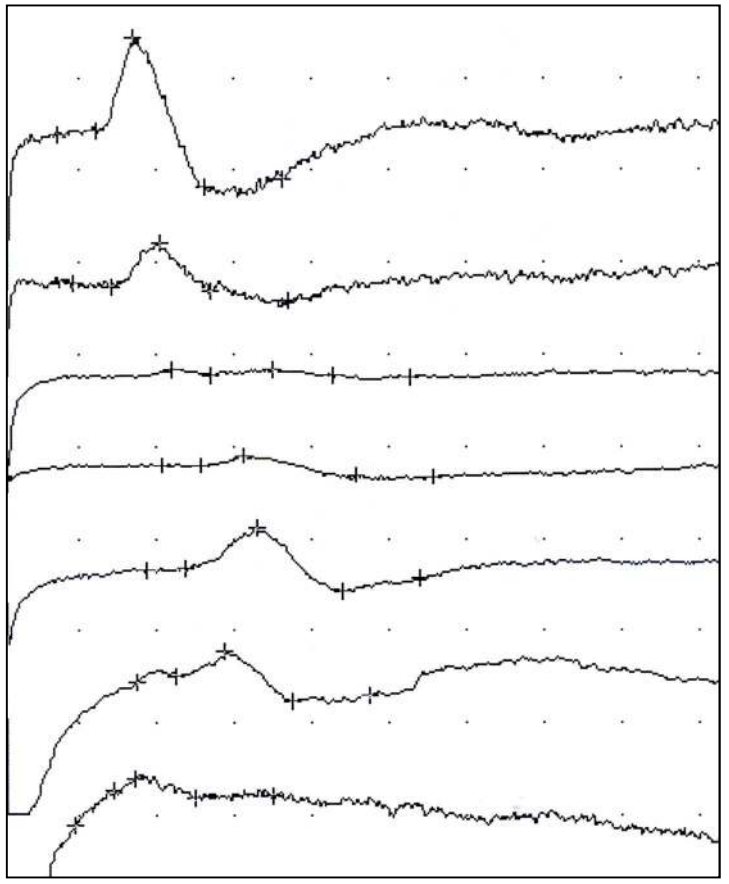
NEUROPHYSIOLOGY


MOTOR CORTEX
+ −
β−
+
α +
−
SENSORY
MUSCLE

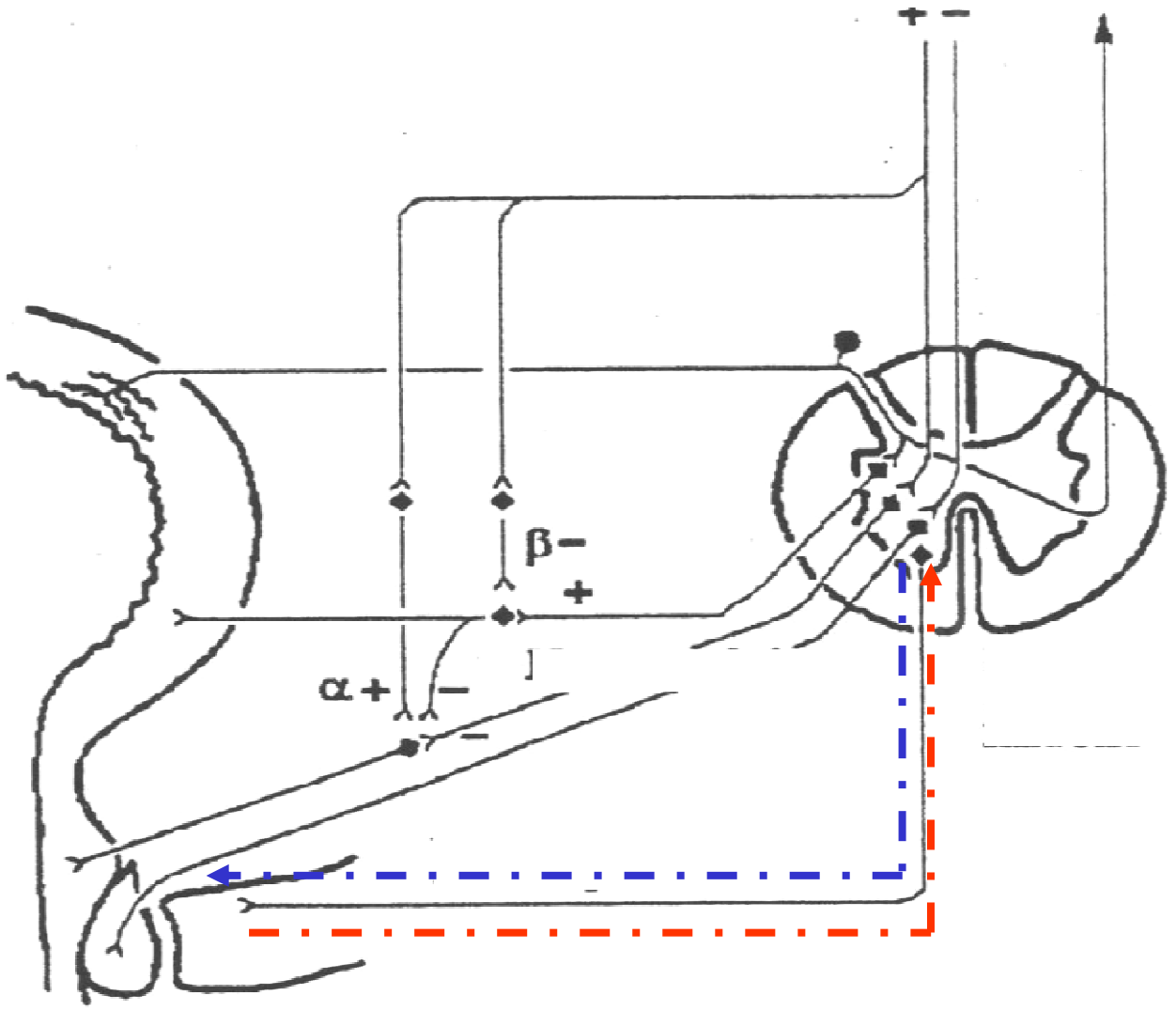
MOTOR CONDUCTION VELOCITY



SENSORY CONDUCTION VELOCITY

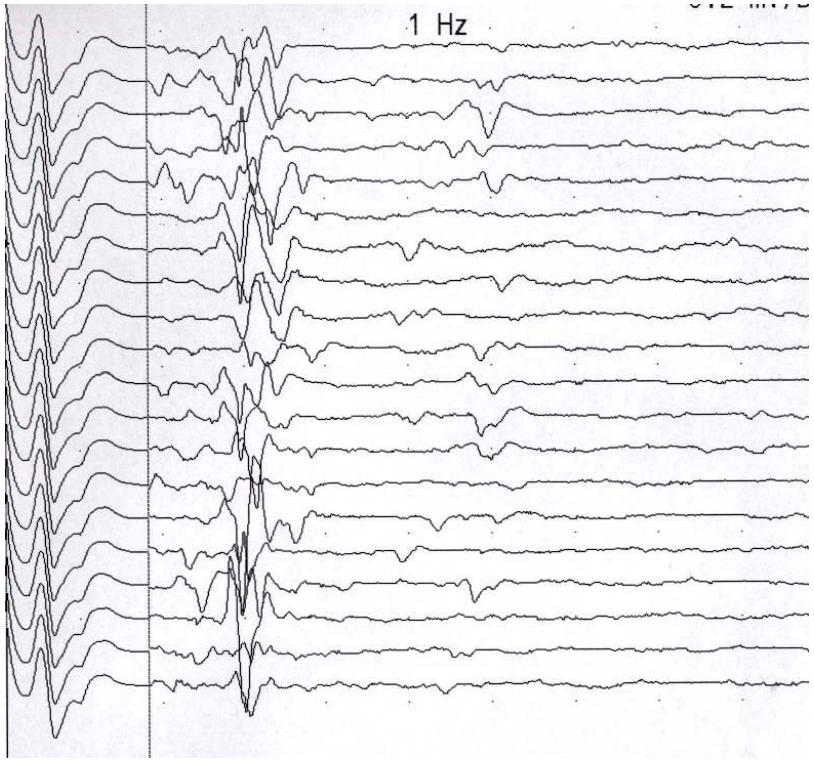


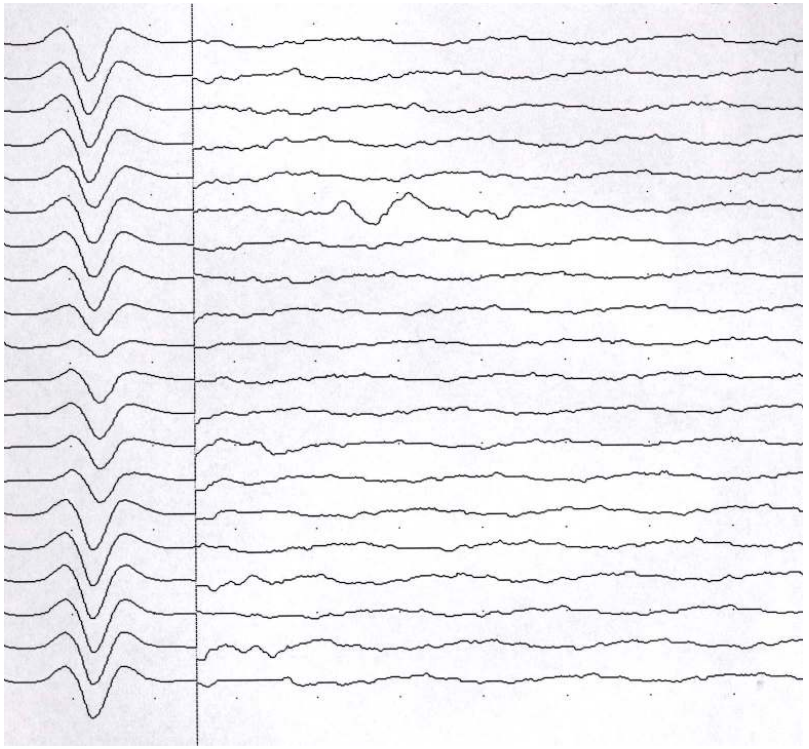
MOTOR CORTEX

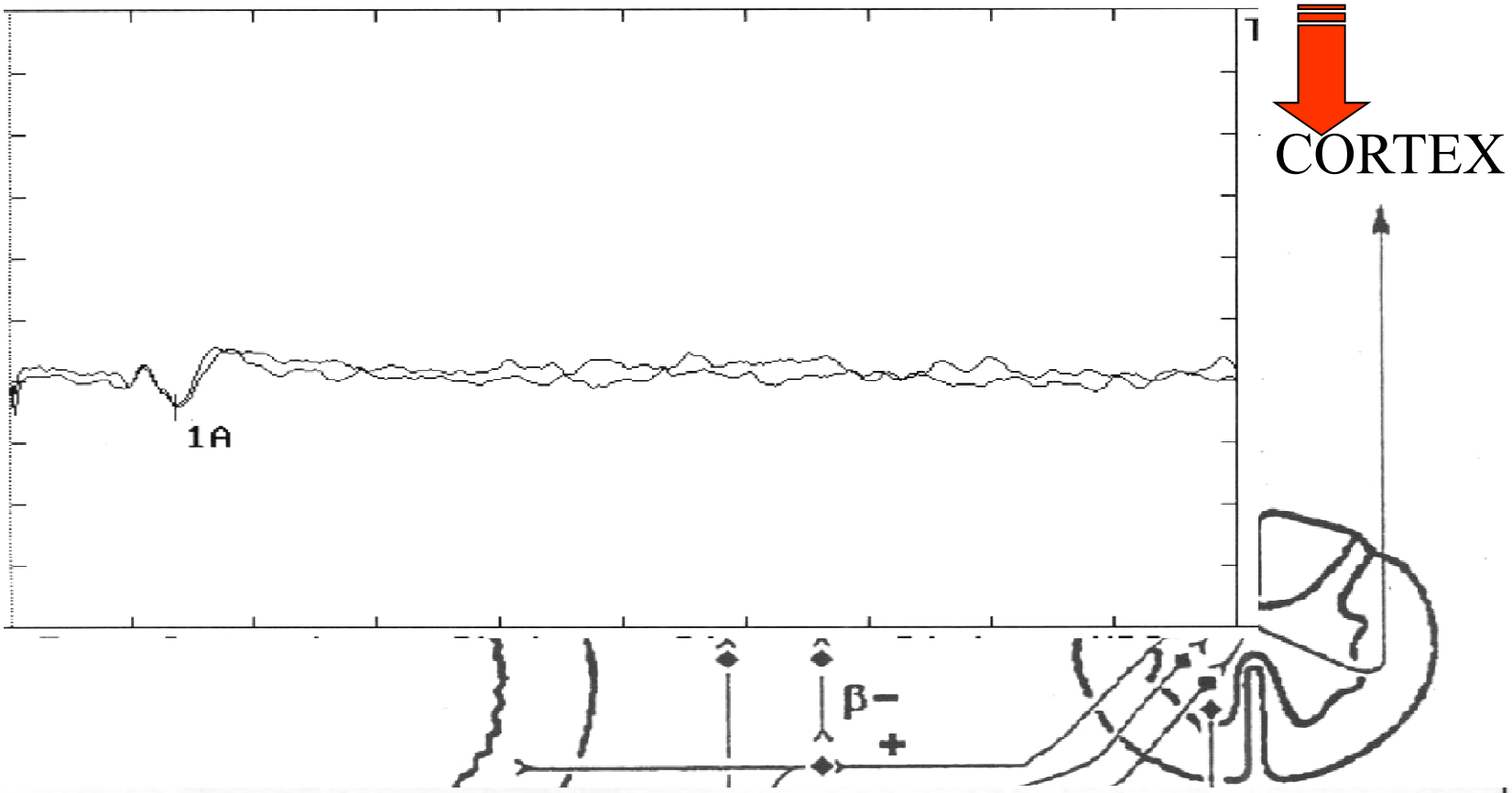


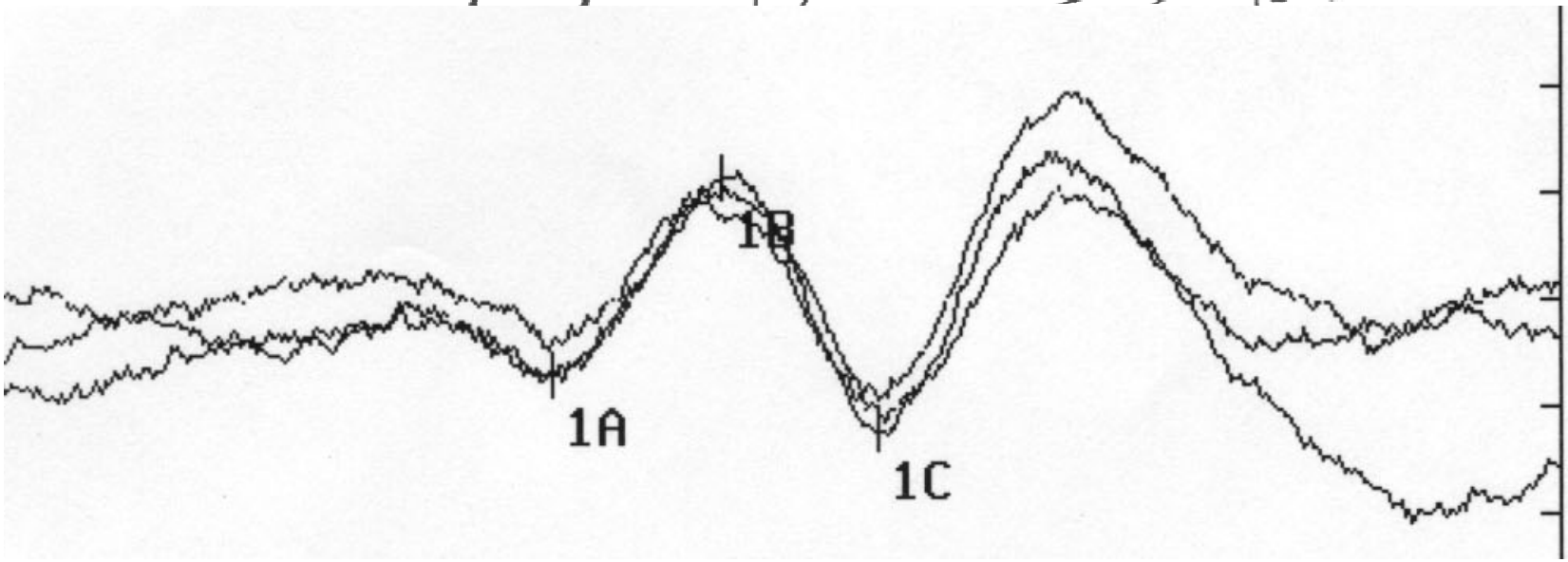
MUSCLE

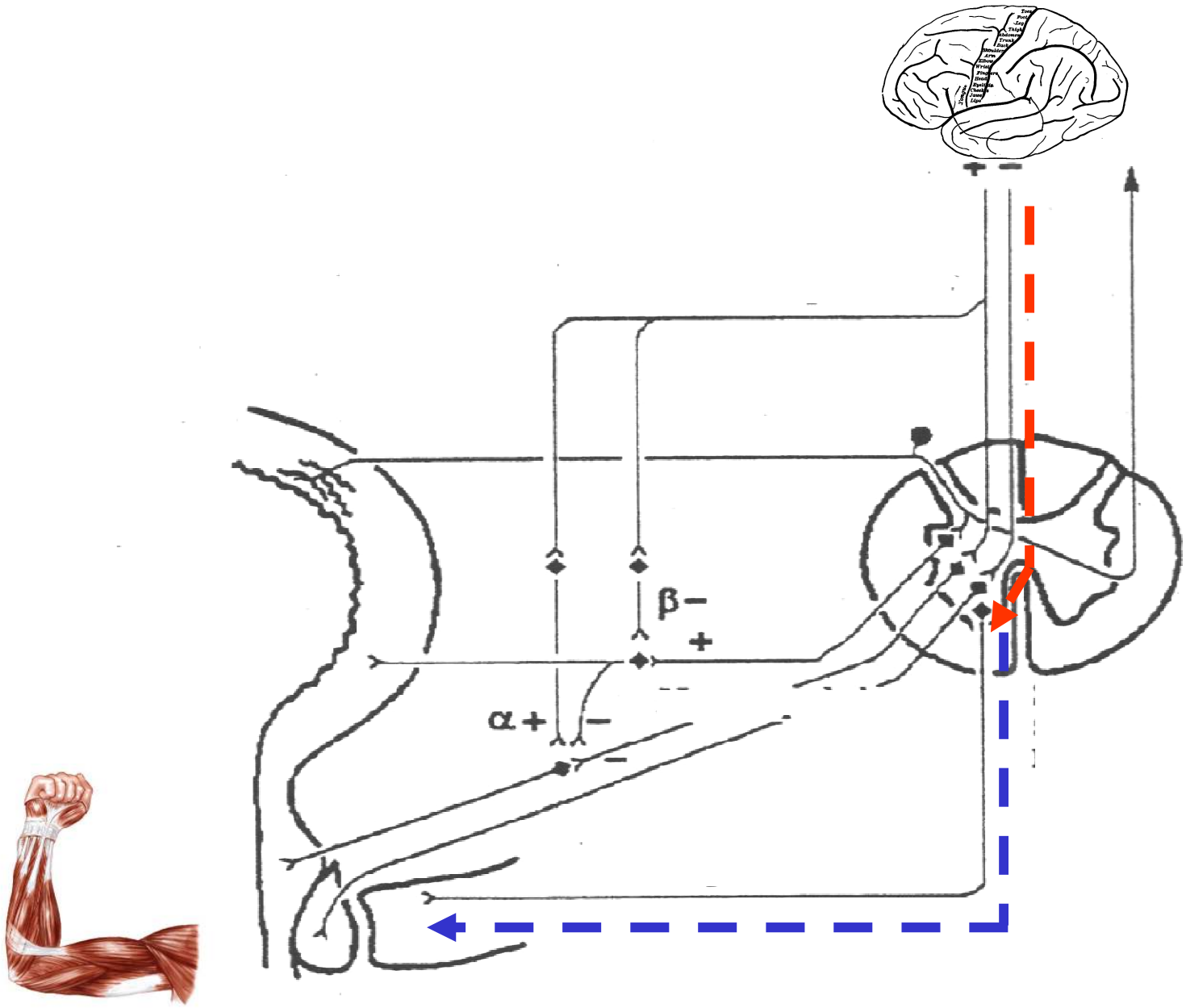
LATE RESPONSES

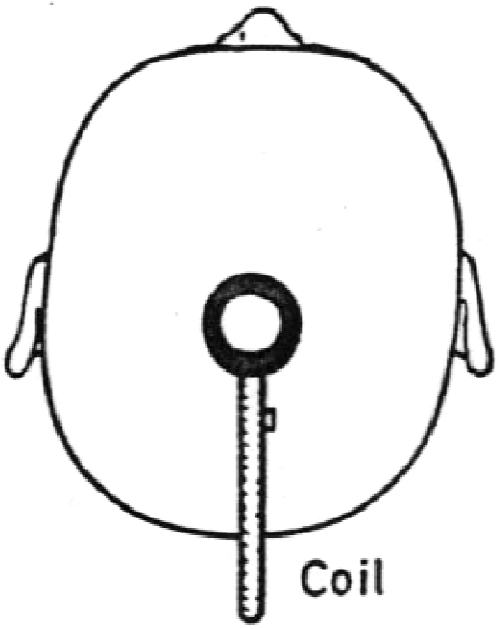


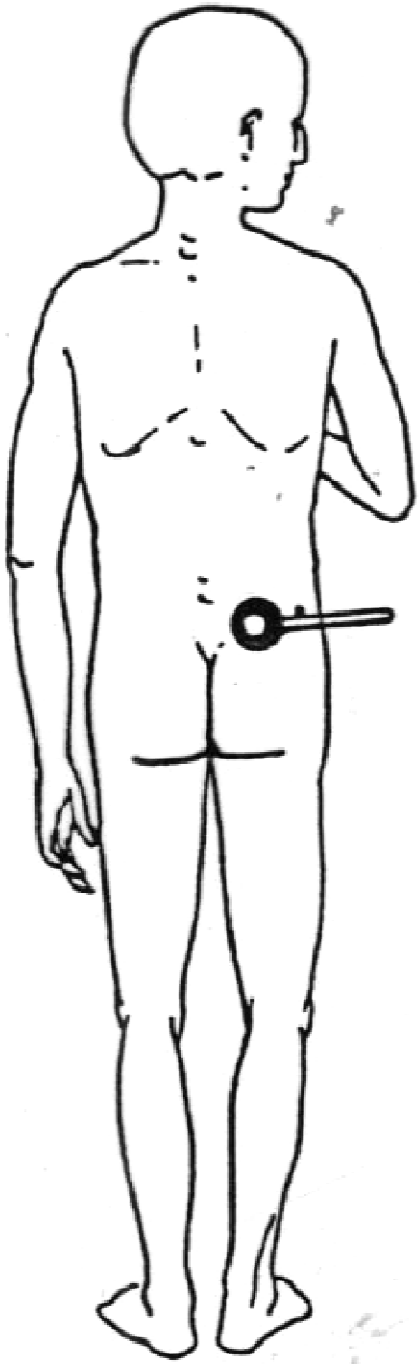



CORTEX
1A
β–
+


1A
1B
1C


β−
+
α+
−
−


Coil



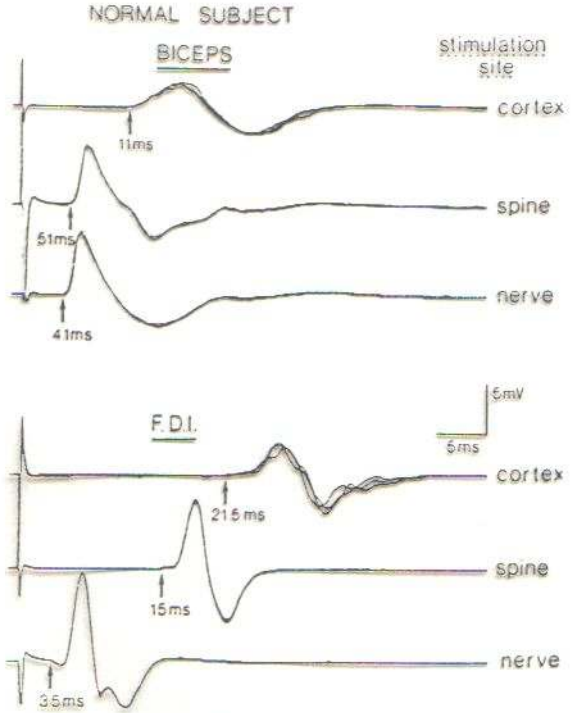


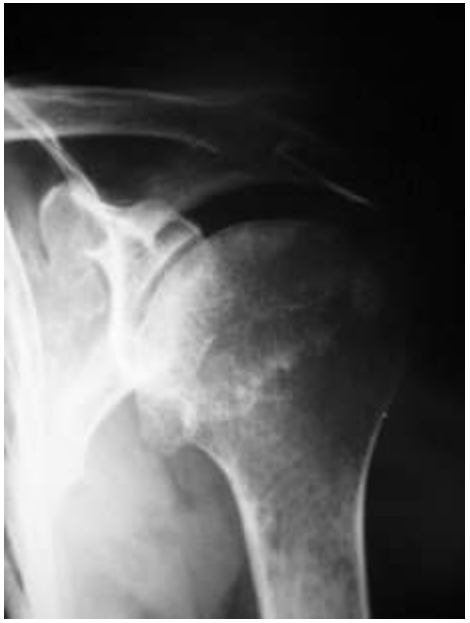
Figure 1: MEPs evoked in biceps and FDI of a normal subject by magnetic stimulation of the motor cortex (upper traces), electrical stimulation over the cervical spine (middle traces) and supramaximal electrical stimulation of musculocutaneous and ulnar nerves (bottom traces). Three individual responses are superimposed on each trace.

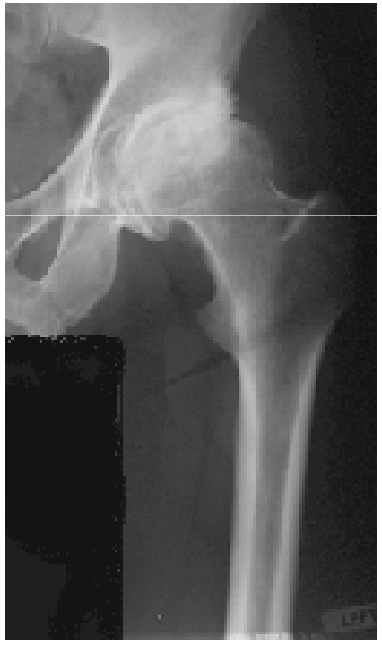
Electromyography
(Grimby et al. 1998).

- EMG may show increased amplitude reflecting an enlarged motor unit
- Nerve conduction studies should reveal normal findings for both motor and sensory nerves, except for the parameters regarding the motor units
- Other diagnoses such as peripheral neuropathy and myopathy can be ruled out after neurophysiological examinations.

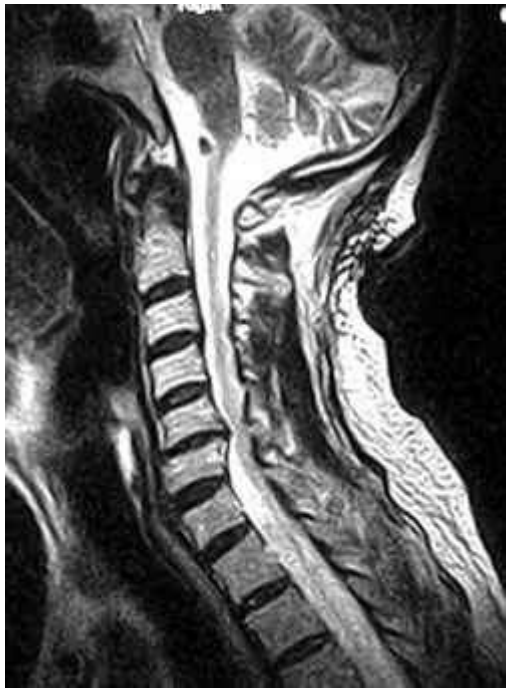
IMAGING

X-ray





Cerebral and Spine MRI

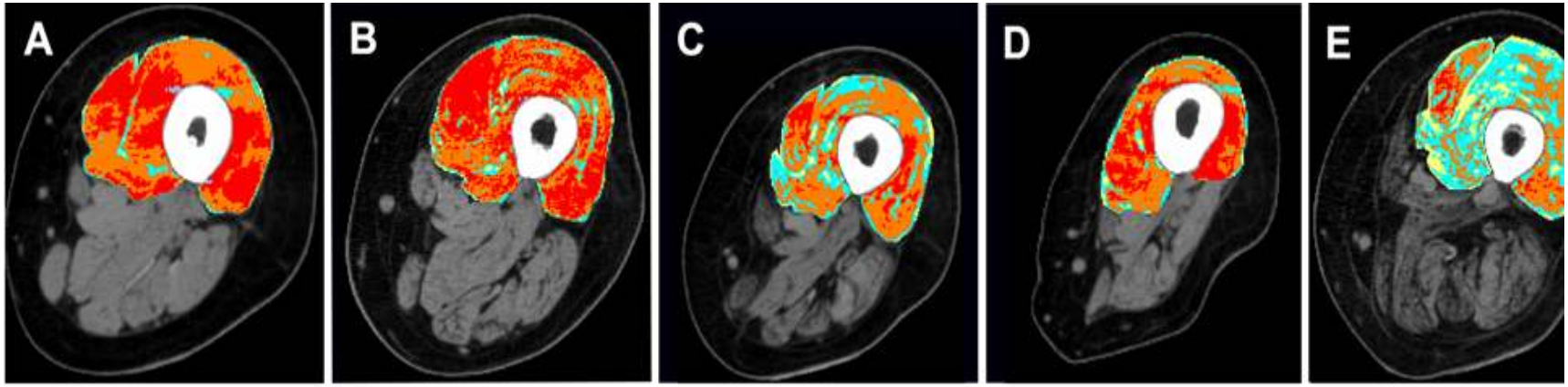


A case of cervical spondylotic amyotrophy resembling post-polio **syndrome**
Isobe T. et al, 2006

Muscle CT scans

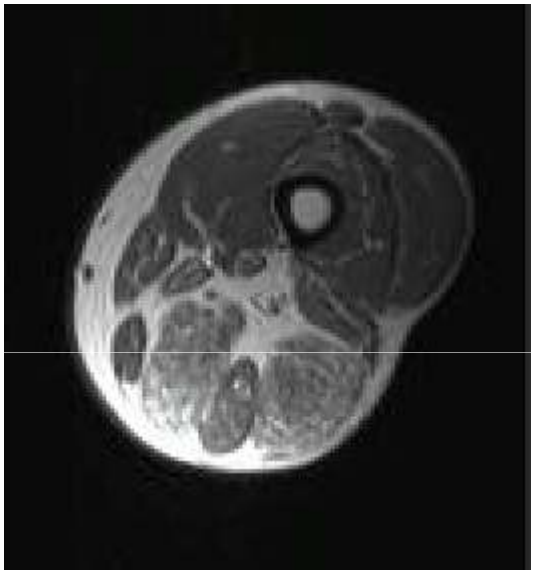
- Computer tomography (CT) scans can be helpful to detect subclinical muscle atrophy

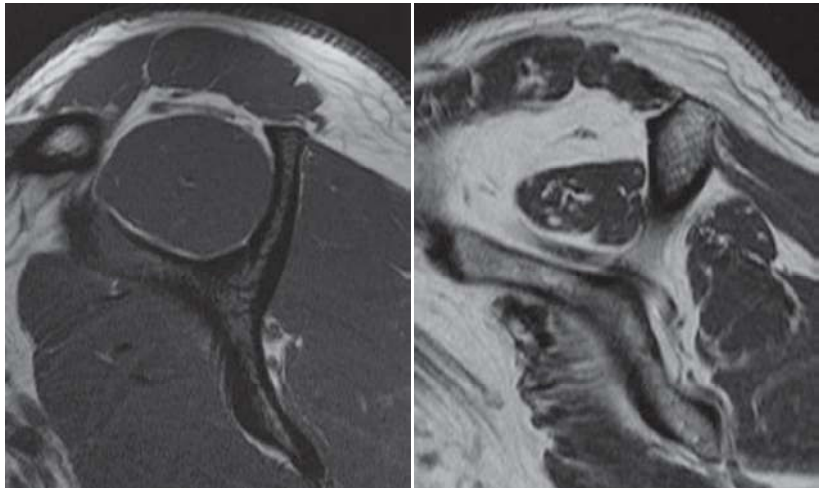
(Ivanyi et al. 1998)



(Kern H et al. Neurorehab Neur Rep 2009)

Muscle MRI





Khoury V. et al, 2008

LABORATORY INVESTIGATIONS

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA - VERONA
DIPARTIMENTO PATOLOGIA E DIAGNOSTICA
U.O.C. LABORATORIO ANALISI dU
Direttore Prof. Gian Cesare GUIDI
Sede di Borgo Roma
U.O. con Sistema Qualita' UNI EN ISO 9001:2008 Certificato n. 194114/LABCC/BR

Referto parziale stampato il 26-08-2011 alle 13:31

MOSCONI CARLO M Nos.: 11014524 49001611
Data di nascita: 29-09-1933 Sezione: Clinica Neurologica OP
N.Sanitario: 602533149 Richiesta del: 26-08-2011

				(Val.riferimento indicativi per sesso e gruppi di eta')
P-AZOTO UREICO	18,00		mg/dL	(8,00 - 22,00)
	6,42		mmol/L urea	(2,85 - 7,85)
P-CREATININA	0,83		mg/dL	(0,60 - 1,30)
	73,3		umol/L	(53,0 - 114,9)
P-BILIRUBINA TOTALE	0,57		mg/dL	(0,20 - 1,10)
	9,7		umol/L	(3,4 - 18,8)
P-CALCIO	9,49		mg/dL	(8,50 - 10,30)
	2,37		mmol/L	(2,12 - 2,57)
P-FOSFATI	3,80	*	mg/dL	(2,20 - 3,70)
	1,22	*	mmol/L	(0,71 - 1,19)
P-CLORO	100		mmol/L	(98 - 107)
P-POTASSIO	3,6		mmol/L	(3,4 - 4,7)
P-SODIO	141,0		mmol/L	(135,0 - 145,0)
P-URATO	4,7		mg/dL	(2,5 - 7,2)
	279,5		umol/L	(148,7 - 428,2)
P-CK	504		U/L	(inf a 50)

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Journal of Neuroimmunology 150 (2004) 139–144

Journal of Neuroimmunology

www.elsevier.com/locate/jneuroim

Prior poliomyelitis—IvIg treatment reduces proinflammatory cytokine production

Henrik Gonzalez[a,b,*], Mohsen Khademi[c], Magnus Andersson[a,c], Fredrik Piehl[c], Erik Wallström[a,c], Kristian Borg[a,d], Tomas Olsson[c]

[a] Department of Clinical Neuroscience, Division of Neurology, Stockholm, Sweden
[b] Department of Rehabilitation Medicine, Danderyd Hospital, Stockholm, Sweden
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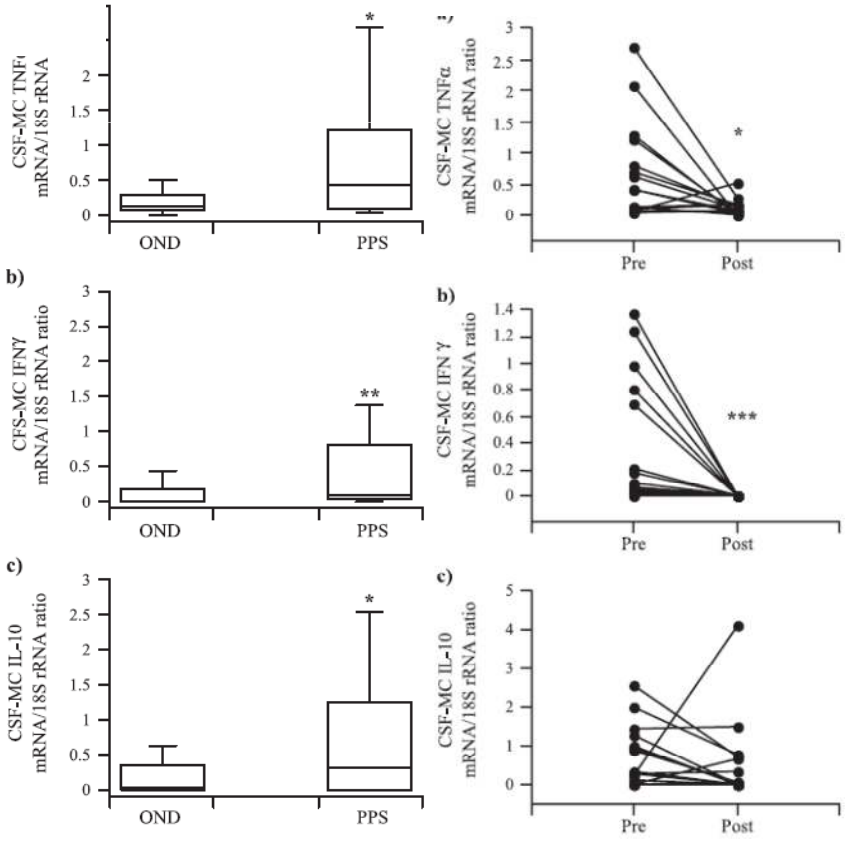
Received 27 October 2003; received in revised form 6 January 2004; accepted 7 January 2004



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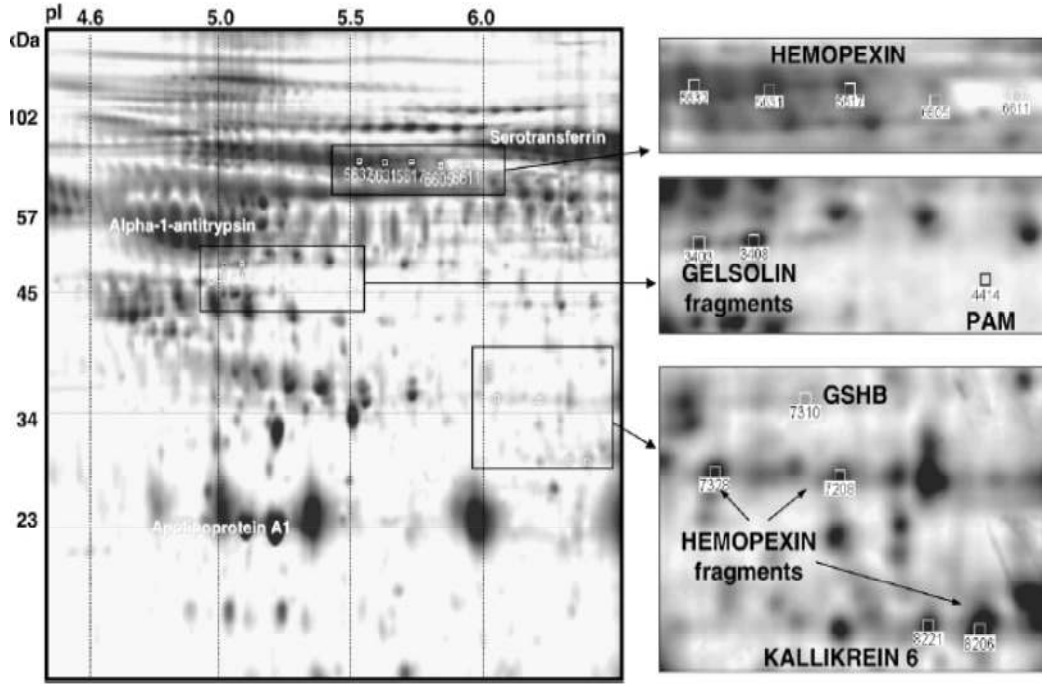
PROTEOMICS

Identification of novel candidate protein biomarkers for the post-polio syndrome — Implications for diagnosis, neurodegeneration and neuroinflammation

Henrik Gonzalez[a,1], Jan Ottervald[b,f,*,1], Kerstin C. Nilsson[c], Niclas Sjögren[d], Tasso Miliotis[e], Helena Von Bahr[e], Mohsen Khademi[f], Bodil Eriksson[g], Sven Kjellström[h], Akos Vegvari[h], Robert Harris[f], György Marko-Varga[h], Kristian Borg[a], Johan Nilsson[i], Thomas Laurell[i], Tomas Olsson[f,1], Bo Franzén[b,1]



Post-polio syndrome patients treated with intravenous immunoglobulin: a double-blinded randomized controlled pilot study

E. Farbu[a,b], T. Rekand[a], E. Vik-Mo[a], H. Lygren[c], N. E. Gilhus[a,d] and J. A. Aarli[a,d]

[a]*Department of Neurology, Haukeland University Hospital, Bergen, Norway;* [b]*Neurocenter, Stavanger University Hospital, Stavanger, Norway;* [c]*Department of Physiotherapy, Haukeland University Hospital, Bergen, Norway; and* [d]*Institute of Clinical Medicine, University of Bergen, Bergen, Norway*

European Journal of Neurology 2007, **14:** 60–65

Table 3 TNF-α, and IL-6 before and after treatment of post polio syndrome (PPS) patients.

	IvIg (mean)	Placebo (mean)	95% CI for the difference	*P*-value
TNF-α, CSF (pg/ml)				
Baseline	1.37	1.97	−0.41 to 1.62	>0.05
1 month	1.10	2.13	0.13 to 1.92	0.028
TNF-α, serum (pg/ml)				
Baseline	1.82	2.24	−1.11 to 1.95	>0.05
1 month	1.93	2.11	−1.36 to 1.71	>0.05
IL-6, CSF, (pg/ml)				
Baseline	1.74	1.41	−1.22 to 0.55	>0.05
1 month	2.33	1.68	−2.1 to 0.79	>0.05

Future Neurol. (2007) 2(4), 451–463

Post-polio syndrome: clinical manifestations and cerebrospinal fluid markers

Michele Fiorini, Gianluigi Zanusso, Andreina Baj, Laura Bertolasi, Antonio Toniolo & Salvatore Monaco†

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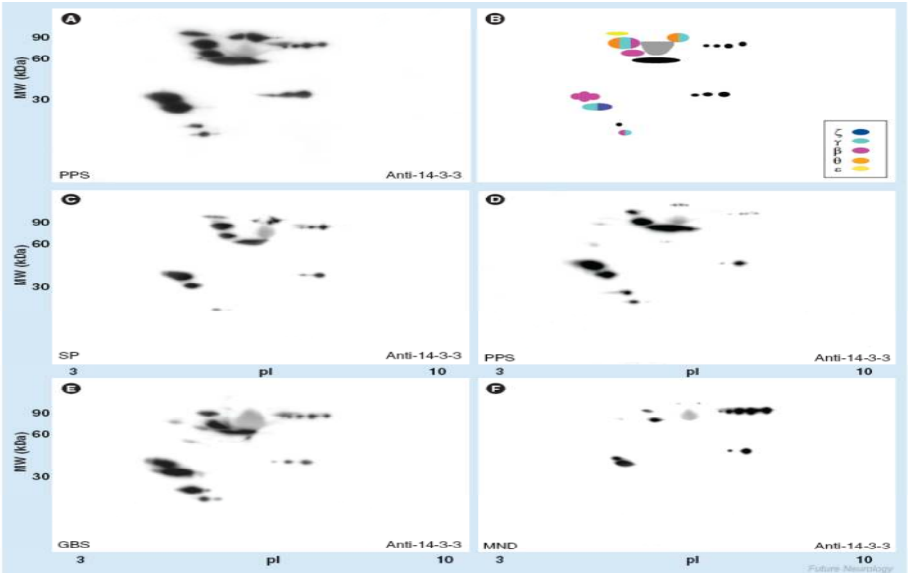
Table 2. Reports of cerebrospinal fluid 14-3-3 protein assay in different neurological disorders.

Disorder	Positive/negative 14-3-3 assay	Ref.
Viral meningoencephalitis	2/7	[68]
	12/24	[69]
Nonviral meningoencephalitis	3/11	[68]
	12/20	[70]
Multiple sclerosis	1/10	[68]
	0/8	[69]
	5/38	[71]
	3/37	[72]
	25/114 (ELISA)	[73]
	24/63	[74]
	14/16	[75]
Alzheimer disease	1/49	[69]
	4/20	[76]
Other dementias	0/5	[68]
	0/14	[69]
	4/31	[76]
Stroke	4/8	[69]
Paraneoplastic diseases	10/70	[77]
Guillain–Barré syndrome	0/5	[68]
	29/38	[78]
Motor neuron disease	0/7	[68]
Noninflammatory neuropathy	0/16 (ELISA)	[73]



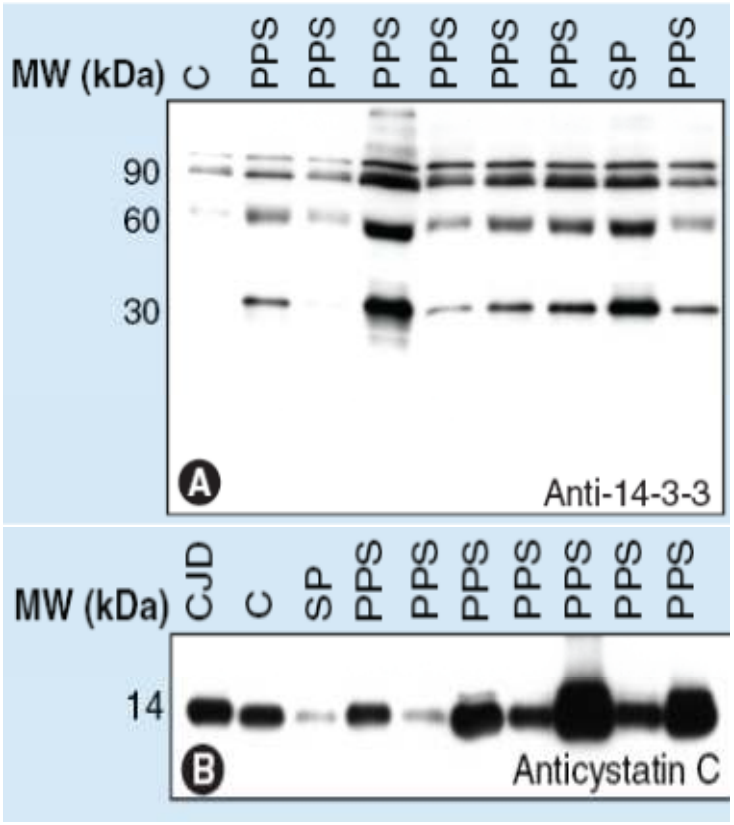
Postpolio Syndrome and CSF Markers

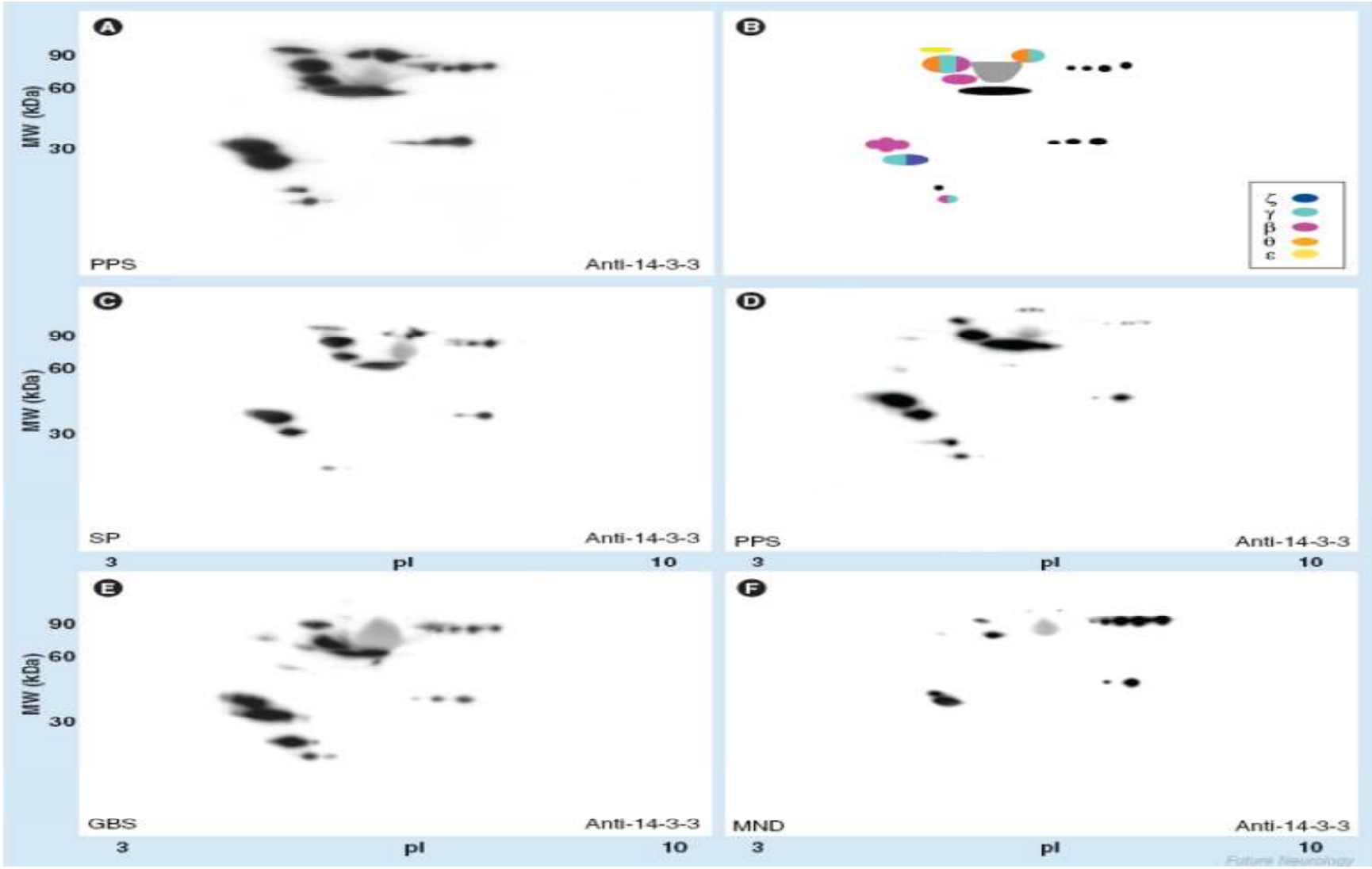
Patients

Table 3. Demographic, clinical and laboratory features of patients.

Patient No.	Diagnosis	Age (years)	CSF protein level (mg/dl)	Oligoclonal Bands	Tau (pg/ml)	1D PAGE 14-3-3	2D PAGE high molecular weight 14-3-3	Cystatin C*
1	Post-polio	52	0.24	nd	374	±	+	0.16
2	Post-polio	73	0.85	nd	115	±	+	0.98
3	Post-polio	50	0.41	nd	<60	±	+	0.22
4	Post-polio	58	0.87	nd	199	+	+	4.66
5	Post-polio	81	0.66	nd	210	+	+	nd
6	Post-polio	57	0.25	nd	<60	±	+	nd
7	Post-polio	52	0.35	nd	198	±	+	1.37
8	Post-polio	66	0.37	+	174	-	+	0.91
9	Post-polio	65	0.37	nd	167	±	+	nd
10	Post polio	51	0.37	nd	195	±	+	nd
11	Post-polio	51	0.24	nd	198	-	+	nd
12	Post-polio	73	0.25	nd	160	±	+	0.32
13	Polio	75	0.15	nd	401	±	+	0.56
14	Post-polio	60	0.21	nd	63	±	+	0.36
15	Polio	54	0.20	+	<60	+	+	0.19
16	Post-polio	54	0.27	nd	86	nd	+	1.99
17	Post-polio	52	0.24	nd	331	nd	+	7.5
18	Post-polio	62	0.22	nd	345	nd	+	11.77
19	Polio	62	0.30	nd	390	+	+	0.15

CSF Analysis





A,D: PPS; C:stable polio; F:GBS; D: ALS
Distinct 14-3-3 isoforms were identified with specific antibodies and are depicted with colors.

Conclusions: CSF Markers in PPS

- 14-3-3 protein levels are increased in the CSF of patients affected with PPS. This finding is more evident by 2D-PAGE analysis likely related to the presence of dimeric forms of 14-3-3 protein.

- 2D-PAGE analysis of 14-3-3 protein shows a pattern similar to that observed in neurological inflammatory disorders but different from ALS

- To provide insights about the inflammatory events occuring in PPS a detailed characterization of distinct 14-3-3 protein isoforms is ongoing.

- However, the low Tau protein levels detectd in PPS exclude an acute or widespread neuronal damage.

Clinical picture

- Asymmetrical and often scattered weakness, involving several segments of the spinal cord,
- No signs of upper motor neuron involvement
- No rapid and severe progressive deterioration.
- Tendon reflexes are often weakened or absent in the same scattered pattern.
- Fasciculations can be observed in the affected muscles, but is not generalized.
- Post-exercise fatigue and decreased muscular endurance during activity
- Muscle pain

History

- Raymond (1875): first case report on new muscle weakness several years after paralytic poliomyelitis (polio). A 19-year old tanner who suffered from new atrophy in his shoulder more than a decade after having passed acute polio for Charcot.

- Polio was considered to be a three-phasic illness starting with acute paralysis, followed by a recovery and subsequently a stable phase with more or less residual weakness.

- This dogma changed as the large numbers of polio survivors in the 20th century grew older and reported new symptoms several decades after the acute illness and data were systematically recorded.

- Halstead (1985): POST-POLIO as a new term to cover all aspects of late consequences occurring several years after acute paralytic polio. The symptoms included were new weakness, generalized fatigue, decreased muscular endurance, muscle pain, joint pain, and cold intolerance.

- Halstead and Dalakas: suggestive criteria and definition

1. Confirmed history of polio
2. Partial or fairly complete neurological and functional recovery after the acute episode
3. Period of at least 15 years with neurological and functional stability
4. Two or more of the following health problems occurring after a stable period: extensive fatigue, muscle and/or joint pain, new weakness in muscles previously affected or unaffected, new muscle atrophy, functional loss, cold intolerance
5. No other medical explanation found
6. Gradual or abrupt onset of new neurogenic weakness

- PPS is a condition following paralytic polio in which the muscle strength and clinical function are slowly deteriorating, without any dramatic loss of muscle strength as in motor neuron diseases.

- Guidelines for diagnosis and management
  - US (MoD) (March of Dimes 2000)
  - Europe (EFNS) (Farbu et al. 2006)

- Very subtle and insidious start.
- Clinical course rather modest, with no devastating progressive weakness (such as in ALS).
- Once the threshold for the neuromuscular compensatory mechanisms is passed, a more stepwise deterioration can be seen.

- Overuse and metabolic stress on enlarged motor units, deterioration of the neuromuscular junction, the normal ageing process and inflammatory changes are thought to contribute to the clinical picture.

- Muscle weakness, atrophy, generalised fatigue, post-exercise fatigue, muscle pain, fasciculations, cramps, cold intolerance, and joint pain dominate.

- Common symptoms in the general ageing population and could be caused by a considerably amount of other conditions and illnesses.

- Primary goal → rule out other possible contributing factors.

The March of Dimes Criteria

- Prior paralytic poliomyelitis with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness, and atrophy of muscles on neurological examination, and signs of denervation on electromyography (EMG).
- A period of partial or complete functional recovery after acute paralytic poliomyelitis, followed by an interval (usually 15 years of more) of stable neurologic function.
- Gradual or sudden onset of progressive and persistent muscle weakness or abnormal muscle fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain. (Sudden onset may follow a period of inactivity, or trauma, or surgery). Less commonly, symptoms attributed to PPS include new problems with swallowing or breathing.
- Symptoms persist for at least a year.
- Exclusion of other neurologic, medical, and orthopaedic problems as causes of symptoms.

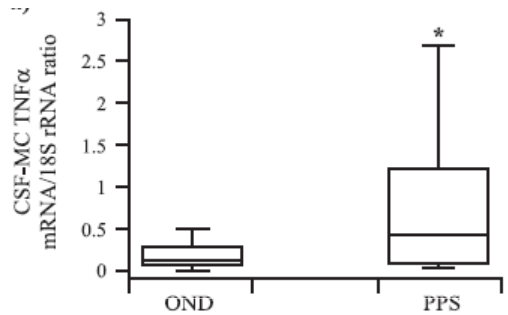
Prior poliomyelitis—IvIg treatment reduces proinflammatory cytokine production

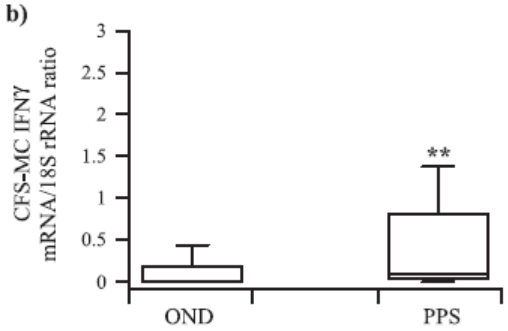
Henrik Gonzalez[a,b,*], Mohsen Khademi[c], Magnus Andersson[a,c], Fredrik Piehl[c], Erik Wallström[a,c], Kristian Borg[a,d], Tomas Olsson[c]

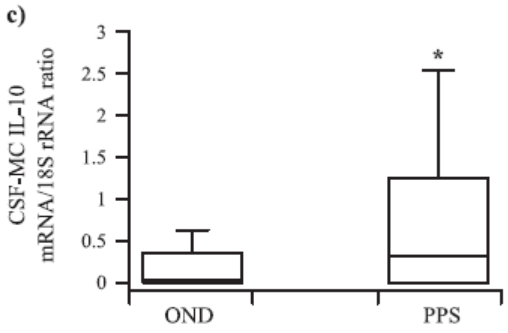
Journal of Neuroimmunology 150 (2004) 139–144

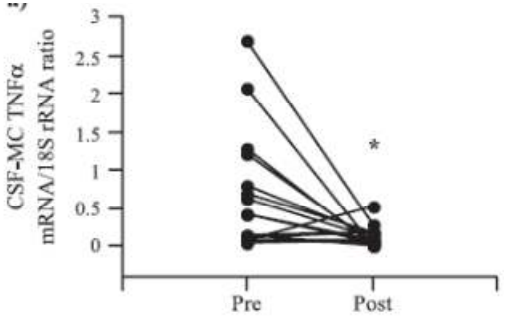
CSF

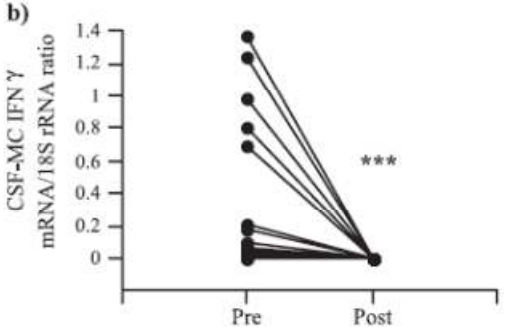
After IvIg treatment

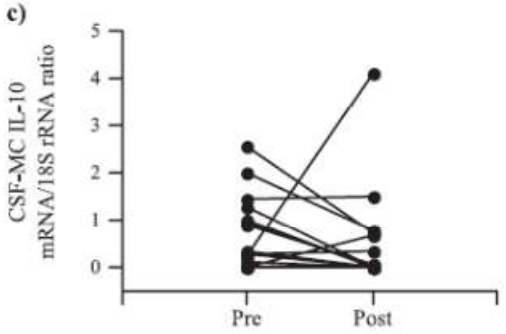












Interpretation

- Kallikrein 6: normally expressed in neurons and oligodendrocyes up-regulated after inflammatory damages. (Expression of neurite outgrowth or toxic to oligodendrocytes)

- Fragments of Gelsolin: Related to an increase of caspase 3 activity and reduction of antiapoptotic effect

- Hemopexin: Expressed in acute phases of CNS damage

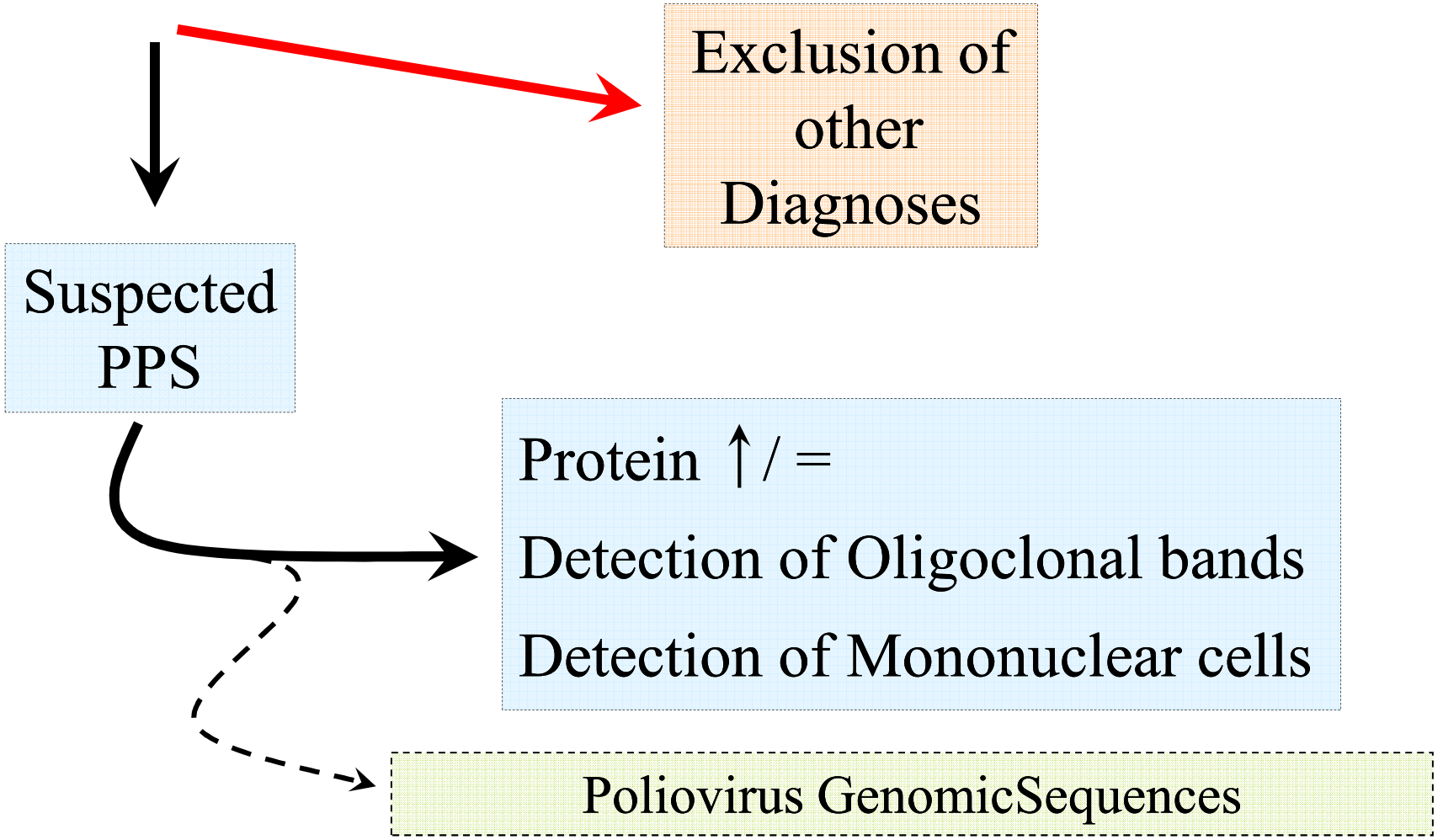
- Expression of a chronic inflammatory CNS damage, possibly related to an autoimmune mechanism or a viral persistence ?????

- These proteins plays a role in the pathophysiology

- Candidate Biomarkers

Standard CSF in Post-Polio Syndrome

CSF Standard



Virology of the post-polio syndrome

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Elisa Dall'ora,
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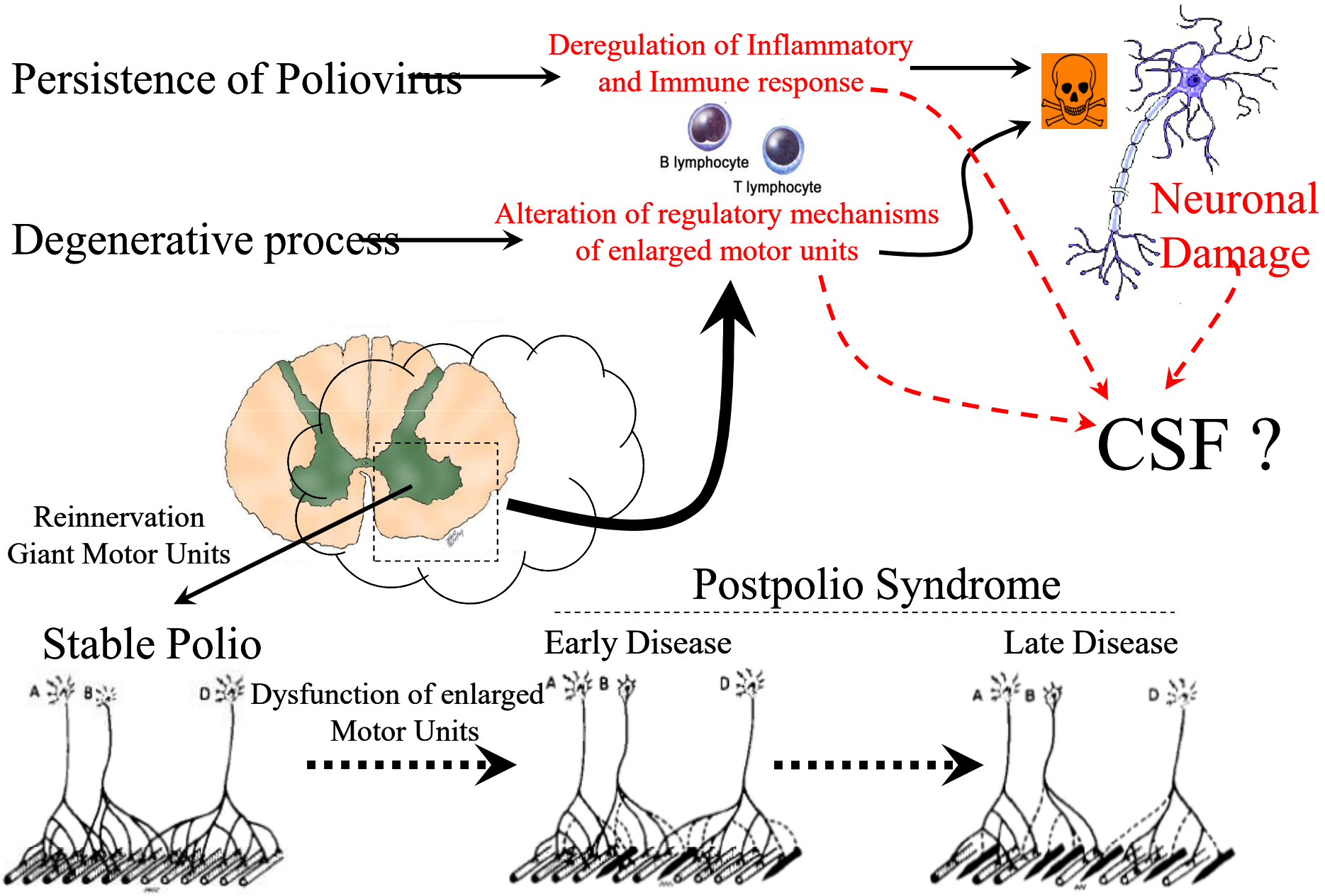
The three poliovirus serotypes (PVs) cause acute paralytic poliomyelitis. Decades after being hit by polio, survivors may develop a condition known as post-polio syndrome (PPS). PPS is characterized by extreme fatigue, progressing muscular weakness and chronic pain. The pathogenesis is unclear and, thus, empirical therapies are employed. PVs are known to be able to persist in infected host cells both *in vitro* and *in vivo*. The understanding of PV genomes has made it possible to set up sensitive and specific molecular tests capable of detecting minute amounts of virus in samples from PPS patients. Current data indicate that complete PV genomes (or genomic fragments) remain present, decades after acute paralysis, in the CNS of these patients. Virus persistence is hypothesized to bring about chronic inflammation, immune-mediated injury and decreased expression of neurotrophic factors. Establishing a pathogenetic link between PV persistence and PPS would be extremely relevant to the development of an etiologic therapy aimed at virus eradication.

Post-polio syndrome

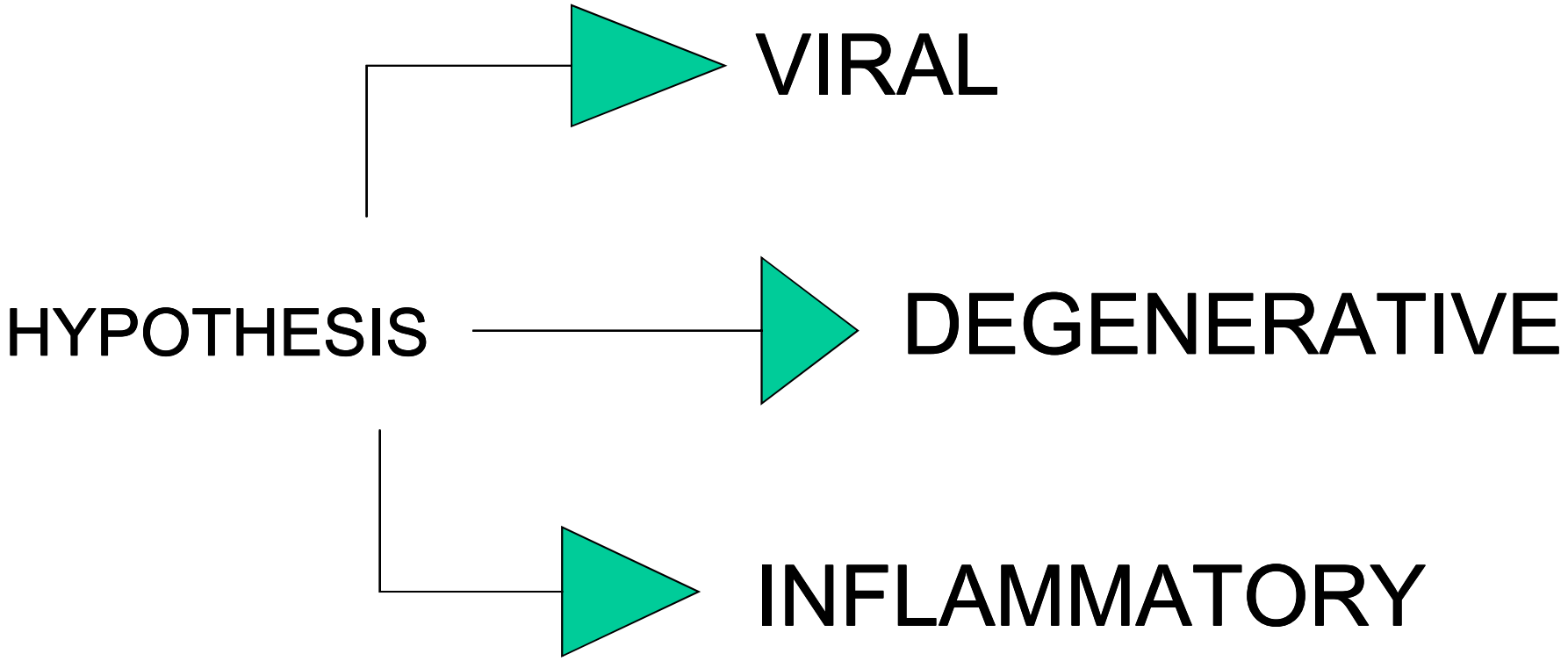
The three poliovirus serotypes (PVs) cause acute

(~740 nucleotides) has a complex secondary structure representing the internal ribosome

Hypothesized Mechanisms leading to Motorneuron Dysfunction



PATHOGENESIS

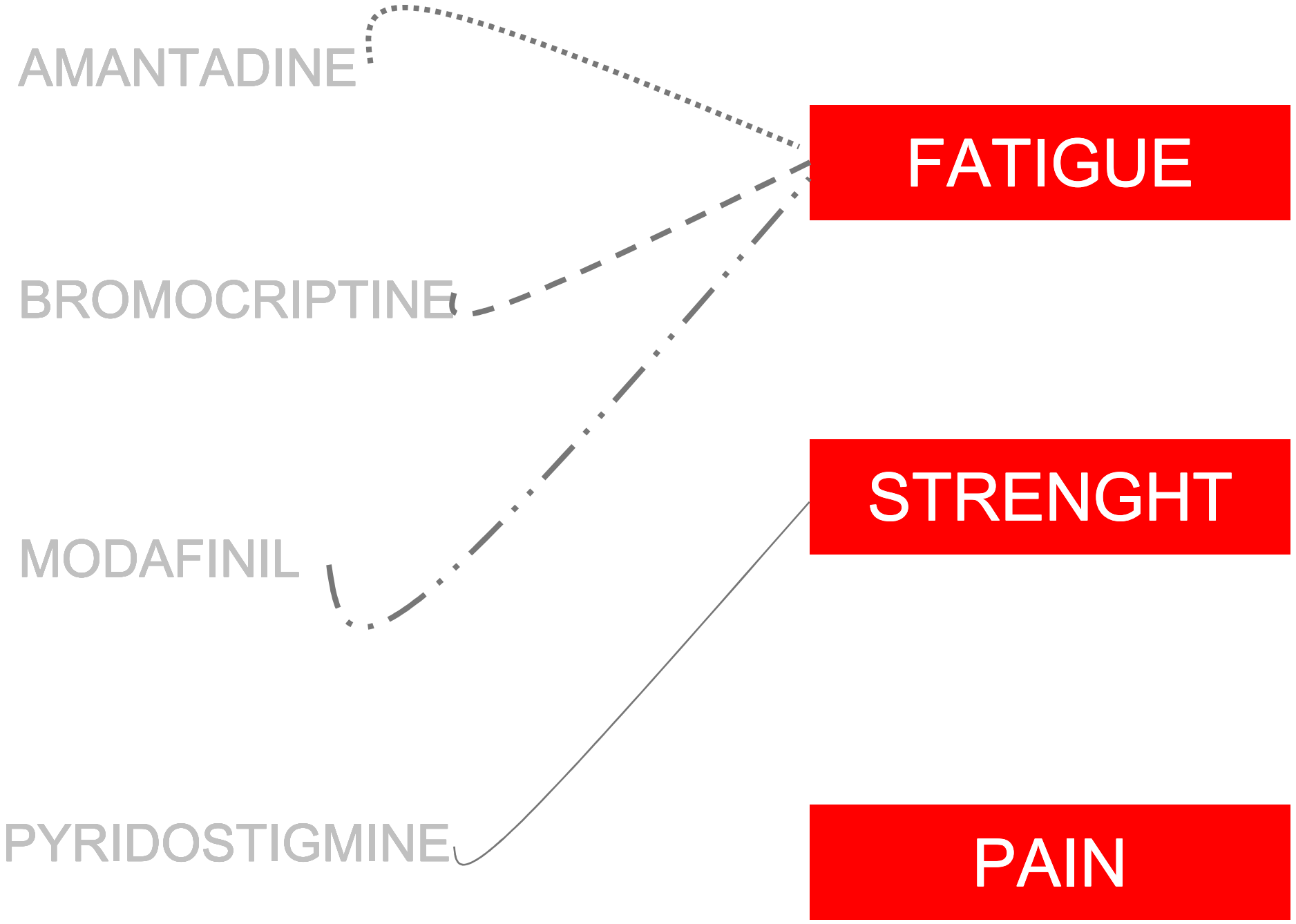


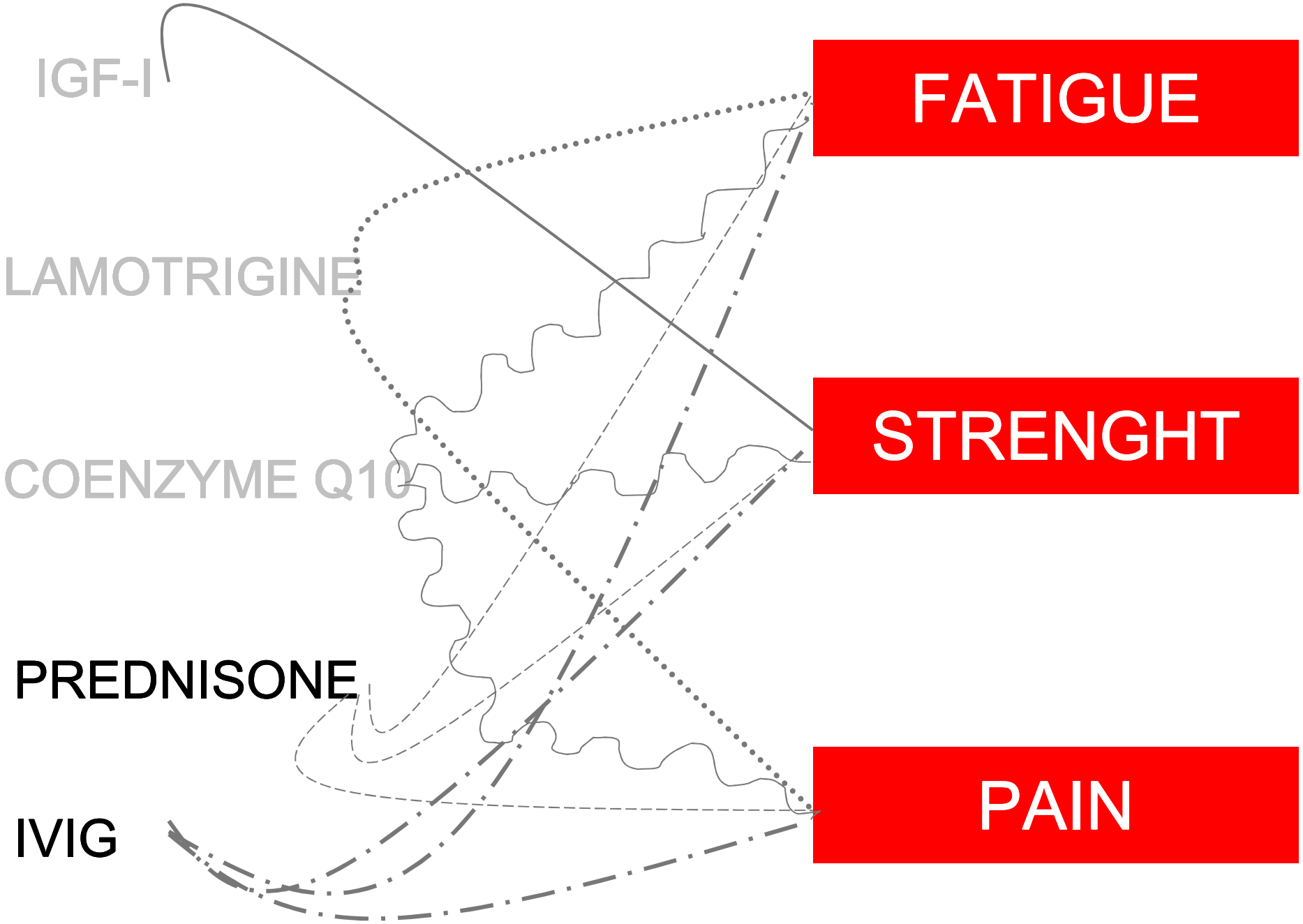
Post-polio syndrome: clinical manifestations and cerebrospinal fluid markers

Michele Fiorini, Gianluigi Zanusso, Andreina Baj, Laura Bertolasi, Antonio Toniolo, Salvatore Monaco

Future Neurology, July 2007, Vol. 2, No. 4, Pages 451-463
(doi: 10.2217/14796708.2.4.451)

14-3-3
Tau
Cystatina C


AMANTADINE
BROMOCRIPTINE
MODAFINIL
PYRIDOSTIGMINE
FATIGUE
STRENGHT
PAIN


IGF-I
LAMOTRIGINE
COENZYME Q10
PREDNISONE
IVIG
FATIGUE
STRENGHT
PAIN

Prior poliomyelitis—IvIg treatment reduces proinflammatory cytokine production Henrik Gonzalez, Mohsen Khademi, Magnus Andersson, Fredrik Piehl, Erik Wallström, Kristian Borg, Tomas Olsson	Ig vena 30 g/die per 3 giorni	16 pz	↓ INF-γ mRNA TNF-α liquor e sangue	6/8 sett
J Rehabil Med 2006; 38: 138–140 SHORT COMMUNICATION EFFECT OF INTRAVENOUS IMMUNOGLOBULIN IN PATIENTS WITH POST-POLIO SYNDROME – AN UNCONTROLLED PILOT STUDY Georgios Kaponides, MD, Henrik Gonzalez, MD, Tomas Olsson, MD, PhD and Kristian Borg, MD, PhD	Ig vena 30 g/die per 3 giorni	14 pz	↑ qualità della vita (=forza e performance fisica)	2 mesi
Intravenous immunoglobulin In postpolio syndrome **Farbu et al** *Tidsskrift for Den norske legeforening*	Ig vena 400mg/ Kg per 5 giorni	1 pz	↑ forza muscolare ↓ fatica	2/3 mesi
Intravenous immunoglobulin for post-polio syndrome: a randomised controlled trial Henrik Gonzalez, Katharina Stibrant Sunnerhagen, Ingar Sjöberg, Georgios Kaponides, Tomas Olsson, Kristian Borg Lancet Neurol 2006; 5: 493–500	Ig vena 30 g/die per 3 giorni	73 pz ter 69 placebo	↑ forza muscolare PASE ↑ VAS ↓	2 mesi dopo il 2° trattamento
Post-polio syndrome patients treated with intravenous immunoglobulin: a double-blinded randomized controlled pilot study E. Farbu, T. Rekand, E. Vik-Mo, H. Lygren, N. E. Gilhus and J. A. Aarli *European Journal of Neurology* 2007, **14:** 60–65	Ig vena 2g/Kg (in 2-4 giorni)	20 pz	↓ VAS	2/3 mesi

- The secondary outcome measures were:
- 1. muscle strength;
- 2. muscle endurance;
- 3. fatigue;
- 4. pain;
- 5. adverse events subdivided into minor adverse events and
- serious adverse events (resulting in cessation of treatment,
- requiring hospitalisation or being life-threatening or fatal).

STUDY PROTOCOL

STUDY TITLE

"IMMUNOGLOBULIN TREATMENT IN "
POSTPOLIO SYNDROME

STUDY DESIGN

Two arms double blind RCT (treatment vs placebo)

INCLUSION CRITERIA

1. Postpolio diagnosis according to Halstead's criteria (Orthopedics 1991; 14: 1209-1217), reconfirmed in 2006 by ENFS
   - anamnesis and neurological examination
   - electrophysiological examination

2. Exclusion of any other neurological, orthopaedic or medical problems as causes of symptoms
   - electrophysiological examination
   - laboratory analysis
   - (orthopaedic examination)
   - (imaging)

Diagnosis of postpolio syndrome

1. History of previous estabilished episodes of paralytic polio
2. Partial or fairly complet recovery
3. Period of functional and clinical stability of at least 15 years
4. Sudden or gradual onset of new symptoms and sings of muscle disfunction:
   - muscle weakness
   - new muscle atrophy
   - muscle or joint pain,
   - loss of muscle function
   - cold intolerance

Electrophysiological examination:

ENG and EMG

- Signs of “ancient” neurogenic reorganization due to previous poliovirus infection
- Signs of new lower motor neuron lesions → reactivation of pathogenic pathway

PESS

- Normal sensory findings;useful tu rule out root or nerve trunk pathology

Further investigations:

Imaging studies: mainly Back bone MRI in order to rule out entrapment or root compression

ORTHOPEDIC EVALUATION: to rule out bone or joint involvement

Esclusion of patients with POST-POLIO SYNDROME and contemporary RADICULOPATHY in the same innervation territories→ **SELECTED POPULATION**

EXCLUSION CRITERIA

- BMI> 30
- Diabetes Mellitus
- Mild or severe heart disease
- Renal Failure
- Hypertension
- History of thromboembolism
- Oral anticoagulant therapy
- Previous IVIG treatment
- IgA deficiency
- Other autoimmune diseases
- Age > 70yrs
- Other causes of controindication ti therapy
- Other causes able to explain the complained symptoms

TREATMENT

- Immunoglobuline e.v. alla dose di 0,4 g/Kg/daily or Placebo (saline) for 5 days
- Direct monitoring by a clinic or a paraclinic involved in the project

PHASE I

1. Selection of patients according to inclusione and exclusion criteria
2. Presentation of the project to the patient which also receives informed consent form
3. Electrophysiological examination :
   - 4 limbs ENG
   - EMG → stable muscle (no variations in the time)
     → healthy muscle (not interested by acute infection)
     → worsened muscle (new muscle weakness after a period of clinical stability of at least 15 years)
   - 4 limbs TMS
   - 4 limbs SEP
4. Laboratory workup:
   - Blood count
   - IgA titration
   - Haepatic and renal function
   - Serology for HIV and haepatitis

PHASE II

Patient's clinical evalutation:

Muscolar Strenght	MRC Dynamic dinamometer
Fatigue	Fatigue severity scale (FSS)
Pain	Analogue Scale (VAS) 101 Point Numerical Rating (101-PNR)
Quality of life	SF-36 (36 item Short-Form)
Muscle function	6 minutes walkin test (6 MWT)

PHASE III

TREATMENT

25 PAZIENTS
IVIG 0,4 g/Kg/daily for 5 consecutive days

25 CONTROLLI
PLACEBO (saline) at the same way

Infusion:
- initial speed: 0,46-0,92 ml/kg/h → 10-20 gtt/min
- maximal speed: 1,85 ml/Kg/h → 40 gtt/min)

PHASE IV

CLINICAL FOLLOW-UP	ELECTROPHYSIOLOGICAL FOLLOW-UP
With: – MRC and Dynamometer – FSS – VAS and 101-PNR – SF-36 – 6 MWT	Mediante: – 4 limbs ENG – 3 muscle EMG – 4 limbs SEP – 4 limbs TMS

2 months

4 months

Estimated period of participation of the patient

6 months

The patient can stop the treatment and leave the study anytime

RANDOMIZATION

- Double blind study
- Randomization codes elaborated with statistical software STATA 9.2 *(HYPERLINK)* by the department of epidemiology and medical statistics, of the Universtity of Verona and delivered to Bussolengo's ASL pharmacist
- Every patients gets a code which he keeps for the duration of the whole study
- Pharmacy of Bussolengo's Hospital prepares the samples: same bags labelled and screened containing venous Ig and saline

MAIN RESPONSE VARIABLES

- PRIMARY END POINT:
  better score of physical component of SF-36 in treated subjects compared with placebo
- SECONDARY END POINT:
  - Increase in muscolar strenght (MRC, Dynamometer)
  - Reduction of fatigue (FSS)
  - Reduction of pain (VAS, 101-PNR)
  - Improvement in muscle function (6 MWT)

Sample's dimention and statical power

Assuming:

- An improvement of at least 4 points in the score of physical component of SF-36 *(Gonzales et al. 2004; Kaponides et al. 2006)*
- Alfa= 0,05
- 80% power
- correlazione tra due misurazioni sullo stesso soggetto di 0,9
- rapporto di randomizzazione 1:1

…we need 21 subjects in every arm

Which will be raised to 25 SUBJECTS in account of eventual dropouts

DATA ANALYSIS

"INTENTION TO TREAT" analysis

Primary and secondary endpoints:

Comparison of differences in the score of the scale used before and after treatment in the two groups by means of

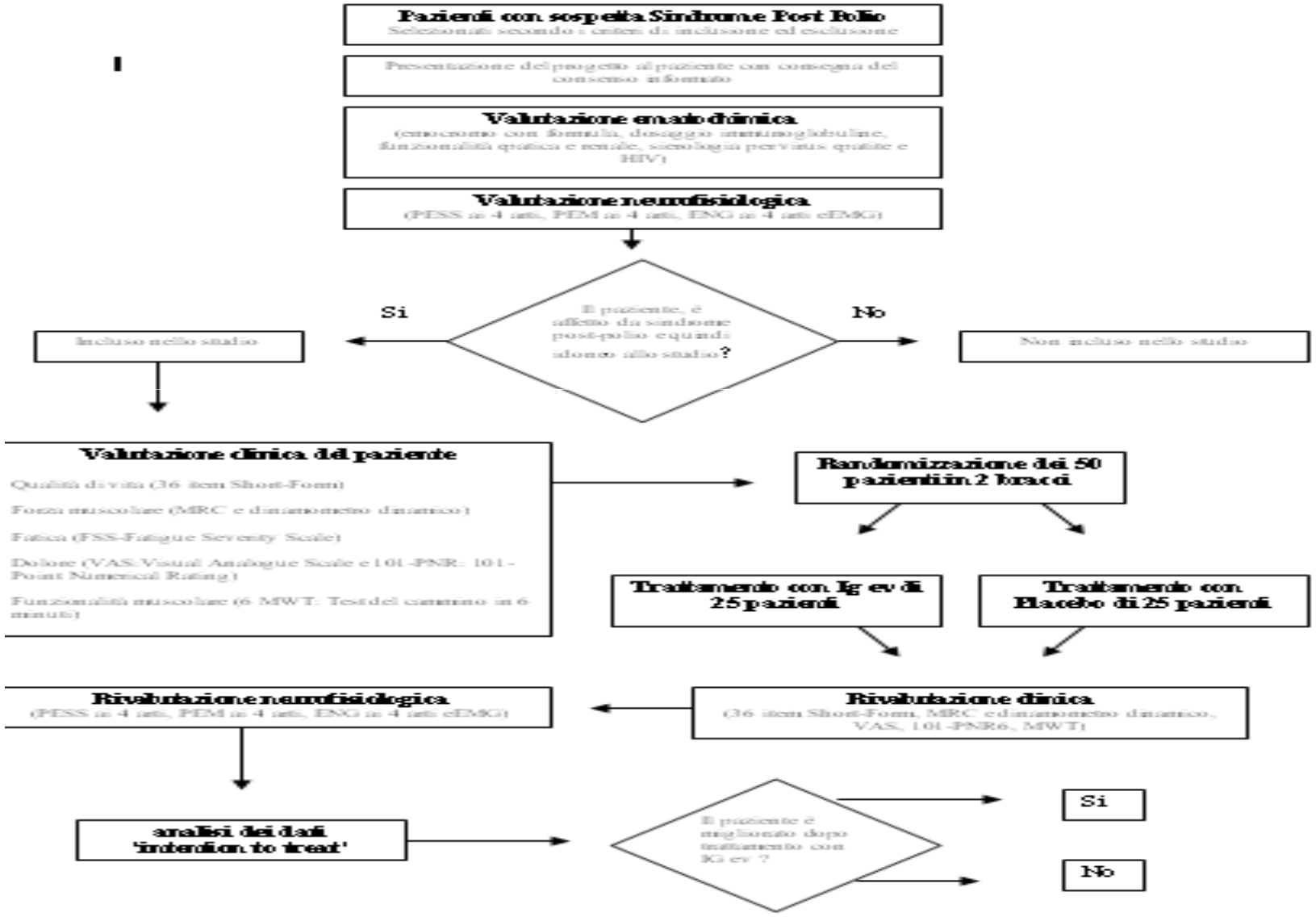
- T-TEST (in case of gaussian distribution)
- TEST of MANN-WHITNEY (in case of non gaussian distribution)

If necesssary check out for biases (eg,severity of pathology, age):

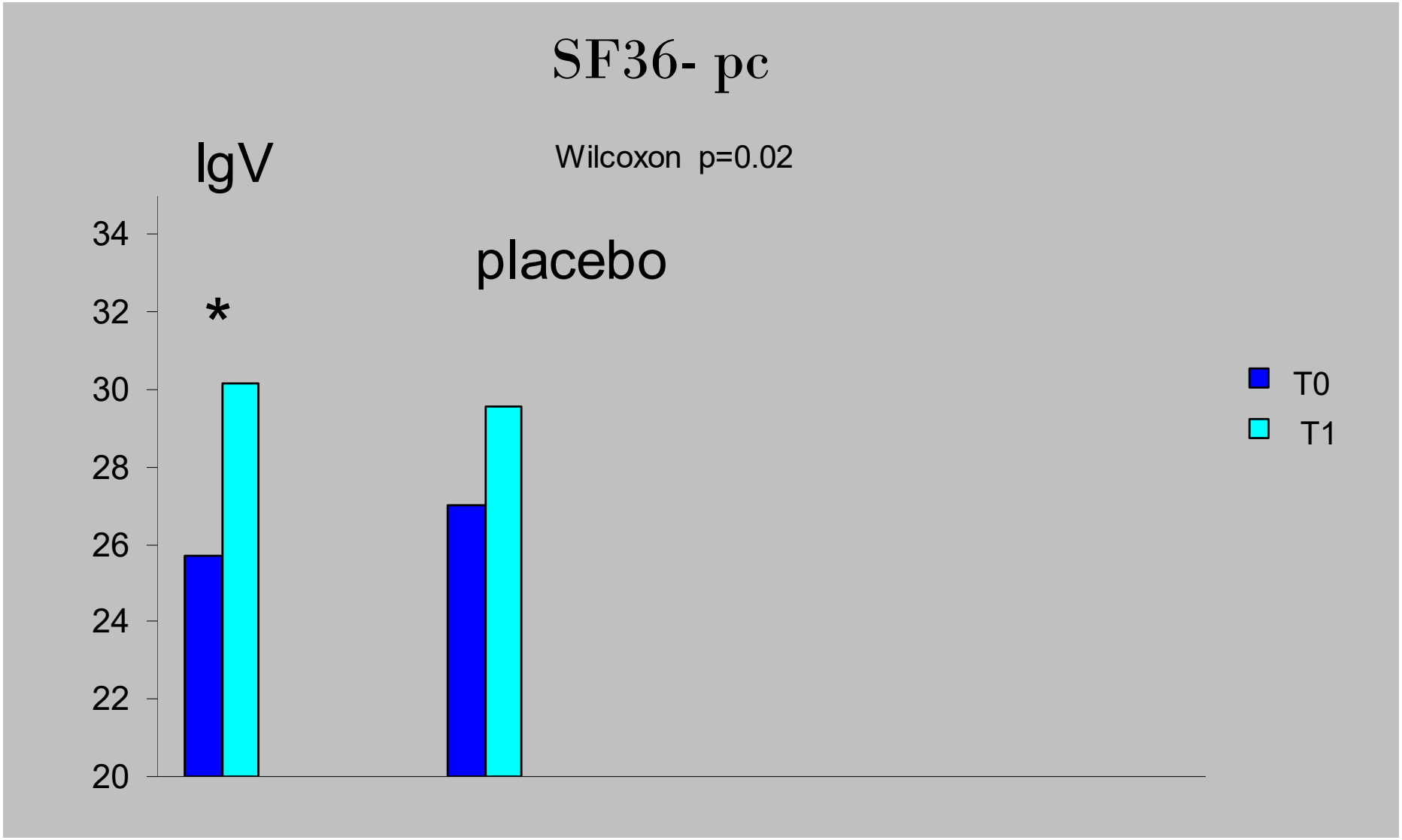
- COVARIANCE ANALYSIS
  - Dependent variable: difference between values in variables before and after treatment/placebo
  - Indipendent variable : group (treatment/placebo); age; disease severity

Statistical analysis by means of software STATA 9.2

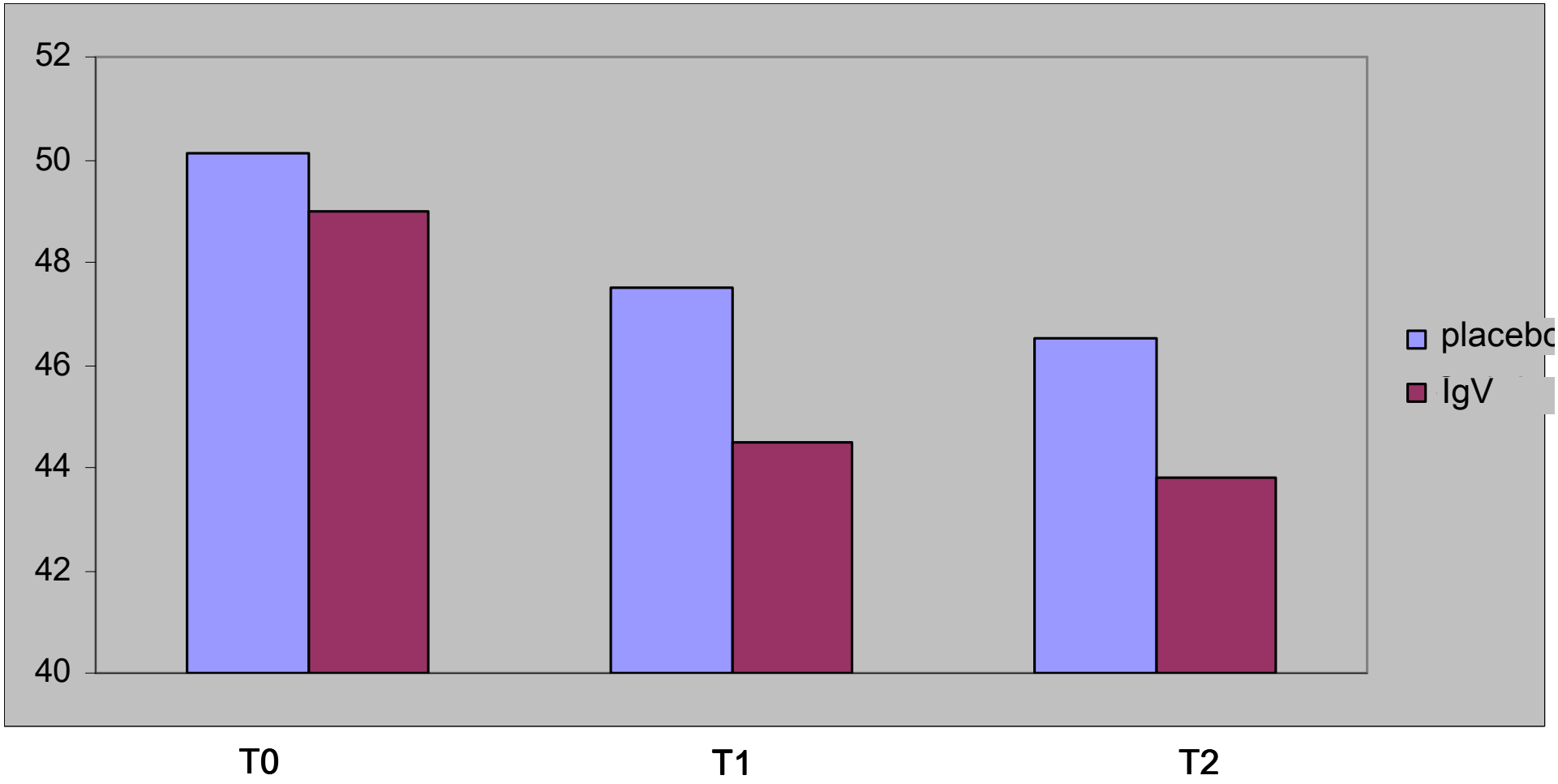
FLOW CHART


Pazienti con sospetta Sindrome Post Polio
Selezionati secondo i criteri di inclusione ed esclusione
Presentazione del progetto al paziente con consegna del consenso informato
Valutazione emato chimica
(emocromo con formula, dosaggio immunoglobuline, funzionalità epatica e renale, sierologia per virus epatite e HIV)
Valutazione neurofisiologica
(PESS su 4 arti, PEM su 4 arti, ENG su 4 arti cEMG)
Si
No
Il paziente, è affetto da sindrome post-polio e quindi idoneo allo studio?
Incluso nello studio
Non incluso nello studio
Valutazione clinica del paziente
Qualità di vita (36 item Short-Form)
Forza muscolare (MRC e dinamometro dinamico)
Fatica (FSS-Fatigue Severity Scale)
Dolore (VAS:Visual Analogue Scale e 101-PNR: 101-Point Numerical Rating)
Funzionalità muscolare (6-MWT: Test del cammino in 6 minuti)
Randomizzazione dei 50 pazienti in 2 bracci
Trattamento con Ig ev di 25 pazienti
Trattamento con Placebo di 25 pazienti
Rivalutazione neurofisiologica
(PESS su 4 arti, PEM su 4 arti, ENG su 4 arti cEMG)
Rivalutazione clinica
(36 item Short-Form, MRC e dinamometro dinamico, VAS, 101-PNR6, MWT)
analisi dei dati 'intention to treat'
Il paziente è migliorato dopo trattamento con Ig ev ?
Si
No

PRIMARY END POINT



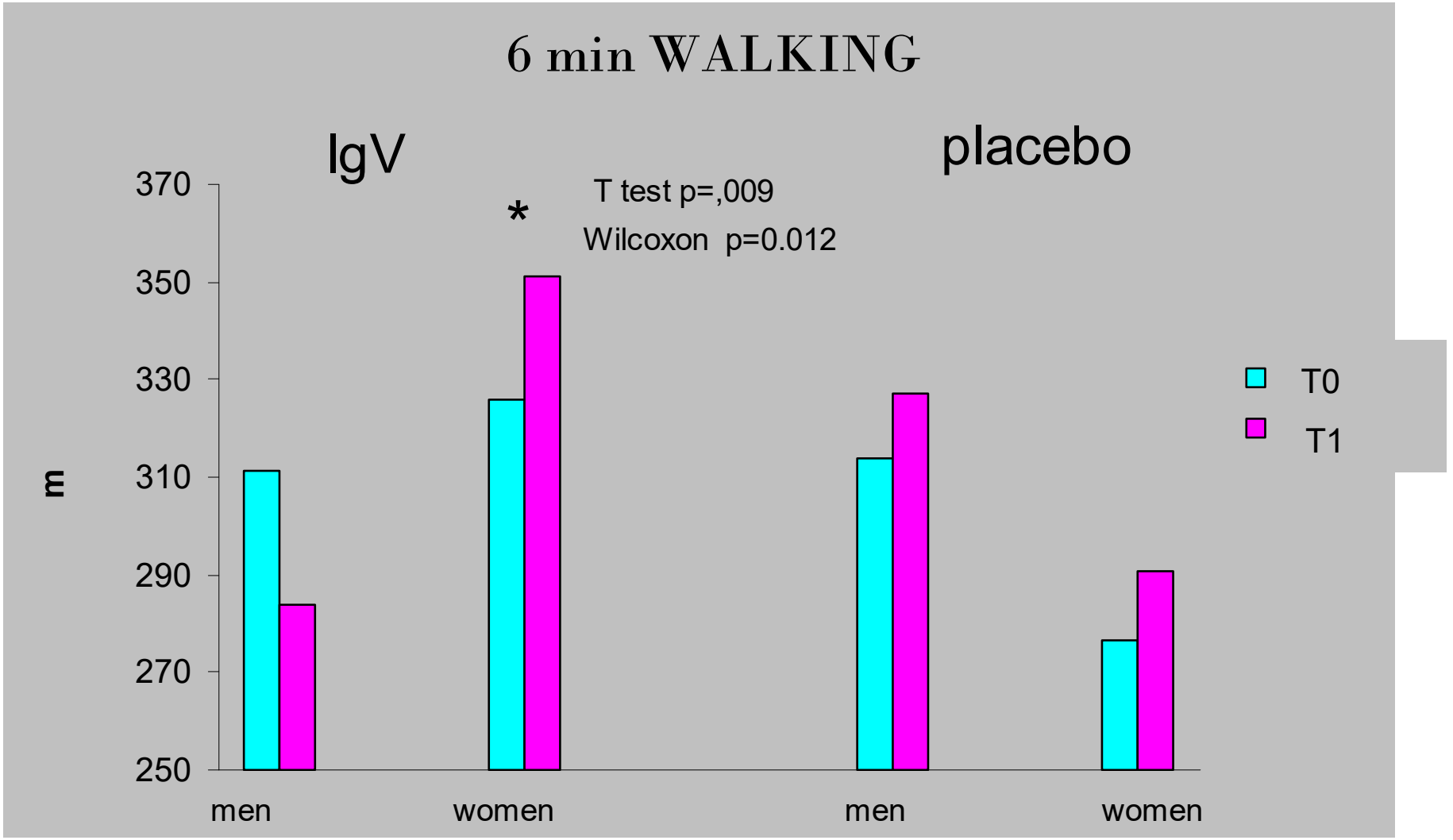
FSS



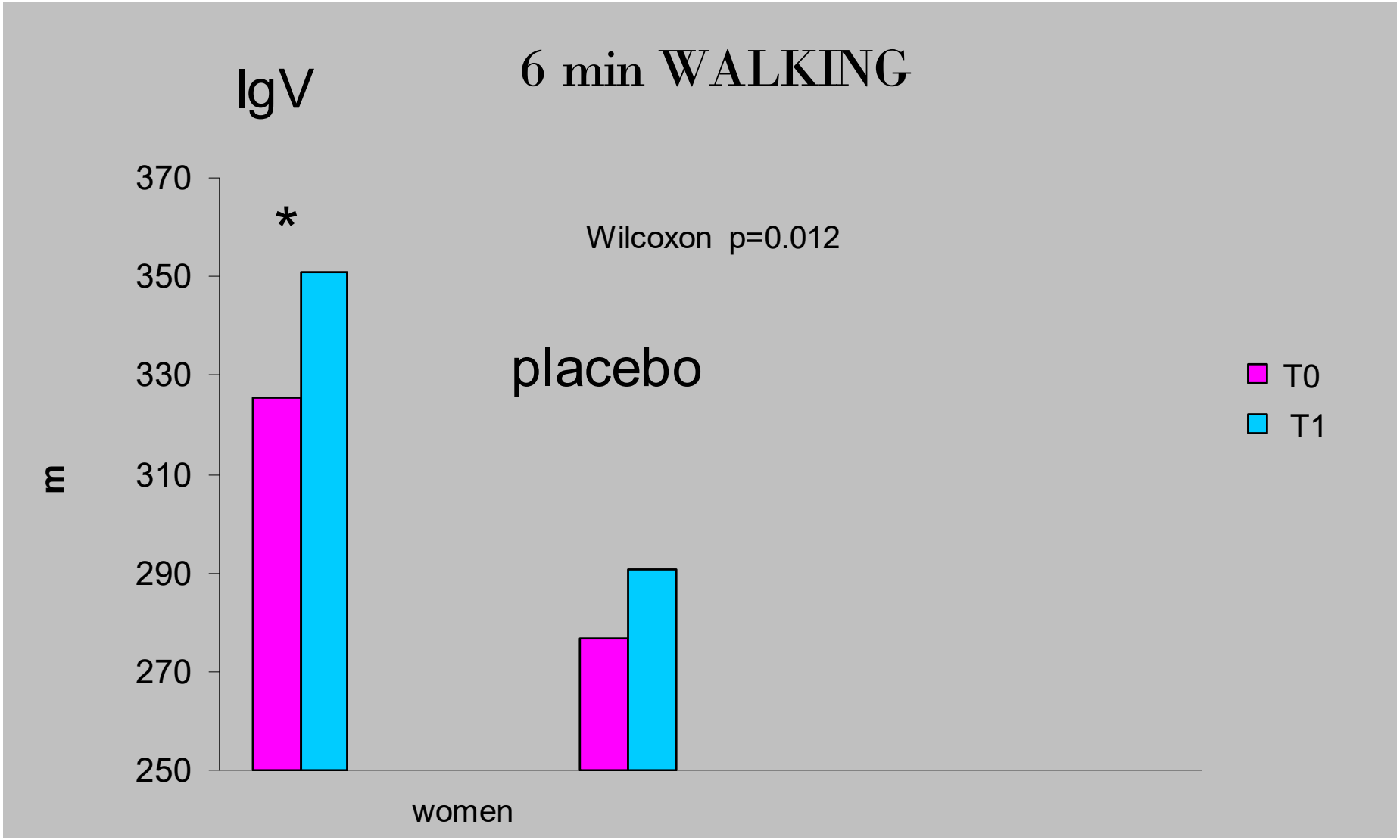
STRATIFIED ANALYSIS

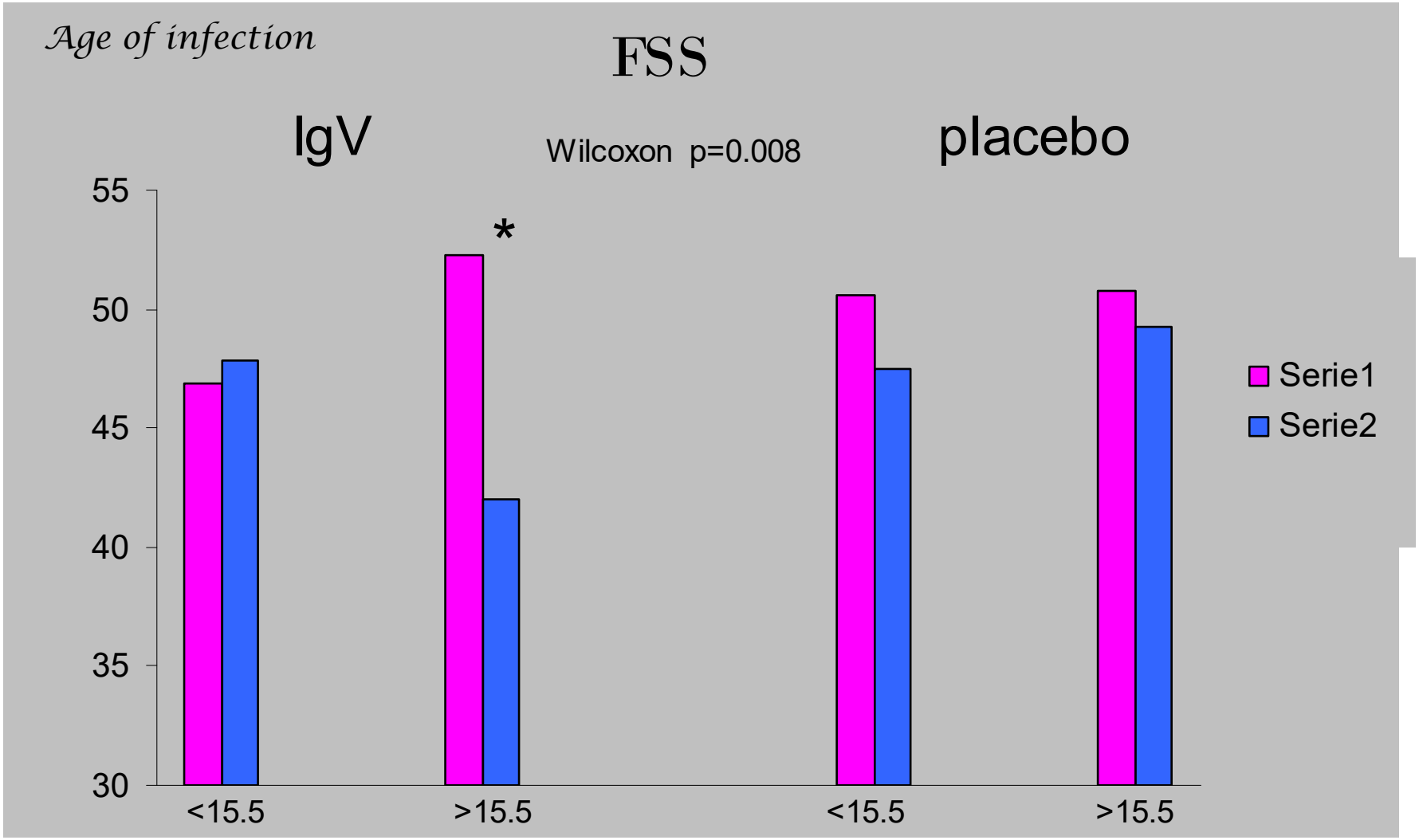
Sex	F	M
Age of infection	<15,5	>15,5
Age of worsening	<50	>50
tempo X trattamento	<7,5	>7,5
FSS T0	<53,5	>53,5
VAS T0	<5,5	>5,5
6 min walking T0	<296,5	>296,5
SF36-pcT0	<24,9	>24,9

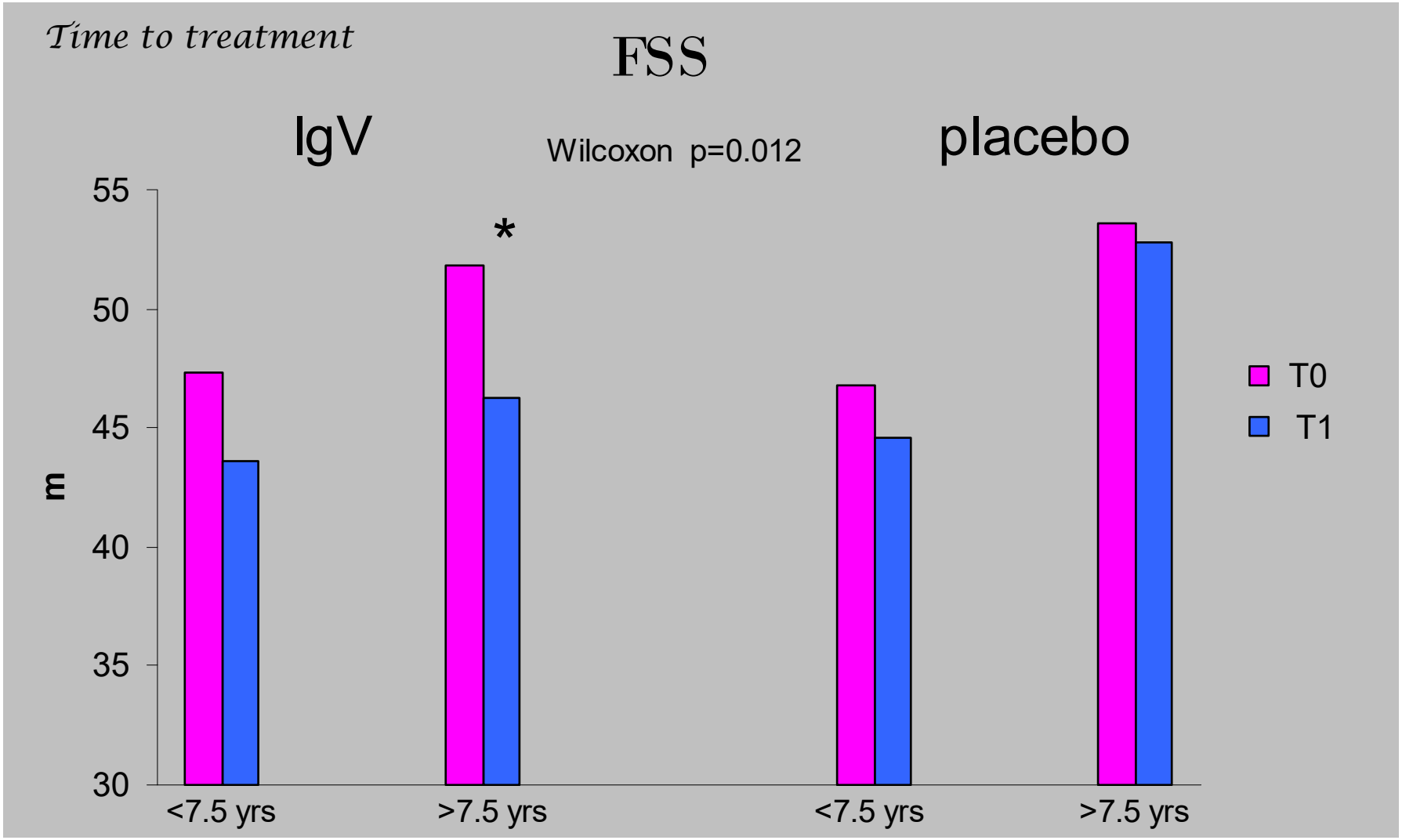
Sex

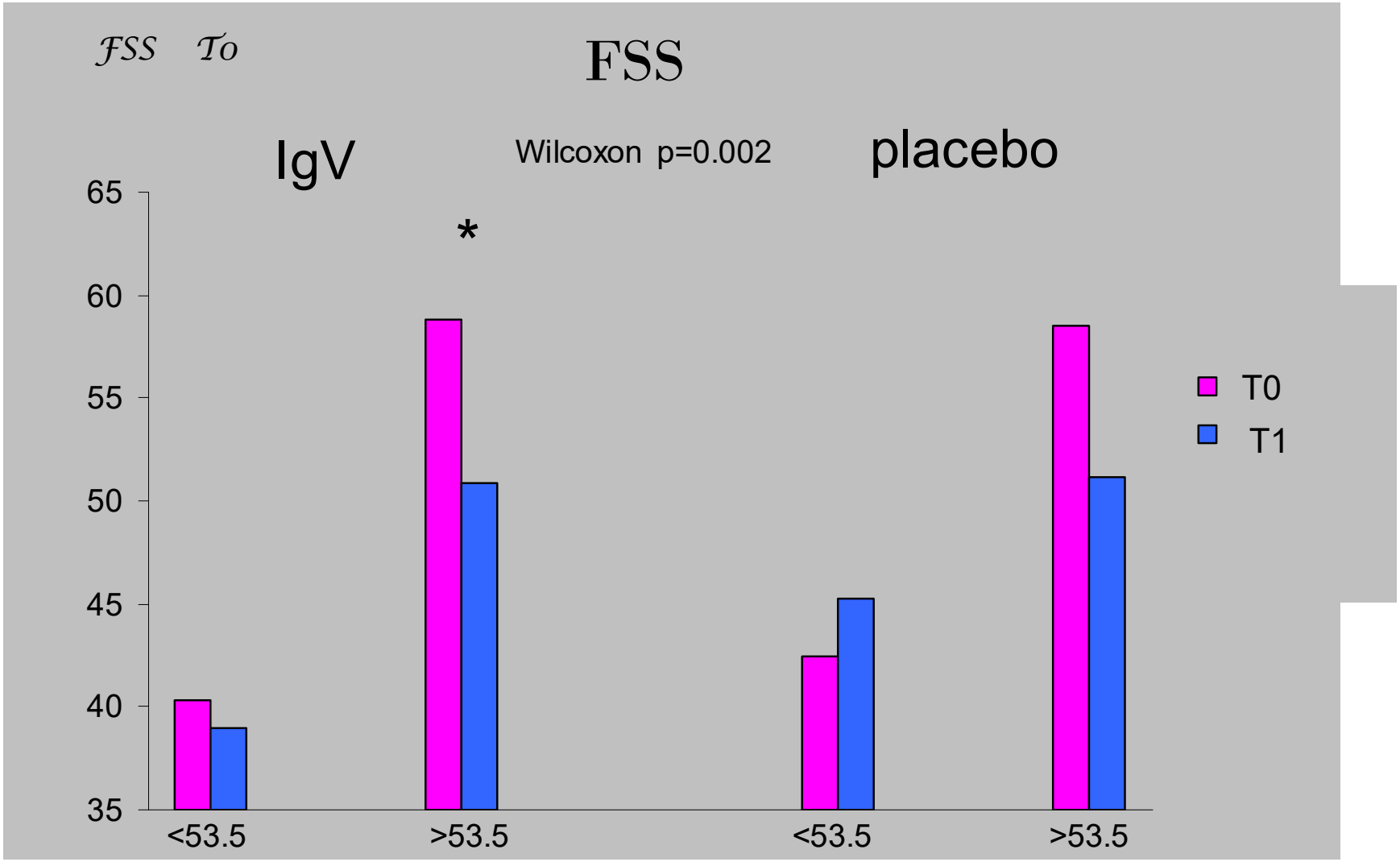

6 min WALKING
IgV
placebo
*
T test p=,009
Wilcoxon p=0.012
370
350
330
310
290
270
250
m
men
women
men
women
T0
T1

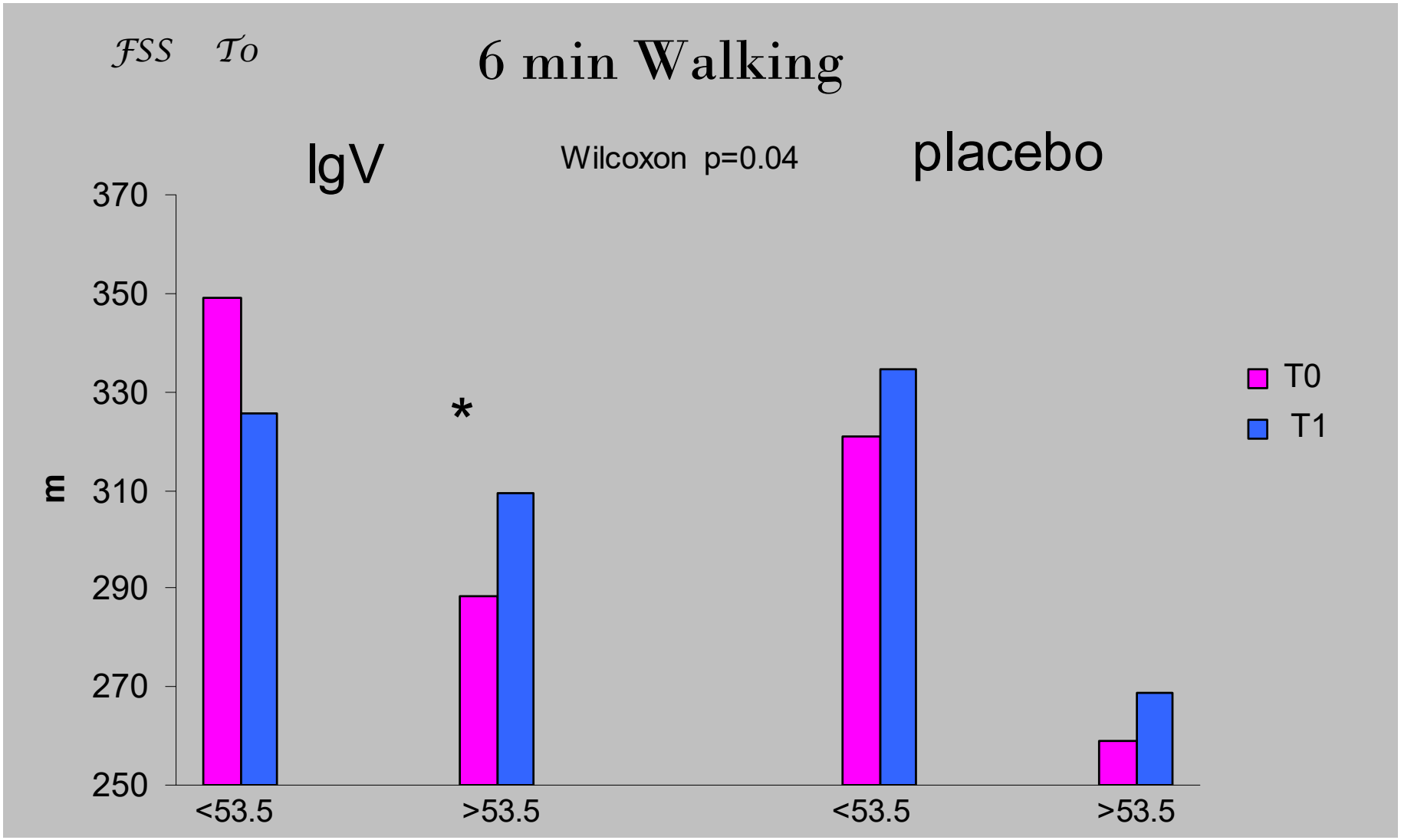
Sex

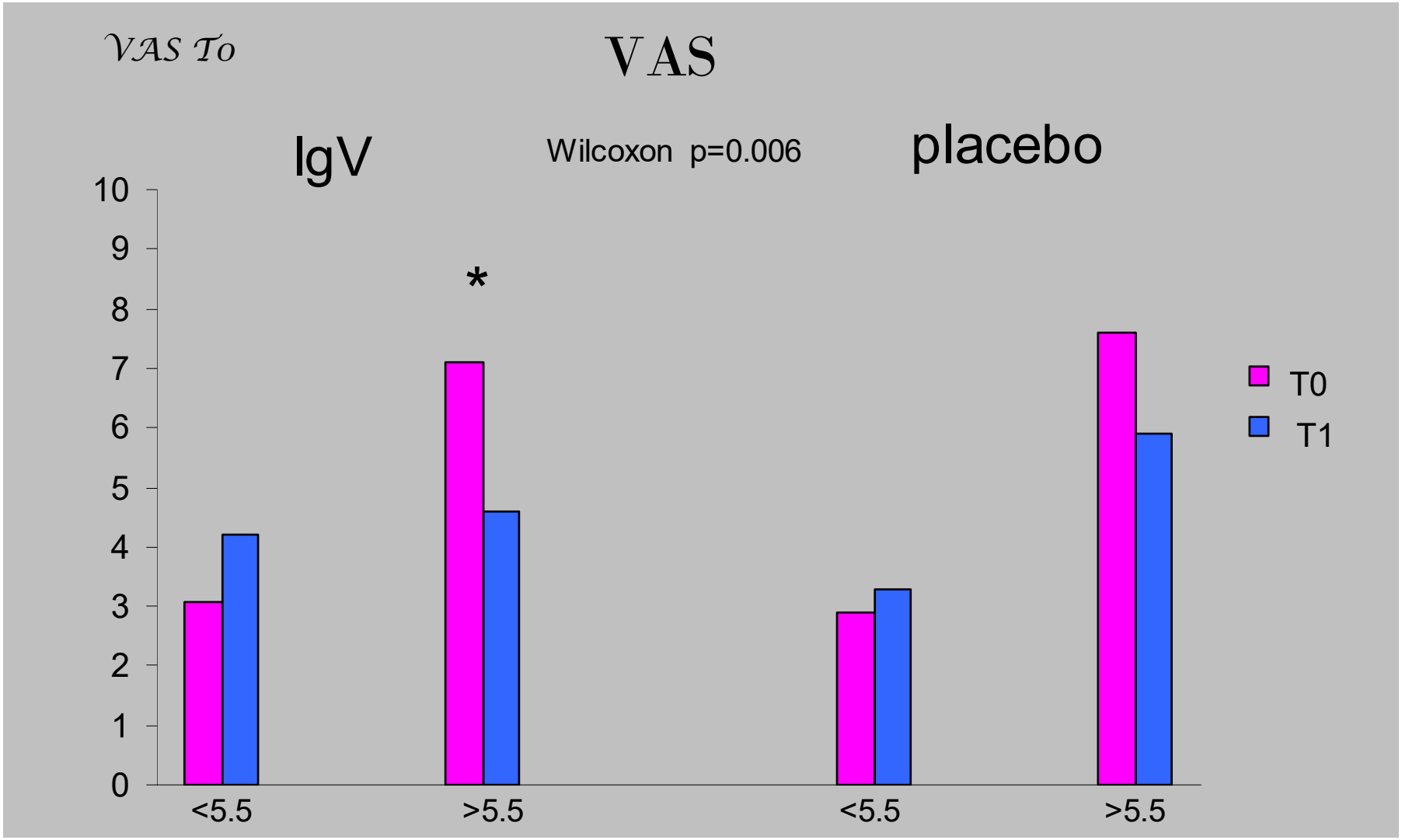

6 min WALKING
lgV
370
350
330
310
290
270
250
m
*
Wilcoxon p=0.012
placebo
T0
T1
women

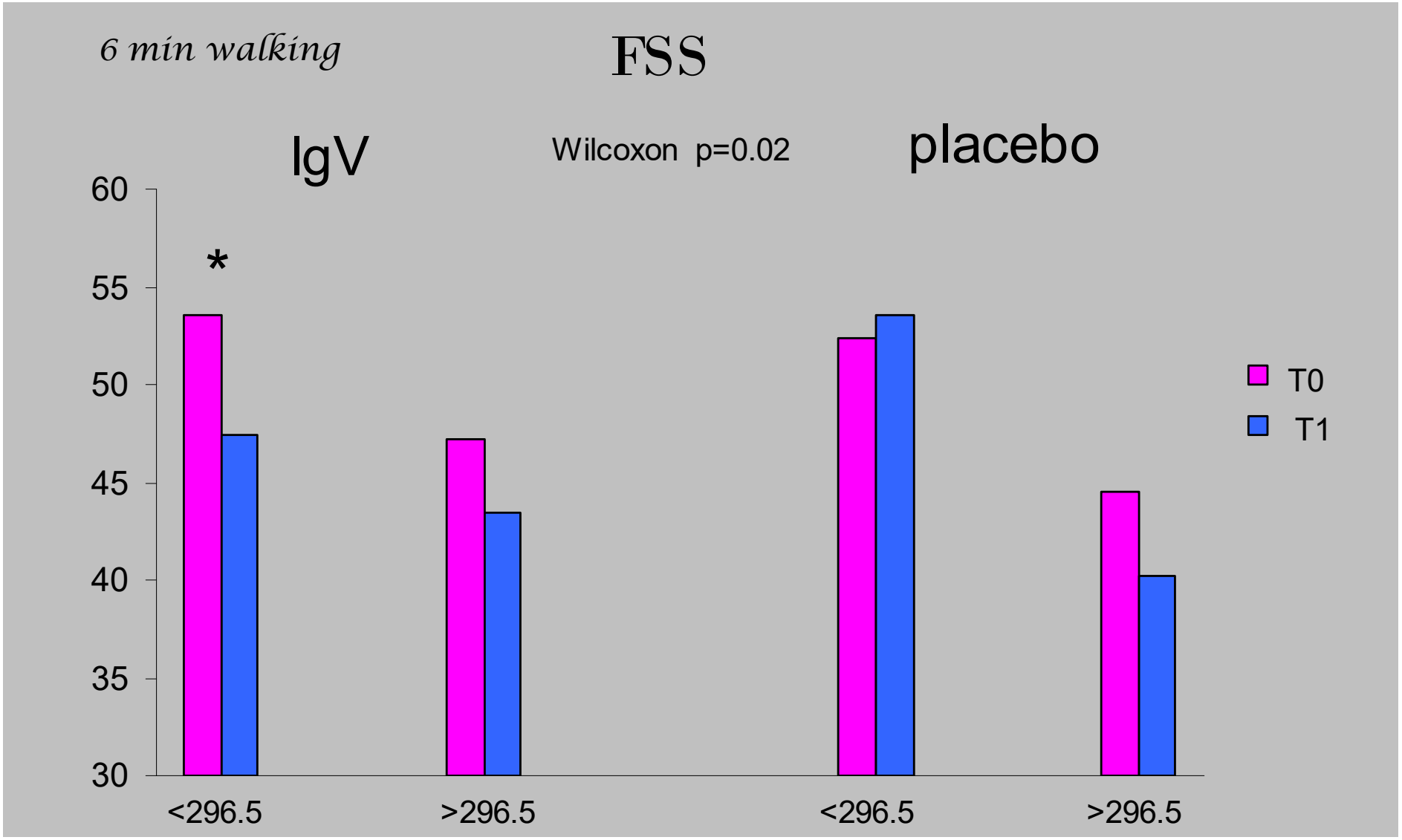

Age of infection
FSS
IgV
Wilcoxon p=0.008
placebo
55
50
45
40
35
30
*
<15.5
>15.5
<15.5
>15.5
Serie1
Serie2


Time to treatment
FSS
IgV
Wilcoxon p=0.012
placebo
55
50
45
40
35
30
m
*
<7.5 yrs
>7.5 yrs
<7.5 yrs
>7.5 yrs
T0
T1


FSS To
FSS
IgV
Wilcoxon p=0.002
placebo
*
65
60
55
50
45
40
35
<53.5
>53.5
<53.5
>53.5
T0
T1

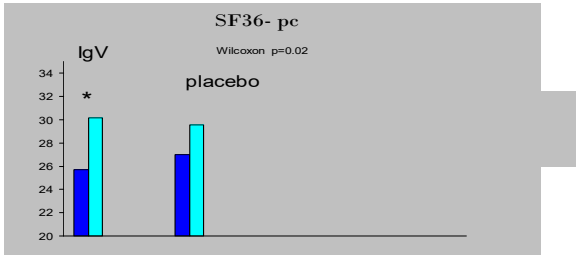

FSS To
6 min Walking
IgV
Wilcoxon p=0.04
placebo
370
350
330
310
290
270
250
m
*
T0
T1
<53.5
>53.5
<53.5
>53.5


VAS To
VAS
IgV
Wilcoxon p=0.006
placebo
10
9
8
7
6
5
4
3
2
1
0
*
<5.5
>5.5
<5.5
>5.5
T0
T1

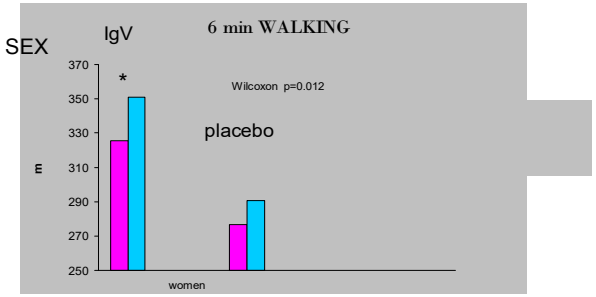

6 min walking
FSS
IgV
Wilcoxon p=0.02
placebo
60
55
50
45
40
35
30
*
<296.5
>296.5
<296.5
>296.5
T0
T1

CONCLUSION

- Primary end point: ig treatment was signifificantly effective

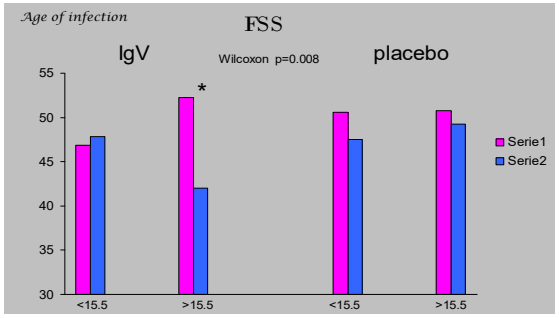


- Compared with males, females have a different response to treatment

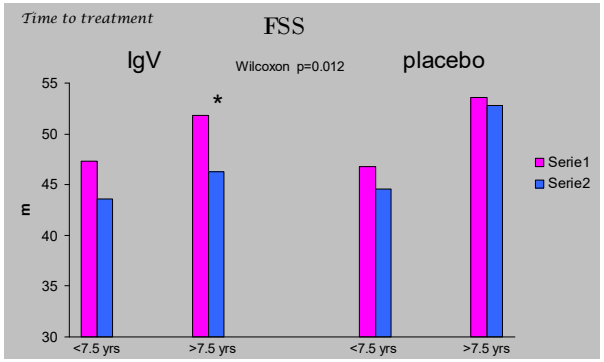


CONCLUSION

• a late acute infection determines a best therapeutical response

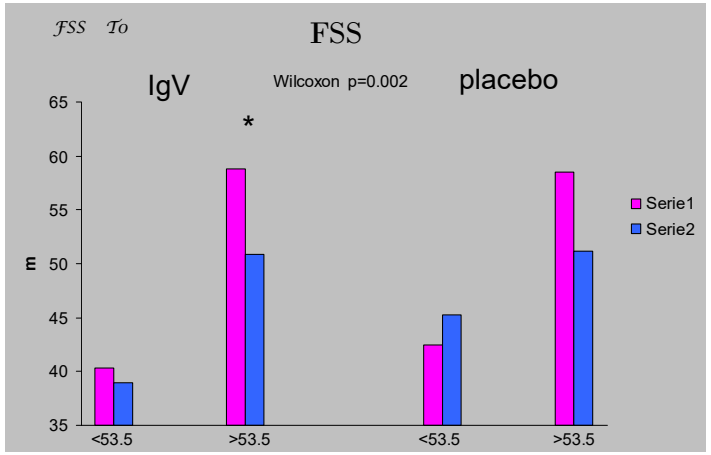


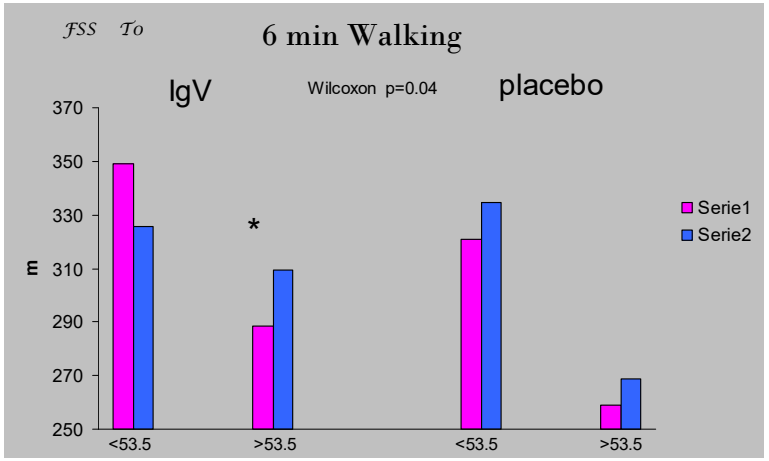
• when treatment is administered after a few years since the beginning of symptoms it seems to be more effective

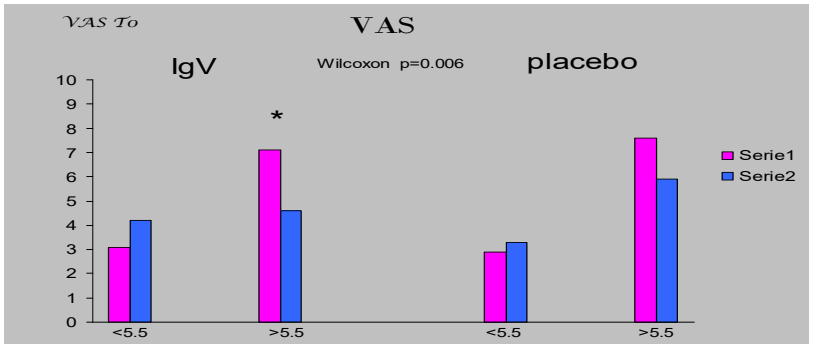


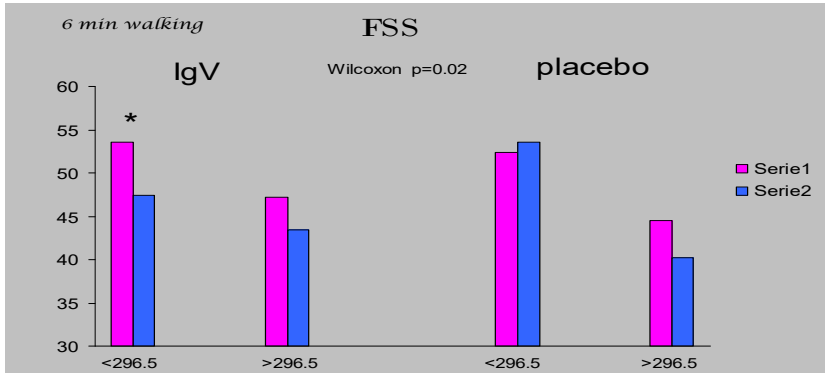
CONCLUSION

- most severe clinical condition receive the greatest benefit from the treatment









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A randomized controlled trial of IV immunoglobulin in patients with postpolio syndrome

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Classification of evidence: Class I evidence indicates that IVIg did not change SF-36 PCS, and Class II evidence indicates that IVIg improved scores on the SF-36 MCS, RP, and RE.