Immunological biomarkers and intervention with immunoglogbulin in the post-polio syndrome

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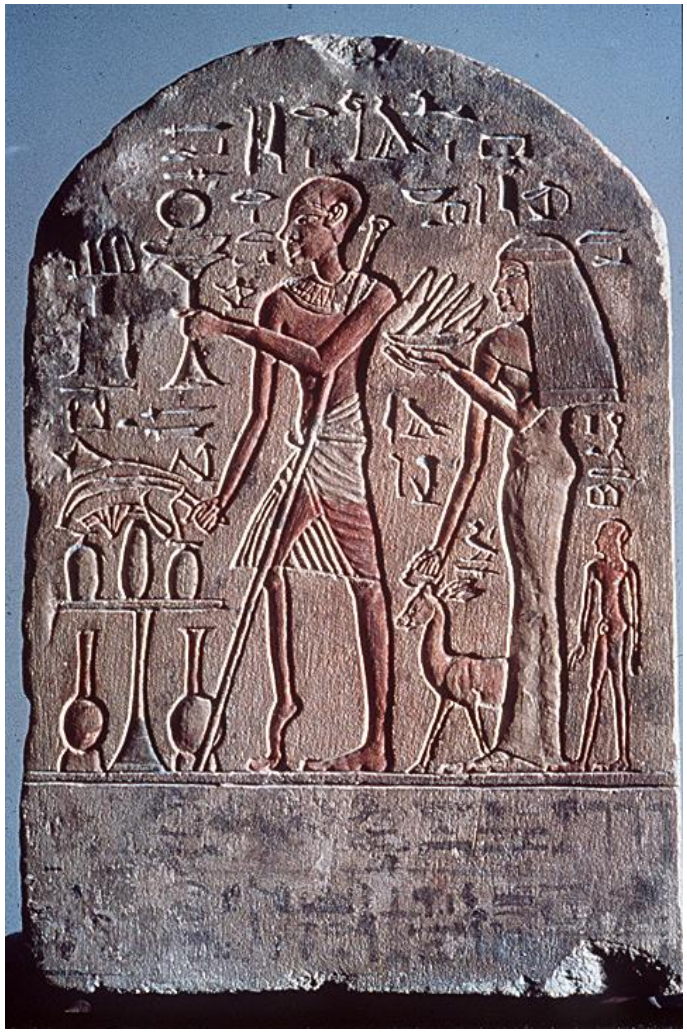
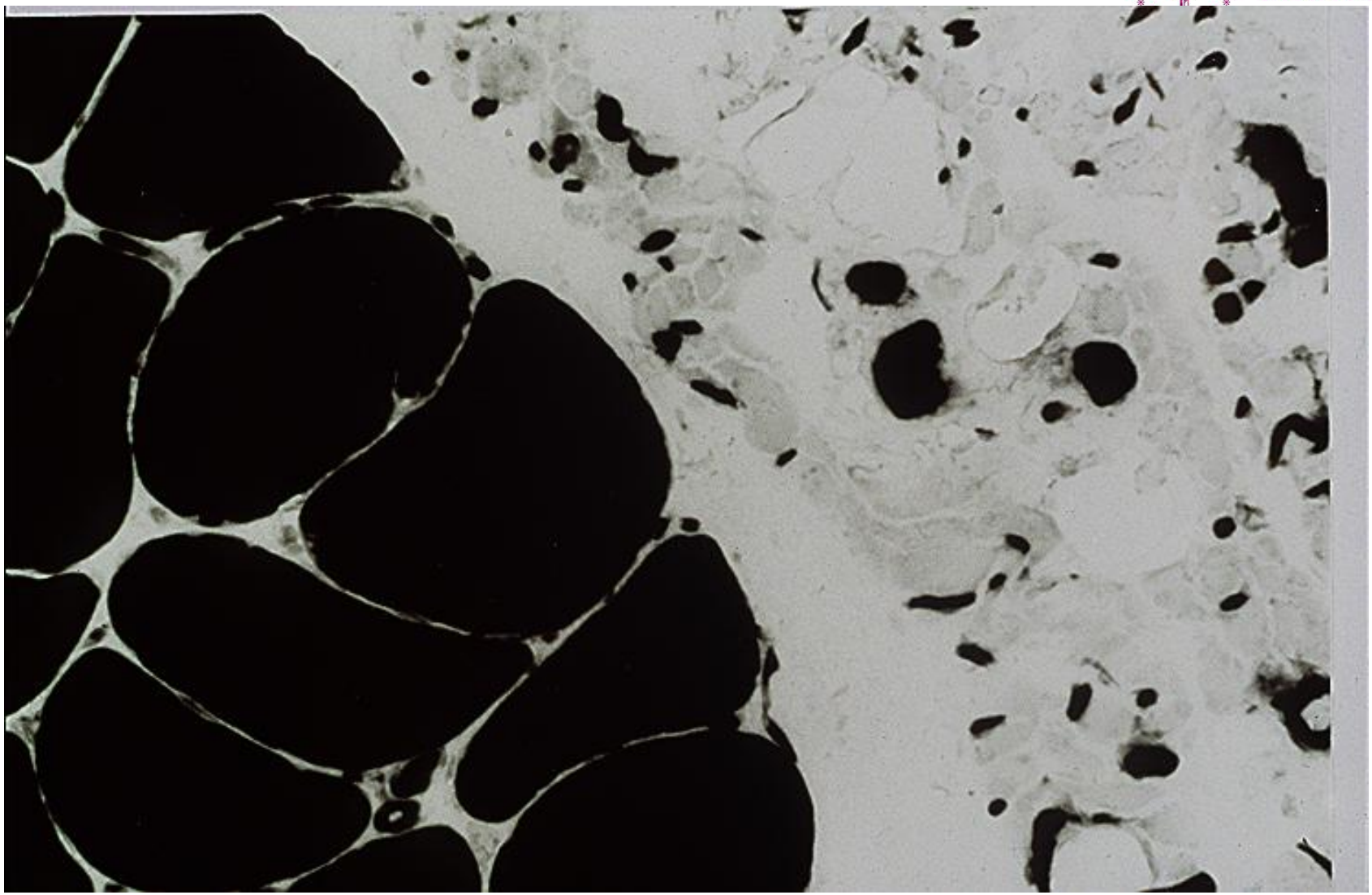



PTU's FORSKERPRIS
2008

Post-polio syndrome – background

- On-going denervation compensated by reinnervation
- Failing capacity to maintain large motor units ie failing capacity to compensate denervation by reinnervation
- Uncompensated denervation leads to decrease of muscle strength



Pathophysiology
denervation-reinnervation

- Overstress of remaining motor units.
- Overuse of remaining motor units.
- Age.
- Amyotrophic lateral sclerosis (ALS).
- Persistent polio virus infection.
- Immunological factors.

PPS-Inflammation

CNS

Dalakas et al 1984,

Sharief et al 1984,1991

PPS-Inflammation

Spinal cord

Pezeshkpour and Dalakas 1987

Miller DC 1995

PPS-Inflammation

Muscle

Dalakas et al 1984

Dalakas 1988, 1995

Semino-Mora and Dalakas 1998

PPS-inflammation

Peripheral blood

Ginsberg et al 1989

PPS-inflammation

Peripheral nerve

Brown and Patten 1987

PPS-inflammation

Cytokines

Gonzalez et al 2002

Farbu et al 2007

Fordyce et al 2008

ELSEVIER

Journal of the Neurological Sciences 205 (2002) 9–13

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Prior poliomyelitis-evidence of cytokine production in the central nervous system

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

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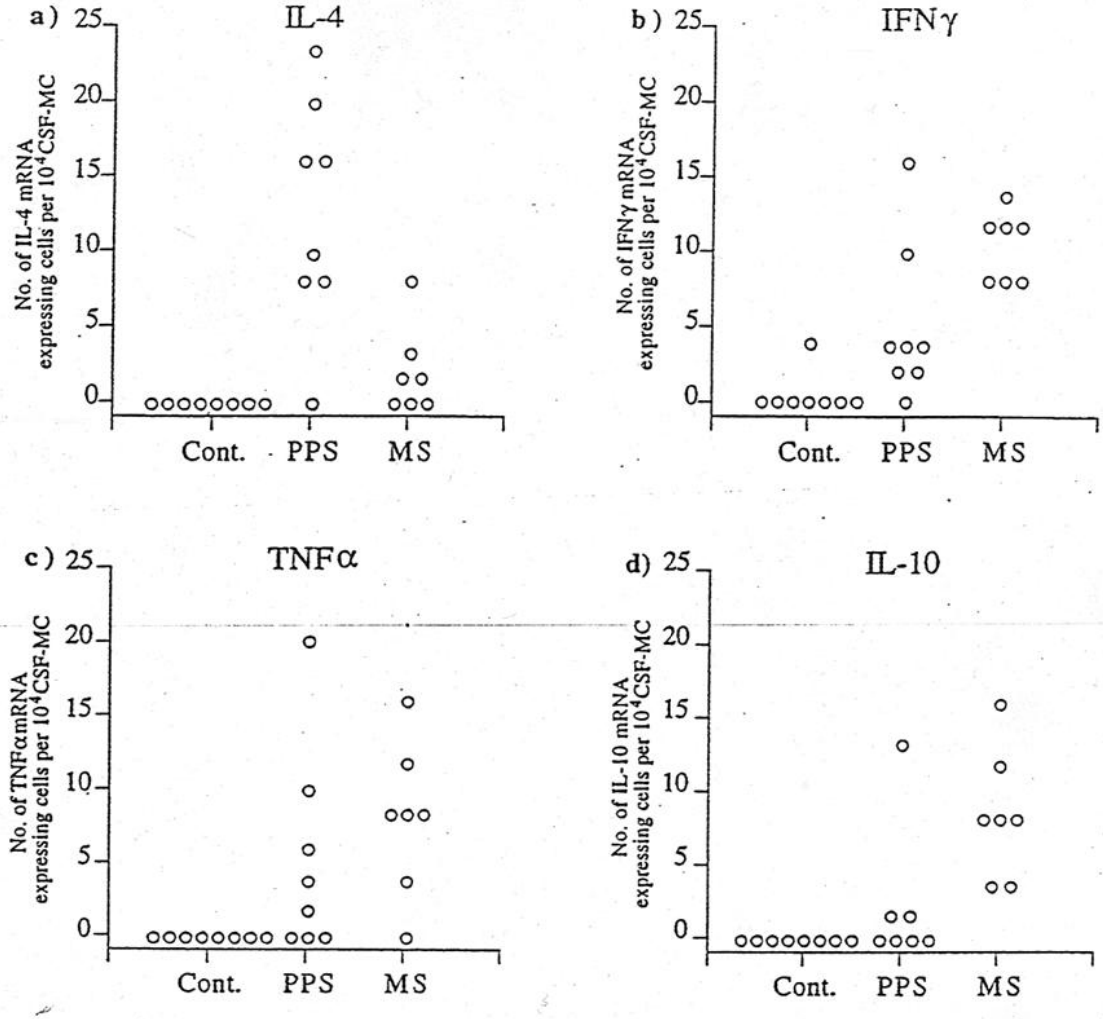
Received 25 October 2001; received in revised form 29 January 2002; accepted 9 April 2002

Figure 1


a) IL-4
No. of IL-4 mRNA expressing cells per 10^4CSF-MC
25
20
15
10
5
0
Cont.
PPS
MS
b) IFNγ
No. of IFNγ mRNA expressing cells per 10^4CSF-MC
c) TNFα
No. of TNFαmRNA expressing cells per 10^4CSF-MC
d) IL-10
No. of IL-10 mRNA expressing cells per 10^4CSF-MC

Immune-modulatory drugs used in PPS

- Cortison
- Interferon
- Immunosuppressants
- Immunotherapy

In order to down-regulate the inflammatory reaction in CNS, 16 post-polio patients were treated with intravenous immunoglobulin (Xepol)

ELSEVIER

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]

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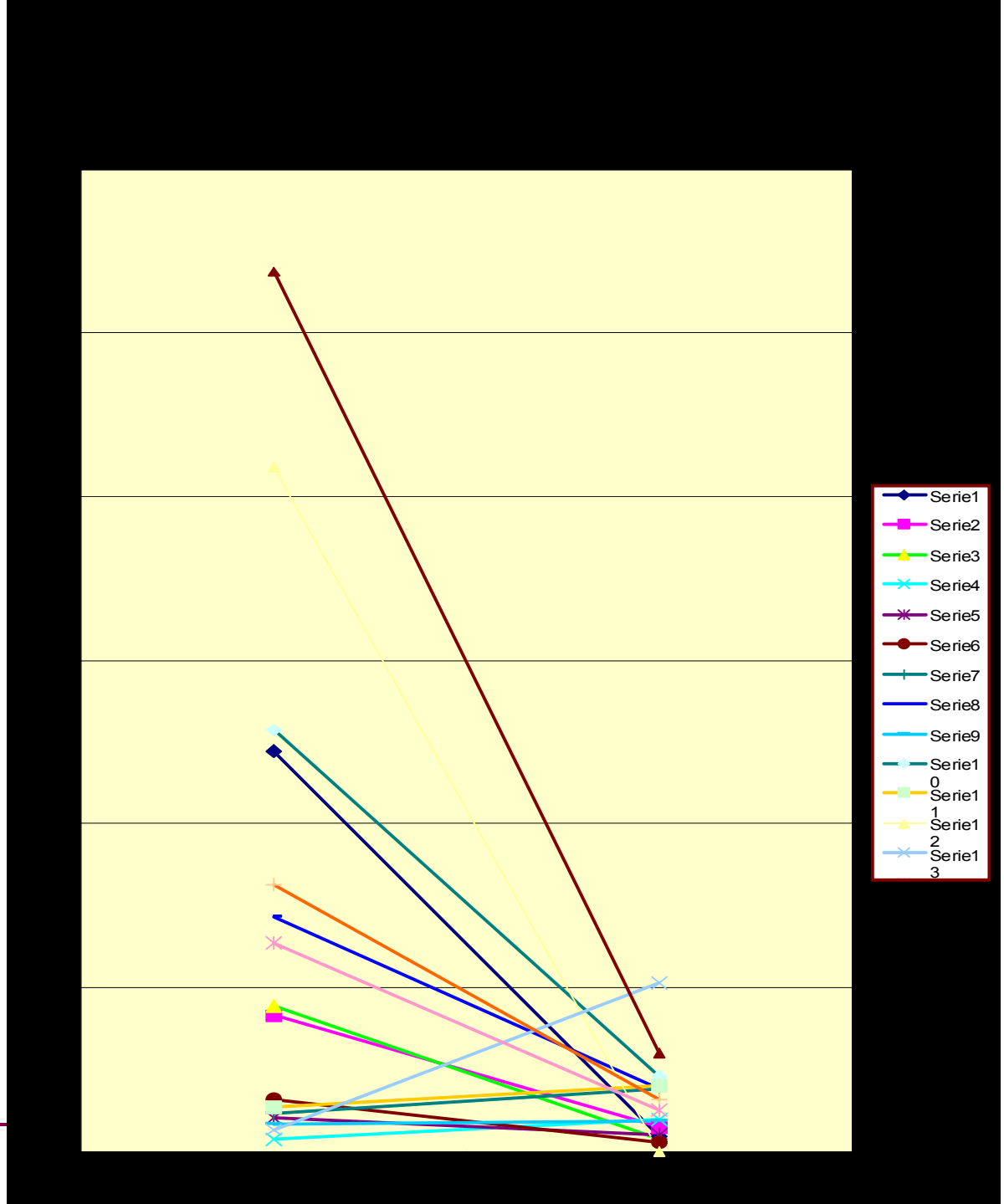
Received 27 October 2003; received in revised form 6 January 2004; accepted 7 January 2004

TNF-α

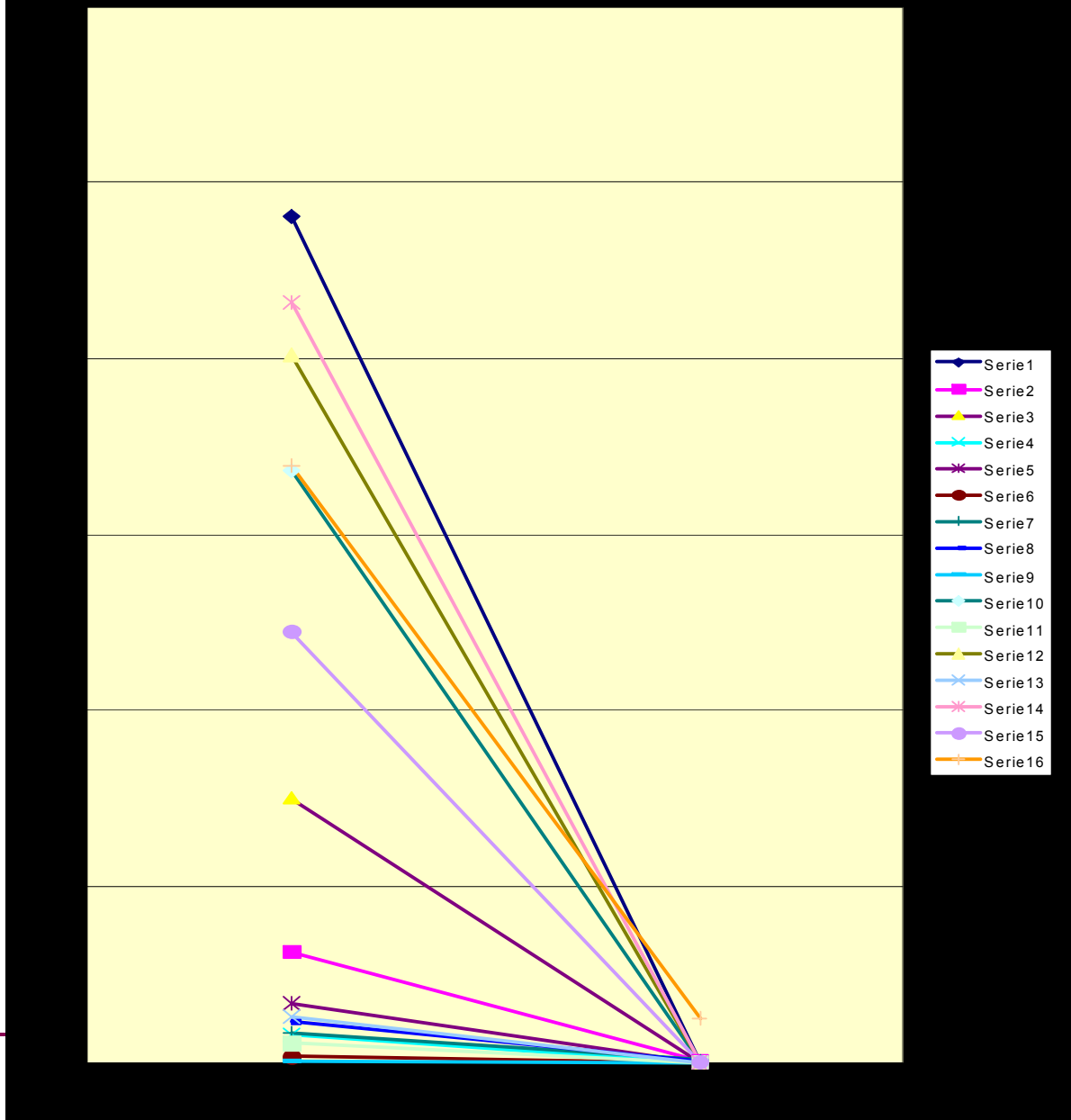
Poliopatients before and after Xepol-treatment

P=0.016



INF-gamma

P=0.00003



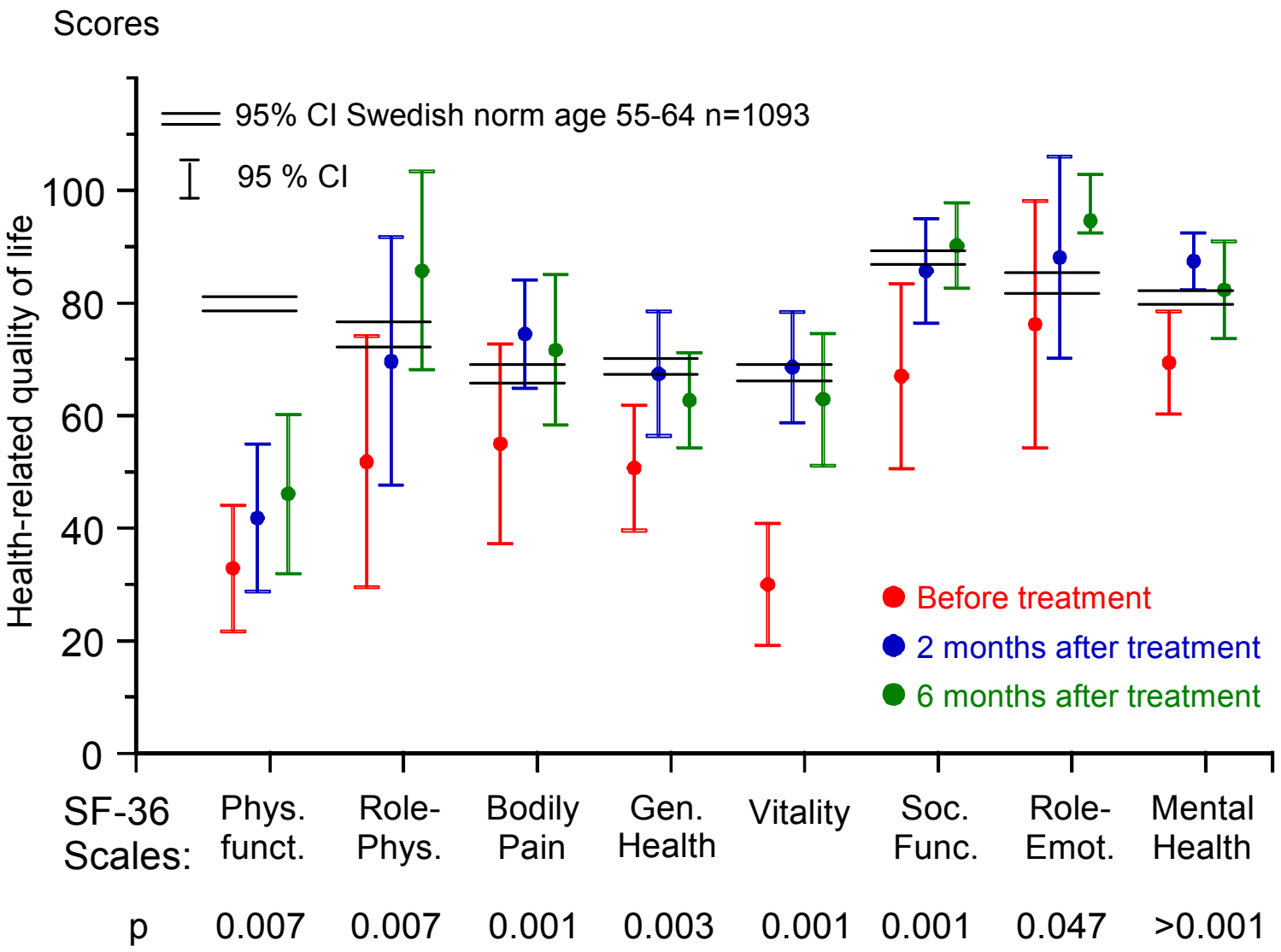
J Rehabil Med
2006, 1–3, PrEview article

SHORT COMMUNICATION

EFFECT OF INTRAVENOUS IMMUNOGLOBULIN IN PATIENTS WITH POST-POLIO SYNDROME – AN UNCONTROLLED PILOT STUDY

Georgios Kaponides, MD[1], Henrik Gonzalez, MD[1], Tomas Olsson, MD, PhD[2] and Kristian Borg, MD, PhD[1]

From the [1]Departments of Public Health Sciences, Division of Rehabilitation Medicine and [2]Neuroimmunology Unit, Center for Molecular Medicine, Karolinska Hospital, Stockholm, Sweden


Scores
95% CI Swedish norm age 55-64 n=1093
95 % CI
Health-related quality of life
100
80
60
40
20
0
Before treatment
2 months after treatment
6 months after treatment
SF-36 Scales:
Phys. funct.
Role-Phys.
Bodily Pain
Gen. Health
Vitality
Soc. Func.
Role-Emot.
Mental Health
p
0.007
0.007
0.001
0.003
0.001
0.001
0.047
>0.001

Multicenter, placebo-controlled, double-blinded study including 142 post-polio patients

Karolinska Institutet

Articles

Intravenous immunoglobulin for post-polio syndrome: a randomised controlled trial

Henrik Gonzalez, Katharina Stibrant Sunnerhagen, Inger Sjöberg, Georgios Kaponides, Tomas Olsson, Kristian Borg

Summary

Background Survivors of poliomyelitis often develop increased or new symptoms decades after the acute infection, known as post-polio syndrome. Production of proinflammatory cytokines within the CNS indicates an underlying inflammatory process, accessible for immunomodulatory treatment. We did a multicentre, randomised, double-blind, placebo-controlled study of intravenous immunoglobulin in post-polio syndrome.

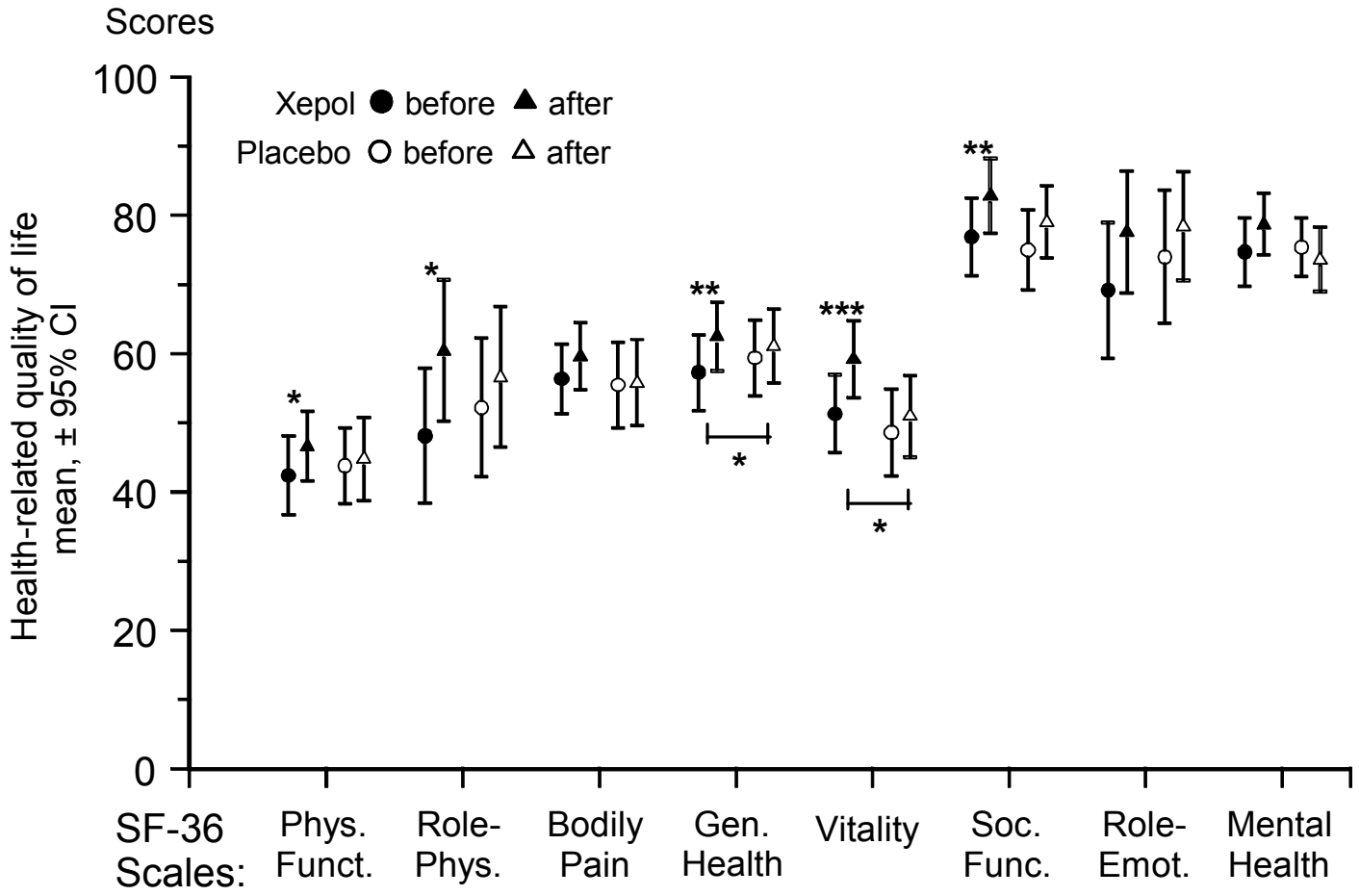
Lancet Neurol 2006; 5: 493–500
Published Online
April 25, 2006
DOI:10.1016/S1474-4422(06)
70447-1

Increase of muscle strength

Treated + 4.3%

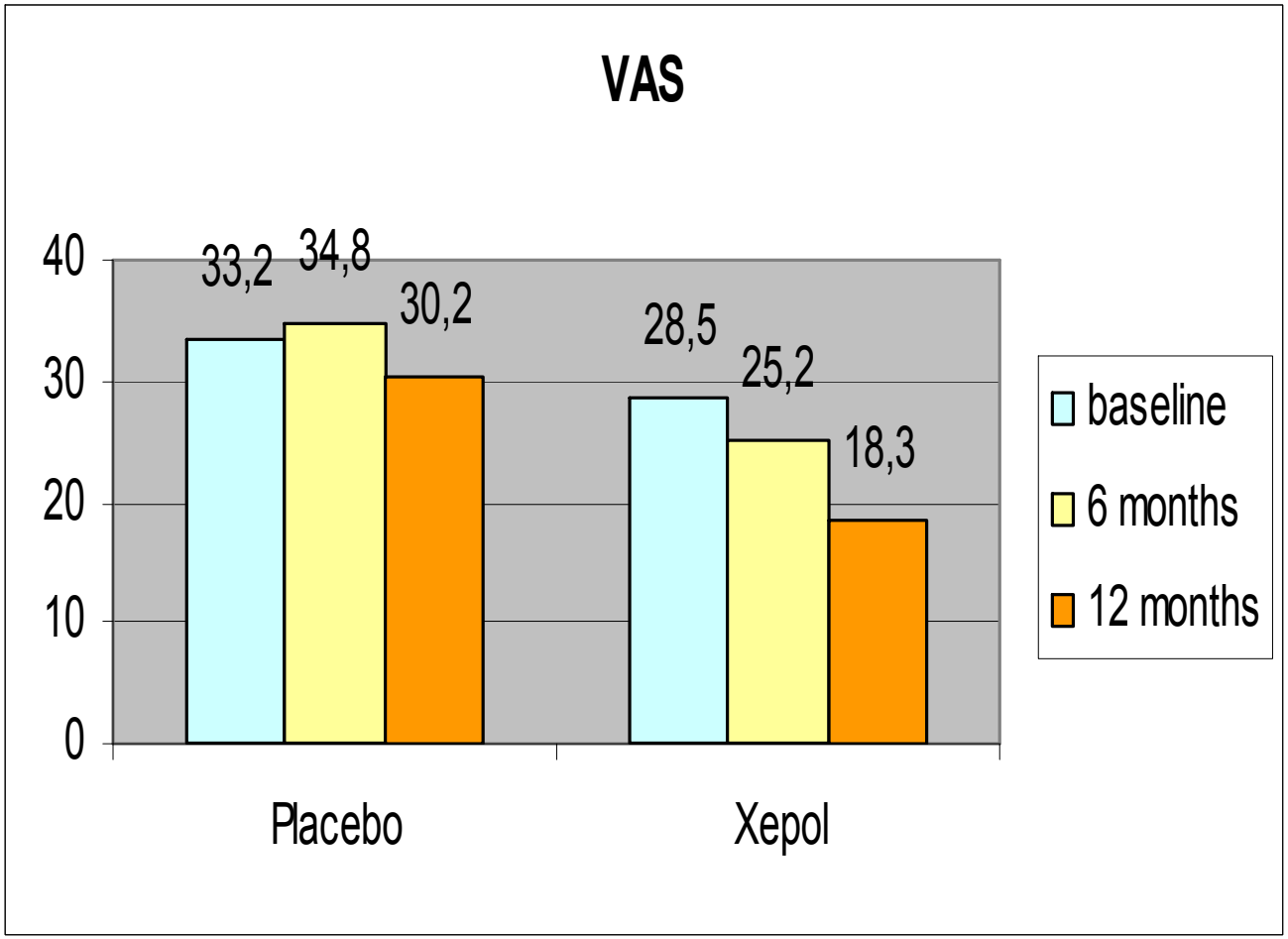
$P < 0.05$

Placebo - 5.7%


Scores
100
80
60
40
20
0
Xepol ● before ▲ after
Placebo ○ before △ after
Health-related quality of life
mean, ± 95% CI
*
*
**
*
***
*
**
SF-36
Scales:
Phys.
Funct.
Role-
Phys.
Bodily
Pain
Gen.
Health
Vitality
Soc.
Func.
Role-
Emot.
Mental
Health

1-year follow-up study

- Still significant decrease of cytokines
- Still significantly better quality of life for physical domains


VAS
40
30
20
10
0
33,2
34,8
30,2
28,5
25,2
18,3
Placebo
Xepol
baseline
6 months
12 months

2.5 year follow-up study

- Cytokine levels ?
- Clinical parameters back to base-line

Werhagen and Borg 2008

- 64 PPS patient treated
- 90 gram IVIG

Werhagen and Borg 2008

- Significant effect of IVIG
- 2/3 of patients had a decrease of pain and fatigue

Werhagen and Borg 2008

- Effect correlated to age and paresis
- Better effect if the patients was < 10 years of age at the acute polio

JOURNAL OF PROTEOMICS 71 (2009) 670–681

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/jprot

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]

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ARTICLE DATA

Article history:
Received 1 October 2008
Accepted 14 November 2008

Keywords:
Post-polio syndrome
Pathophysiology
CSF
Proteomics
Biomarkers
Diagnosis

ABSTRACT

Survivors of poliomyelitis often develop increased or new symptoms decades after the acute infection, a condition known as post-polio syndrome (PPS). The condition affects 20–60% of previous polio patients, making it one of the most common causes of neurological deficits worldwide. The underlying pathogenesis is not fully understood and accurate diagnosis is not feasible. Herein we investigated whether it was possible to identify proteomic profile aberrations in the cerebrospinal fluid (CSF) of PPS patients.

CSF from 15 patients with well-defined PPS were analyzed for protein expression profiles. The results were compared to data obtained from nine healthy controls and 34 patients with other non-inflammatory diseases which served as negative controls. In addition, 17 samples from persons with secondary progressive multiple sclerosis (SPMS) were added as relevant age-matched references for the PPS samples.

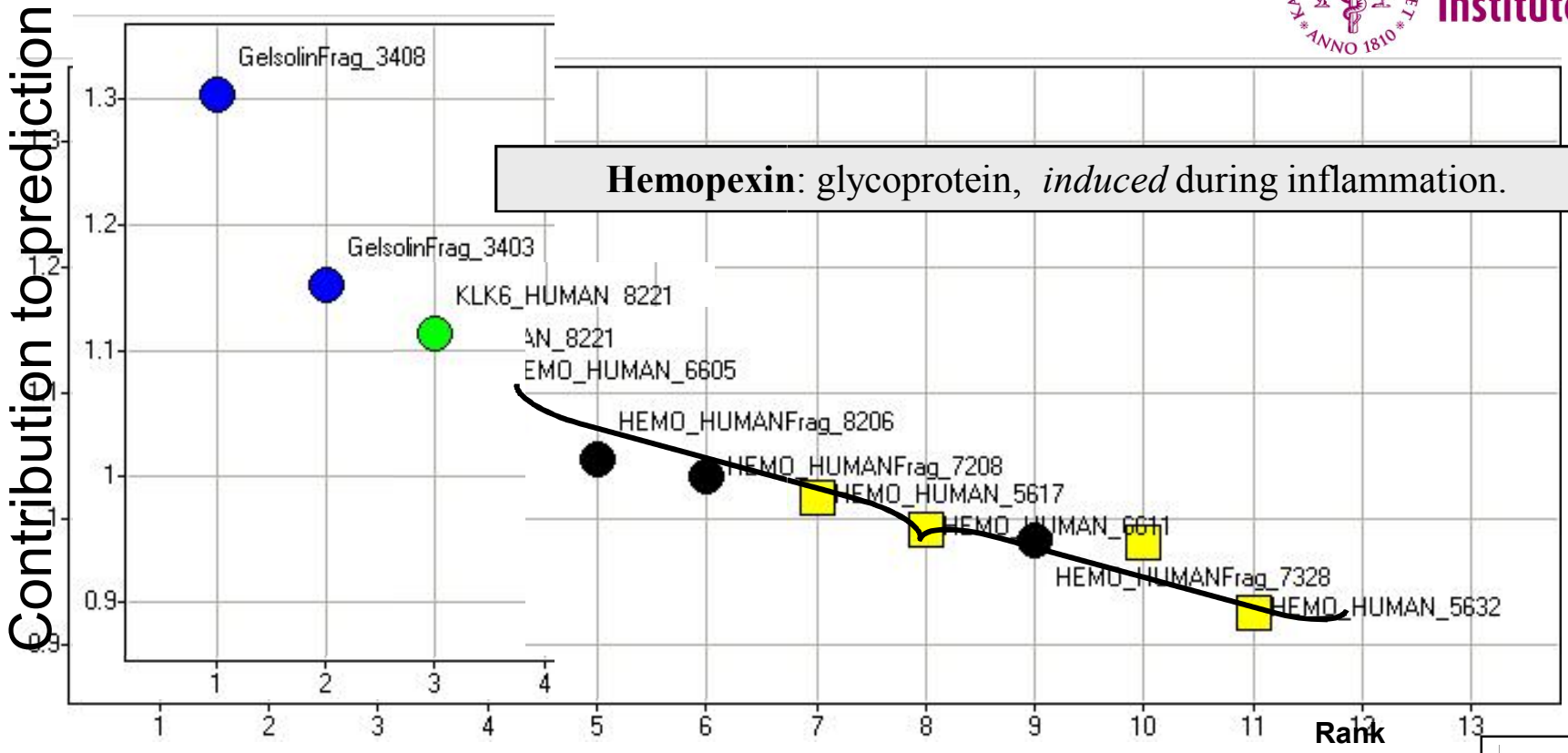
The CSF of persons with PPS displayed a disease-specific and highly predictive ($p=0.0017$) differential expression of five distinct proteins: gelsolin, hemopexin, peptidylglycine alpha-amidating monooxygenase, glutathione synthetase and kallikrein 6, respectively, in comparison with the control groups. An independent ELISA confirmed the increase of kallikrein 6.

Gonzales et al 2009 - a proteomic study of CSF

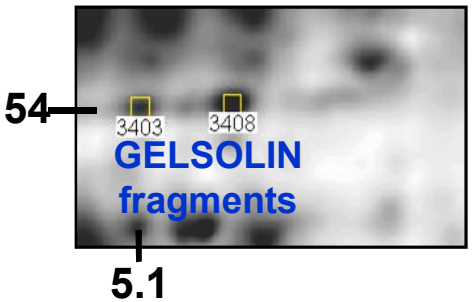
- Disease specific differential expression of 3 proteins
- Involved in neuroinflammation and/or apoptosis

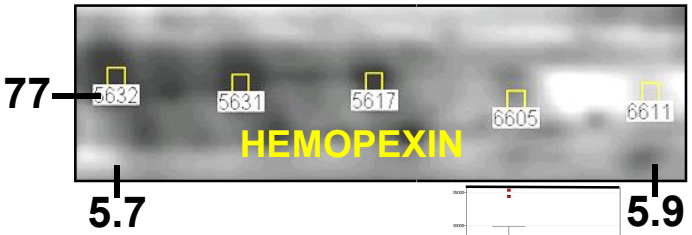
Identification of predictive proteins

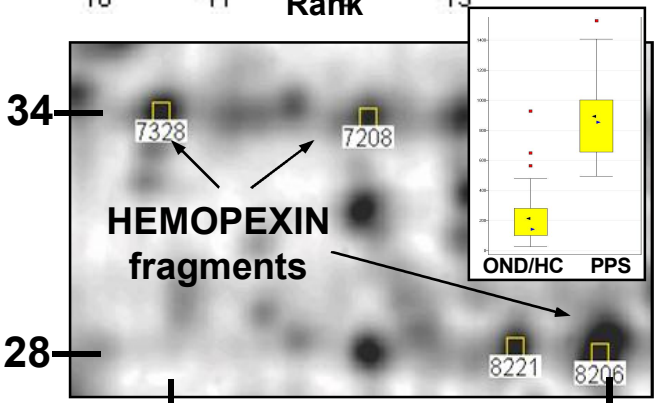
Karolinska Institutet

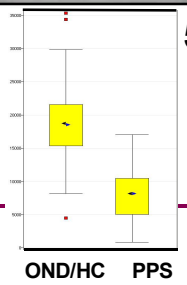


Hemopexin: glycoprotein, *induced* during inflammation.

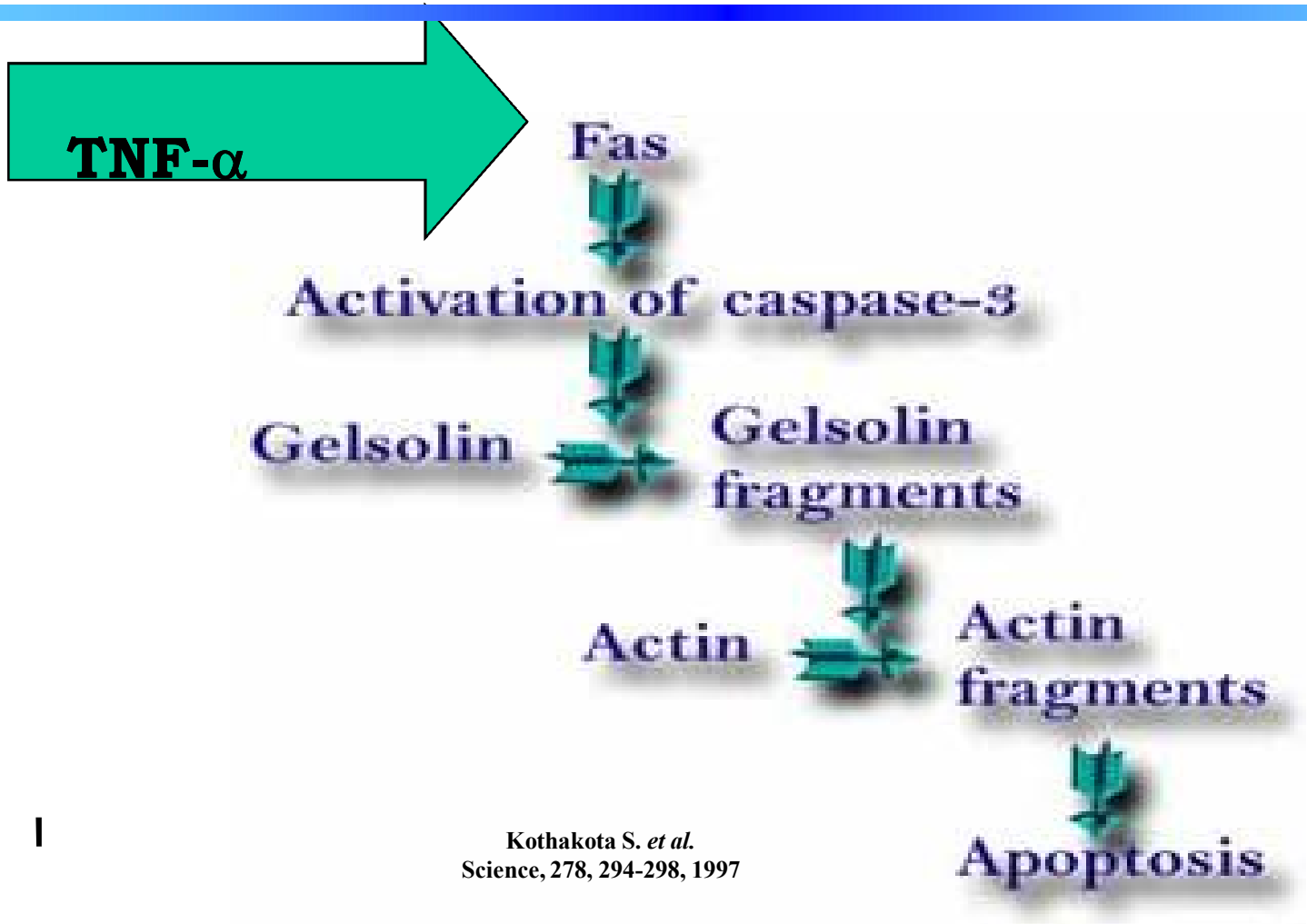








Inflammatory cascade - Gelsolin - cell death



Kothakota S. *et al.*
Science, 278, 294-298, 1997

Other studies

- Farbu et al 2007.
  TNF-alfa increase, effect on pain after 3 months.

- Open study, Stockholm end 2009.

- Fordyce et al 2008
  TNF-alfa increase correlated to pain, no intervention

Summary

- Post-polio patients have an increase of cytokines in the CSF indicating an inflammation in the CNS
- The inflammation is down-modulated by means of treatment with intravenous gammaglobulin
- Clinically, the down-modulated inflammation leads to an increased muscle strength and a better quality of life, mainly for the general health and vitality domains, as well as for pain and fatigue
- Recent studies suggest that there are specific biomarkers for PPS in CSF and blood

IS IT NECESSARY TO DOWN-MODULATE THE INFLAMMATION ?

Cytokines have a harmful effect on motoneurones

YES !

- Improvement of motor function
- Increased vitality and general health
- Decrease of pain and fatigue
- Avoiding the natural course
- Avoiding neurodegeneration

GRIFOLS

PHARMALINK

ASTRA-ZENECA

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