

Does Inflammation cause the Post Polio Syndrome? Implications for therapy!



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IMMUNOPATHOGENESIS OF THE POST-POLIO SYNDROME

Probably an old question







Polio



- Singel-stranded **RNA-virus**.
- 1-2% of the polio-infected got **paralytic polio**.
- Survivors **recovers** during a period of years and, some to full or almost full function.
- After restitution most have a long time of **stability**, followed by sudden or stepwise alternatively very slow **progressive disability**.
- 20 000 persons have today disabilities after paralytic polio in Sweden.

POLIOVIRUS properties

- Picornavirus
- Subgroup-enterovirus
- 3 serotypes
- RNA-virus
- icosahedral capsid
- No envelope
- size: 25 nm



POLIOVIRUS serotypes

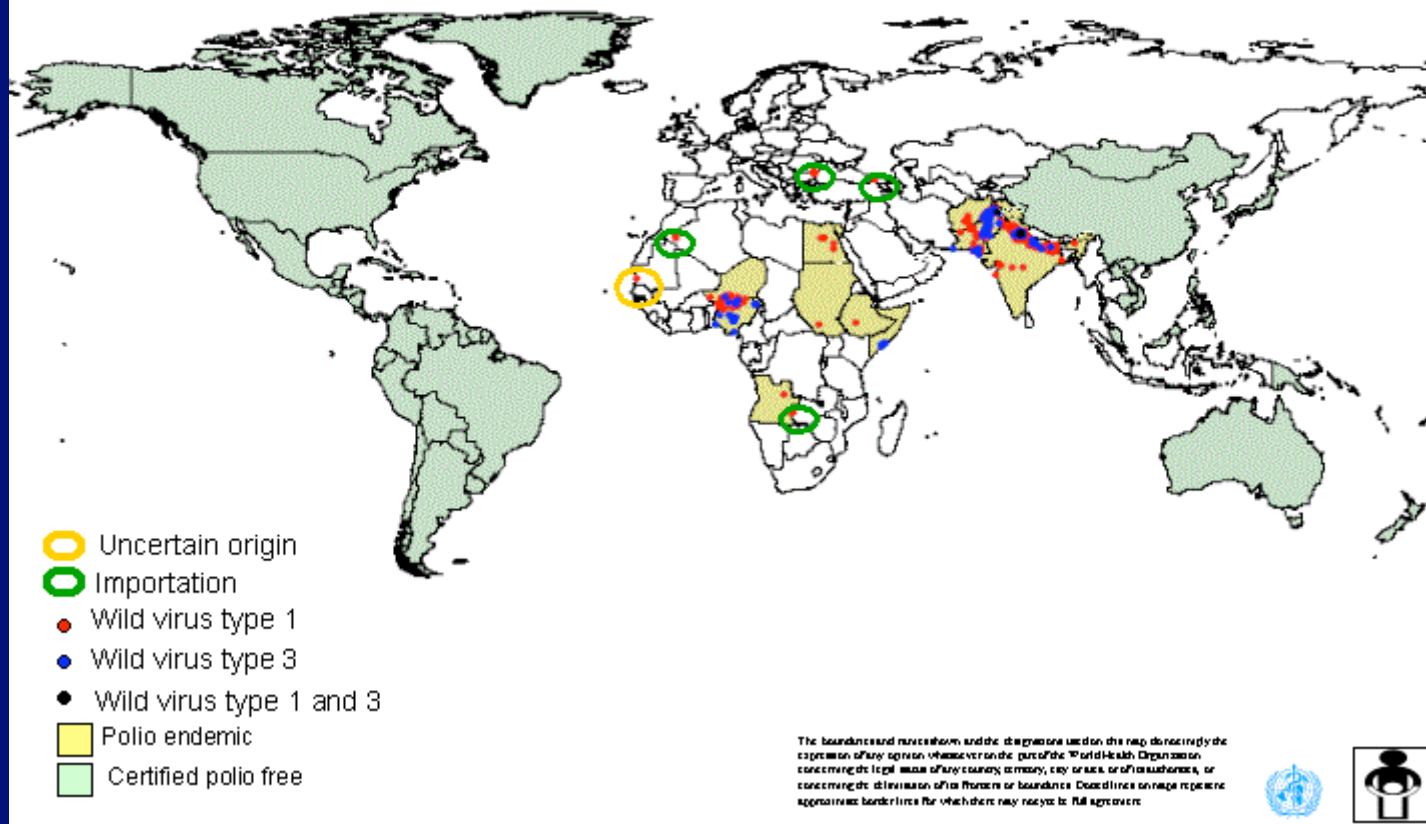
- Serotype 1 (Brunhilde)
- Serotype 2 (Lancing)
- Serotype 3 (Leon)



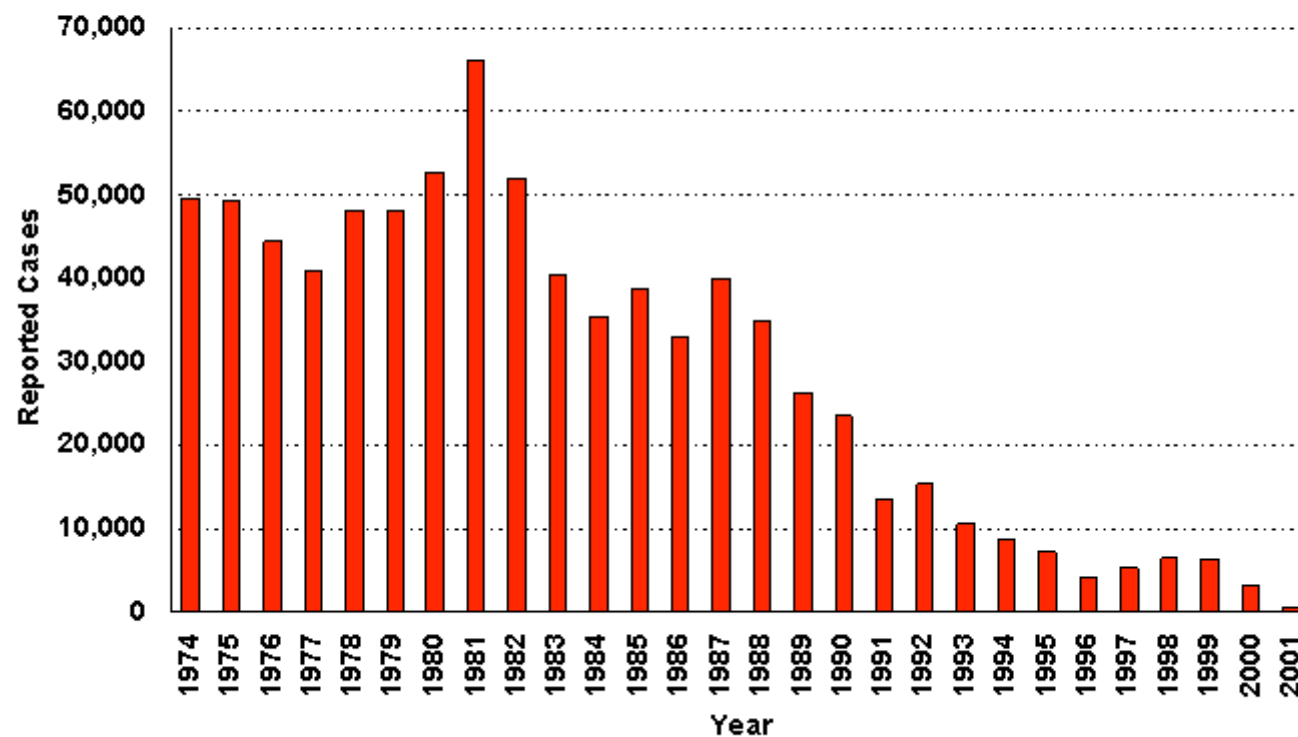
EPIDEMIOLOGY



Wild poliovirus , 2001



Global annual reported polio cases, 1974-2001



TRANSMISSION



- Fecal-oral
- direct person-to-person contact
- contact with infected secretions from the nose or mouth
- contact with infected feces.

TRANSMISSION



- The virus enters through the **mouth and nose**
- Multiplies in the **throat and intestinal tract**, and then
- Is absorbed and spread through the **blood and lymph system**.
- **Incubation** ranges from **5 to 35 days** (average 7 to 14 days).

ACUTE POLIOINFECTION

- There are three basic patterns of polio.
- A. subclinical infections, B. nonparalytic, and C. paralytic infection.
- Approximately 95% of these are subclinical infections, which may go unnoticed.
- Clinical poliomyelitis affects the CNS (brain and spinal cord) and is divided into nonparalytic and paralytic forms.
- It may occur after recovery from a subclinical infection.

C. PARALYTIC POLIOMYELITIS

- **Fever, occurring 5 to 7 days before other symptoms.**
- **headache**
- **stiff neck and back**
- **muscle weakness , asymmetrical**
- **rapid onset**
- **progresses to paralysis.**
- **location depends on where the spinal cord is affected.**
- **Abnormal sensation of an area**



C PARALYTIC POLIOMYELITIS

- sensitivity to touch, mild touch may be painful
- difficulty beginning to urinate
- constipation
- bloated feeling of abdomen
- swallowing difficulty
- muscle pain



C. PARALYTIC POLIOMYELITIS

- muscle contractions or spasms, particularly in the calf, neck or back
- breathing difficulty
- irritability or poor temper control
- positive babinski reflex



POLIOMYELITIS diagnostics

- The disorder may resemble encephalitis, and it may affect the cranial nerves and cause difficulty with facial expression, swallowing, chewing, and so on. It may also cause choking or difficulty breathing.
- **Viral cultures** of throat washings, stools, or cerebrospinal fluid (CSF) **confirm the diagnosis.** Routine CSF examination may be normal or show slight increase in pressure, protein, and white blood cells.

TREATMENT

- The goal of treatment is to **control symptoms** while the infection runs its course.
- Lifesaving measures, particularly **assistance with breathing**, may be necessary in severe cases.

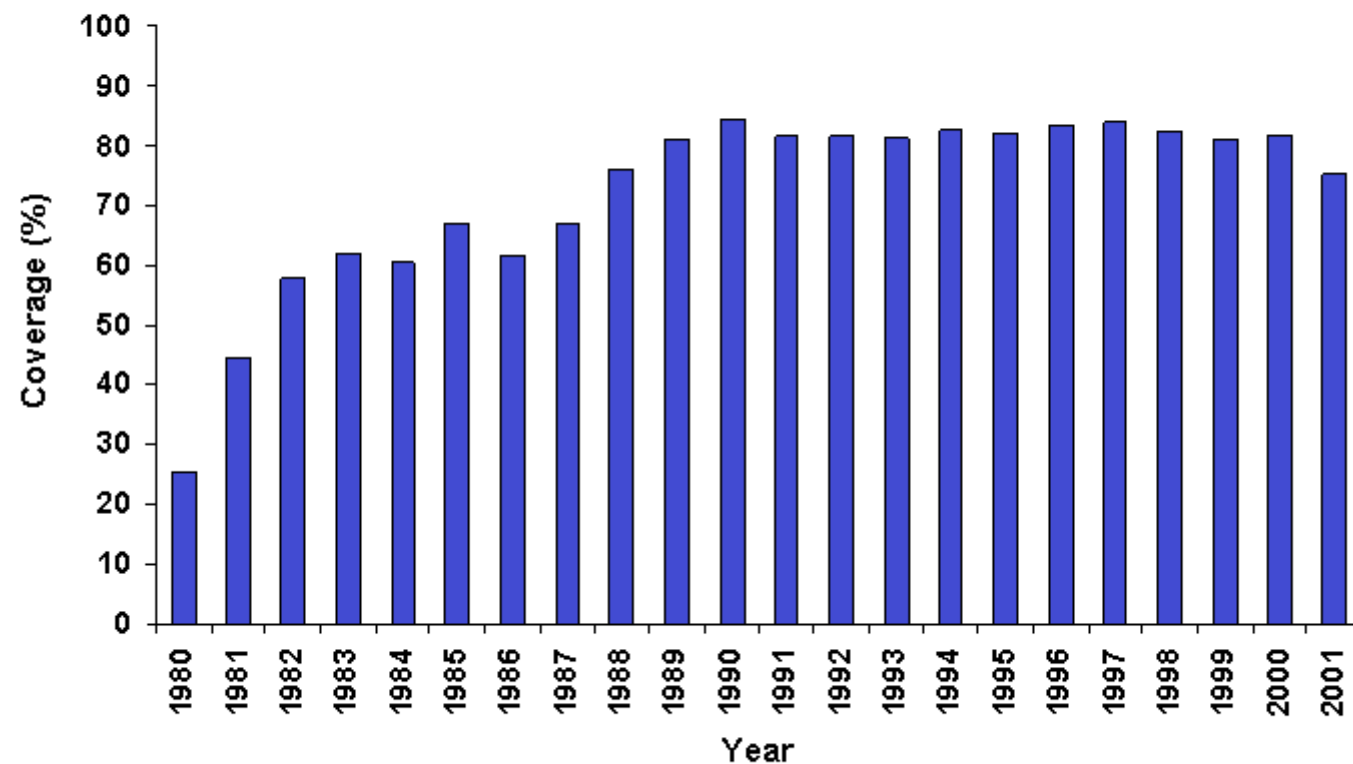


LABORATORY diagnostics

- **Virusisolation**
- **Sequence typing**
- **Serology as a compliment**



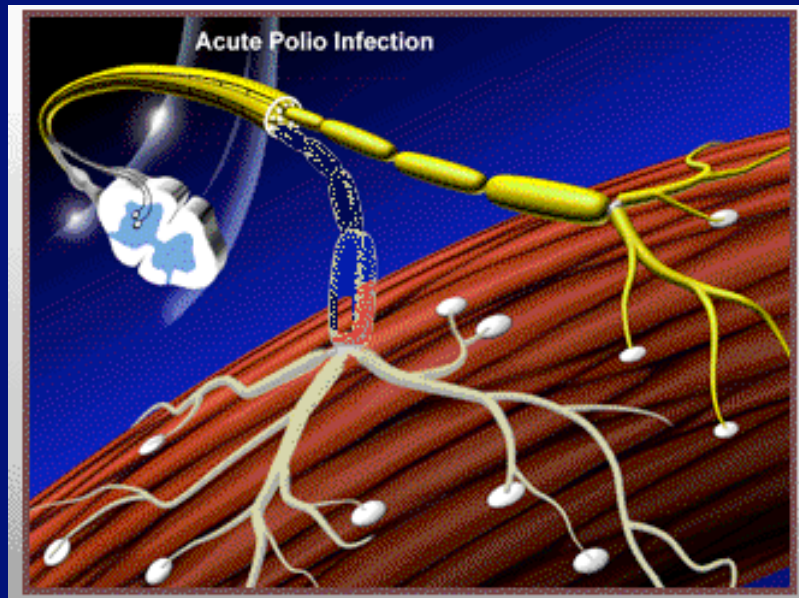
Global coverage with 3 doses of polio vaccine among infants, 1980-2001



Affects the moto-neurons

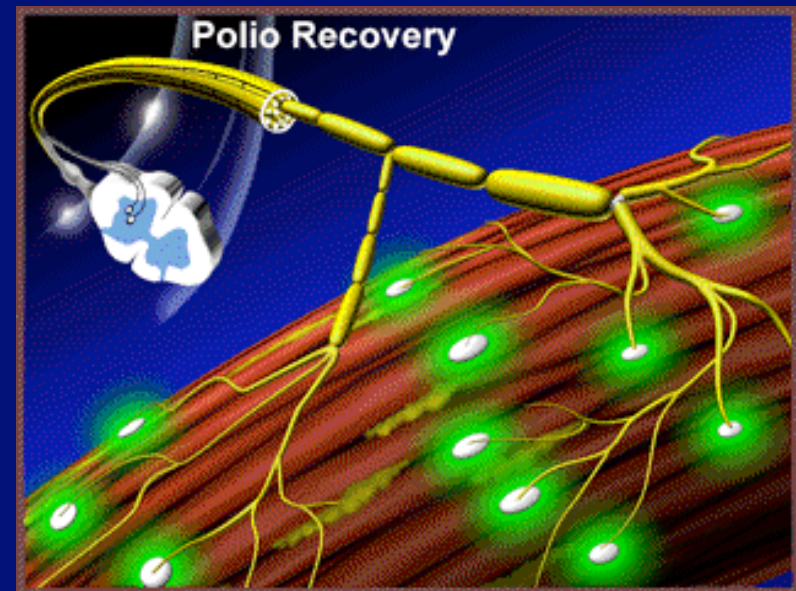


Denervation

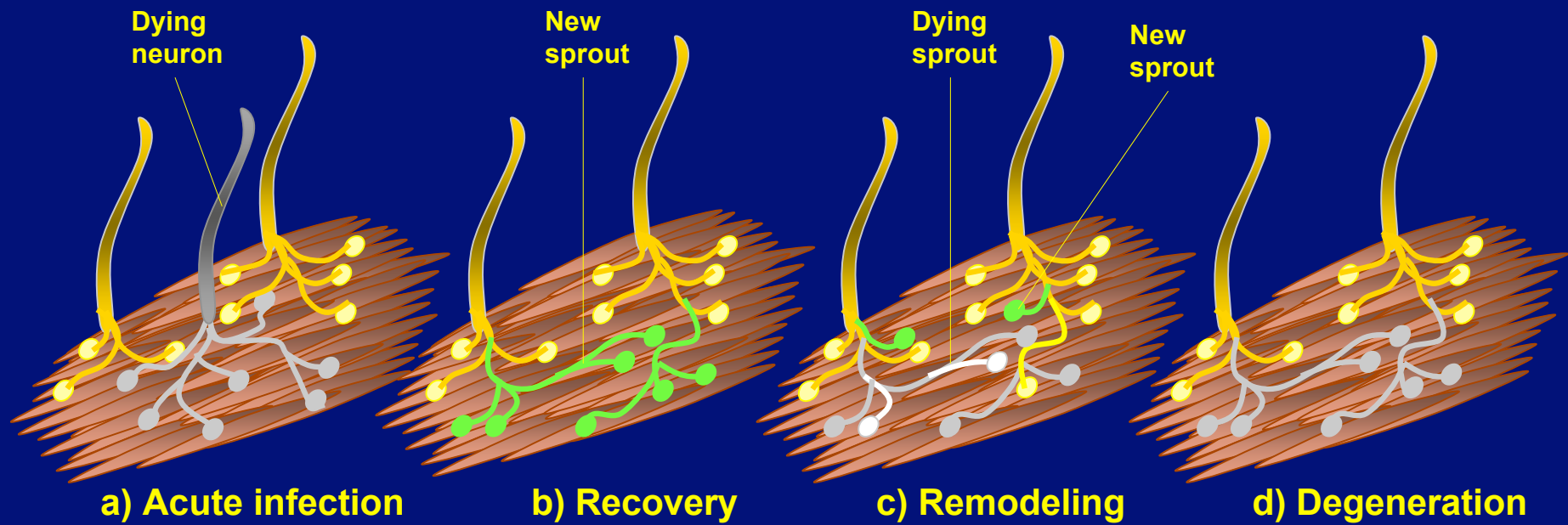


Reinnervation

=> large motor-units



Degeneration of motor neurons in PPS



Late effects of POLIO

(PostPolio Syndrome = PPS)

- **Fatigue**.....muscular/central
- **Pain**.....perifer/central
- **Progressive muscular weakness**
- **Restrictive pulmonary dysfunction**
- +a variety of other symptoms that could not be explained by some other reason

Cause of PPS?

- Overstress of remaining motor neurons, in combination with normal aging?
- Persistent poliovirus?
- Chronic inflammation?

Previous data on inflammation

- Dalakas, 1984, 1985 inflammation in spinal cord in autopsy cases.
- Sharief et al, 1984, 1991, Inflammatory CSF changes.

Cytokines

- Peptide molecules, secreted by inflammatory cells. enabling intercellular communication and effector functions
- Acts paracrinely- determine cellular expression, body fluid levels tell little.
- Accurate production pivotal in defence against infection.
- Defence has a price, tissue damage

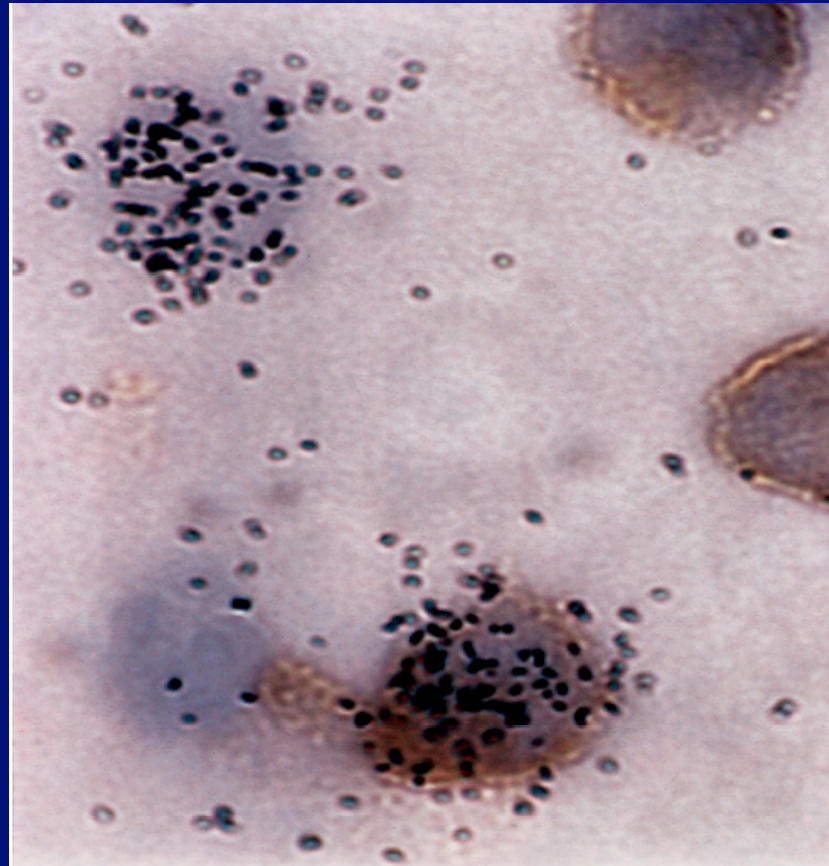
T1 cytokines

- TNF α , Interferon γ
- Delayed type hypersensitivity reactions
- Enables killing of intra-cellular parasites-viruses, Tb
- Activates macrophages
- Probably instrumental in diseases such as rheumatoid arthritis, multiple sclerosis
- Numerous effects: fever, pain, chachexia

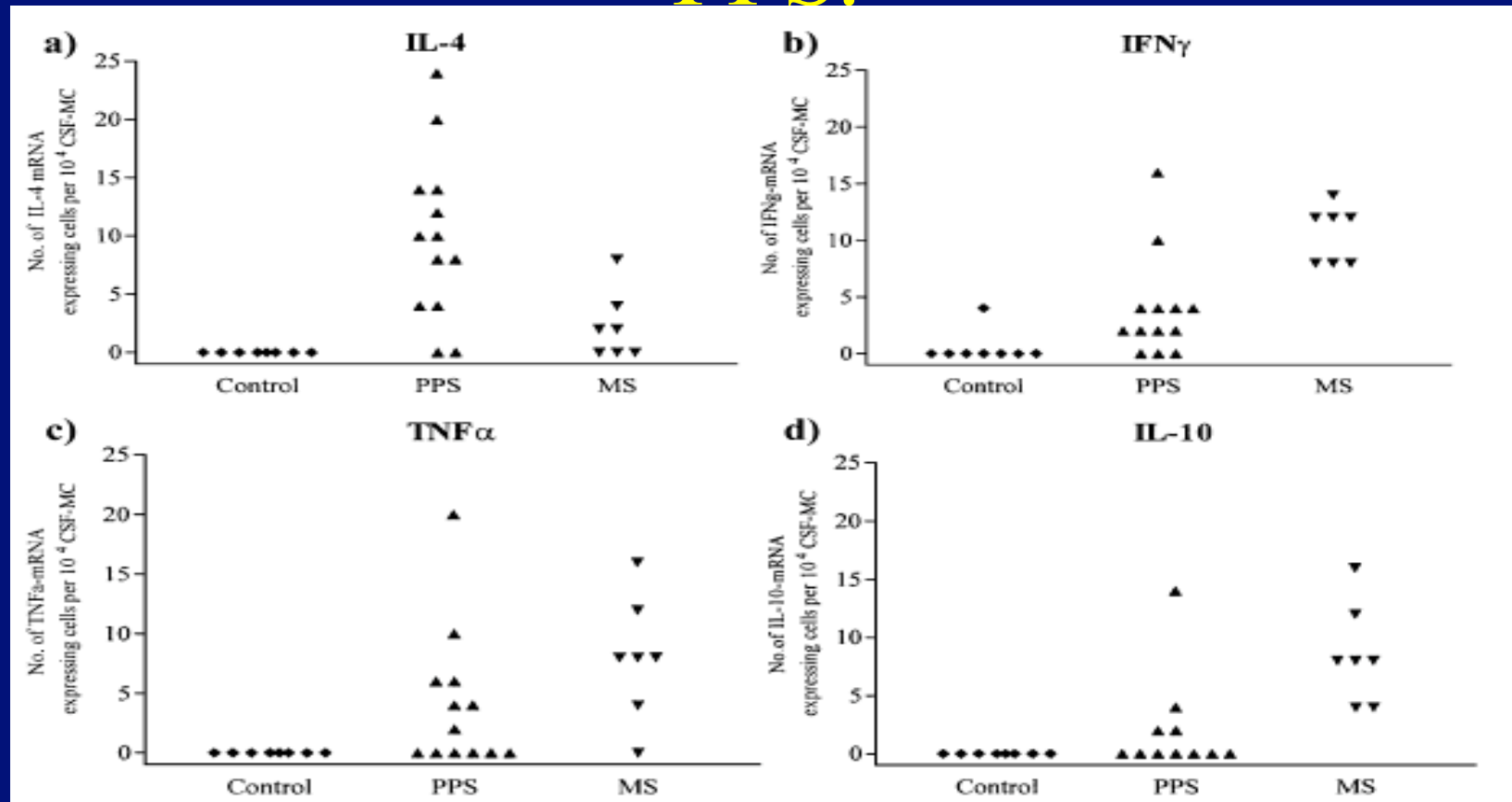
T2 cytokines

- Interleukin 4,5, 10 and 13
- Support B cell differentiation and function
- Instrumental in allergy and asthma

mRNA expression of IFN γ in lymphocytes

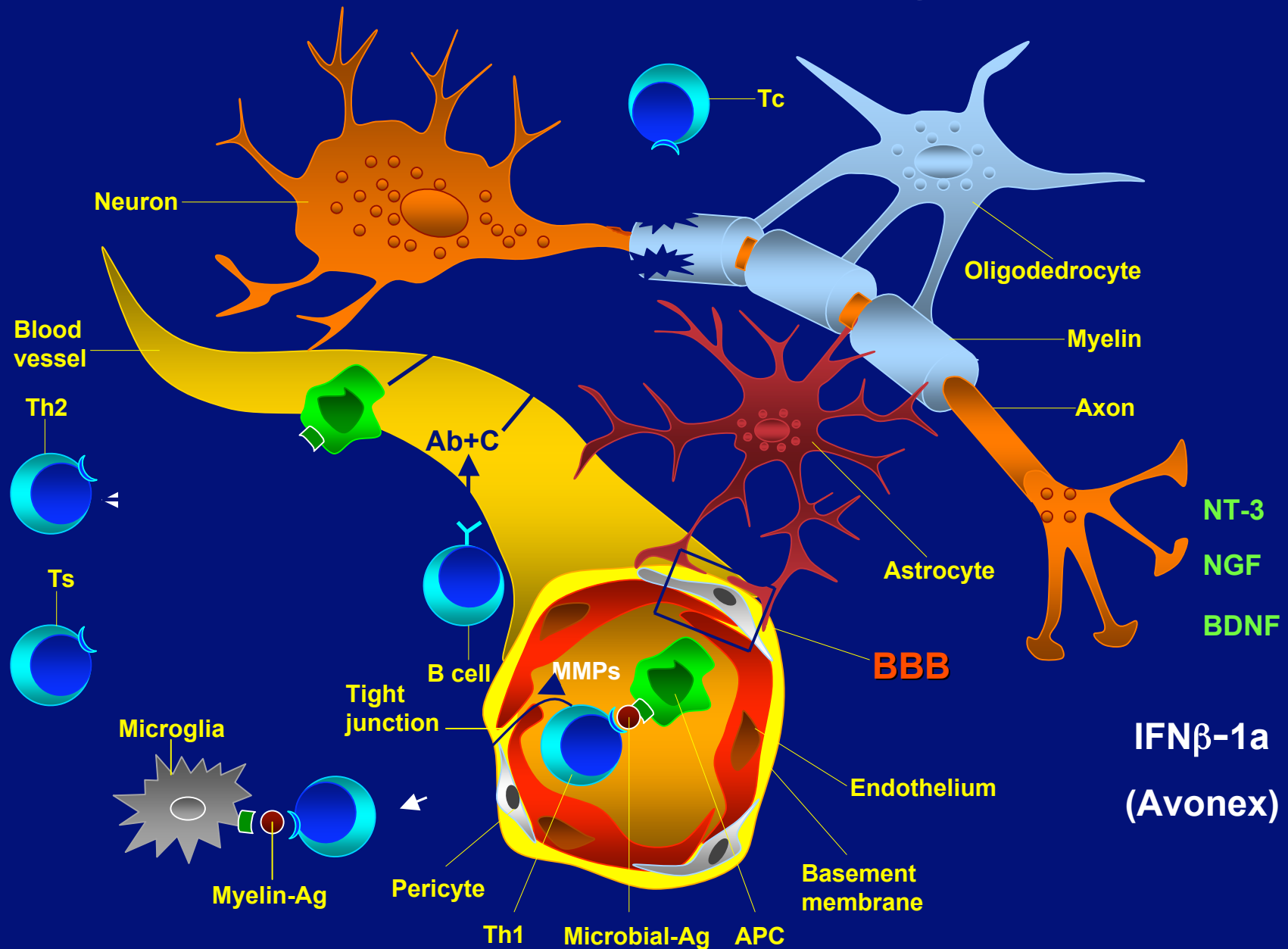


Increased cellular expression of Cytokines in CSF of persons with PPS.

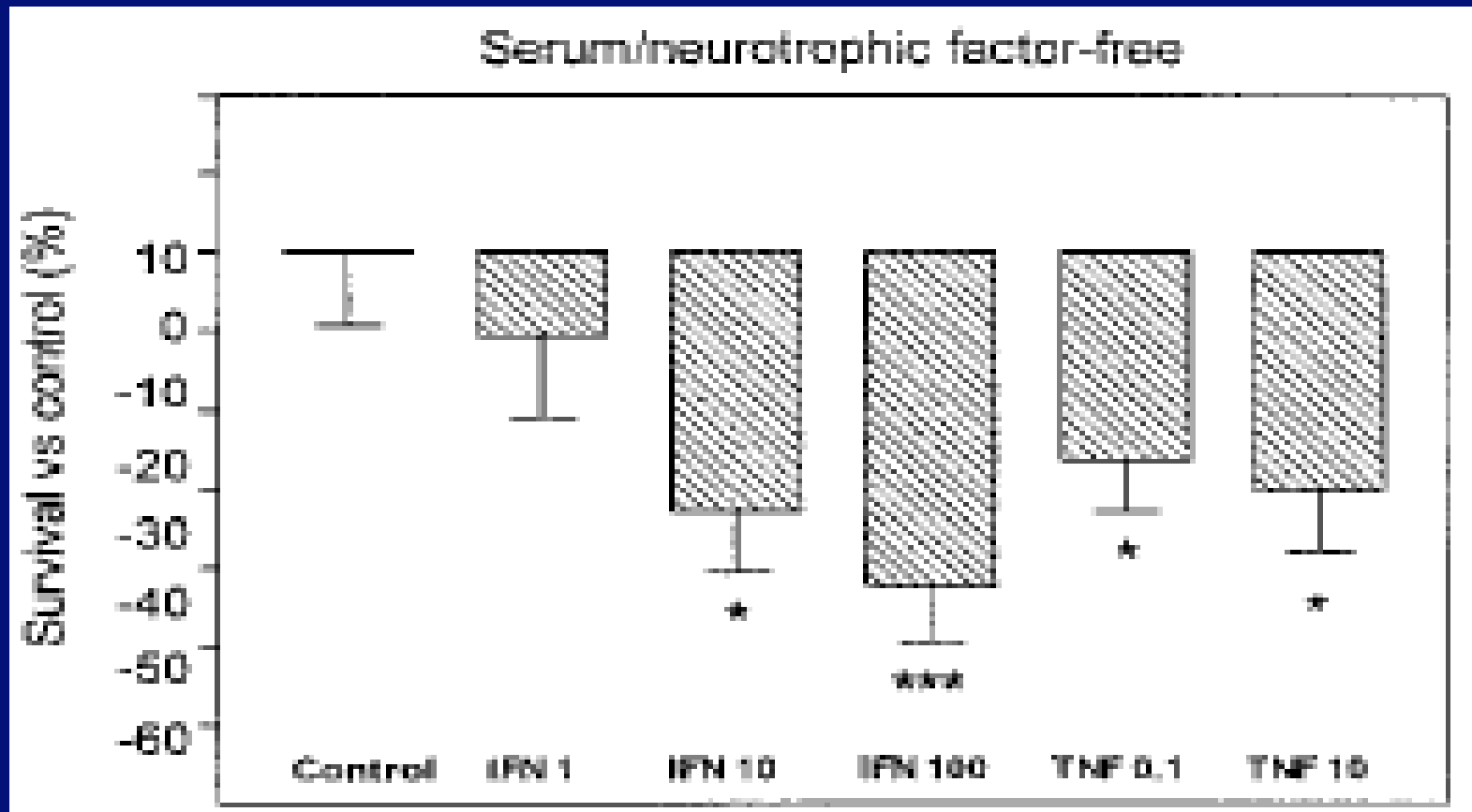




A model of MS immunopathogenesis



IFN γ and TNF α can kill motor neurons.



Reasons for chronic intrathecal overproduction of cytokines in PPS?

- Persistent poliovirus?
- Abberant, autoimmune reaction?
- Secondary epiphenomenon to neurodegeneration?
- Immunomodifying treatments may give hints.

PILOT II



- † 16 patients with Late effects of Polio
- † Mean age : 58.5 years .
- † **Cytokines in CSF** measured by real timePCR before treatment.
- † New LP 6-10 weeks after treatment.
- † **Physical variables and QOL-questionnaire** were analysed .

Polio patients vs OND's

OND / PPS

TNF- α -CSF $P=0,0162$ $P<0,02$

IFN- γ -CSF $P=0,0001$ $P=0,0001$

IL-10-CSF $P=0,0121$ $P<0,02$

TNF-PB $P=0,0234$ $P<0,03$

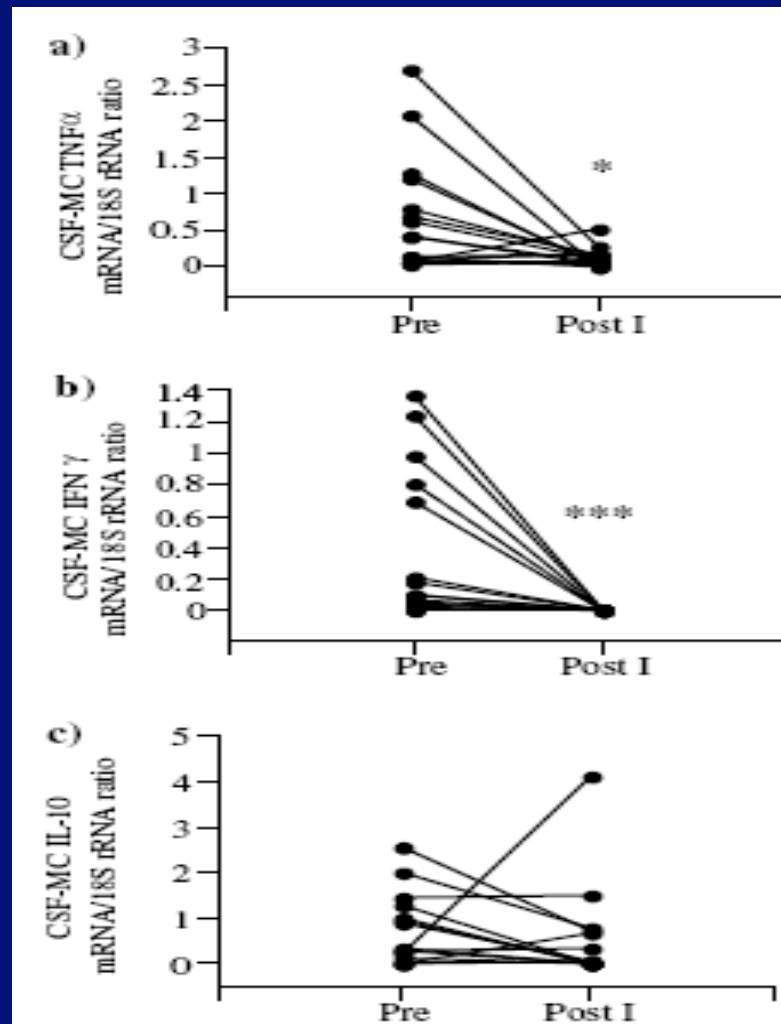
IFN-PB $P=0,3706$

IL-10-PB $P=0,7852$

IL-4-PB $P=0,0976$

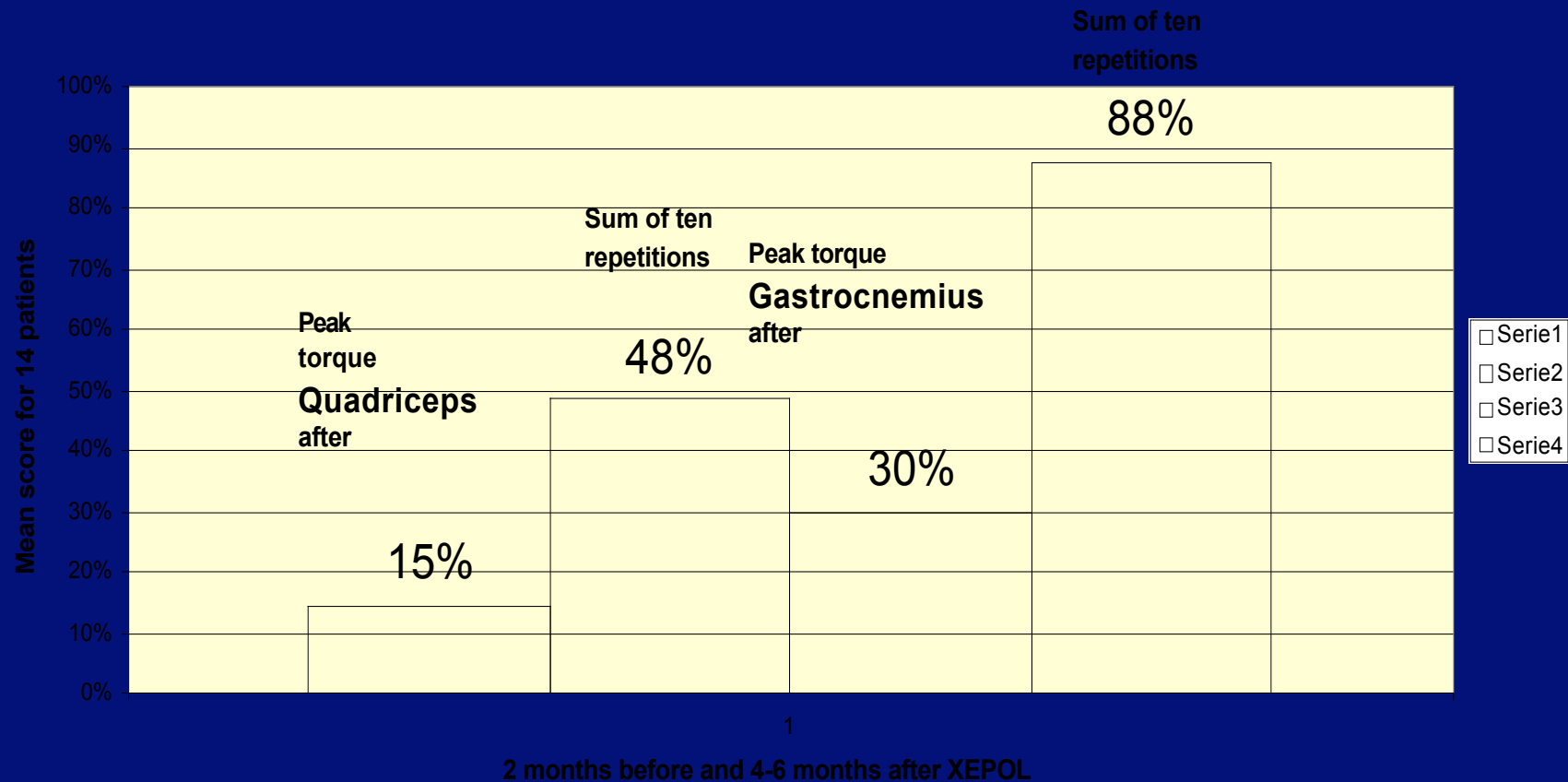
t test

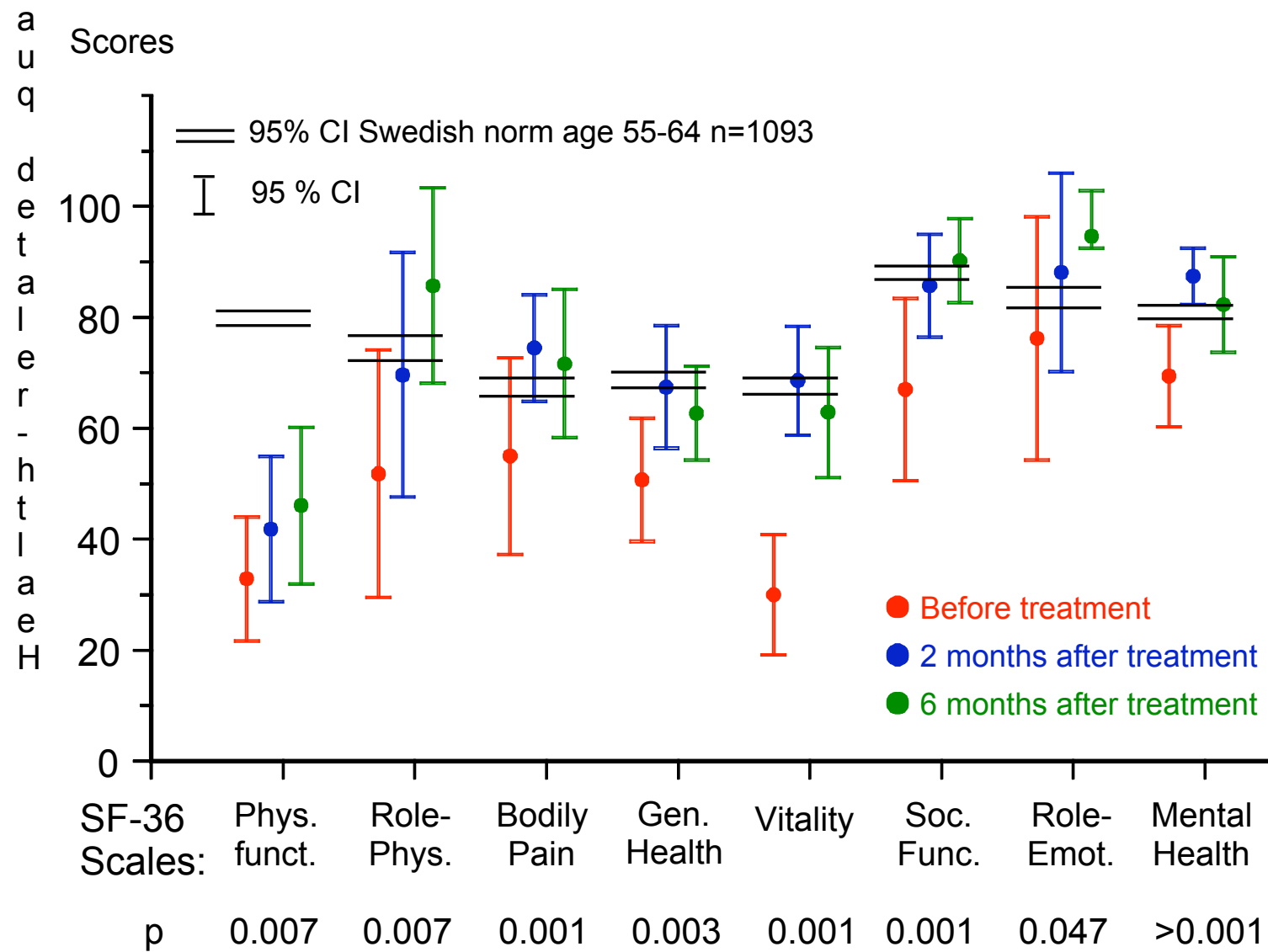
IVIG-Xepol dampens Cytokine production in PPS



Muscle-strength

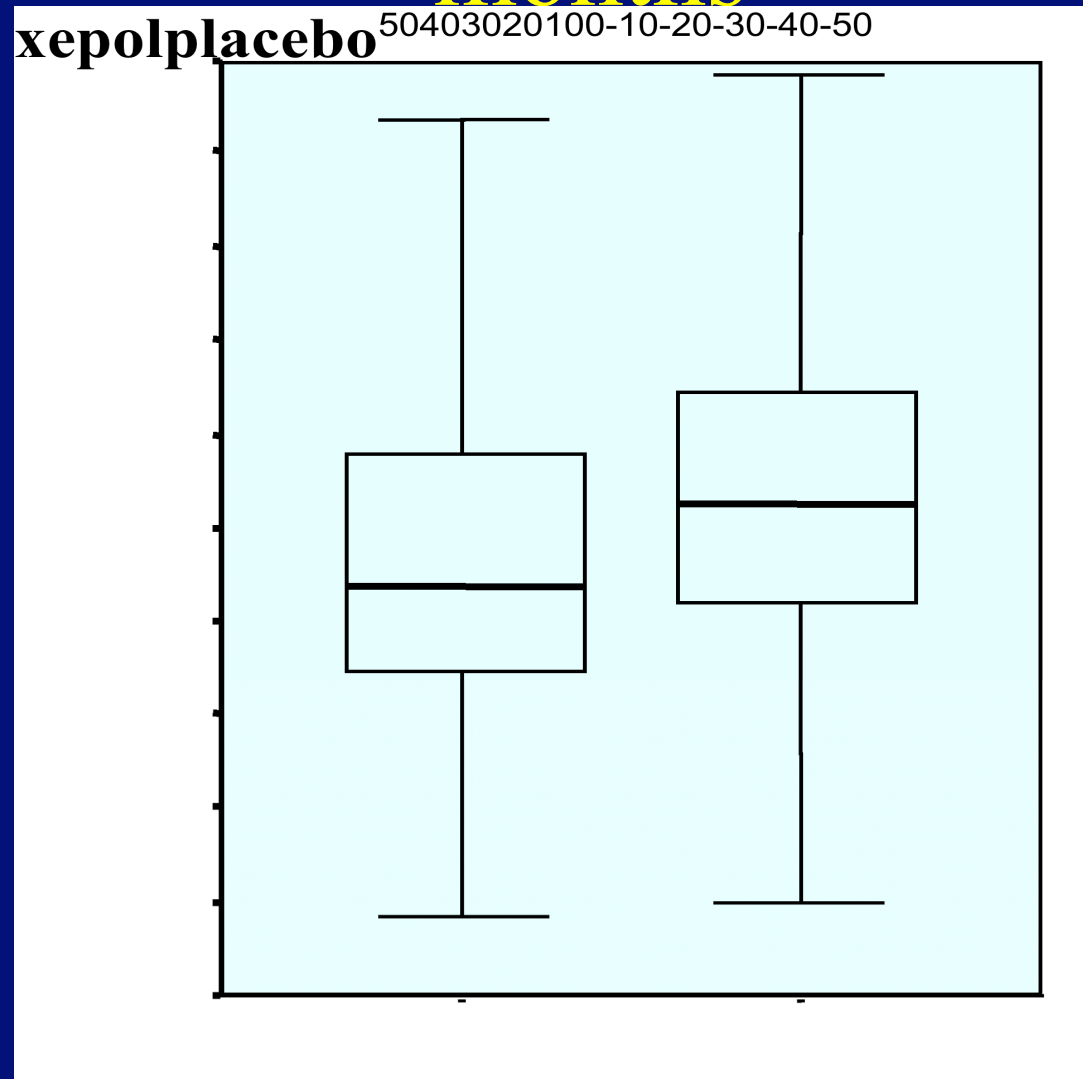
INCREASE IN MUSCLE STRENGTH
AND DECREASED FATIGUE
BIODEX

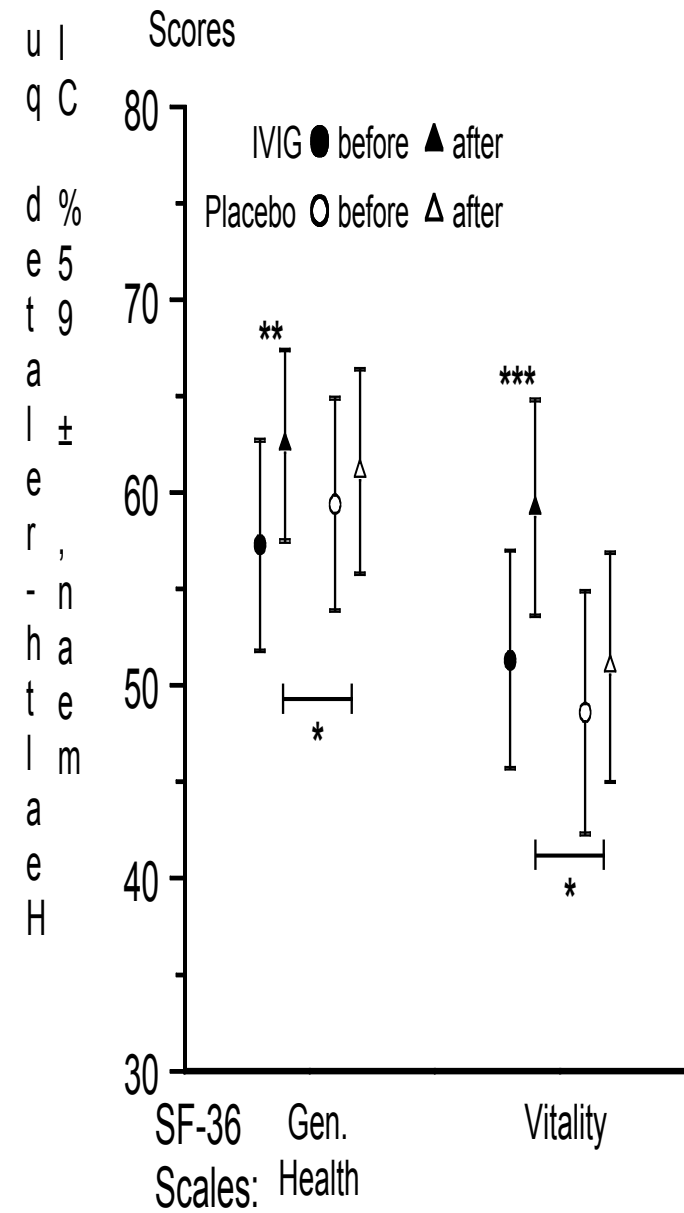
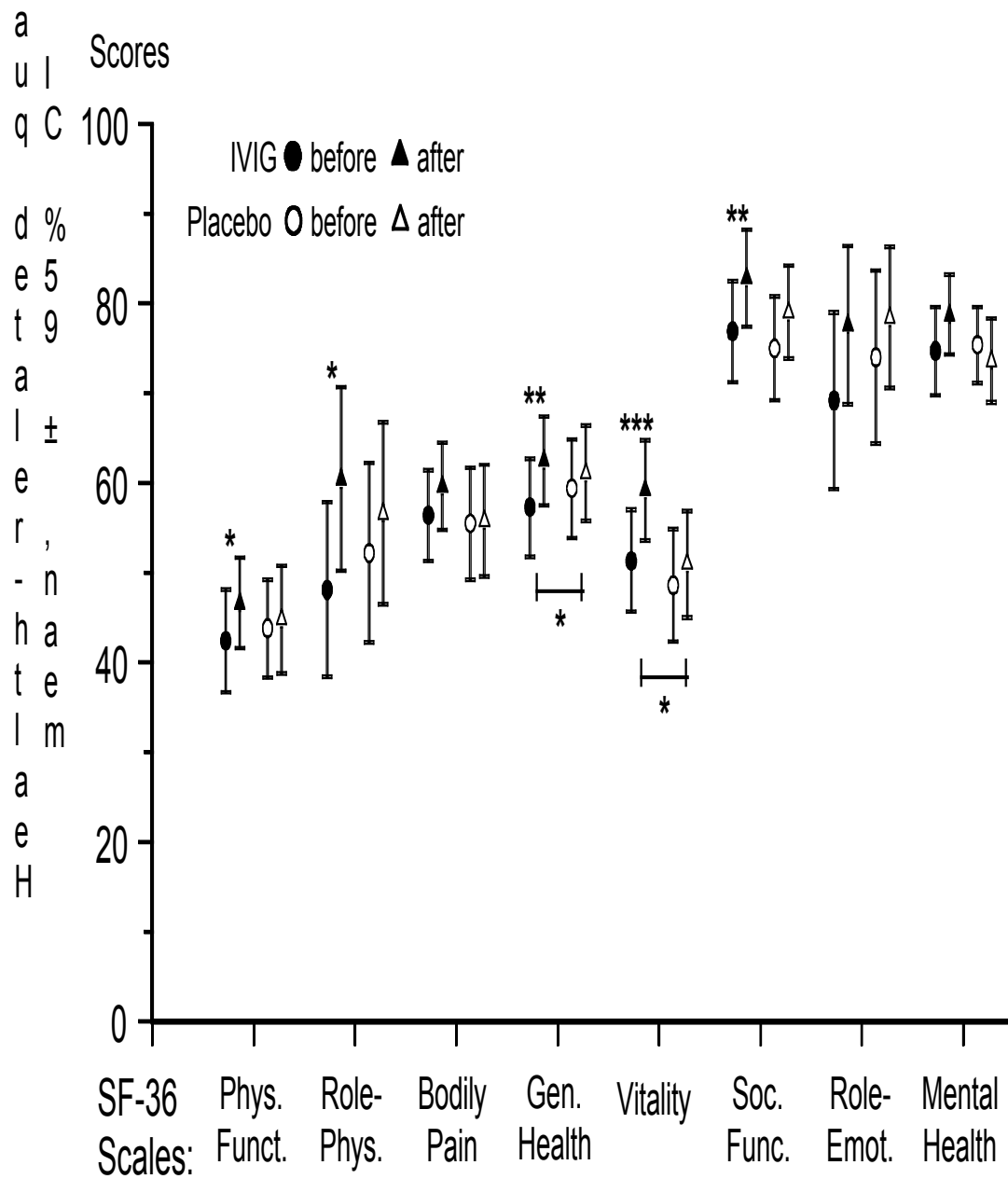




Multicenter, placebo-controlled,
double-blinded study including
135 post-polio patients

Muscle Strength, % change over 6 months





A double blind placebo controlled trial with IVIG

- **An increased muscle strength and a better quality of life, mainly for the general health and vitality domains**
- **Remarkable in view of the long term nature of PPS.**

Remaining issues

- Dose and dosing intervals? One year intervals seem optimal.
- Selection of responders? Any help from CSF cytokine expression?
- Other more specific immunomodulating principles?
- Mechanism of action?

PPS immune study group

- Kristian Borg
- Henrik Gonzalez
- Magnus Andersson
- Mohsen Khademi
- Erik Wallström
- Fredrik Piehl
- Tomas Olsson