Dr. Bart C. Jacobs

Erasmus MC, Rotterdam

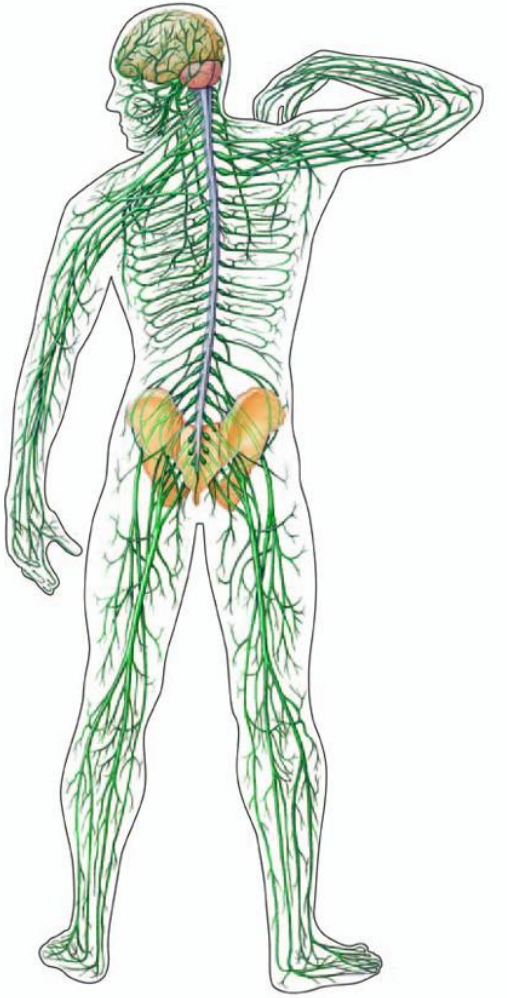
The Netherlands

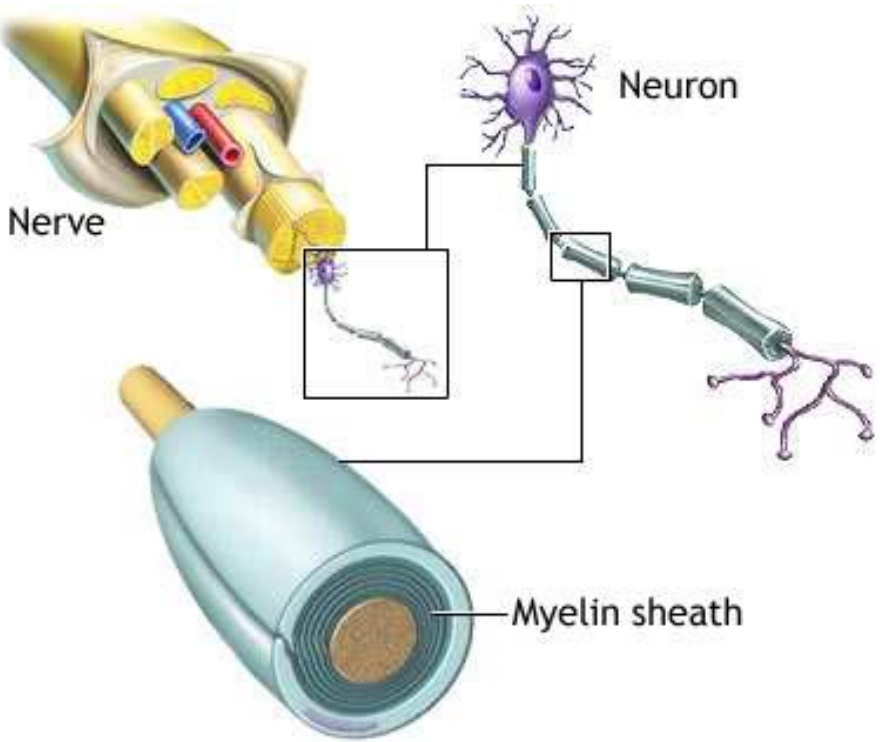
The alphabet soup of inflammatory neuropathies

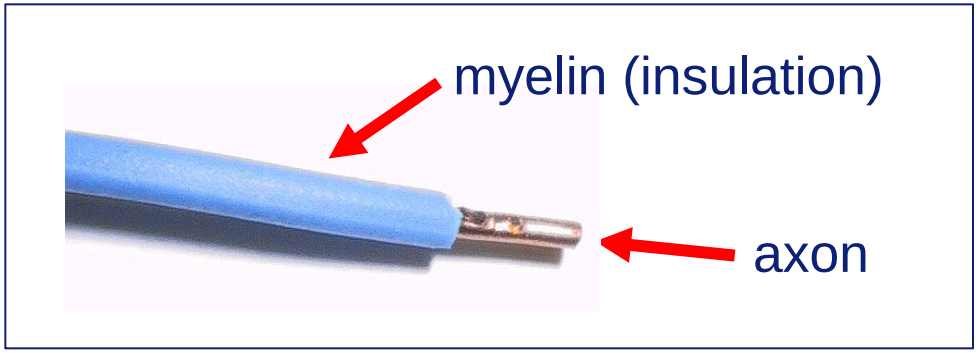
Diseases	Diagnostics	Treatments	Research
Acute • GBS • AIDP • AMAN • MFS • A-CIDP **Chronic** • CIDP • MMN • LSS • DADS • MADSAM • CANOMAD • MGUS-NP	• LP • CSF • EMG • MAG • GM1 • GD1a • GD1b • GQ1b	• IVIg • PE	• IGOS • I-SID

Erasmus MC

Peripheral nervous system

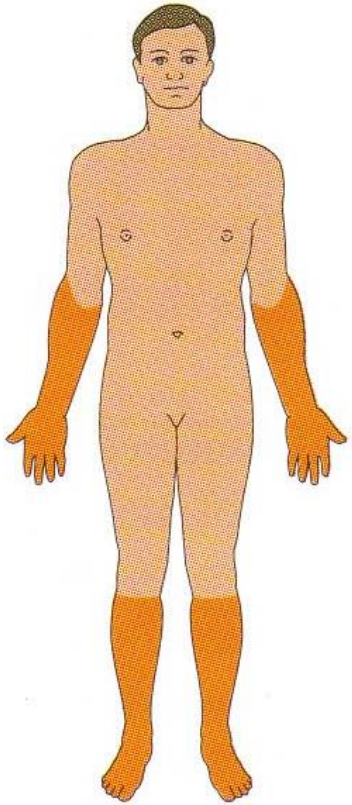






Normal nerves Neuropathy

- Muscle strength → Weakness
  - limbs, face → limbs, face
  - breathing → respiratory failure
  - swallowing → swallowing
- Sensation → No or abnormal sensation
  - touch → numbness
  - pain → pain, cold
  - coordination → ataxia
- Reflexes → Low or absent reflexes

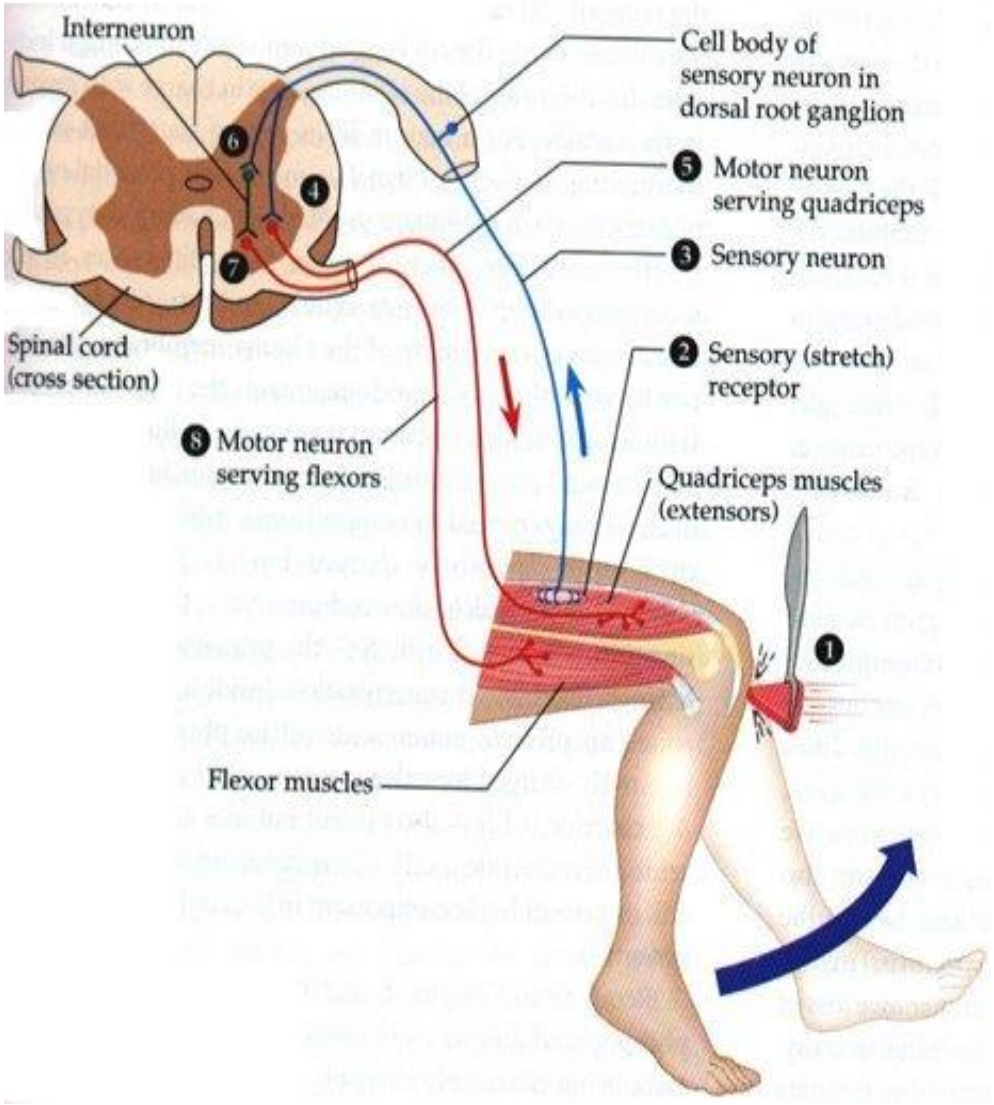


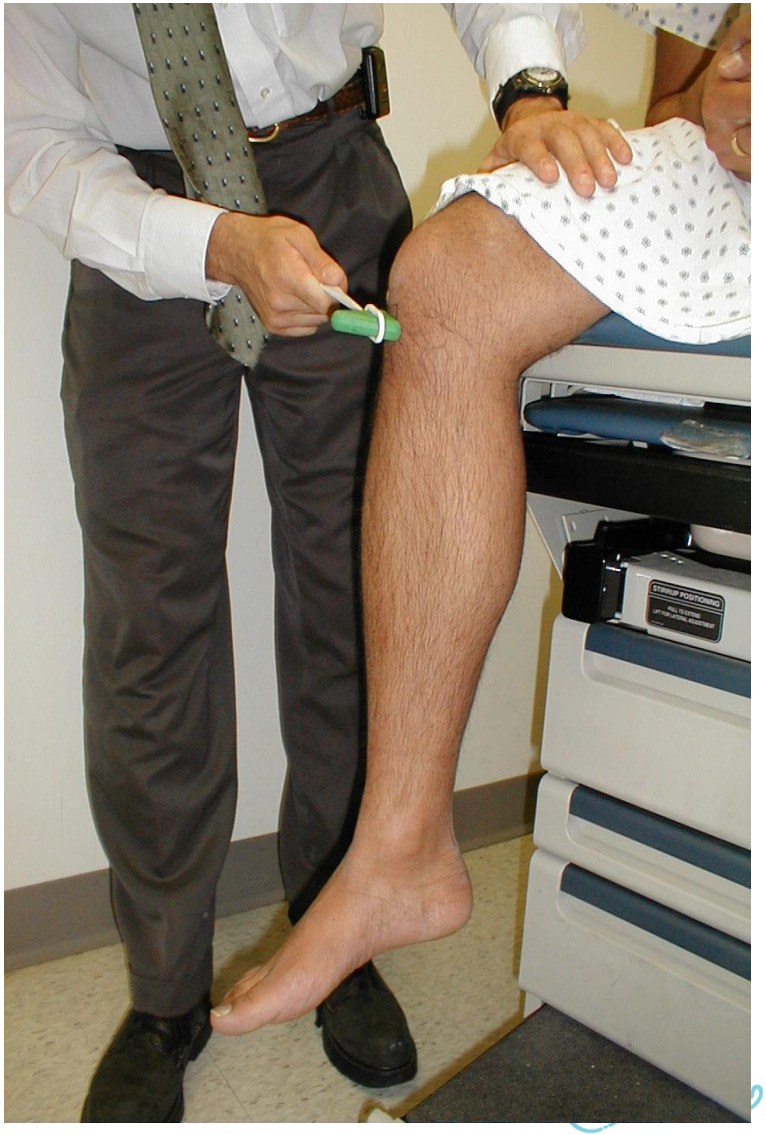
Erasmus MC

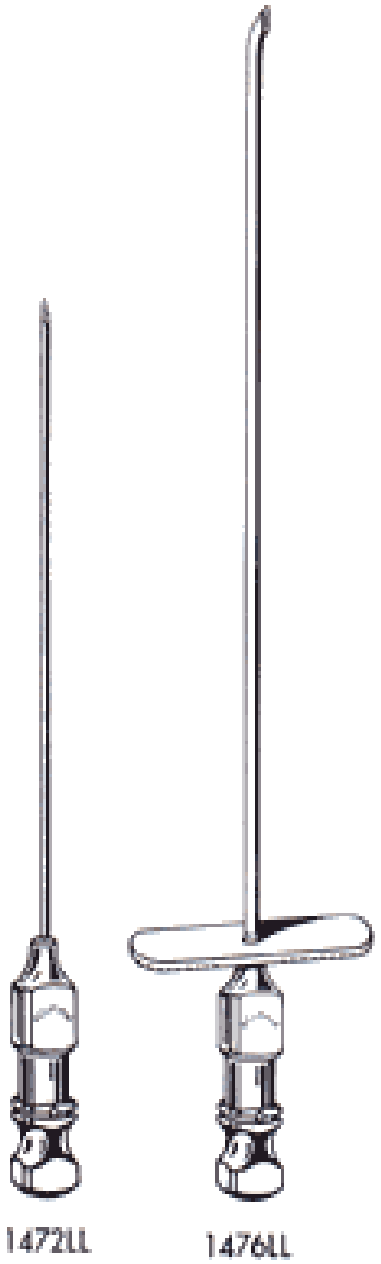
Reflex hammer

Erasmus MC

Knee jerk reflex



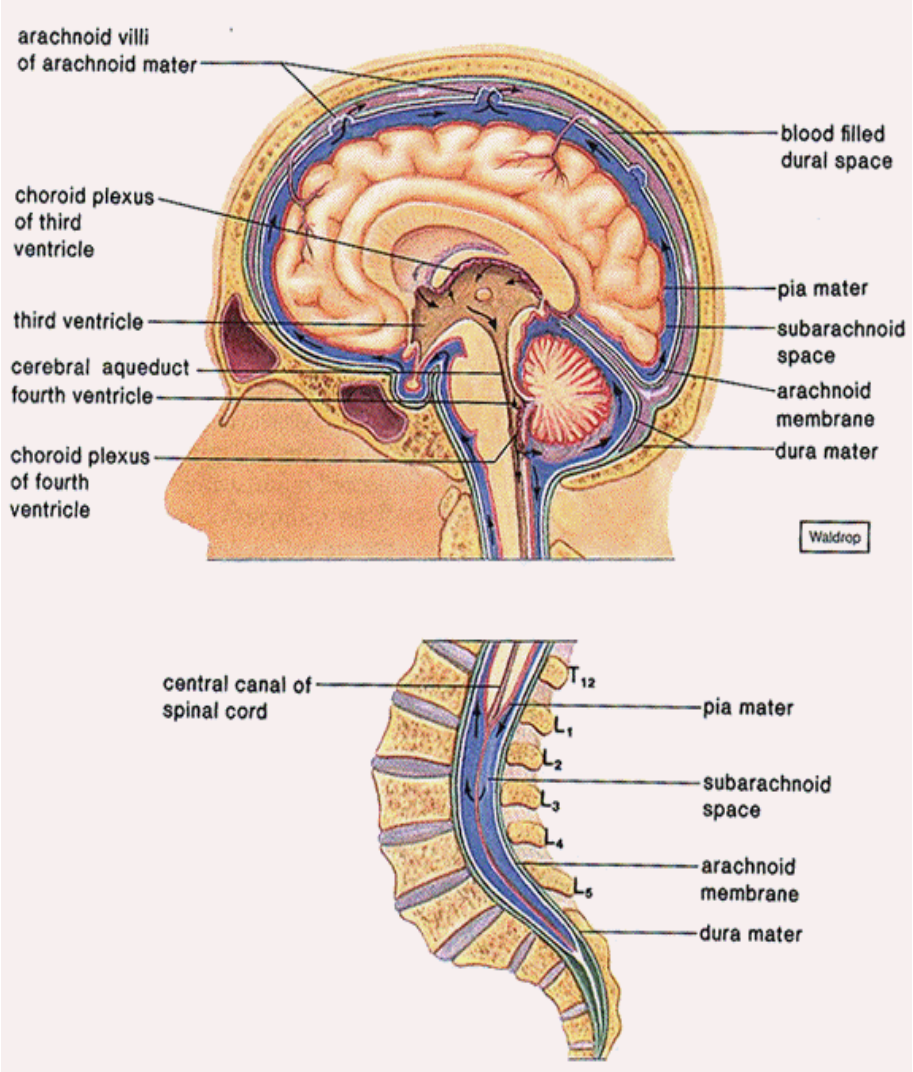


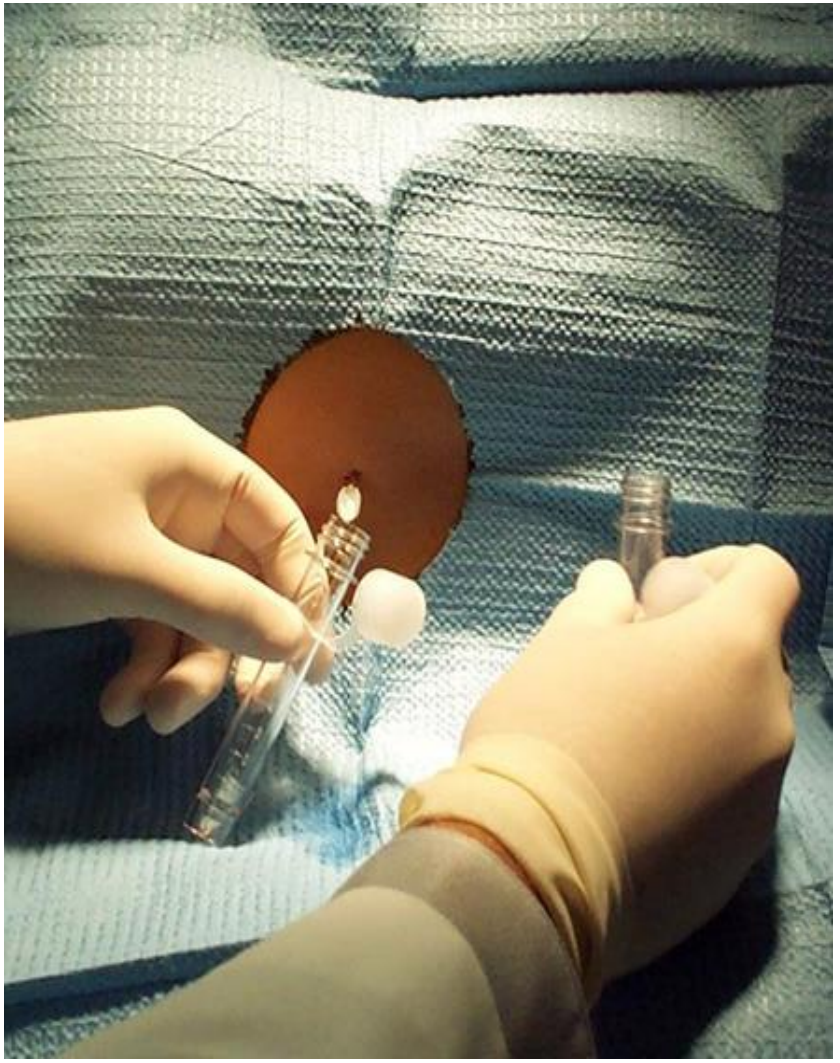


1 inch

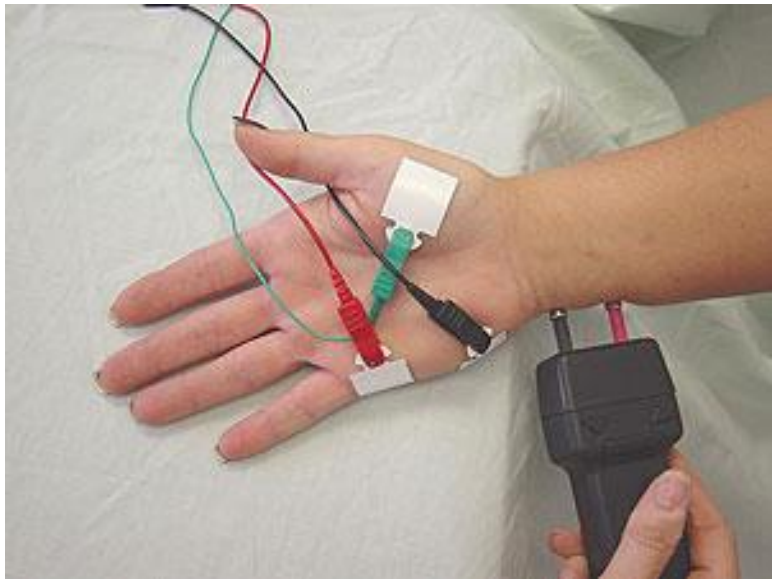
Erasmus MC

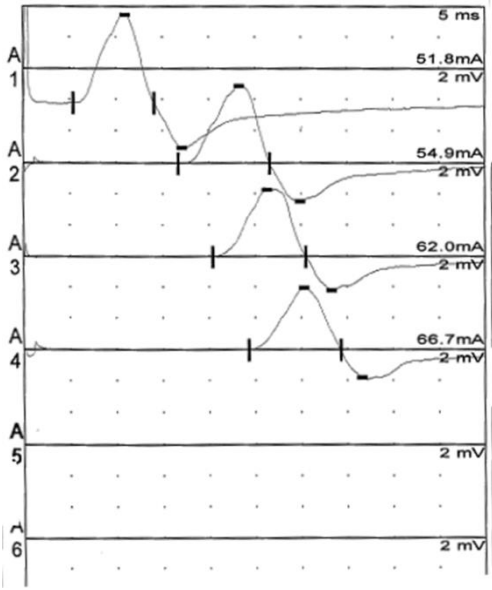
Lumbar punction (LP) and cerebrospinal fluid (CSF)





Nerve electrophysiology and -myogram (EMG)



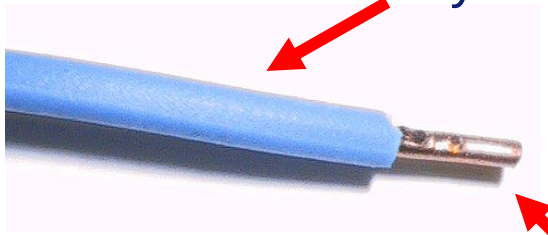


Recording Site : M.Abd.dig.V

Stimulus Site	Lat1 ms	Dur ms	Amp mV	Area mVms	Temp °C
A1: pols	5.3	8.7	8.6	24.5	31.5
A2: el.di	16.6	9.9	7.4	24.1	32.0
A3: el.pr	20.3	10.1	6.6	22.6	32.0
A4: oksel	24.2	10.0	5.8	19.5	33.0
A5: Erb					
A6:					

Segment	Dist mm	CV m/s	CVco m/s	rAmp %	rArea %
M.Abd.dig.V-pols	60				
pols-el.di	280	24.7	30.4	86.0	98.4
el.di-el.pr	90	24.3	30.0	88.6	93.9
el.pr-oksel	80	20.5	24.3	88.1	86.3
oksel-Erb					

Myelin damage (demyelination)



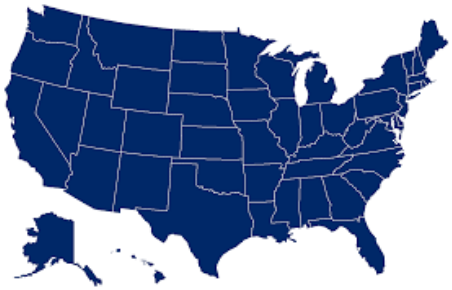
Axon damage (degeneration)

Erasmus MC

Patients with inflammatory neuropathies in USA

estimations based on data from The Netherlands

	New this year	Total alive with/after disease
GBS	3,000 - 4,000	60,000 - 80,000
MFS	100 - 200	2,000 - 4,000
CIDP	400 - 500	8,000 - 10,000
MMN	100 - 200	2,000 - 4,000
Total	**3,500 - 5,000**	**70,000 - 100,000**



Population: 320 million

Erasmus MC

Guillain-Barré syndrome (GBS)

(1916) Bull Mem Soc Med Hop Paris, 40, 1462-70

G. Guillain

J-A. Barré

A. Strohl

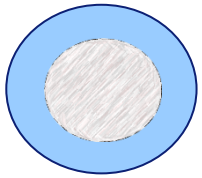
Guillain-Barré syndrome (GBS)

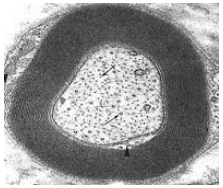
- All ages, but increasing with age
- More frequent in males than females
- Rapidly progressive and potentially life-threatening
- Symmetrical weakness and sensory symptoms in legs and arms
- Frequently painful
- 25% respiratory failure requiring ventilation at ICU
- 15% autonomic dysfunction
- Large variation in clinical course between patients

Erasmus MC

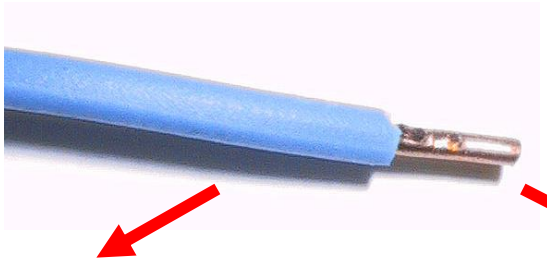
Two main subtypes of GBS

Cross-section

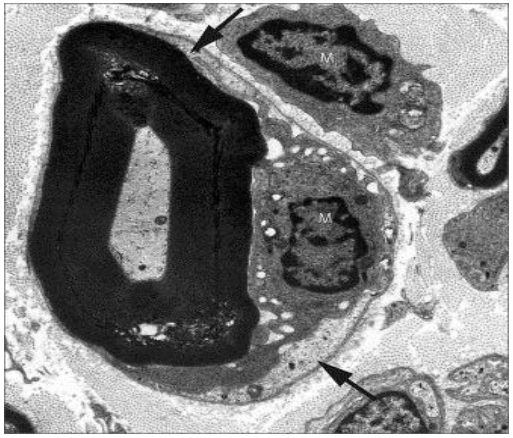




Normal nerve

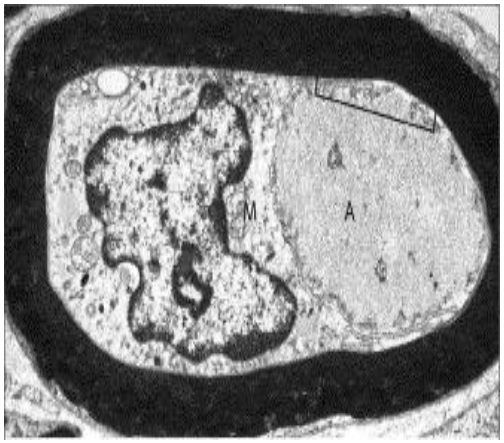


Damaged myelin



Acute inflammatory demyelinating polyneuropathy (AIDP)

Damaged axon



Acute motor (sensory) axonal neuropathy (AMAN) (AMSAN)

Miller Fisher syndrome (MFS)

- Three typical characteristics
  - Weakness muscles for eye movements (double vision)

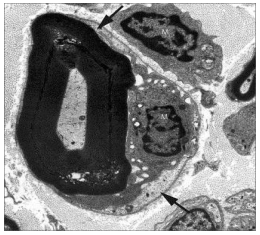
    - Often with drooping eyelids and facial weakness
  - Poor balance and coordination with clumsy walking (ataxia)
  - On physical examination: loss of tendon reflexes

- Variant of GBS, but no weak of the limbs

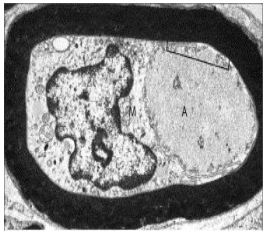
Erasmus MC

Guillain-Barré syndrome

- AIDP



- AMAN

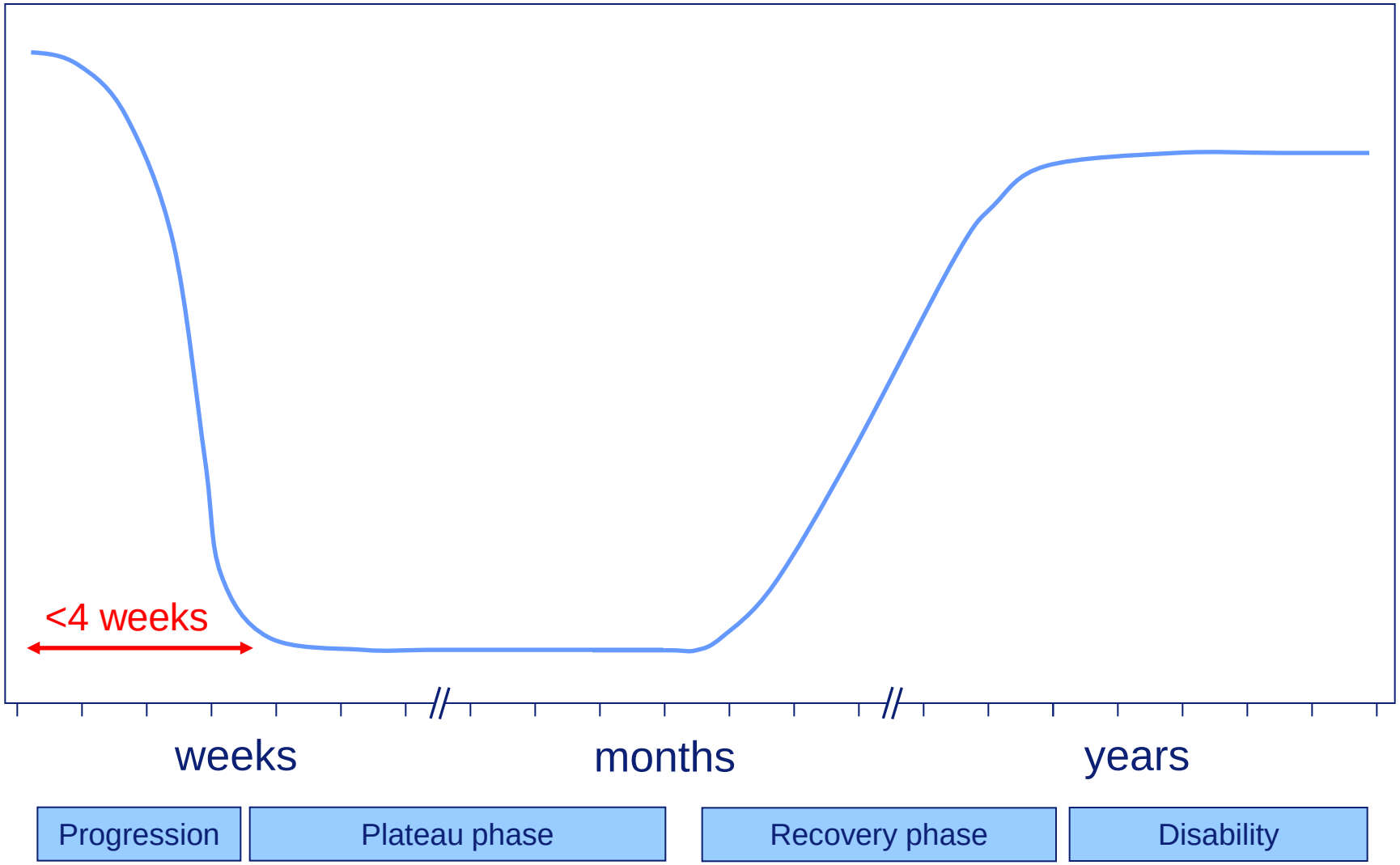


- MFS
- Other variants
- AMSAN

Motor + sensor

Erasmus MC

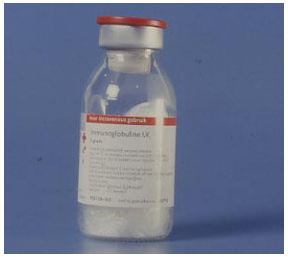
Typical clinical course of GBS



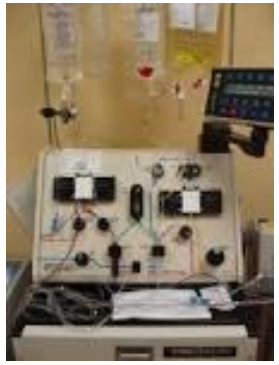
Treatment of GBS

- Supportive care
  - Artificial ventilation
  - Pain medication
  - Prevention complications
- Specific treatments
  - Immunoglobulins (IVIg)
  - Plasma exchange (PE)
- Rehabilitation and physiotherapy

IVIg

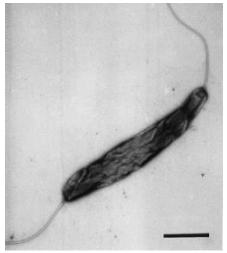
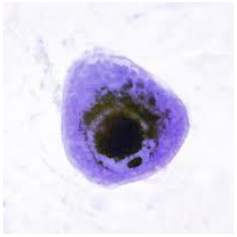
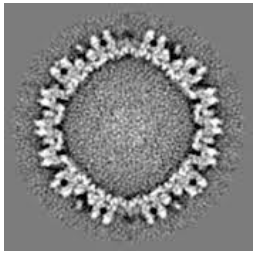
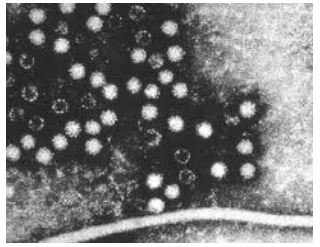


PE



Erasmus MC

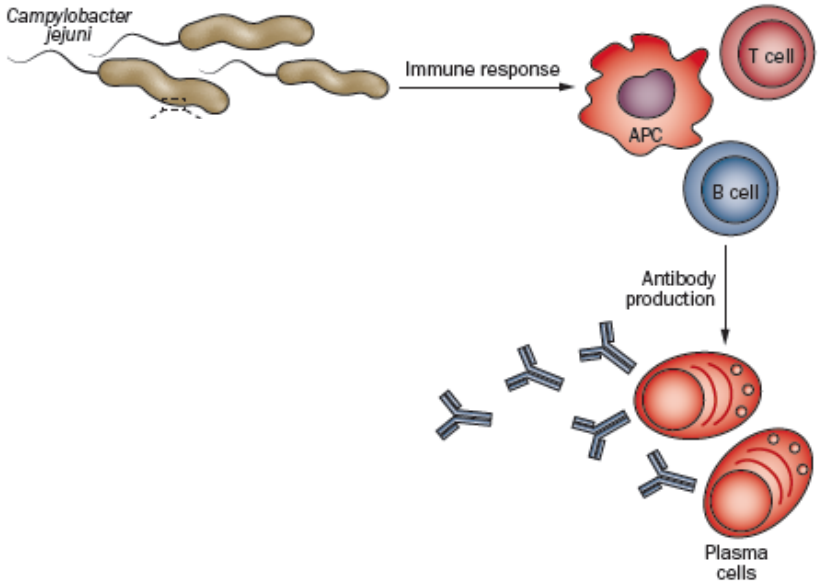
Infections that can cause GBS

Campylobacter bacteria	Cytomegalo virus	Epstein-Barr virus	Mycoplasma bacterie	Hepatitis E virus
				
Gastro-intestinal infection	Respiratory tract infection	Infectious monocucleosis (‘kissing disease’)	Respiratory tract infection	Hepatitis
30%	15%	10%	5%	5%

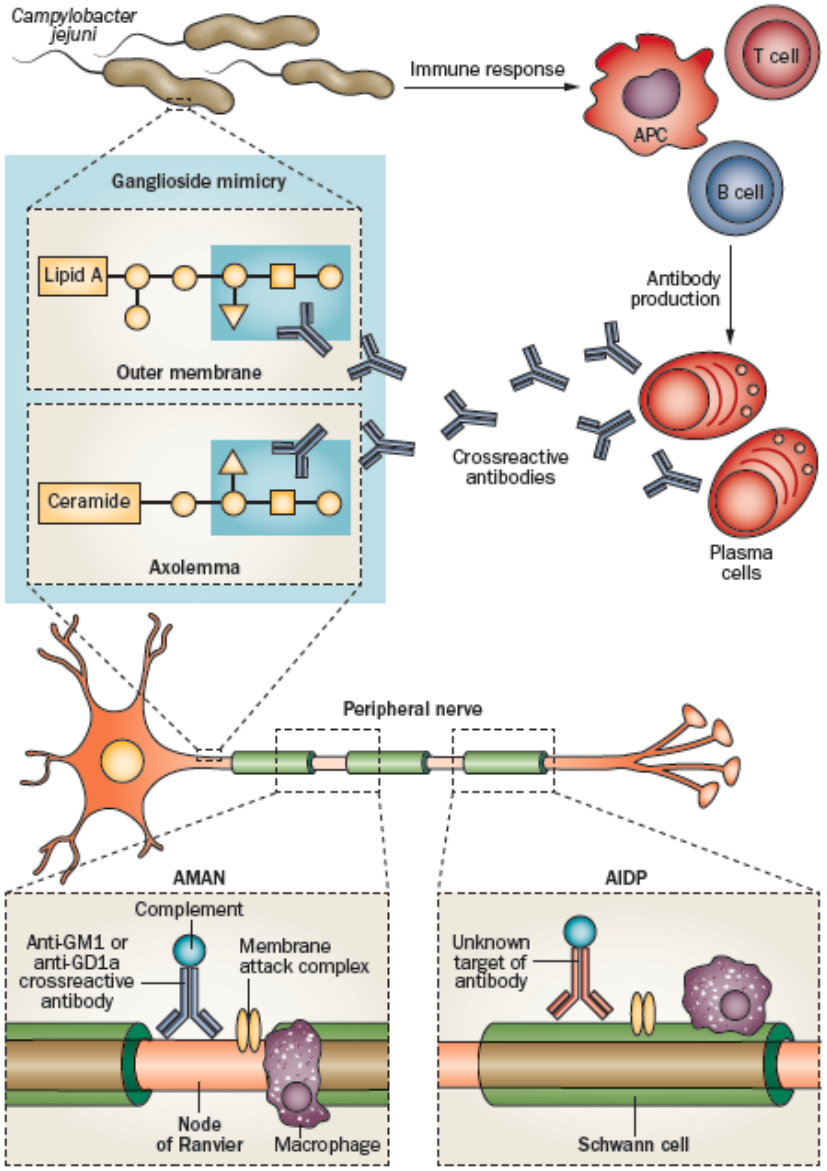
GBS

Erasmus MC

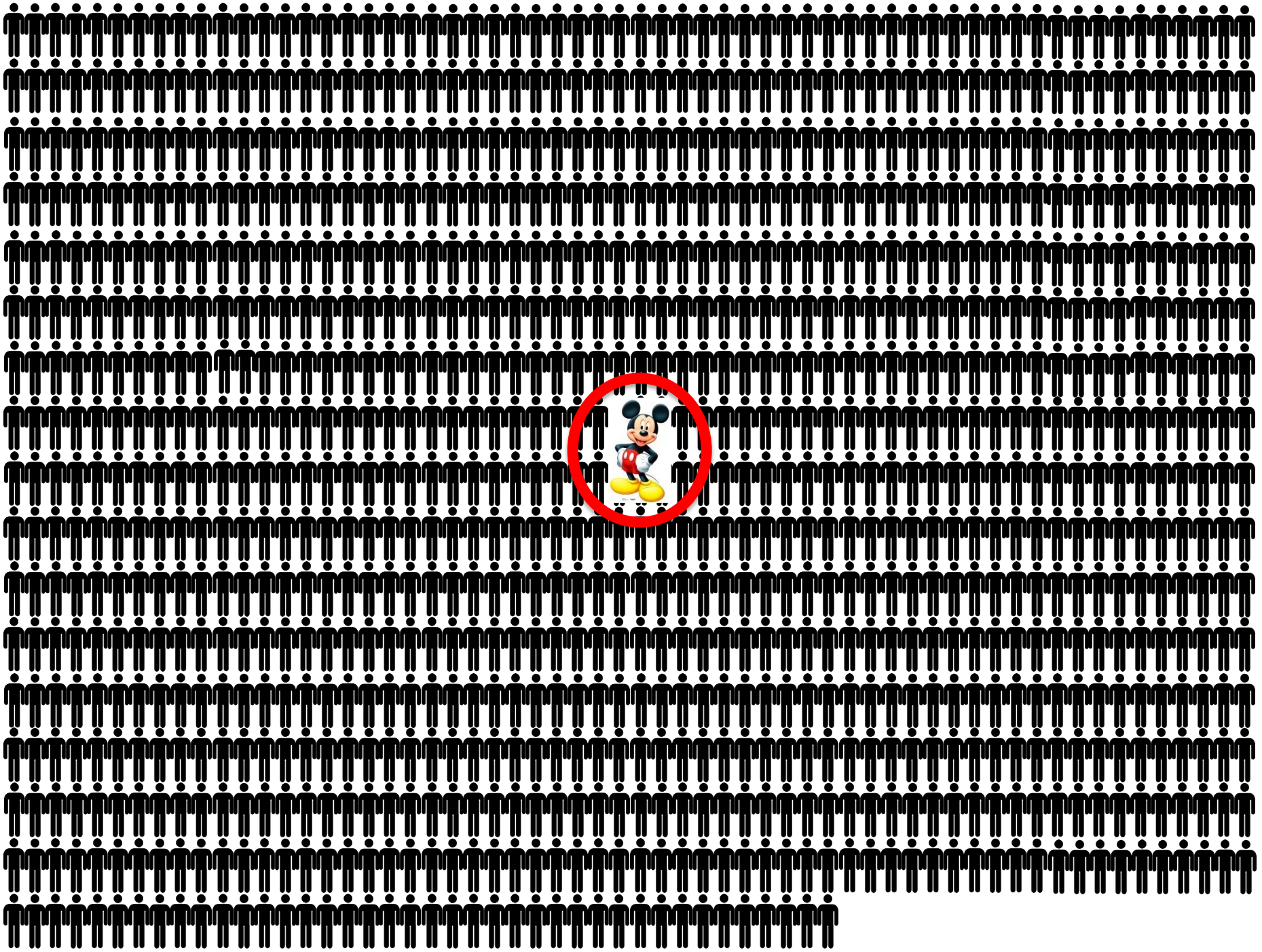
Infections that trigger immune responses to nerves



Infections that trigger immune responses to nerves



Erasmus MC



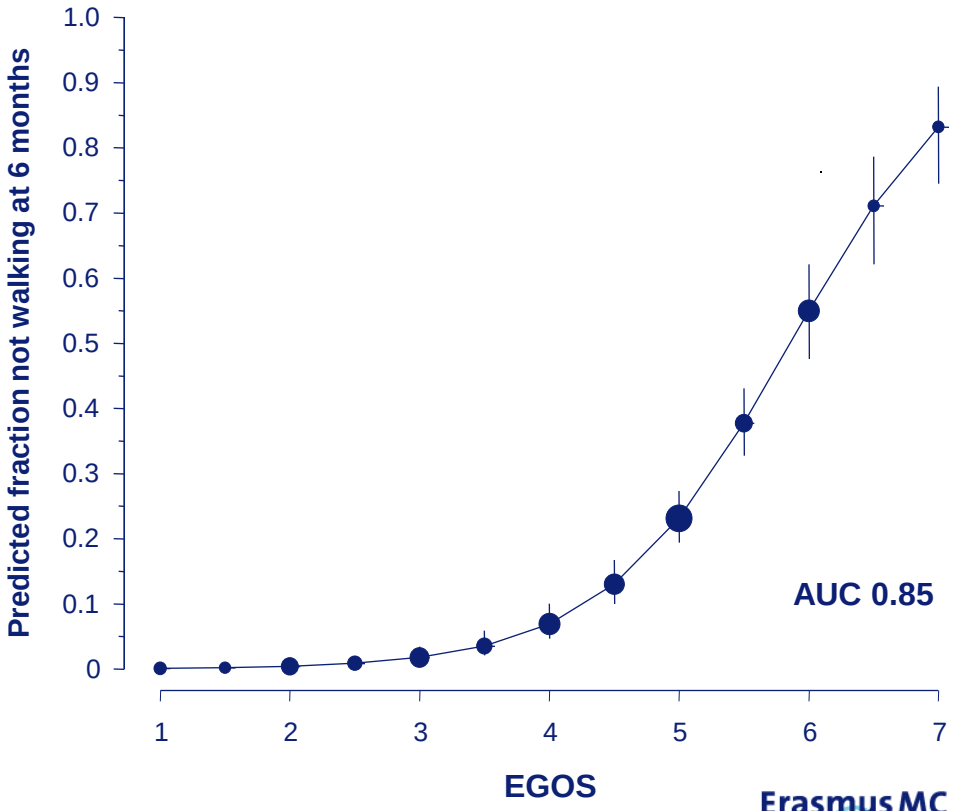
Predicting recovery of GBS in individual patients

van Koningsveld et al. Lancet Neurol 2007

Erasmus GBS outcome score (EGOS)

Predictors	Categories	Score
Age (years)	≤40	0
	41-60	0.5
	>60	1
Diarrhoea (≤ 4 weeks)	absent	0
	present	1
GBS disability score (at 2 weeks)	0-1	1
	2	2
	3	3
	4	4
	5	5
EGOS		**1 - 7**

Chance unable to walk at 6 months according to EGOS (N=762)



Erasmus MC

Chronic inflammatory demyelinating poly(radiculo)neuropathy (CIDP)

Erasmus MC

CIDP

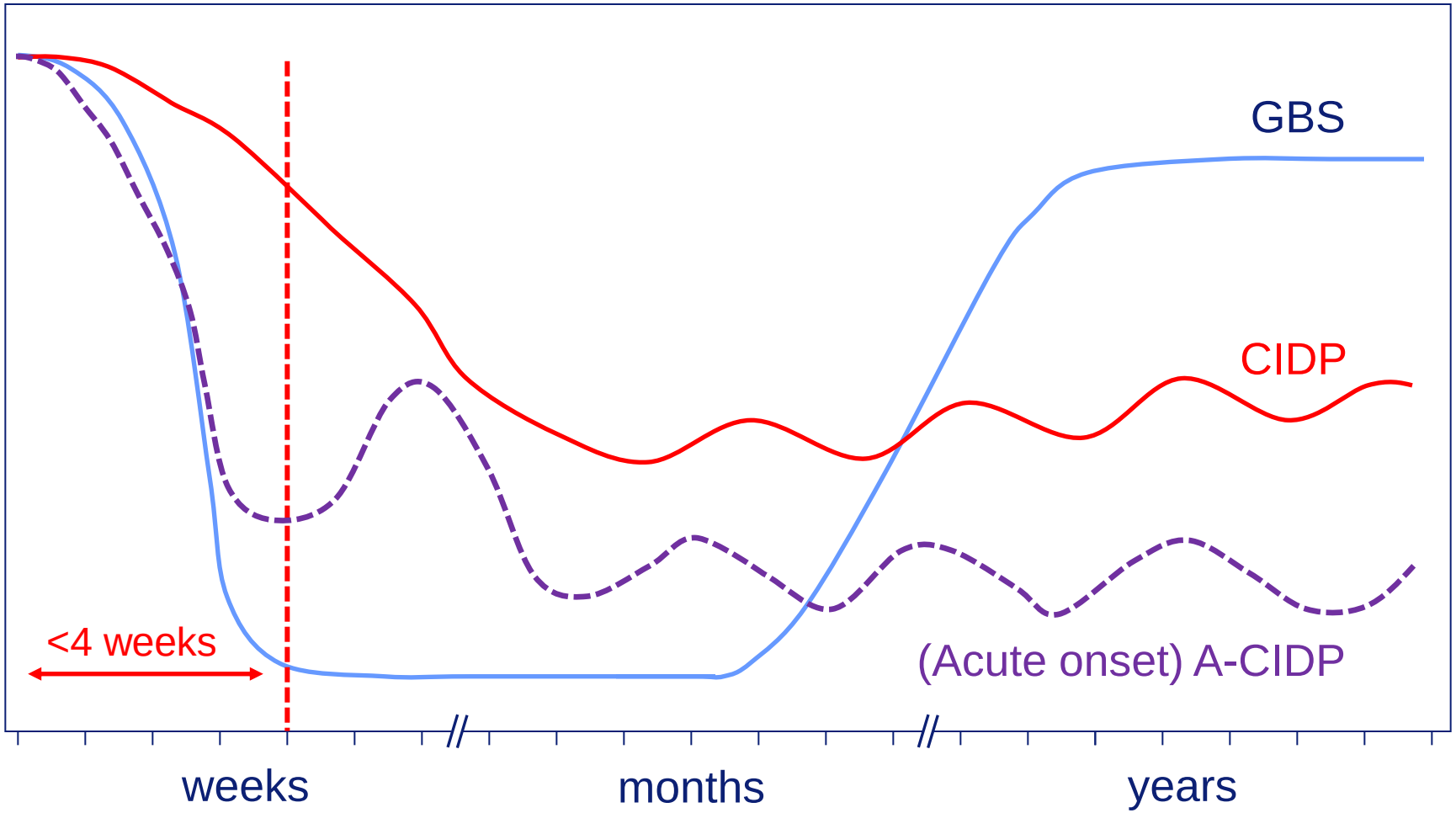
- **Clinical features:**
  - Slow onset (disease progression > 8 weeks)
  - Symmetrical weakness and sensory deficits
  - Legs more involved than arms
  - Sometimes cranial nerve involvement

- **Diagnosis:**
  - Neurological exam
  - Blood tests (to exclude other diseases)
  - Spinal tap
  - Nerve electrophysiology

- **Treatments:**
  - Immunoglobulins (IVIg)
  - Corticosteroids
  - Plasma exchange (PE)

Erasmus MC

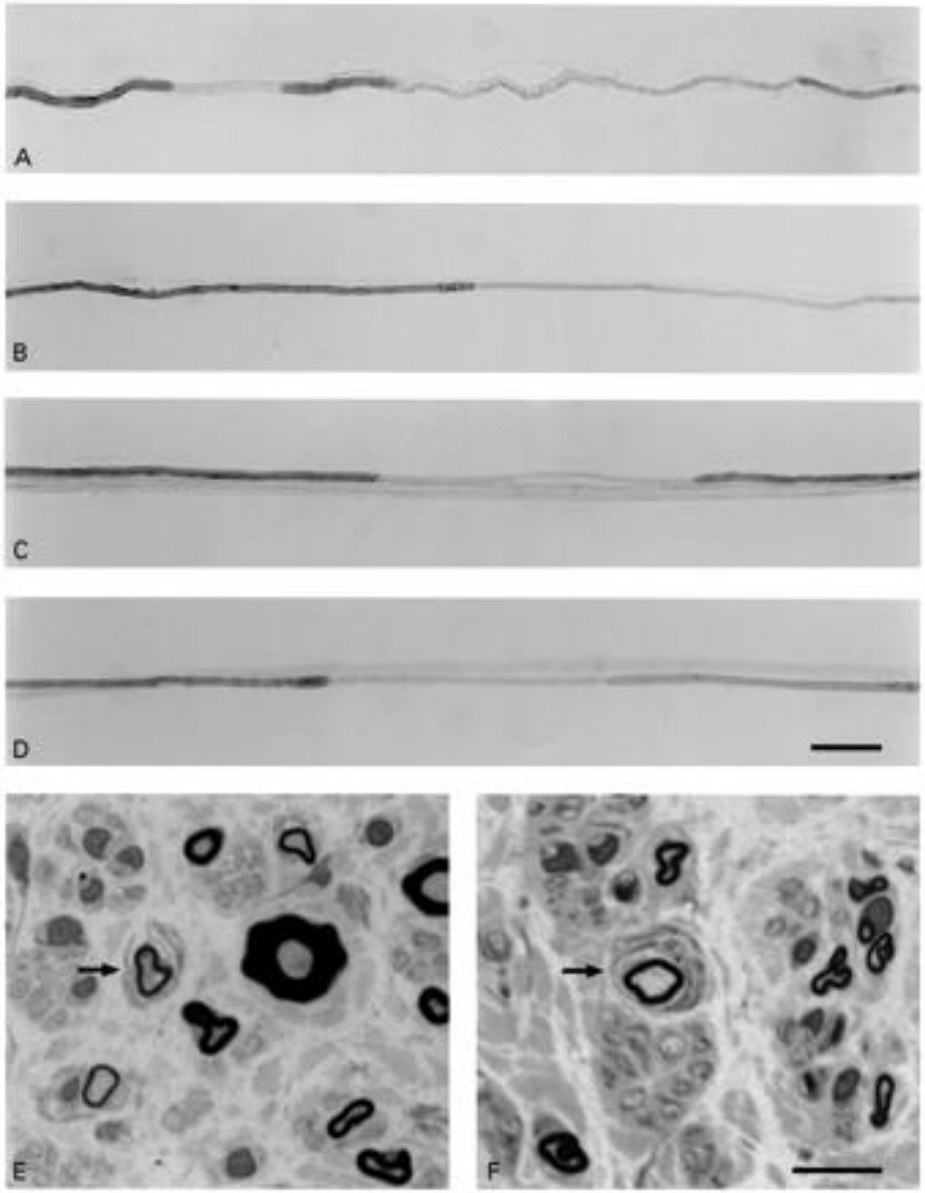
Typical clinical course of GBS and CIDP



Peripheral nerves of a patient with CIDP

Myelin damage

‘Union bulbs’



Bosboom et al., 2001

Right diagnosis and treatment?

- Important to excluded other causes of neuropathy:
  - Hereditary neuropathy
  - Diabetes-related polyneuropathy
  - Paraprotein- or MAG-related polyneuropathy
  - Chronic idiopathic axonal polyneuropathy

- Most patients respond to treatment (at least to some extent).

- CIDP may recover, so try reduce or stop therapy regularly.

- Discriminate between:
  - active CIDP requiring treatment
  - inactive CIDP with residual damage

Erasmus MC

Multifocal Motor Neuropathy (MMN)

Erasmus MC

MMN

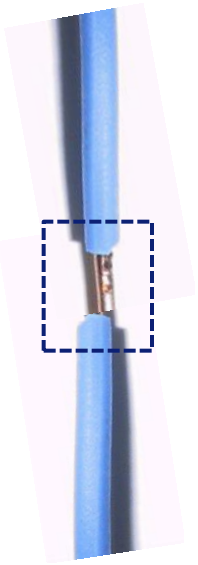
- **Clinical features:**
  - Slow onset
  - Asymmetrical (stepwise involvement specific motor nerves)
  - Weakness in legs more than arms
  - Rarely sensory symptoms (at later stages)

- **Diagnosis:**
  - Neurological exam
  - Blood tests (antibodies to GM1)
  - Spinal tap
  - Nerve electrophysiology

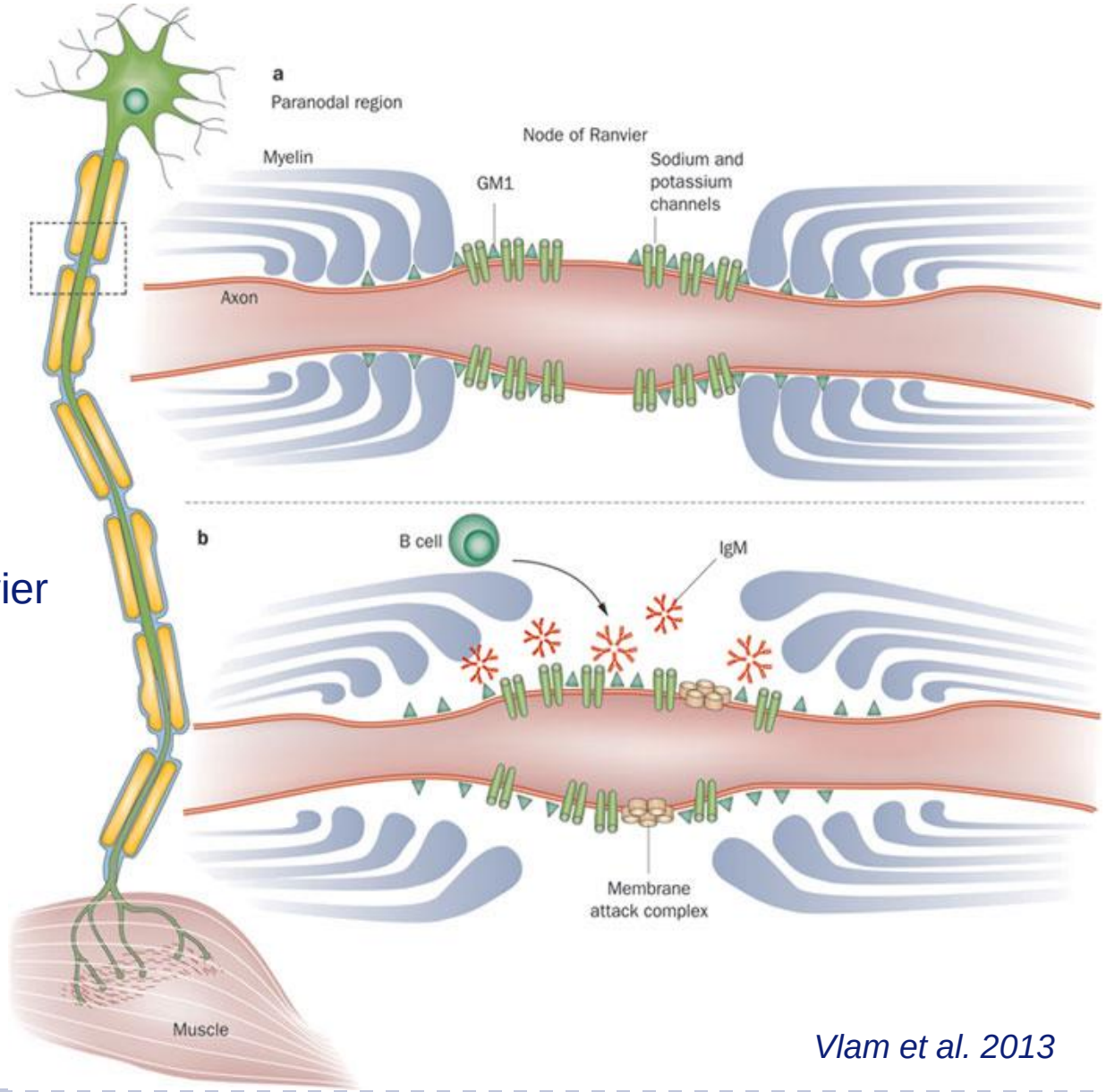
- **Treatments:**
  - Immunoglobulins (IVIg)

Erasmus MC

Disease mechanism of MMN

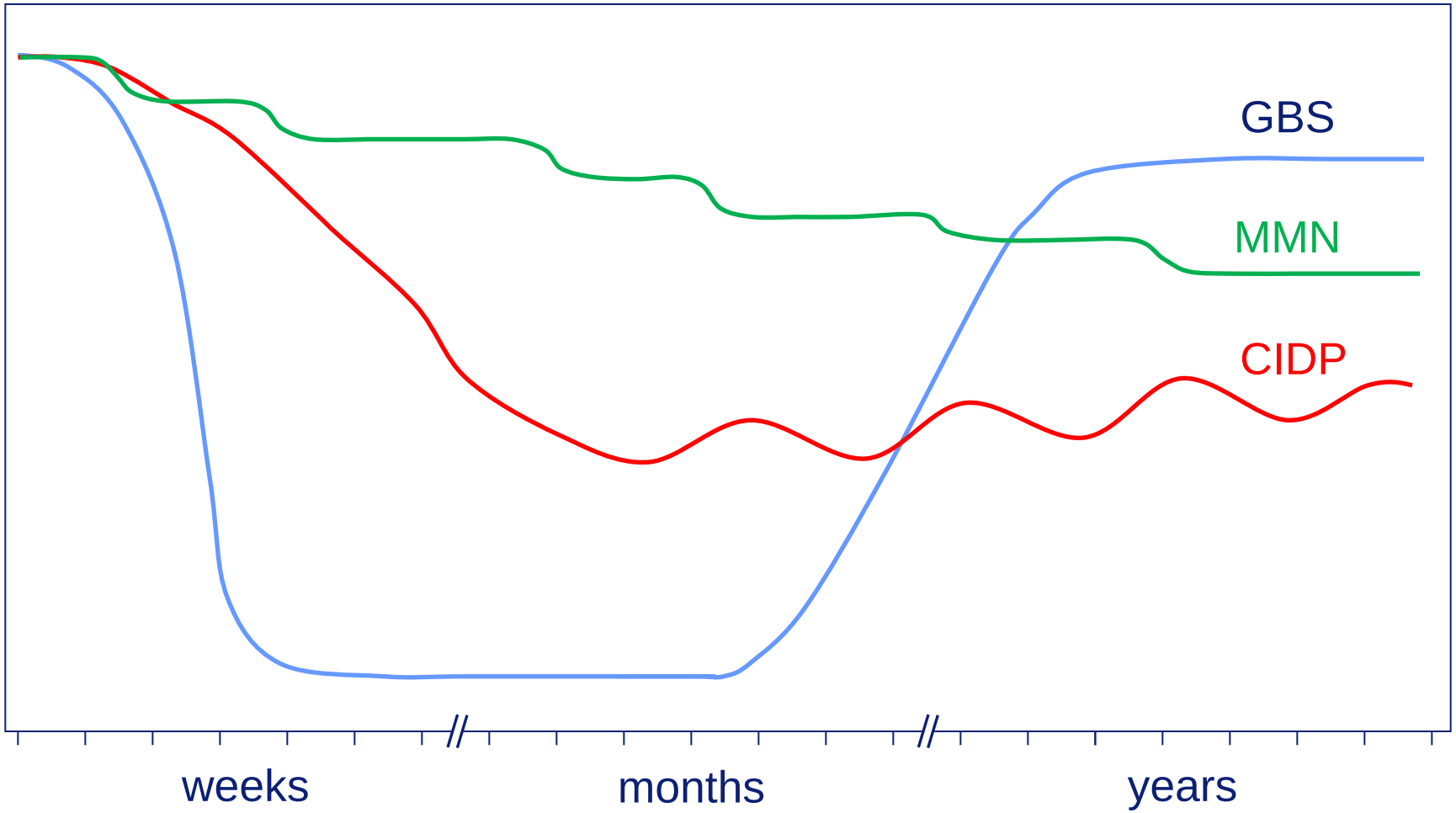


Node of Ranvier



Vlam et al. 2013

Typical clinical course of GBS, CIDP and MMN



Differences between GBS, CIDP and MMN

	GBS	CIDP	MMN
Onset	sudden	slow	slow
Distribution	symmetric	symmetric	asymmetric
Weakness	legs + arms	legs > arms	arms > legs
Sensory deficits	usually	usually	rare
Effective therapy	IVIg, PF	IVIg, steroids, PF	IVIg
Course	single episode (95%)	relapsing-remitting, chronic	persistent

Gaps in current knowledge

- No risk factors known, so all persons may develop these neuropathies.
- Not known in many patients which targets attacked by immune system (especially in AIDP en CIDP).
- No 100% accurate diagnostic tests, so still complex diagnoses.
- Treatable diseases, but only when diagnosed early.
- Highly variable response to treatments between patients.
- Little known about long-term effects and how to treat these.

Erasmus MC

International GBS Outcome Study

International GBS Outcome Study (IGOS)

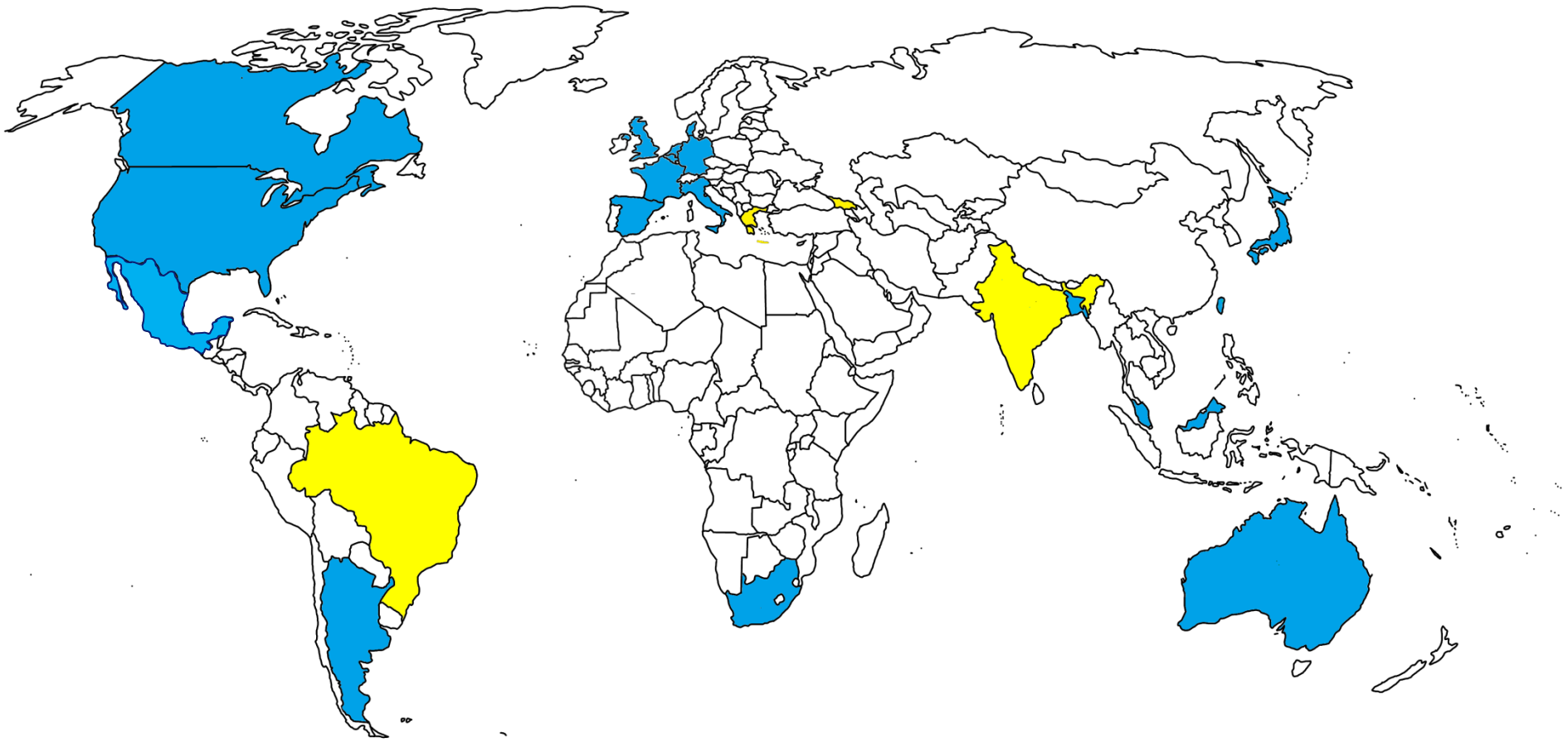
- **Study objectives**
  - Find infections and genes that cause GBS
  - Find factors that determine clinical course and outcome in individual patients
  - Develop better treatments for individual patients
- **Patients**
  - All patients with GBS (and variants) in acute phase (first 2 weeks)
  - More than 1000 patients will participate
- **Design**
  - Prospective study with follow-up of each patients of 1-3 years
  - Collection of clinical data and blood samples
  - 3 new treatments tested
    - International Second IVIg Dose (I-SID) study

IGOS

Inflammatory Neuropathy Consortium (INC)

INC meeting in June 2012 in Rotterdam

IGOS: a worldwide study



- Inclusion of patients
- In process of IRB approval

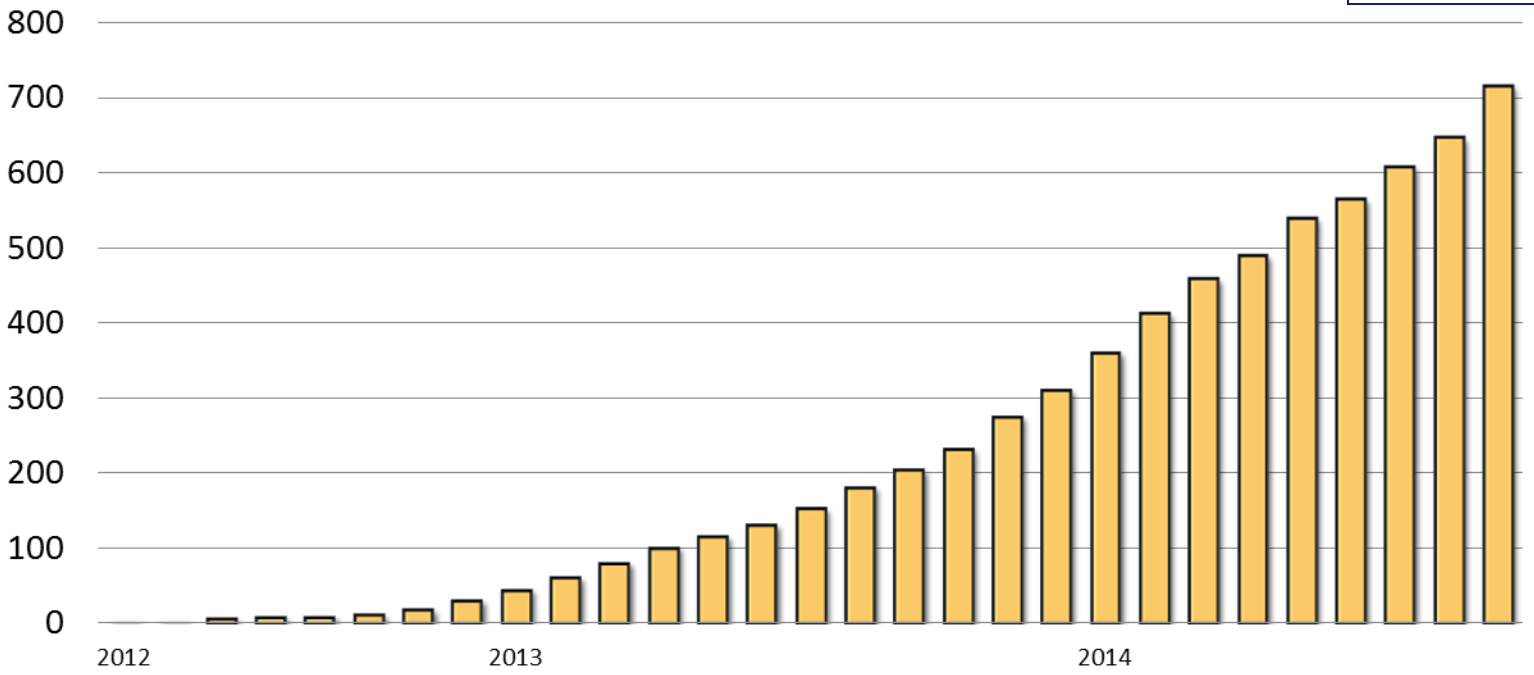
- 18 participating countries
- 142 participating centers

IGOS

Number of patients participating in IGOS

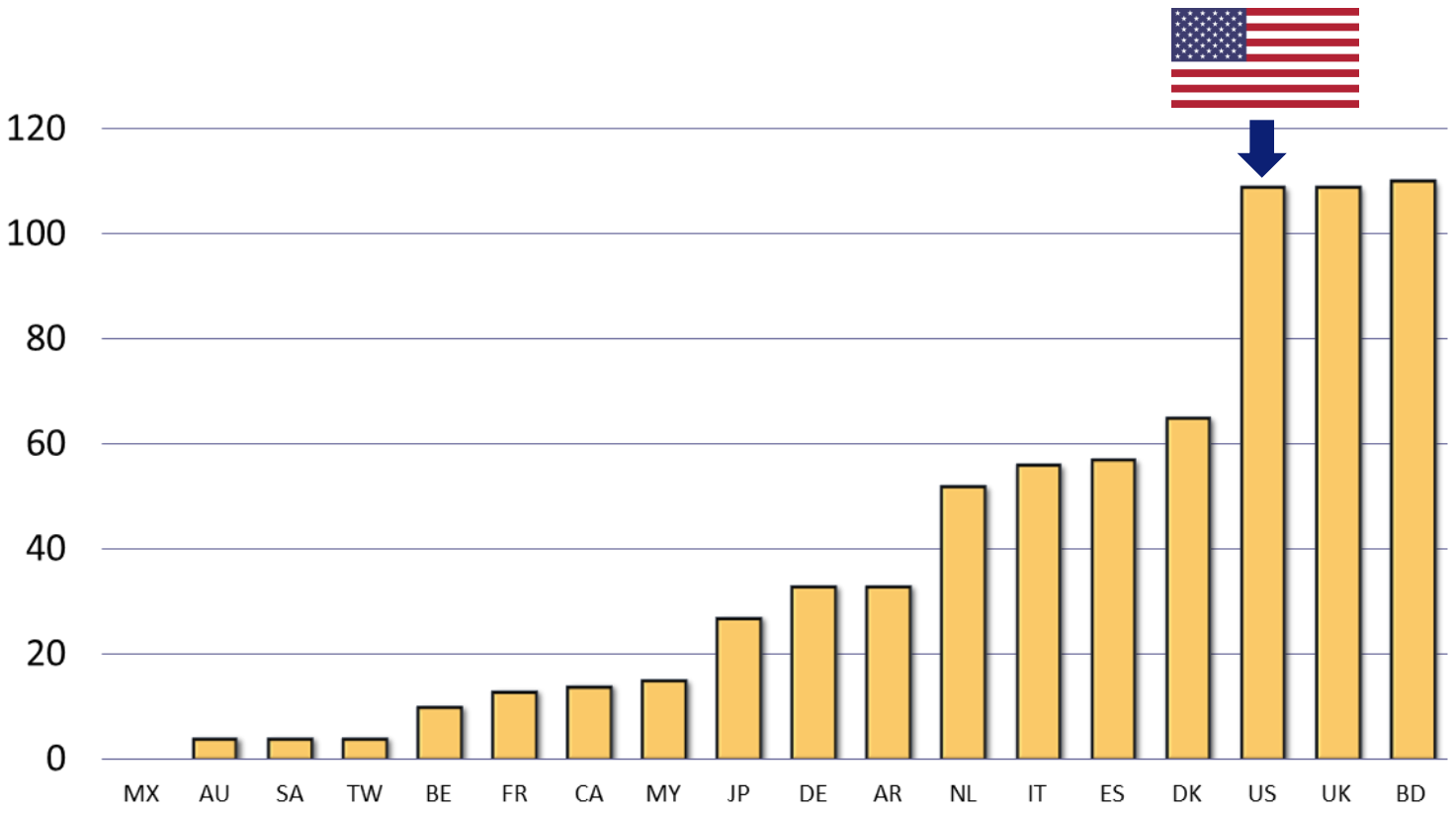
update October 28th , 2014

715 patients



Number of inclusions per country

update October 28th, 2014



What will IGOS deliver?

- Largest data and biobank ever collected for GBS research.
- Better understanding of the risk factors for developing GBS.
- Prediction of disease course and handicap in individual patients.
- First clues how to adjust treatment in individual patients.
- International collaboration between clinicians and experts.
- Training of young researchers and clinicians.
- Network for similar studies in CIDP, MMN and other neuropathies.

Erasmus MC

What could you do to support IGOS?

- Continue to participate as a patient in the research project.
- Financial support via GBS-CIDP Foundation International.

Erasmus MC

Thanks to:

- All patients and relatives involved in research projects
- Research team in Rotterdam
- IGOS Consortium
- Financial support:

GBS|CIDP Foundation International

GBS·CIDP

Erasmus MC Universitair Medisch Centrum Rotterdam

GRIFOLS

CSL Behring

If you can dream it, you can do it.

Walt Disney