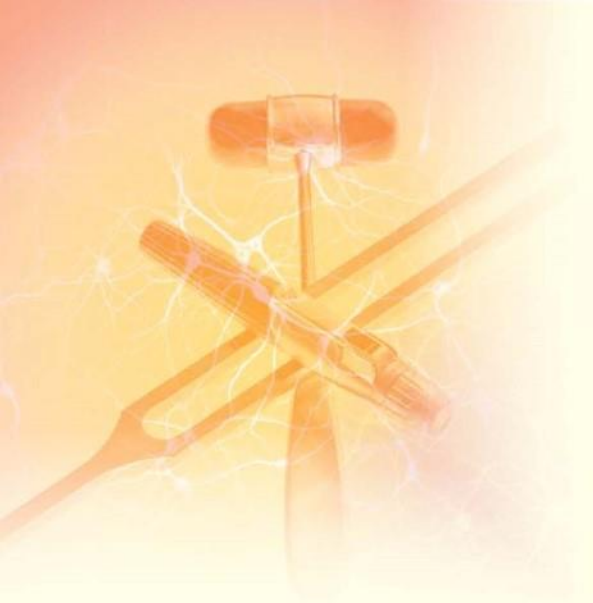


Vnetne nevropatije

Uroš Rot

Klinični oddelek za bolezni živčevja
Nevrološka klinika

MALA ŠOLA NEVROLOGIJE

univerzitetni klinični center ljubljana

Vnetne nevropatije

- imunski odziv proti mielinu ali aksonu
- imunski odziv proti drobnemu žilju, ki prehranjuje živec
- uspešno zdravljenje s kortikosteroidi in imunosupresivi
- nezdravljene vodijo v precejšnjo prizadetost

Table 1 Differential diagnosis of inflammatory peripheral neuropathies: idiopathic inflammatory neuropathy

- Acute
  - Acute inflammatory demyelinating polyradiculoneuropathy
  - Acute motor axonal neuropathy
  - Acute motor–sensory axonal neuropathy
  - Fisher Syndrome and other regional variants
    - Pharyngeal–cervical–brachial
    - Paraparetic
    - Facial palsies
    - Pure oculomotor
  - Functional variants of Guillain–Barré syndrome
    - Pure dysautonomia
    - Pure sensory Guillain–Barré syndrome
    - Ataxic Guillain–Barré syndrome
- Subacute
  - Subacute inflammatory demyelinating polyradiculoneuropathy
- Chronic
  - Chronic inflammatory demyelinating polyradiculoneuropathy
  - Multifocal motor neuropathy with conduction block
  - Chronic relapsing axonal neuropathy
  - Chronic ataxic sensory neuronopathy

Table 2 Differential diagnosis of inflammatory peripheral neuropathies: paraproteinaemia associated with neuropathy

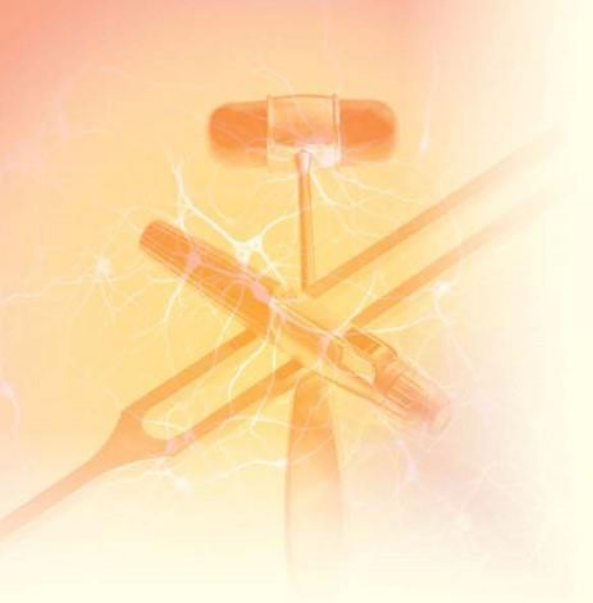
- Multiple myeloma
- Solitary myeloma (osseous and extraosseous)
- Lymphoma
- Chronic lymphocytic leukaemia
- Waldenström macroglobulinaemia (lymphoplasmacytoid lymphoma)
- Cryoglobulinaemia
- Cold agglutinin disease
- Primary amyloid light chain amyloidosis
- Monoclonal gammopathy of undetermined significance

Table 3 Differential diagnosis of inflammatory peripheral neuropathies: vasculitic causes of neuropathy

- Primary vasculitis
  - Microscopic polyangiitis
  - Polyarteritis nodosa
  - Churg–Strauss disease
  - Wegener vasculitis
  - Non-systemic vasculitic neuropathy (isolated nerve vasculitis)
  - Temporal arteritis
- Systemic autoimmune diseases with associated vasculitis
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Sjögren syndrome
  - Mixed connective tissue disease
- Other
  - Serum sickness
  - Infectious, malignant, related to chemotherapy

Table 4 Differential diagnosis of inflammatory peripheral neuropathies: other inflammatory neuropathies

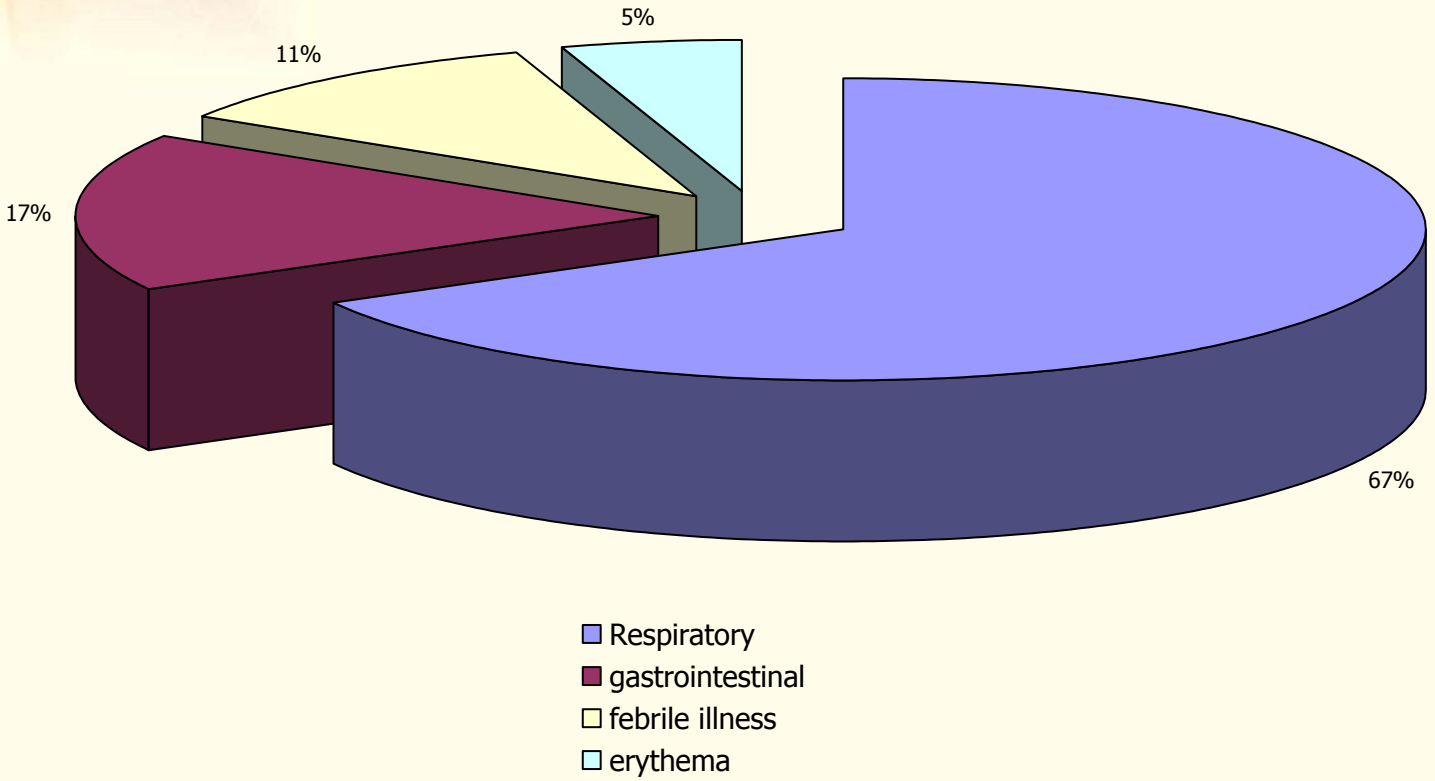
- Inflammatory neuropathy associated with infection
  - HIV neuropathies, including cytomegalovirus neuropathy
  - Leprosy
  - Lyme disease
  - Chagas disease
- Granulomatous conditions
  - Sarcoidosis
- Paraneoplastic
  - Subacute sensory neuropathy/neuronopathy—small-cell lung carcinoma and anti-Hu Abs
  - Other paraneoplastic tumour-antibody syndromes
- Metabolic
  - Diabetic lumbosacral plexopathy



Pregled predavanja

- sindrom Guillain-Barre
- kronična vnetna demielinizacijska polinevropatija in oblike
- vaskulitične nevropatije

GBS


5%
11%
17%
67%
Respiratory
gastrointestinal
febrile illness
erythema

GBS in cepljenje proti gripi

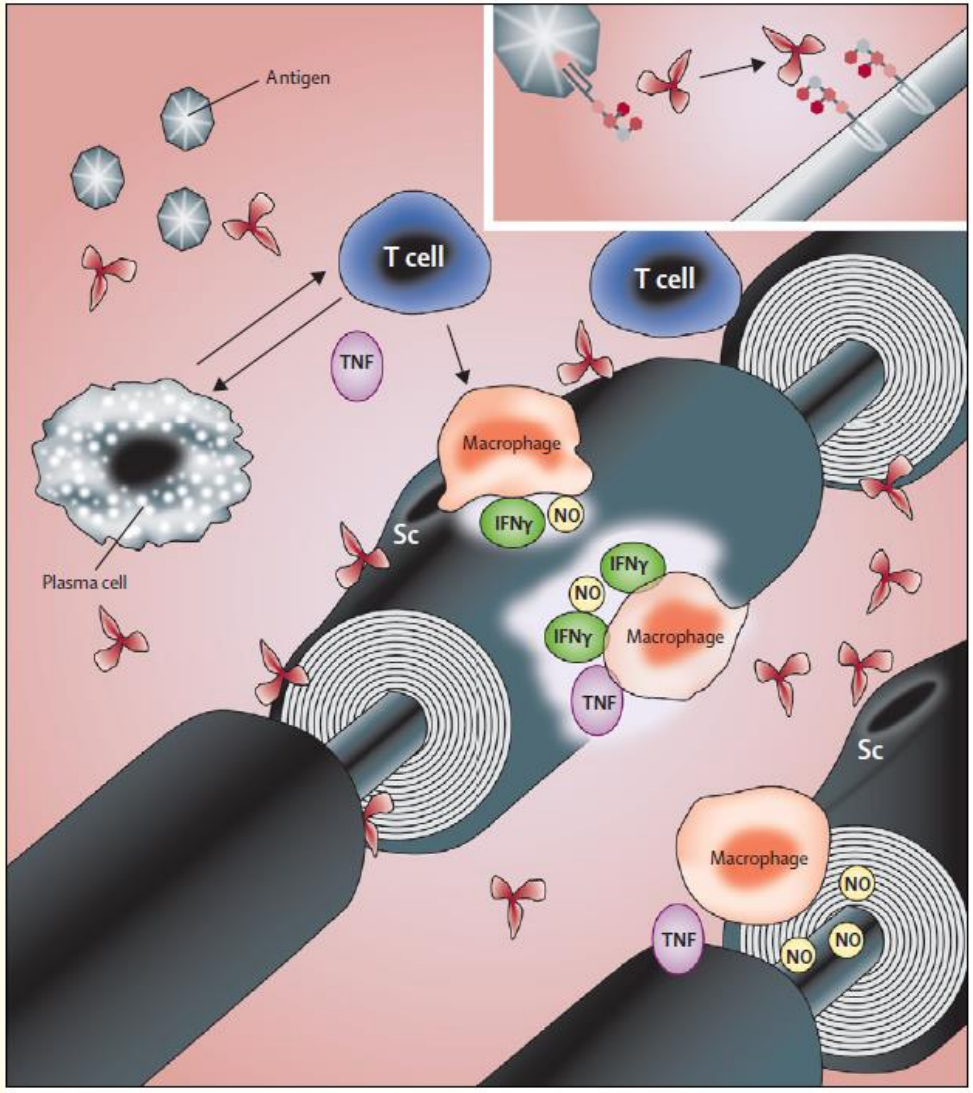
	Vaccination seasons	Study location	Study design	Vaccine or WHO recommended composition[101]	Outcomes and conclusions
Schonberger et al[5]	1976–77	USA	Nationwide active surveillance programme	A/NJ/76 (H1N1)	Significantly elevated rates of GBS within 6 weeks of vaccination (8·8 additional GBS cases per million vaccines)
Marks and Halpin[93]	1976–77	OH, USA	State-wide active surveillance programme	A/NJ/76 (H1N1)	Higher rate for GBS among vaccine recipients than among unvaccinated individuals (13·3 per million *vs* 2·6 per million). Fewer people with GBS had a history of antecedent infection
Safranek et al[92]	1976–77	MI and MN, USA	Review of state-wide active surveillance data (case records) and acute-care databases	A/NJ/76 (H1N1)	Increased relative risk of GBS within 6 weeks of vaccination (8·6 excess cases of GBS per million recipients in MI, 9·7 per million in MN), but not beyond 6 weeks
Hurwitz et al[95]	1978–79	USA (except MD)	Nationwide surveillance programme	A/Texas/1/77 (H3N2), A/USSR/90/77 (H1N1), and B/Hong Kong/05/1972	No increased risk for GBS
Kaplan et al[94]	1979–80, 1980–81	USA	Nationwide surveillance programme	A/Texas/1/77 (H3N2), A/USSR/90/77 (H1N1), A/Bangkok/01/1979 (H3N2), A/Brazil/11/78 (H1N1), and B/Singapore/222/79	No increased risk of GBS
Roscelli et al[99]	1980–88	USA*	Self-controlled case series method to assess data from US Army health statistics database	Various	No increased risk of GBS
Haber et al [91]	1990–2003	USA	Nationwide passive surveillance programme	Various	Decrease in yearly reporting rates for GBS after influenza vaccination from 1990 to 2003. Possible causal association
Stowe et al[7]	1990–2005	UK	Self-controlled case series method to assess data from primary-care database	Various	No increased risk of GBS within 90 days
Hughes et al[97]	1992–2000	UK	Self-controlled case series method to assess data from primary-care database	Various	No or minimally increased risk of GBS within 42 days†
Juurlink et al[98]	1992–2004	ON, Canada	Data from health-insurance database for a universal influenza immunisation programme	Various	Significantly increased relative incidence of GBS within 2–7 weeks, but no significant increase in hospital admissions
Vellozzi et al[96]	1990–2005	USA	Nationwide passive surveillance programme	Various	No increased risk for GBS associated with influenza vaccine
Lasky et al[100]	1992–94	IL, MD, NC, WA, USA	Hospital discharge summaries, telephone interview	Various	One additional case of GBS per million vaccinees

GBS=Guillain-Barré syndrome. *US Army. †For influenza and other vaccines.

Table 2: **Guillain-Barré syndrome after influenza immunisation**

Lehmann et al, 2010

Hipotetičen mehanizem nastanka GBS



Lehmann et al, 2010

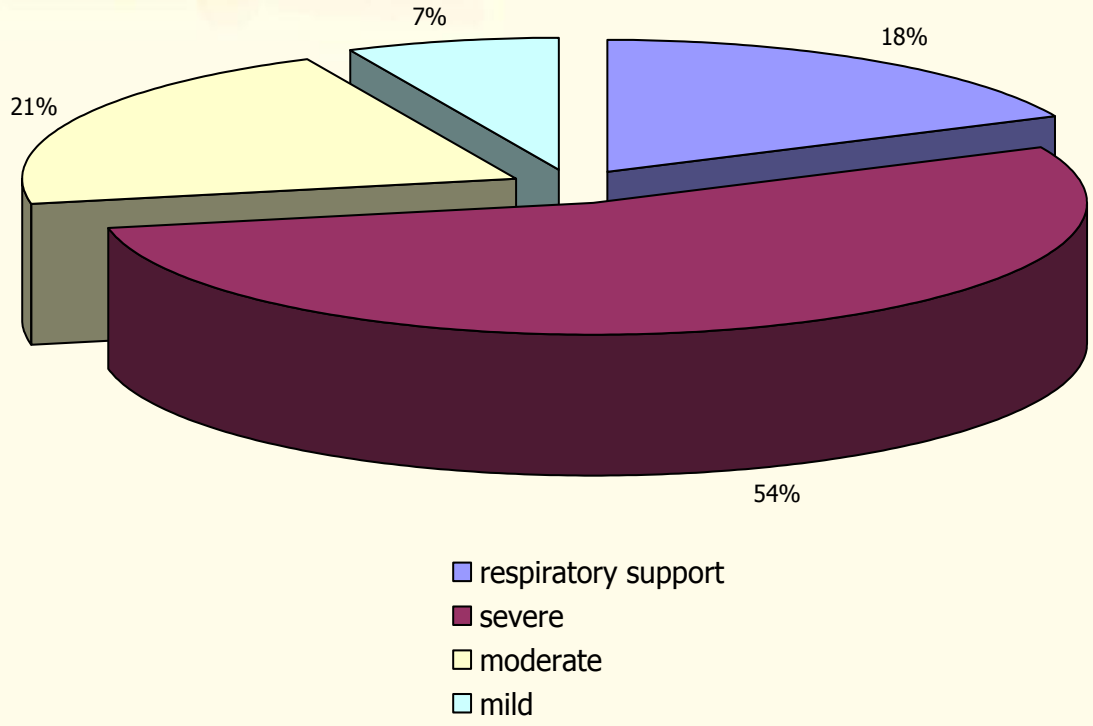
MJ, 66 let

- teden dni pred sprejemom mravljinčenje v podplatih, ki se je razširilo do kolen
- drevenenje prstov rok
- šibke noge, klecanje, spotikanje
- Status: ugasli refleksi na rokah, simetrična šibkost fleksorjev kolkov in dorzifleksorjev stopal, ugasli refleksi na nogah. Slabši občutek za dotik po nogah do kolen in po dlaneh. Hoja racajoča, nezanesljiva.

Klinična slika GBS

- ugasli refleksi 28/28 (100%)
- simetričnost izpadov 26/28 (93%)
- senzorični simptomi 18/28 (64%)
- senzorični znaki 18/28 (64%)
- bolečina 12/28 (43%)
- prizadetost možganskih živcev 7/28 (25%)

Prizadetost ob sprejemu (n=28)



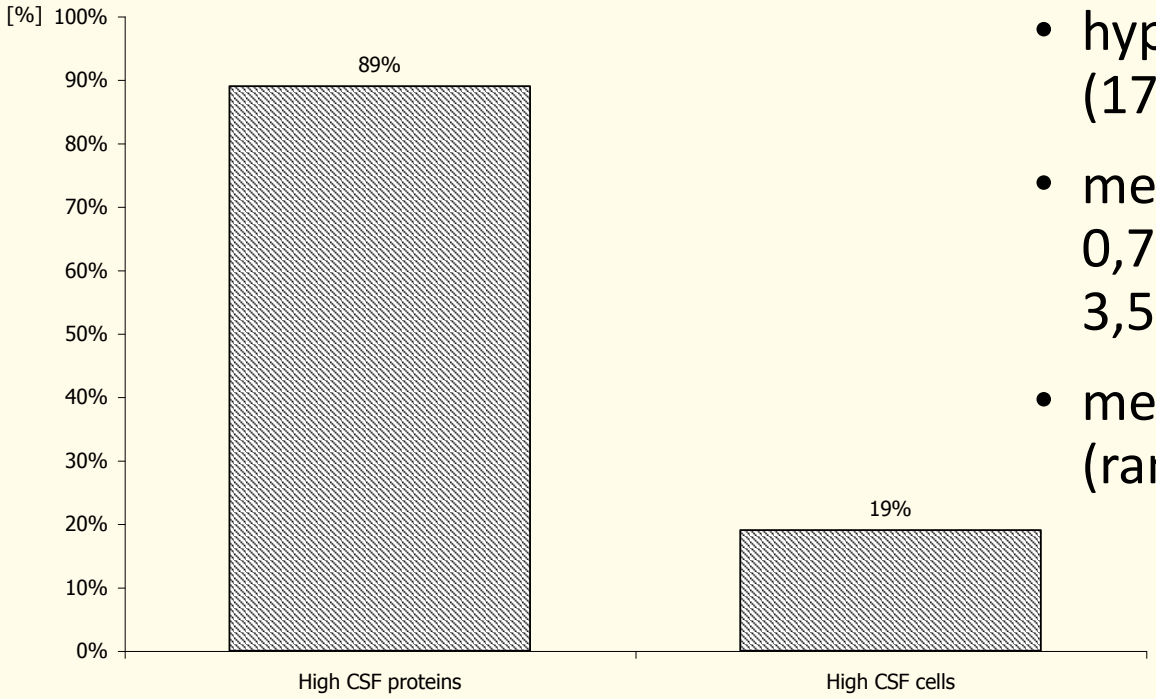
huda, ni sposoben hoje
zmerna, hodi ob opori

MJ, 66 let

- EMG: upočasnjene prevodne hitrosti prevajanja po motoričnem nitju (levi n. medianus 29 m/s, levi n tibialis 32 m/s), podaljšanji končni časi prevajanja, odsotni valovi F
- Likvor: proteini 0,72 g/l, 1 celica/mm3

Preiskave pri GBS

Albumino-cytologic dissociation in our GBS patients



- hyponatremia 4/24 (17%)
- median CSF protein level 0,77 g/l (range 0,29 – 3,5)
- median CSF cells 2/mm^3 (range 0 – 21)

EMG določi ´obliko´ GBS

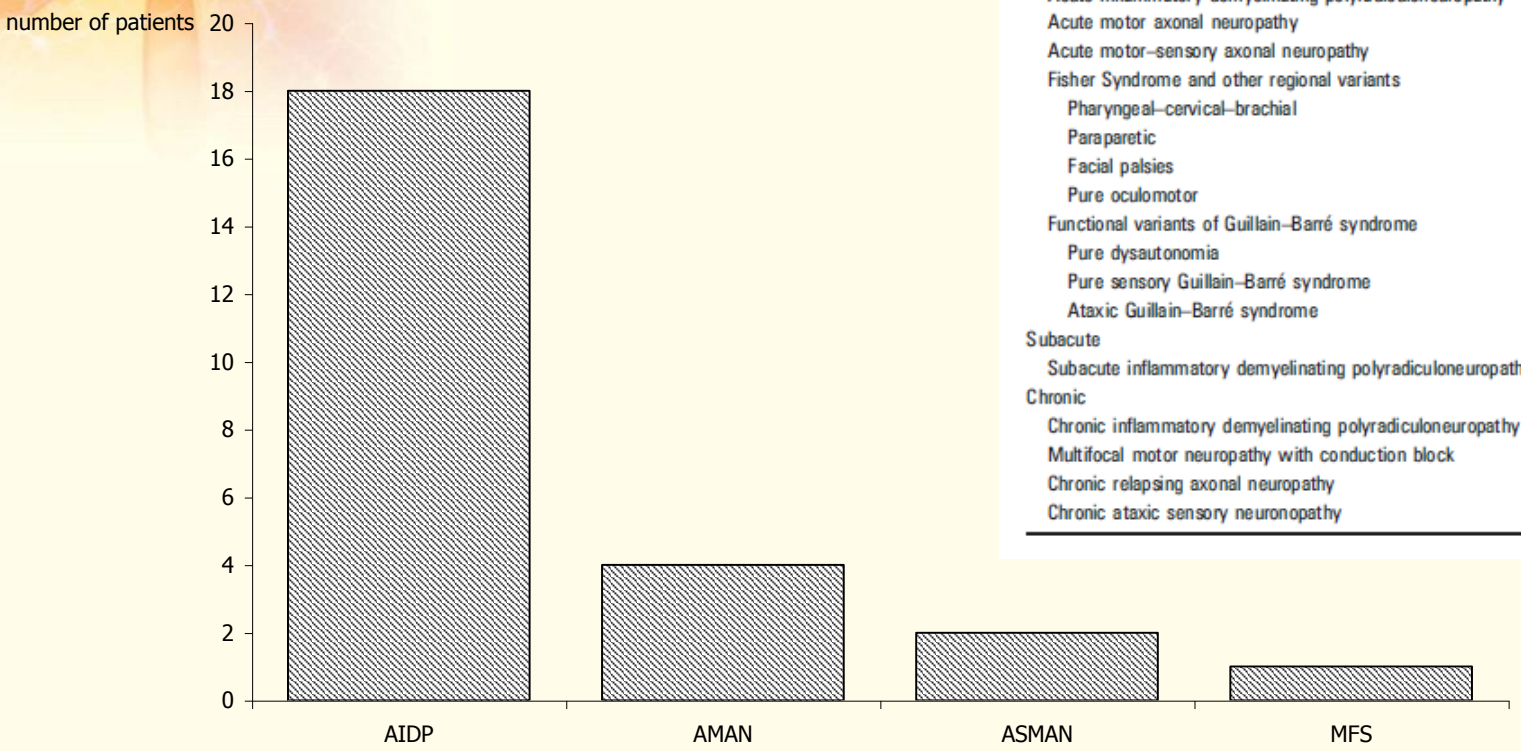


Table 1 Differential diagnosis of inflammatory peripheral neuropathies: idiopathic inflammatory neuropathy

Acute
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Paraparetic
Facial palsies
Pure oculomotor
Functional variants of Guillain–Barré syndrome
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Ataxic Guillain–Barré syndrome
Subacute
Subacute inflammatory demyelinating polyradiculoneuropathy
Chronic
Chronic inflammatory demyelinating polyradiculoneuropathy
Multifocal motor neuropathy with conduction block
Chronic relapsing axonal neuropathy
Chronic ataxic sensory neuronopathy

MJ, 66 let - zdravljenje

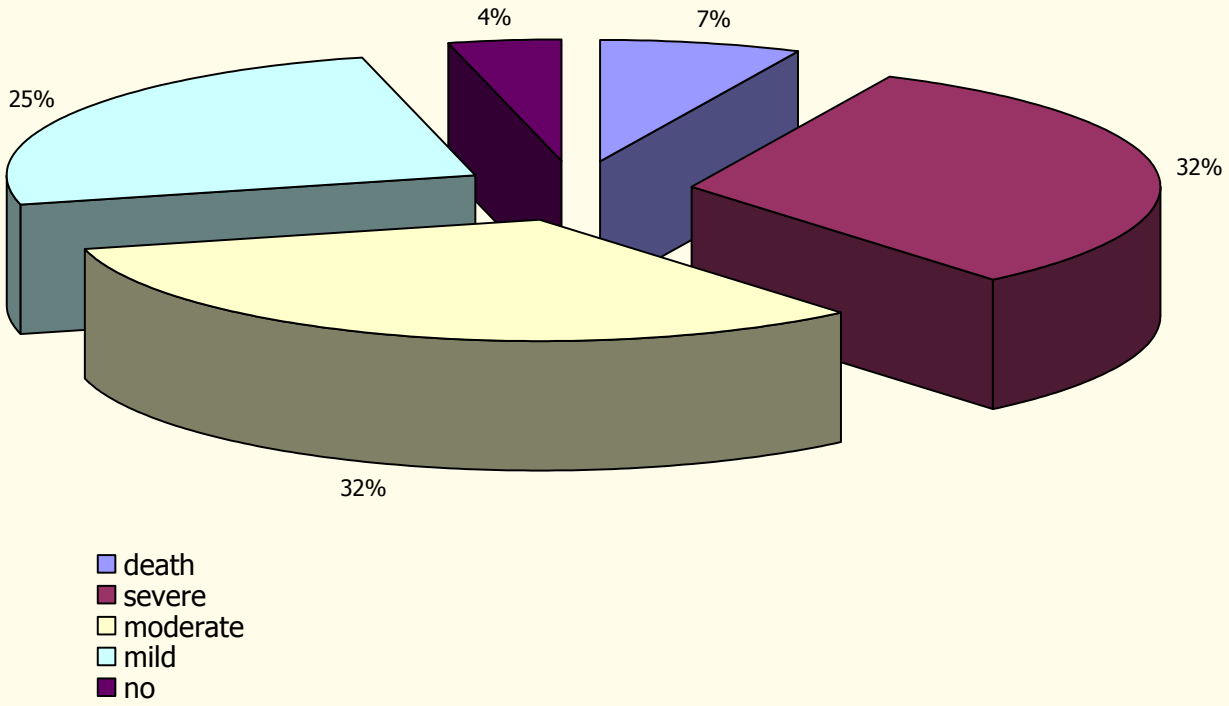
- IVIG 2g/kg 5 dni
- pregabalin 2x150 mg
- FTH
- URI Soča po 20 dneh

Zdravljenje GBS

- humani imunoglobulini 2 g/kg 2-5 dni 25/28 (89%), zdravimo prizadete bolnike (izpolnilo merila 19/25 (76%)
- plazmafereze (3 naši bolniki)
- simptomatsko zdravljenje
  - FTH (100%)
  - analgetiki (83%)
  - heparinoidi (80%)
  - ONIT (18%)

Prognoza GBS

- 50% Soča
- 33% zdravilišče
- 80% dobra p
- 5% umre



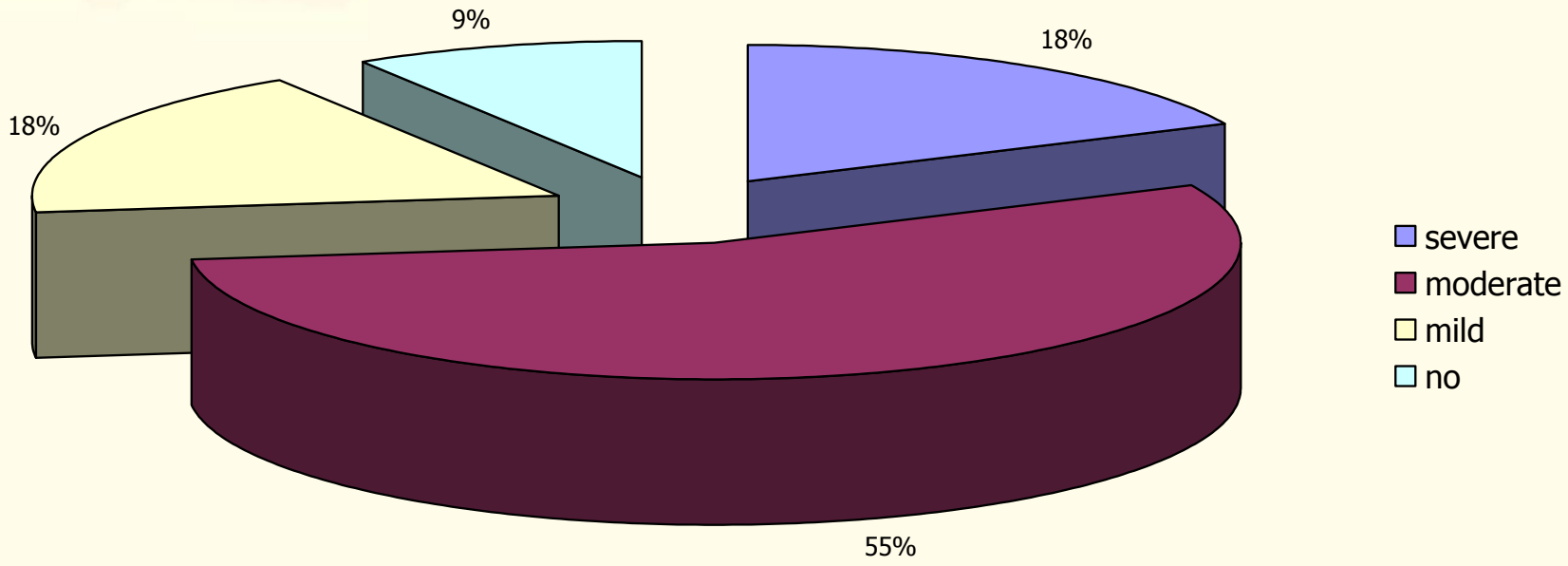
Družinski zdravnik in GBS

- najpogostejši vzrok ohlapne ohromelosti, običajno hospitalizacija => ustrezna napotitev z oznako NUJNO
- 10% ponovitev GBS
- prizadeti bolniki po hospitalizaciji
  - okužbe
  - GVT
  - bolečine
  - preležanine

Kronična vnetna demielinizacijska polinevropatija (CIDP)

- idiopatska in sekundarna (hematološke bolezni, HIV, hepatitis B, SLE)
- napredujoča bolezen, včasih slabšanja v zagonih
- simetrična proksimalna in distalna šibkost, ki se razvije v nekaj mesecih, parestezije
- brez prizadetosti možganskih živcev, bolečin
- EMG: žariščna demielinizacija, likvor: albumino-citološka disociacija
- Th: steroidi, IVIG, PE, citostatiki (azatioprin)
- manj ugodna prognoza pri starejših, boljša pri mlajših, ki se odzovejo na zdravljenje

Prizadetost pri bolnikih s CIDP (n=11)



Zdravljenje naših bolnikov s CIDP

steroidi 10/11 (91%)

IVIG 6/11 (55%)

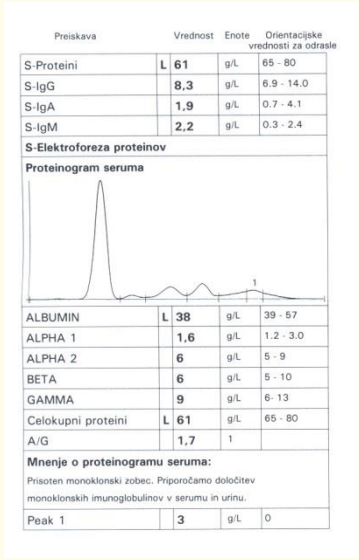
PE 2/11 (18%)

azatioprin 1/11 (9%)

kombinacija 5/11 (45%)

Variante CIDP

- multifokalna motorična nevropatija z bloki
  - asimetrična, roke, zgolj motorična prizadetost, odzivnost le na zdravljenje z IVIG
- CIDP ob MGUS
  - Pretežno senzorična, anti-MAG protitelesa, slaba odzivnost na zdravljenje, včasih uspešen rituksimab (anti-CD20)



Preiskava		Vrednost	Enote	Orientacijske vrednosti za odrasle
S-Proteini	L	61	g/L	65 - 80
S-IgG		8,3	g/L	6.9 - 14.0
S-IgA		1,9	g/L	0.7 - 4.1
S-IgM		2,2	g/L	0.3 - 2.4
S-Elektroforeza proteinov				
Proteinogram seruma				
ALBUMIN	L	38	g/L	39 - 57
ALPHA 1		1,6	g/L	1.2 - 3.0
ALPHA 2		6	g/L	5 - 9
BETA		6	g/L	5 - 10
GAMMA		9	g/L	6 - 13
Celokupni proteini	L	61	g/L	65 - 80
A/G		1,7	1	
Mnenje o proteinogramu seruma: Prisoten monoklonski zobec. Priporočamo določitev monoklonskih imunoglobulinov v serumu in urinu.				
Peak 1		3	g/L	0

CIDP in družinski zdravnik

- redke bolezni
- obdobni pregledi pri hematologu pri CIDP ob MGUS, ker bolezen lahko napreduje v maligno paraproteinemijo
- zapleti terapije
  - steroidi (AH, ulkus, katarakta, osteoporoza => nadzor nad preventivnim zdravljenjem, pregledi)
  - AZT (slabost, bruhanje, hepatopatija, pankreatitis)
  - ciklofosfamid (hemoragični cistitis, levkopenija => prošnja kontrolni hemogram čez 10 dni; febrilna nevtropenija)

Vaskulitične nevropatije

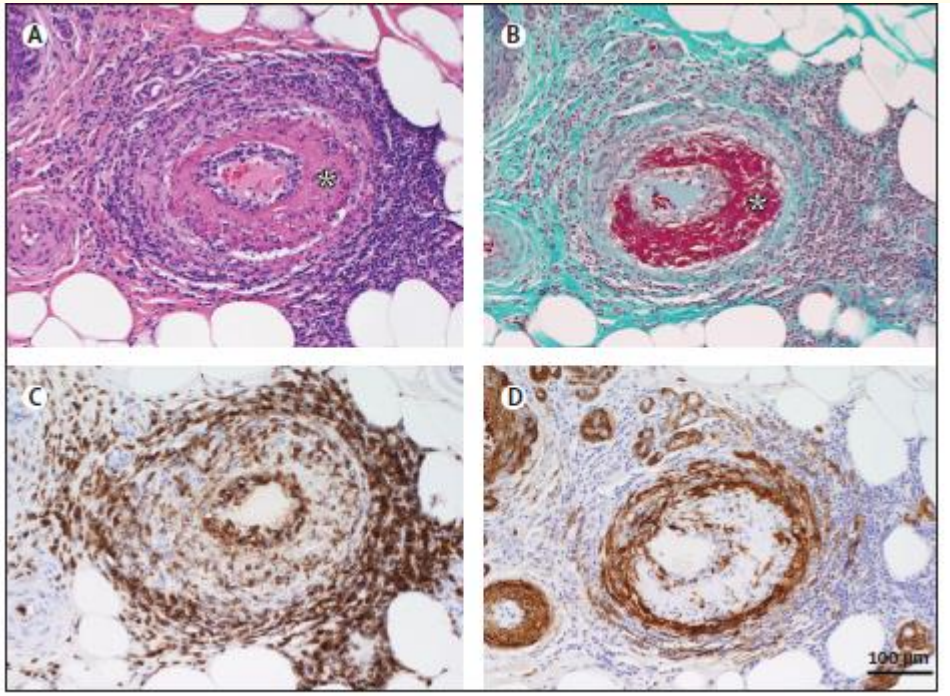
***Panel 1*: Classification of vasculitides associated with neuropathy**

I Primary systemic vasculitides (mostly nerve large arteriole)
1 Predominantly small vessel vasculitis
  a Microscopic polyangiitis*
  b Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis)*
  c Wegener's granulomatosis (granulomatosis with polyangiitis)*
  d Essential mixed cryoglobulinaemic (non-HCV)
  e Henoch-Schönlein purpura (IgA vasculitis)
2 Predominantly medium vessel vasculitis
  a Polyarteritis nodosa
3 Predominantly large vessel vasculitis
  a Giant cell arteritis

II Secondary systemic vasculitides associated with one of the following (mostly nerve large arteriole)
1 Connective tissue diseases
  a Rheumatoid arthritis
  b Systemic lupus erythematosus
  c Sjögren's syndrome
  d Systemic sclerosis
  e Dermatomyositis
  f Mixed connective tissue disease
2 Sarcoidosis
3 Behçet's disease
4 Infection (such as HBV, HCV, HIV, CMV, leprosy, Lyme disease, HTLV-I)
5 Drugs
6 Malignancy
7 Inflammatory bowel disease
8 Hypocomplementemic urticarial vasculitis syndrome

III Non-systemic or localised vasculitides (mostly nerve microvasculitides)
1 Non-systemic vasculitic neuropathy (includes non-diabetic radiculoplexus neuropathy and some cases of Wartenberg's migrant sensory neuritis)
2 Diabetic radiculoplexus neuropathy
  a Diabetic lumbosacral radiculoplexus neuropathy
  b Diabetic cervical radiculoplexus neuropathy
  c Diabetic thoracic radiculopathy
  d Painless diabetic motor neuropathy
3 Localised cutaneous or neuropathic vasculitis
  a Cutaneous polyarteritis nodosa
  b Others

Reproduced from reference 6, by permission of John Wiley & Sons. ANCA=antineutrophil cytoplasmic antibody. HCV=hepatitis C virus. HBV=hepatitis B virus. CMV=cytomegalovirus. HTLV=human T-lymphotropic virus. *ANCA-associated vasculitides.



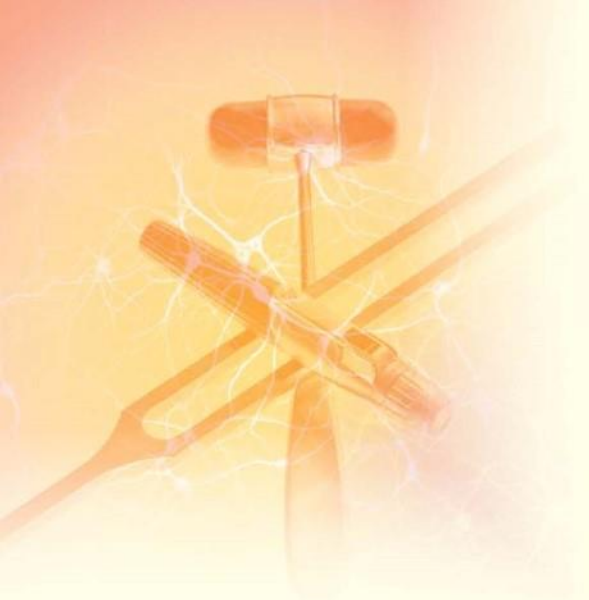
Gwhatmey et al, 2014

Vaskulitične nevropatije

- mononevropatija ali multipla mononevropatija
- bolečina
- aksonska prizadetost
- ena redkih indikacij za biopsijo živca
- agresivno zdravljenje
  - steroidi
  - ciklofosfamid

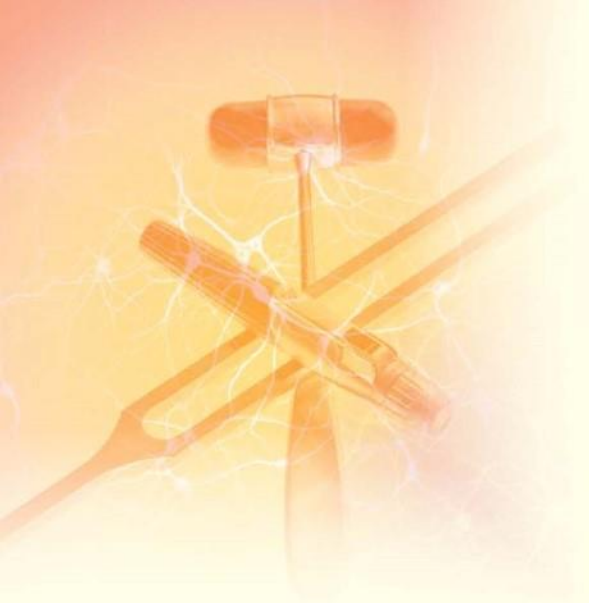
Zaključek

- redke bolezni, najpogostejši GBS, ki pogosto precej prizadene bolnika, a ima dolgoročno ugodno prognozo
- Vloga družinskega zdravnika:
  - prepoznavanje simptomov in usmerjanje, saj bolezni učinkovito zdravimo
  - poznavanje zapletov bolezni in zapletov dolgotrajne terapije z imunosupresivi in kortikosteroidi



Terapija izbora GBS:

A. kortikosteroidi
B. humani imunoglobulini
C. plazmafereze
D. imunosupresivi



GBS in CIDP je skupno:

A. obe bolezni zdravimo s kortikosteroidi
B. pri obeh bolezni so neredko prizadeti možganski živci
C. pri obeh boleznih EMG pokaže znake žariščne demielinizacije
D. pri obeh boleznih je pogosto prisotna tudi bolečina

56-letna gospa, ki se zdravi zaradi revmatoidnega artritisa je nenadoma začutila bolečino v predelu podlakti in kmalu opazila, da ne more iztegniti zapestja in prstov rok. Najverjetneje gre za:

A. parezo sobotne noči
B. GBS
C. multižariščno motorično nevropatijo z bloki v prevajanju
D. vaskulitično nevropatijo (mononevritis)