
- Prion diseases
- Guillain-Barré syndrom
- Chronic inflammatory demyelinating polyneuropathy

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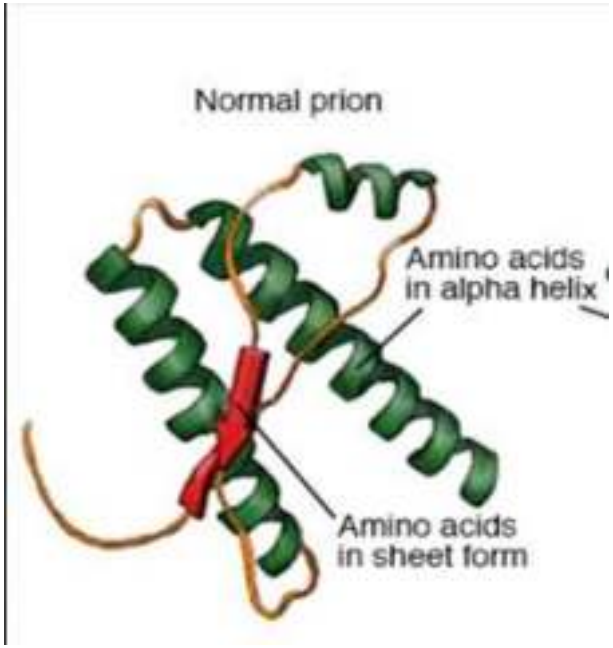
Prions

- Prions are infectious agents that consist of proteins but not DNA or RNA,

- They appear to produce their lethal effects by duplicating their shapes and accumulating in tissues.



Prion diseases

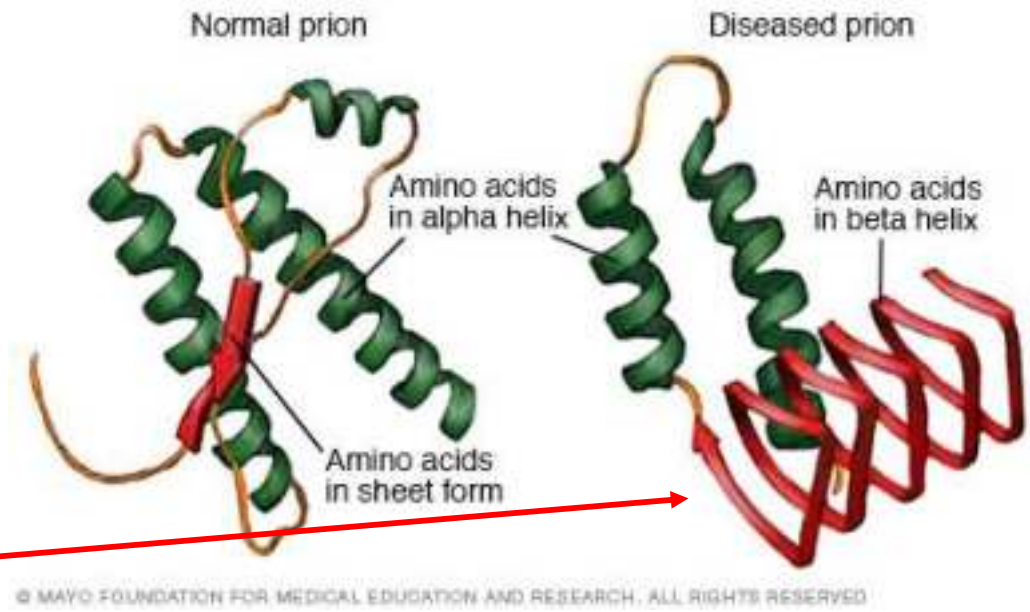
- fatal neurodegenerative diseases affecting both humans and animals

- characterized by the conversion of the cellular prion protein PrP^{C} to an abnormal, insoluble and partially protease-resistant isoform called scrapie prion protein (PrP^{SC})

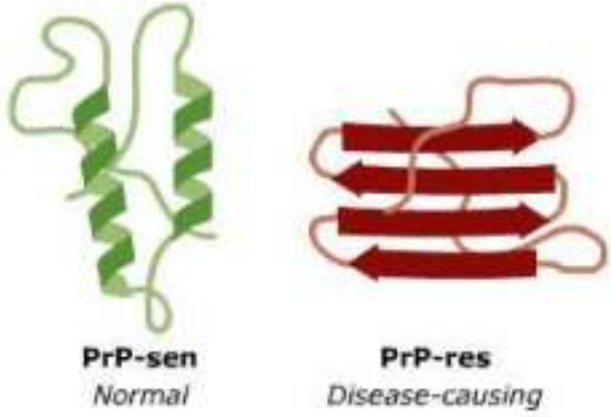
- Normal prion protein PrPc – encoded by the prion gene (PRNP) on human chromosome 20
- The function - role in anti-oxidant systems and cellular coper metabolism

Prion diseases

- Upon conversion of normal PrP^{C} to the pathological isoform of PrP^{SC}, the number and sequence of amino acids do not change, but conformational changes occur.

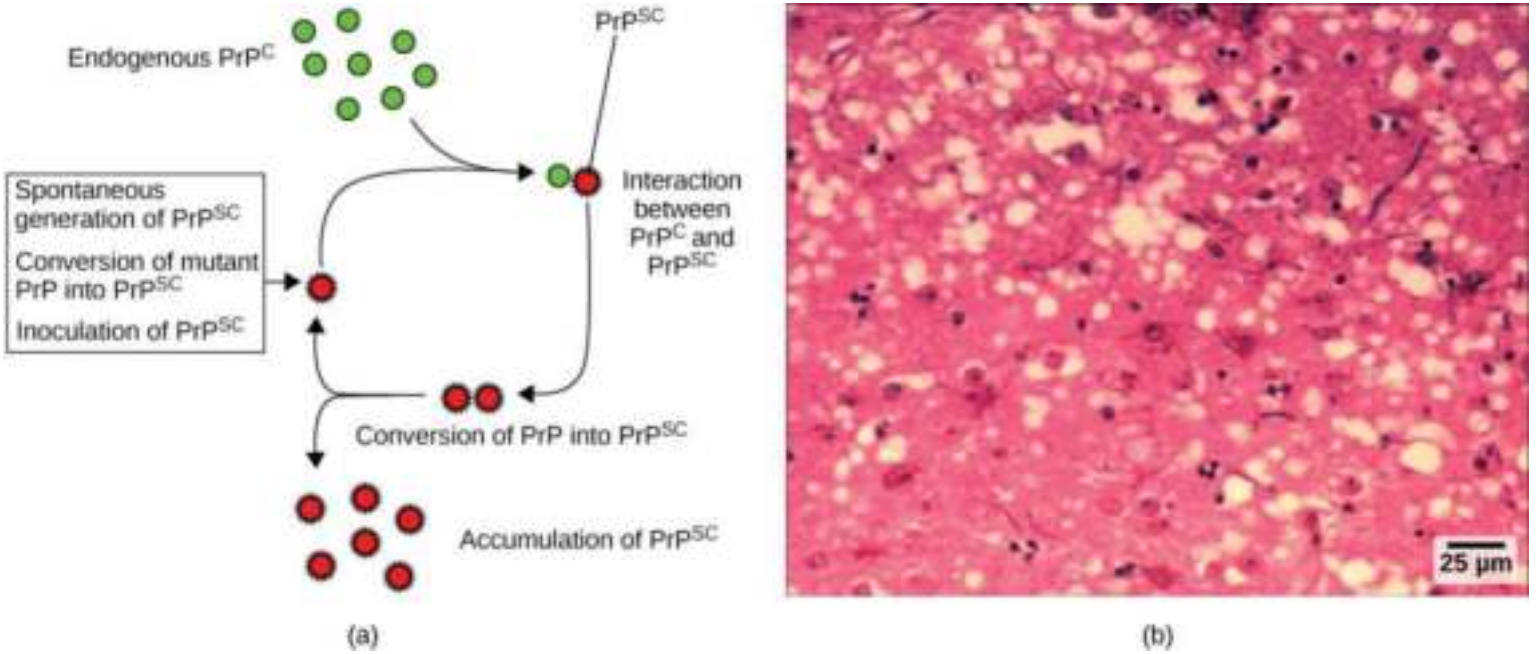


- PrP^{SC} binds to PrP^{C} and converts it to PrP^{SC} in a not-known manner



Prion diseases

- There is a chain reaction in which PrP^{SC}s accumulate in nerve cells, they are damaged, they are vacuolated and subsequently die
- Prions are also stored in the extracellular space, where they form the so-called amyloid plaques
- Spongiform change is the most consistent histological abnormality observed in cases of prion disease, reflected in the more traditional term "spongiform encephalopathy"
- Spongiform change is characterised by a fine vacuole-like appearance in the neuropil – granulovacuolar degeneration

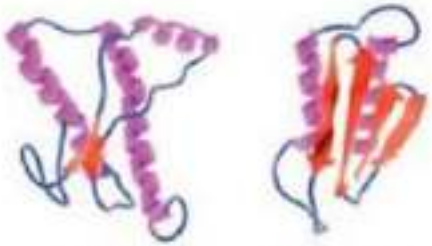


modification of work by Dr. Al Jenny, USDA APHIS; scale-bar data from Matt Russell

How Creutzfeldt-Jakob disease works

CAUSE

Creutzfeldt-Jakob disease is caused by abnormal proteins called prions that are not killed by standard methods for sterilizing surgical equipment.



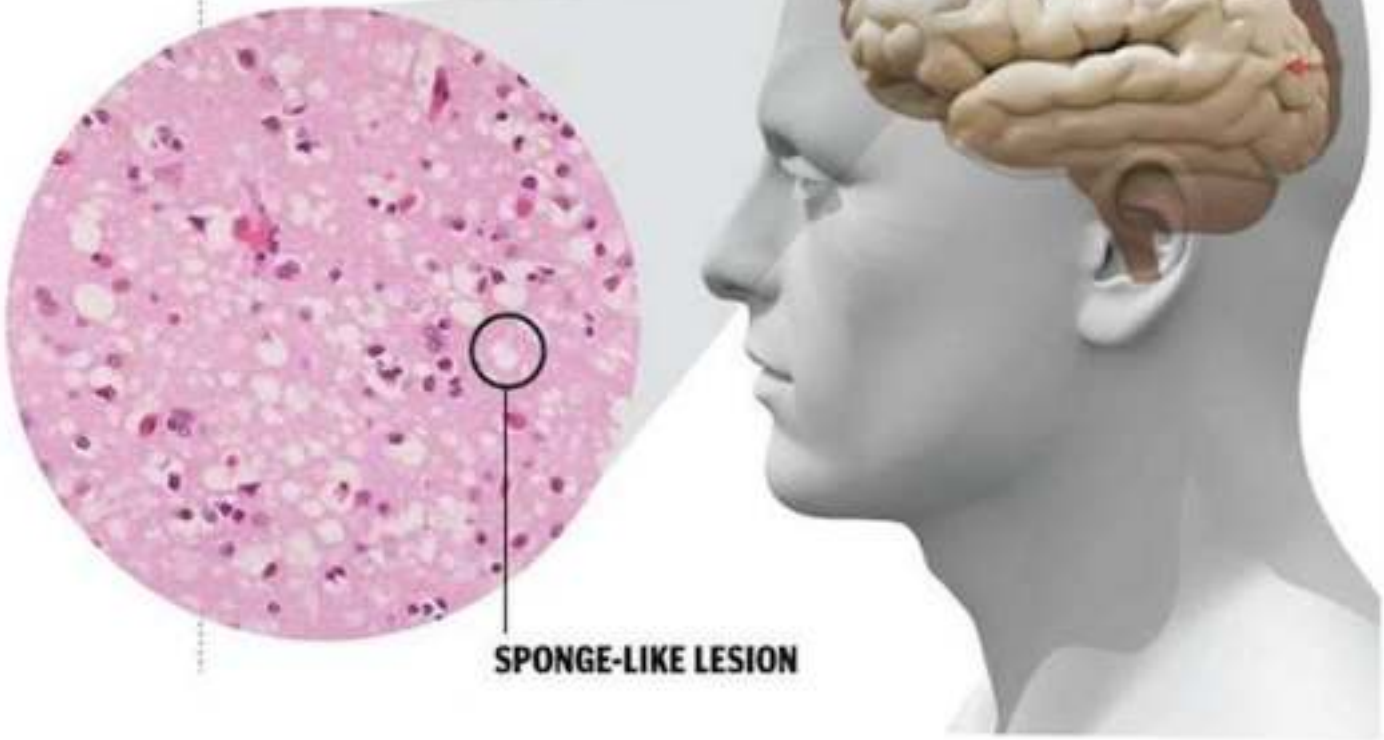
NORMAL HUMAN PROTEIN

DISEASE-CAUSING PRION

As prions build up in cells, the brain slowly shrinks and the tissue fills with holes until it resembles a sponge.

CONSEQUENCES

Those affected lose the ability to think and to move properly and suffer from memory loss. It is always fatal, usually within one year of onset of illness.



Prion diseases

- In most people with prion disease, the cause is unknown
- in several diseases the disease is caused by transmission from a known source of infection
- 10-15% of patients have a genetic form of the disease either due to a point mutation or due to the insertion of octapeptide repeats (OPR) in the prion protein gene (PRNP)
- The three most common forms are: Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI) and Gerstmann-Sträussler-Scheinker syndrome (GSS)

Creutzfeldt-Jakob disease

- Incidence - 1-2 / 1 000 000 inhabitants per year
- sporadic - in about 85% of patients
- the genetic form (gCJD) also called familial is less common - due to a number of mutations (point mutations, insertions, deletions) in the PRNP gene

  The familial form is autosomal dominant
- The rest consists of acquired forms - iatrogenic CJD (iCJD) and a new variant (vJCD)

Creutzfeldt-Jakob disease

- Codon 129 of the PRNP gene contains a polymorphism (ATG / GTG) that encodes methionine (M) or valine (V)

- The polymorphism itself is not pathogenetic, but a homozygous variant of MM increases the risk of sCJch (approximately 72% for MM, 17% for VV) while the heterozygous genotype appears to be protective.

Creutzfeldt-Jakob disease

- Iatrogenic – CJD was transmitted by neurosurgical instruments, EEG electrodes during stereotactic examinations and corneal transplantation

- The new variant originated from bovine spongiform encephalopathy (BSE), which does not occur at present

Creutzfeldt-Jakob disease – clinical picture

- Cognitive deficit – rapidly progressive dementia, ataxia, visual disorders
- Myoclonus is present in some patients and is more common in the later stages of the disease
- Extrapyramidal symptoms
- Incontinence, gradual loss of independence with bed restraint
- In the terminal stage, dysphagia is often associated, which cause aspiration pneumonia as the cause of death.
- Mutism,
- The average duration of the disease is 4.5 to 7.4 months.

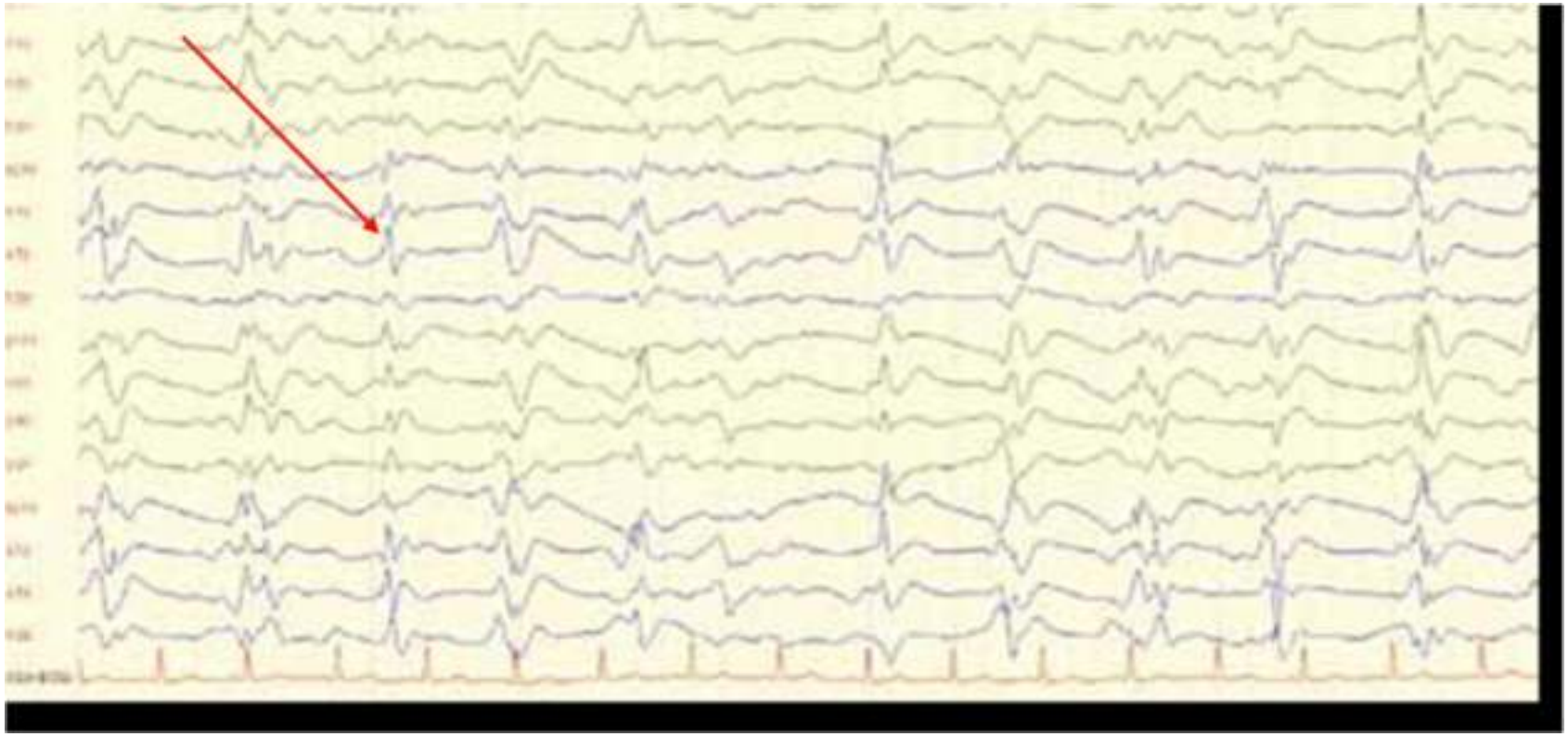
Creutzfeldt-Jakob disease – diagnostic criteria

Definite CJD	Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western Blot confirmed protease-resistant PrP; and/or presence of scrapie-associated fibrils
Probable CJD	Rapidly progressive dementia; and at least two out of the following four clinical features: 1 Myoclonus 2 Visual or cerebellar signs 3 Pyramidal/extrapyramidal signs 4 Akinetic mutism AND a positive result on at least one of the following laboratory tests: 1 A typical EEG (periodic sharp wave complexes) during an illness of any duration; and/or 2 A positive 14.3.3 cerebrospinal fluid (CSF) assay in patients with a disease duration of less than 2 years 3 Magnetic resonance imaging (MRI) high signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) AND without routine investigation indicating an alternative diagnosis
Possible CJD	Progressive dementia; and at least two out of the following clinical features: 1 Myoclonus 2 Visual or cerebellar signs 3 Pyramidal/extrapyramidal signs 4 Akinetic mutism AND the absence of a positive result for any of the three laboratory tests that would classify a case

WHO a MRI-CJD konsorcium

sCJD – EEG

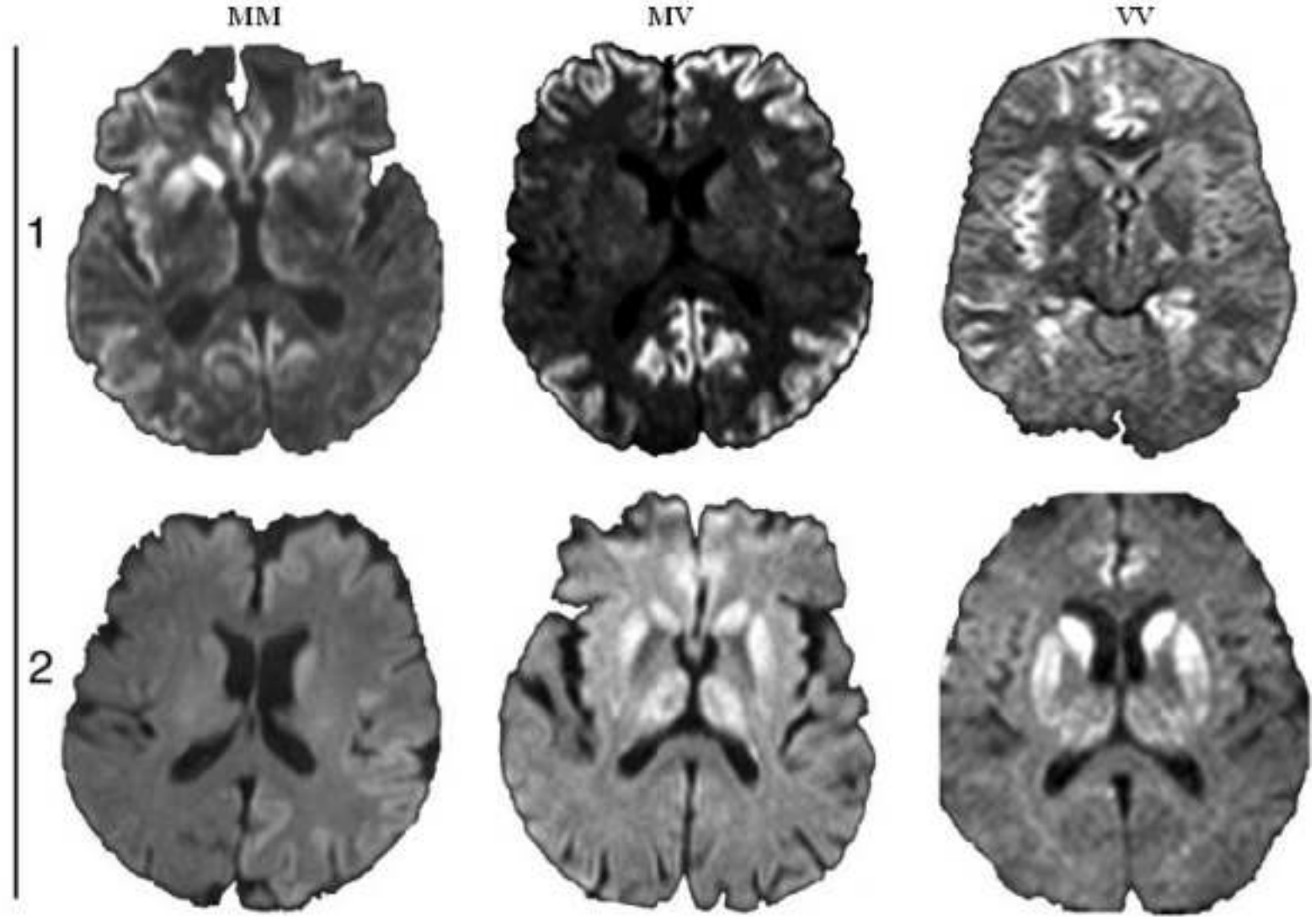
- Period sharp waves complexes



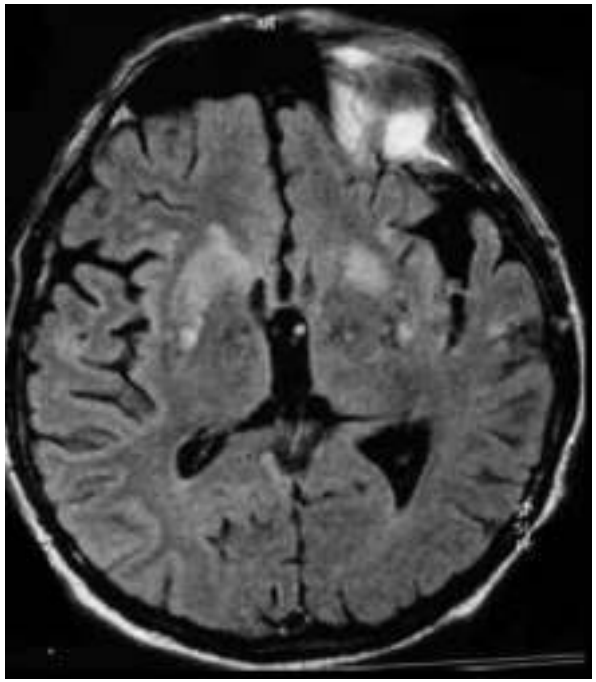
sCJD – MRI

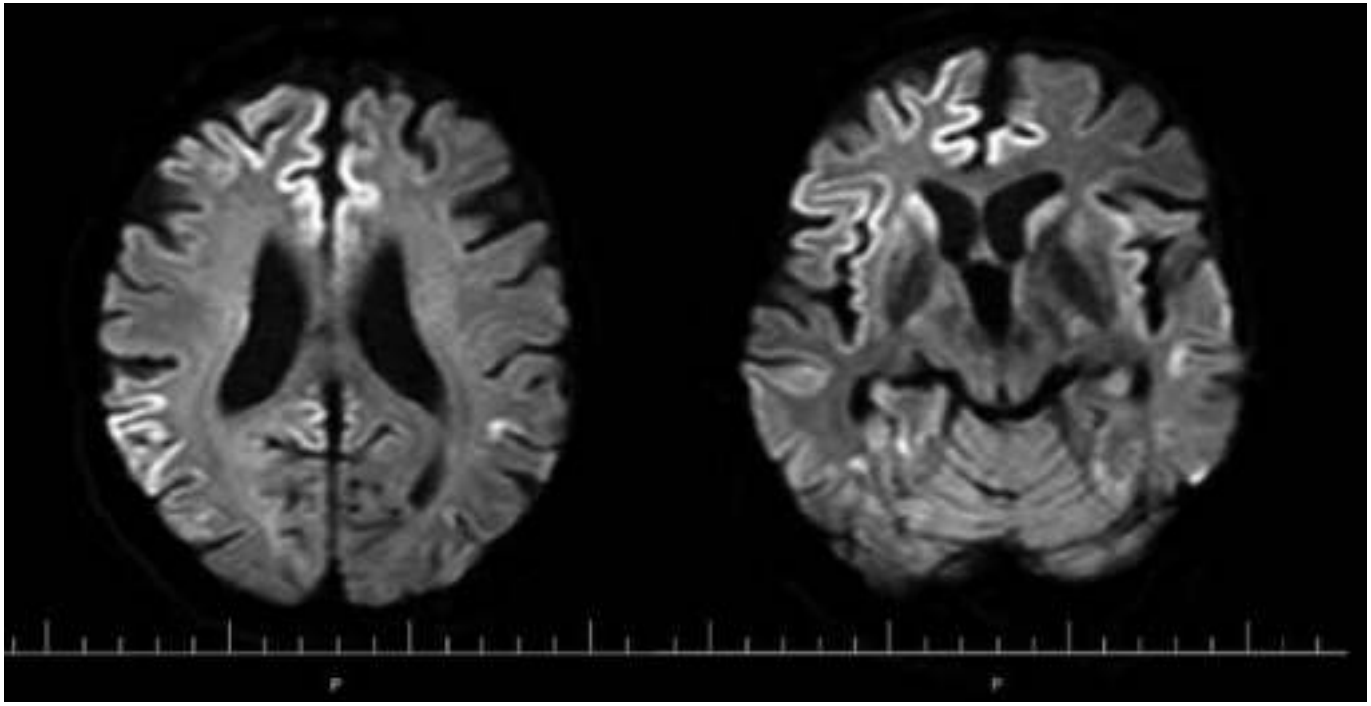
- DWI MRI and FLAIR sequence have the highest sensitivity and specificity
- Increased signal strength in:
- more than three cortical areas of the brain
- hippocampus
- in any of the basal ganglia
- in any nucleus of the thalamus
- in the cerebellum

sCJD - MRI



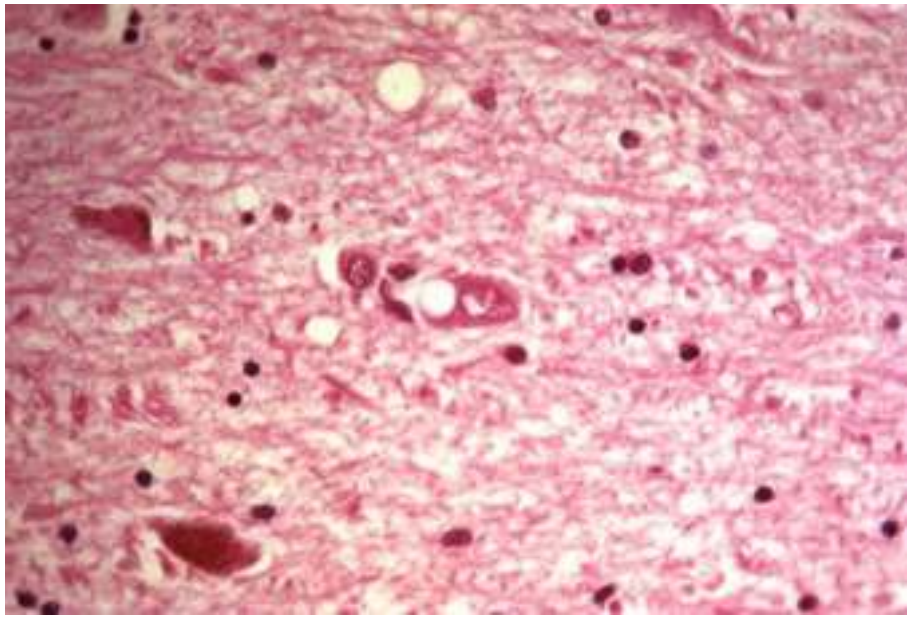
sCJD - MRI



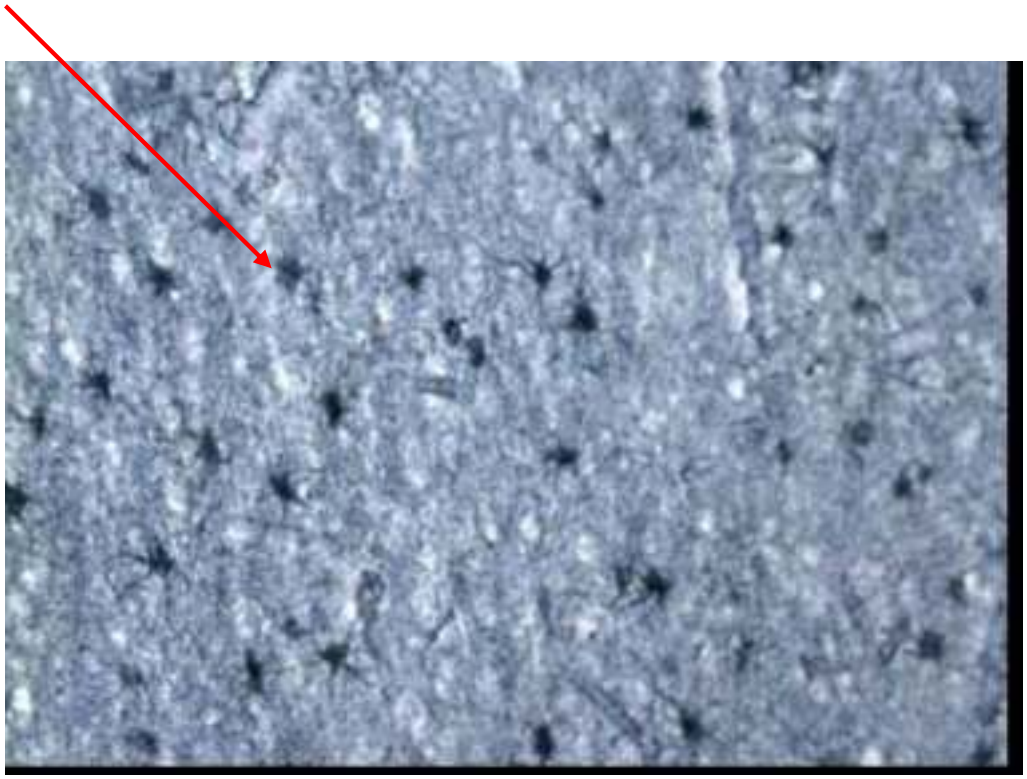


sCJD – diagnostics

Spongiform changes



Patological PrP



Zapožičané z N árodného referenčného centra pre prionové choroby, Slovenská zdravotnícka univerzita, Bratislava

sCJD – CSF

- CSF
- Protein 14-3-3
- Normal protein being released to CSF due to the destruction of nerve tissue, including brain hemorrhage, cerebral infarction, brain tumors, inflammatory CNS diseases, and other nerve tissue damage.
- Not specific for CJD
- Tau protein is ↑
- S100b protein and neuron specific enolase (NSE)
- Genetic testing – most common mutation – E200K

sCJD – diagnostics

- Definitive diagnosis - based on
- neurohistological examination of brain tissue
- supplemented by immunohistochemical methods made with several types of antibodies and by the western blot method, which verify the presence of pathologically altered prion protein in the tissue.

sCJD – diagnostics

- Using a test for prion diseases known as Real-Time Quaking-Induced Conversion (RT-QuIC),
- scientists analyzed skin tissue
- RT-QuIC correctly detected abnormal prion protein in each CJD patient sample tested and in none of the non-CJD group.

Genetic CJD

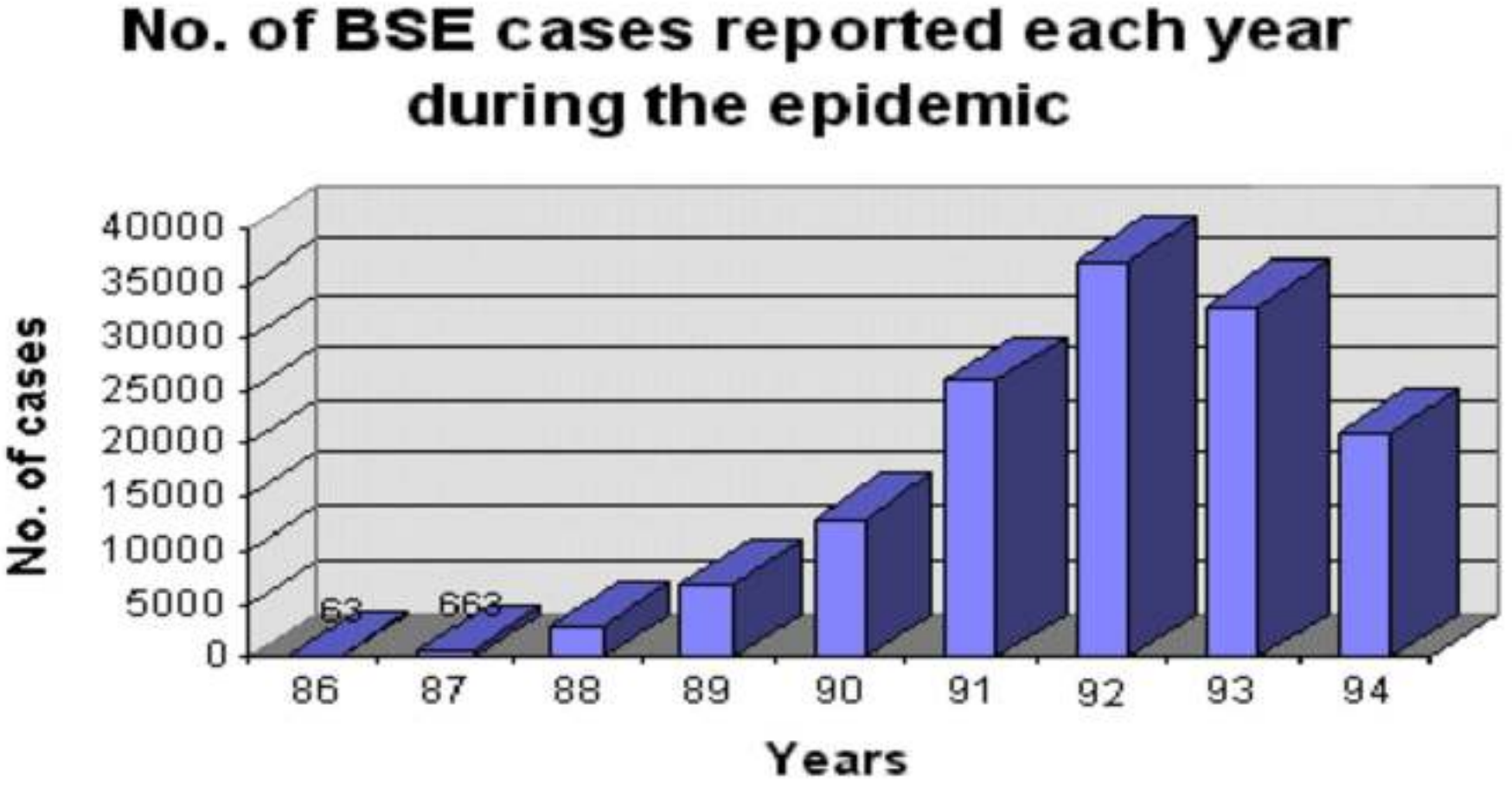
- The most often mutation – E200K-129M haplotyp

- The largest population was registered with the Libyan and Tunisian Jews, Chile and also in Slovakia where the specific relationship of E200K mutation to CJD was confirmed for the first time

nvCJD

- First time – in GB in 1996
- Due to consumption of beef contamined by the agent of bovine spongiform encephalopathy (BSE)
- Young age at onset of ilness (27-50)
- Main difference - the etiological agent was also found in peripheral lymphatic organs, which significantly increases the risk of transmission.

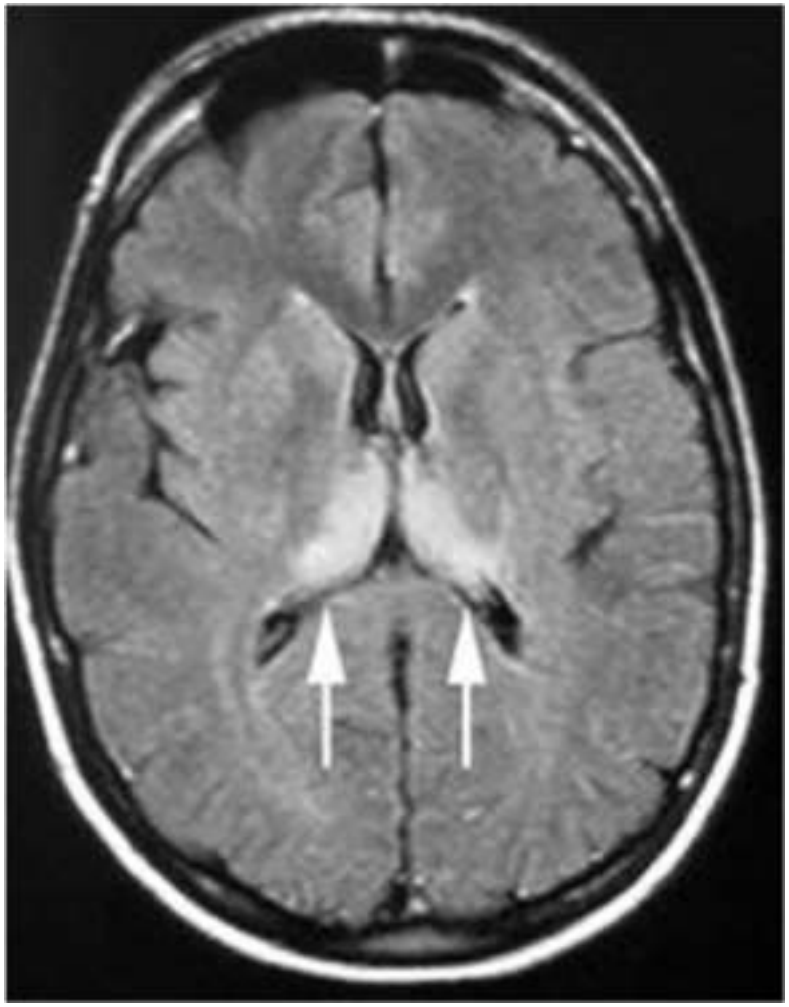
Bovine spongiform encephalopathy



nvCJD

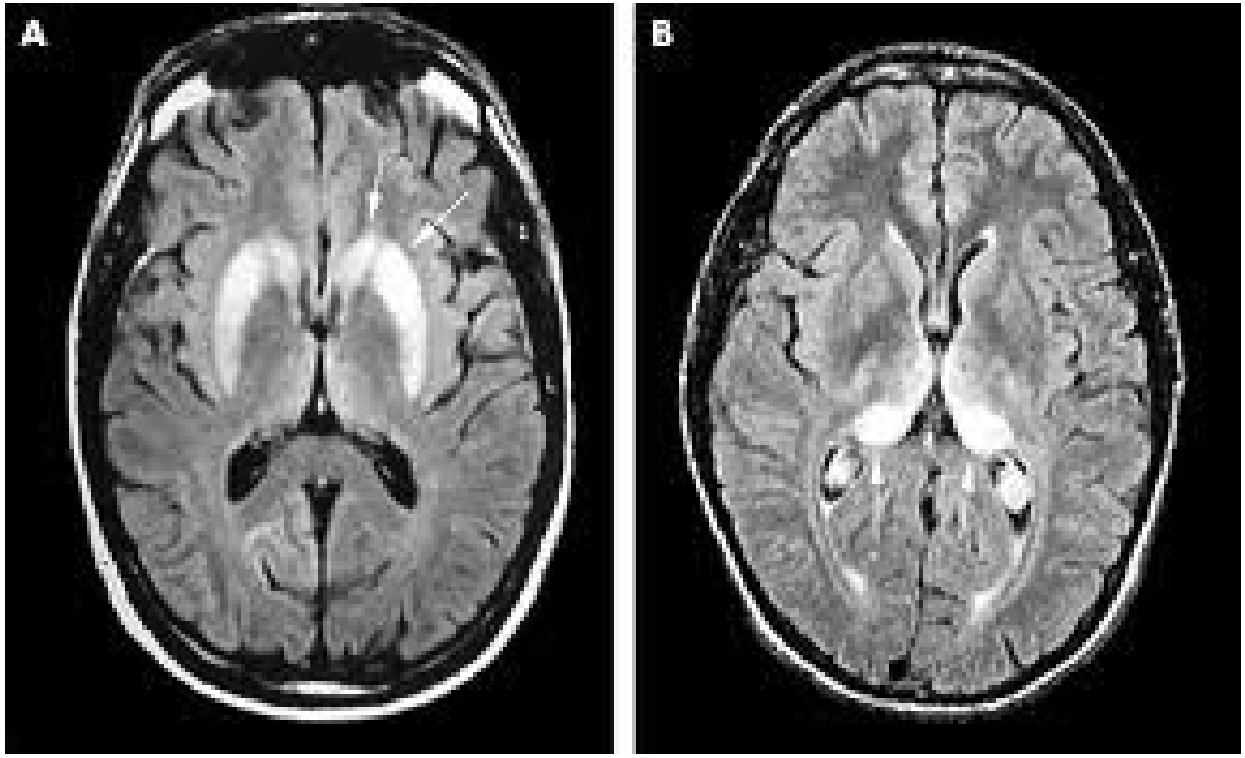
- Neurological symptoms – 6 month after psychiatric symptoms
- Clinical feature
- Dysartria, ataxia, memory problems, involuntary movements, myoklonus, chorea, dystonia
- Dementia
- Duration of the disease - around 14 months (6-39 months).
- MRI – pulvinar talami sign

nvCJD - MRI



MRI

sCJD nvCJD



Diferential diagnosis

- all rapidly progressing dementias (RPD)
- Alzheimer's disease
- Frontotemporal dementia, Corticobasal degeneration and dementia with Lewy bodies
- Autoimmune dementias that are treatable
- autoimmune limbic encephalitis
- Steroid-responsive encephalopathy associated with autoimmune thyroiditis - Hashimoto's encephalitis
- Viral and bacterial infections NS
- Tumors
- Vascular dementia

Gerstmann-Sträussler-Scheinker sy (GSS)

- Beginning between 45-50 years
- Slow developing ataxia
- Mental deterioration
- Dementia, myoclonus, duration 5-10 years
- Point mutation of codon 102, 105, 117, 145, 198, 217

Fatal familiar insomnia (FFI)

- Autonomic and endocrine dysfunction
- Insomnia (during the day of somnolence)
- Unexplained disorders of temperature, cardiovascular activity, respiration regulation
- Later - pyramidal, extrapyramidal symptoms, cerebellar ataxia, myoclonus
- Duration 1-2 years
- Codon mutation 178

Guillain-Barré syndrome

- Guillain-Barré syndrome

  ≠ only

- AIDP - Acute inflammatory demyelinating polyradiculoneuropathy

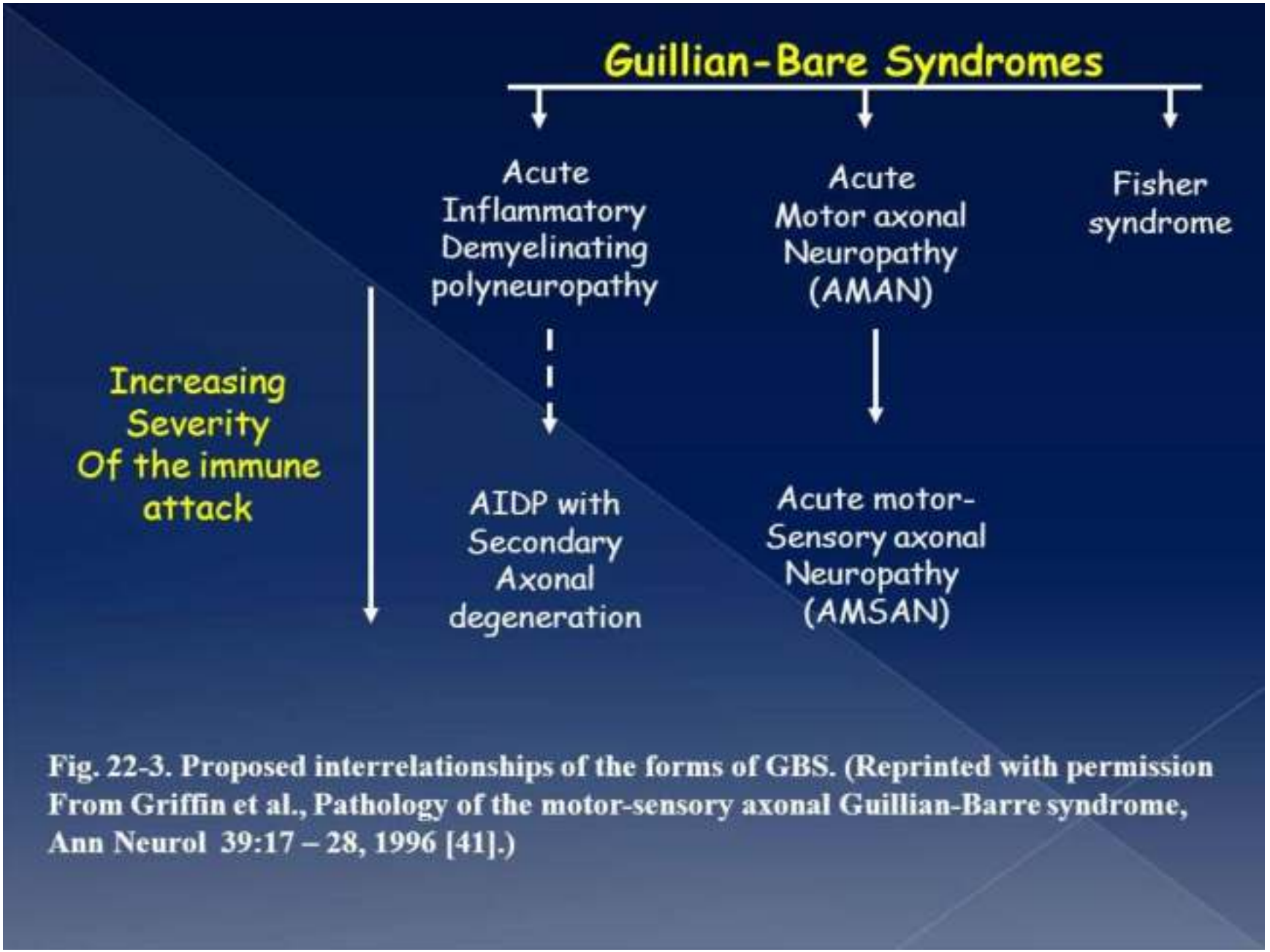
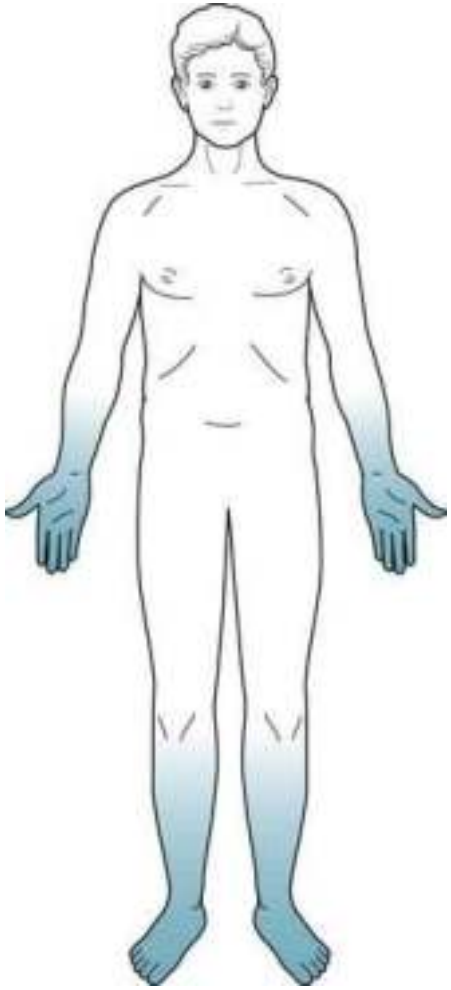


Fig. 22-3. Proposed interrelationships of the forms of GBS. (Reprinted with permission From Griffin et al., Pathology of the motor-sensory axonal Guillian-Barre syndrome, Ann Neurol 39:17 – 28, 1996 [41].)

G-B syndrome

- The disease manifested by acute mild paralysis characterized by
- symmetrical limb weakness
- hyporeflexia or areflexia
- which reach maximum within 4 weeks
- Sensitivity disorders – symmetrical numbness, paraesthesia which begin distally



G-B syndrome

- Epidemiology
- 0.81-1.89 / 100,000 / year, men: women - 3: 2

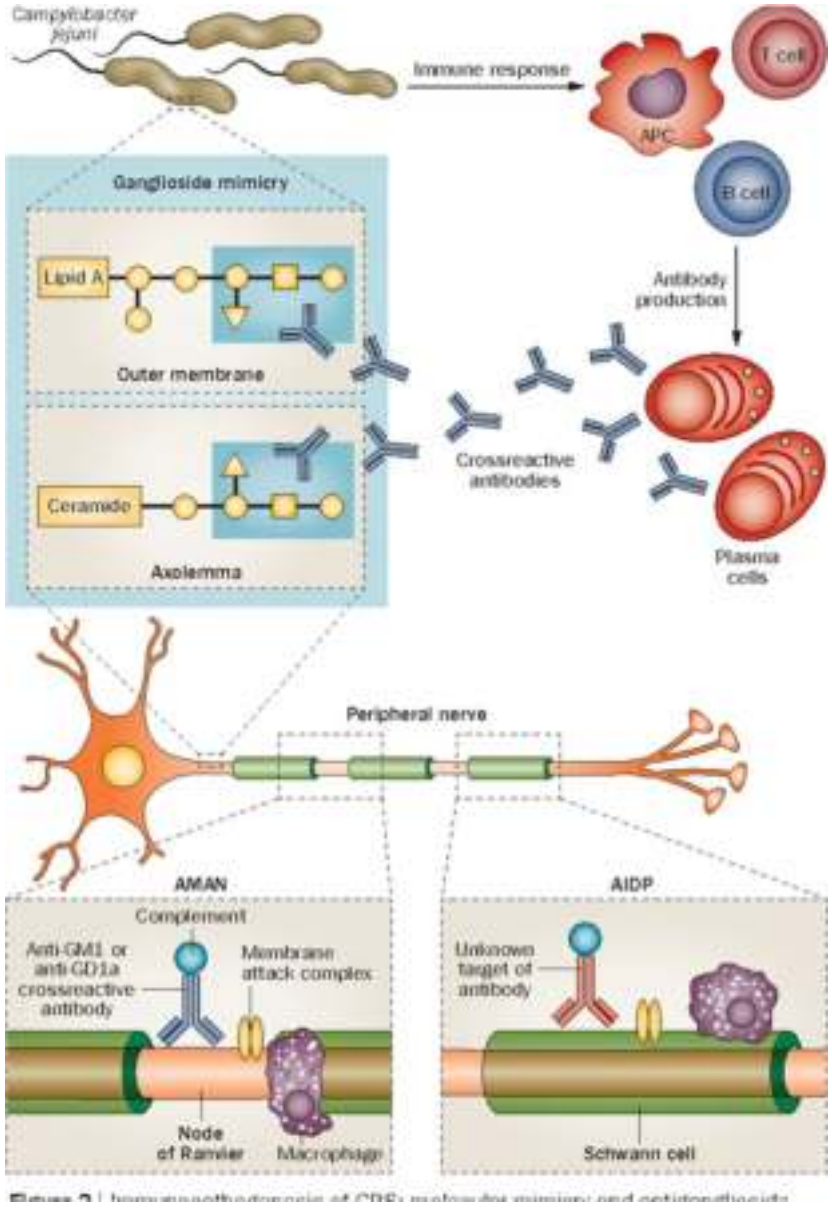
- The most common forms:
- AIDP (acute demyelinating polyneuropathy)
- AMAN - acute motor axonal neuropathy
- MFS - Miller-Fisher syndrome

G-B syndrome – pathogenesis

- Autoimmune disease arising from an aberrant immune response against various components of peripheral nerve fibers
- Impaired humoral and cell-mediated immunity
- The disease develops through a respiratory or GIT infection

G-B syndrome – pathogenesis

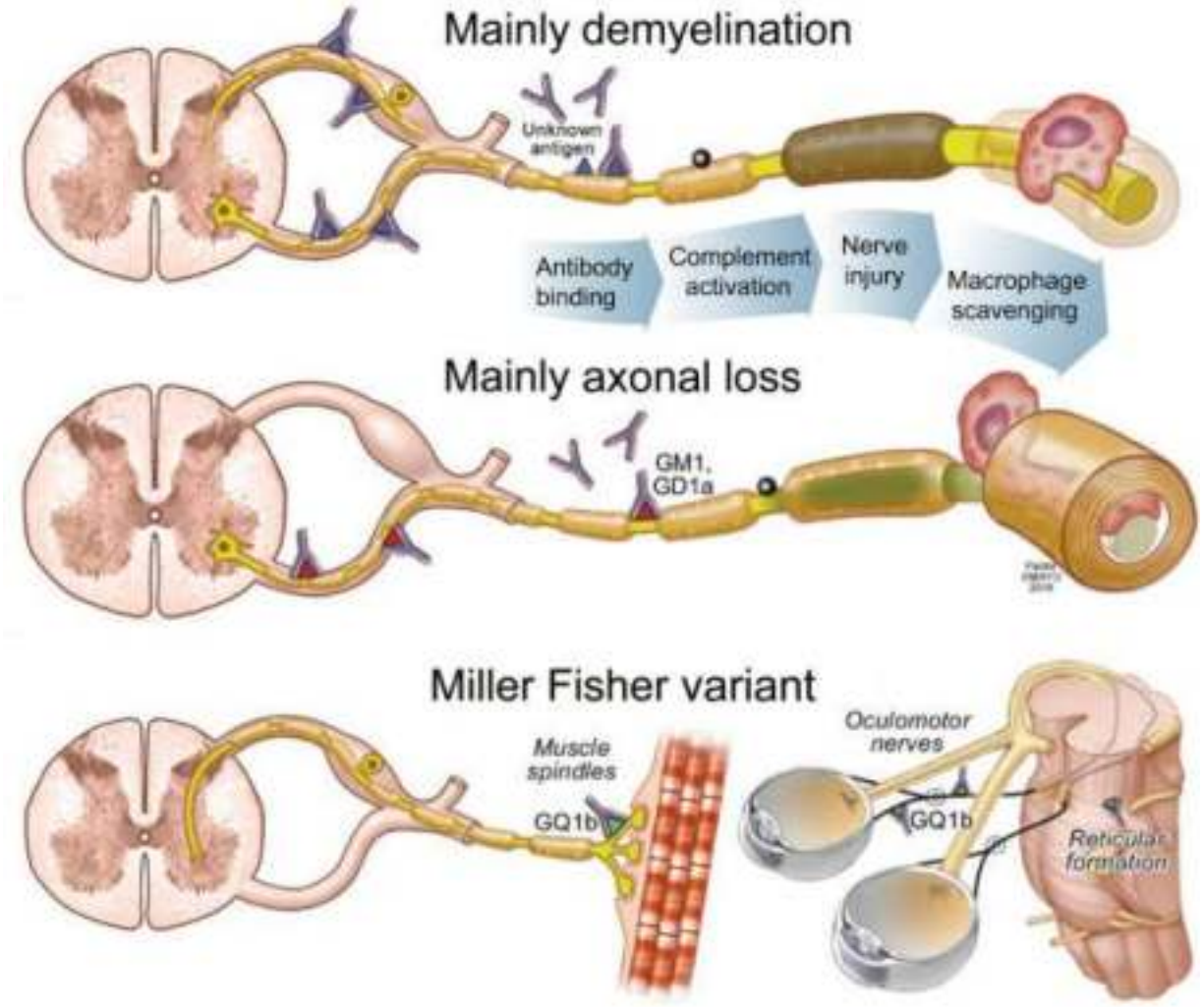
- In about half of the patients - Campylobacter jejuni (gastroenteritis)
- Other pathogens - cytomegalovirus, E-B virus, H. influenza and others
- It can occur after vaccination against H1N1 flu or Covid-19 infection



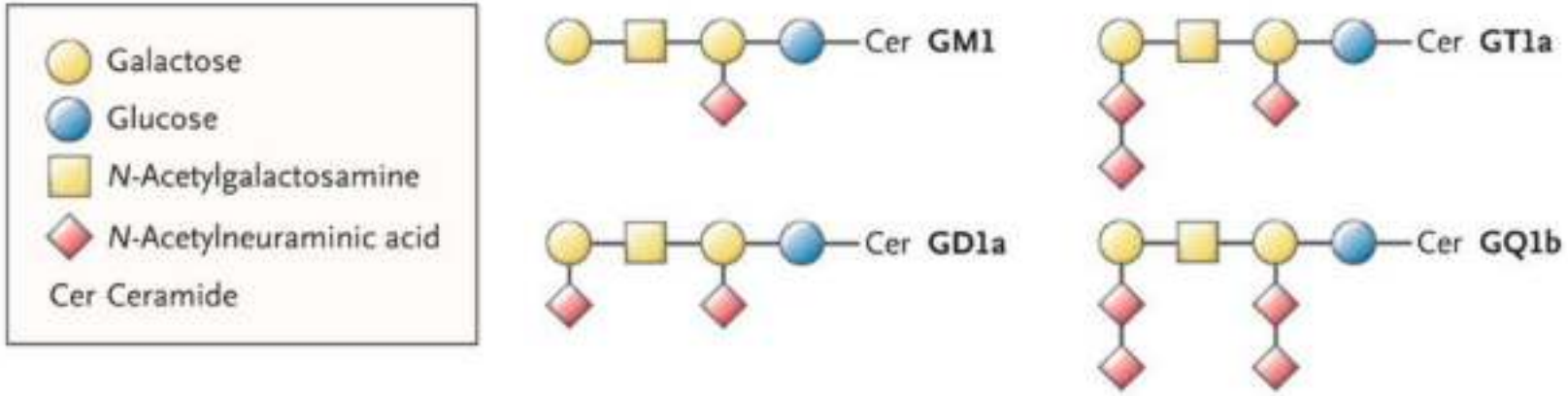
G-B syndrome – pathogenesis

- AIDP - specific mechanism of action is not known, GM2 antibodies
- AMAN - antibodies against gangliosides - GM1 (axonal form),
- Antibodies against GQ1b - Miller Fisher
- Complement activation - contribution to neurodegeneration

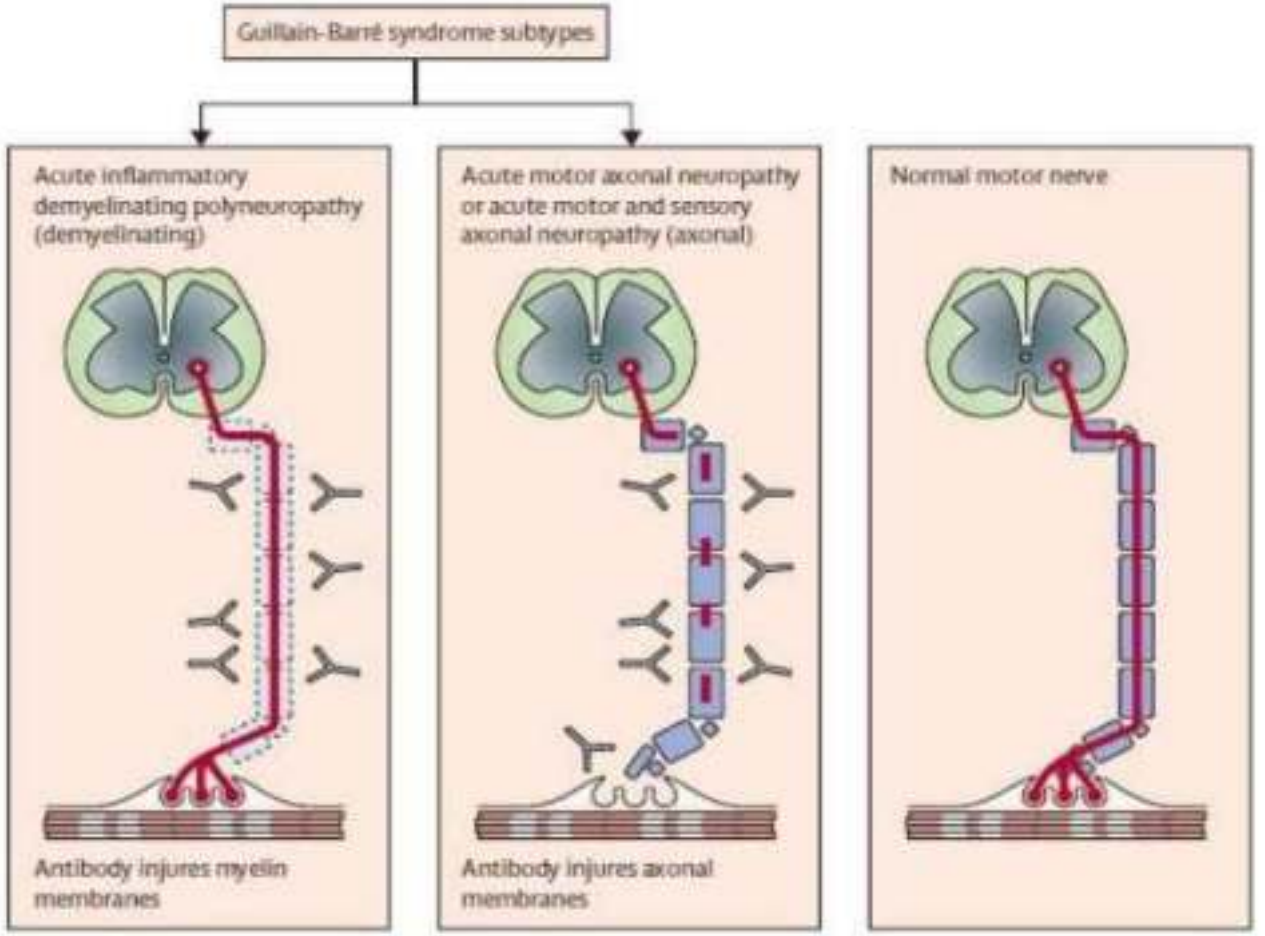
G-B syndrome – pathogenesis



Subtypes and variants	IgG autoantibodies to
Guillain–Barré syndrome	
Acute inflammatory demyelinating polyneuropathy	None
Facial variant: Facial diplegia and paresthesia	None
Acute motor axonal neuropathy	GM1, GD1a
More and less extensive forms	
Acute motor–sensory axonal neuropathy	GM1, GD1a
Acute motor-conduction-block neuropathy	GM1, GD1a
Pharyngeal–cervical–brachial weakness	GT1a > GQ1b >> GD1a
Miller Fisher syndrome	GQ1b, GT1a
Incomplete forms	
Acute ophthalmoparesis (without ataxia)	GQ1b, GT1a
Acute ataxic neuropathy (without ophthalmoplegia)	GQ1b, GT1a
CNS variant: Bickerstaff's brain-stem encephalitis	GQ1b, GT1a



G-B syndrome – pathogenesis



G-B syndrome – clinical picture

- Rapid, progressive, symmetrical limb weakness, paraesthesia, decreased or absent tendom reflexes
- Paresthesias spread proximally
- 50% of patients - involvement of the cranial nerves, especially the peripheral lesion of n.VII., sometimes swallowing disorders
- Frequent acral pain, and painful paraesthesia
- 25% - respiratory insufficiency - a patient with G-B sy should therefore be hospitalized at ICU (rapid progression of the clinical picture)

G-B syndrome – clinical picture

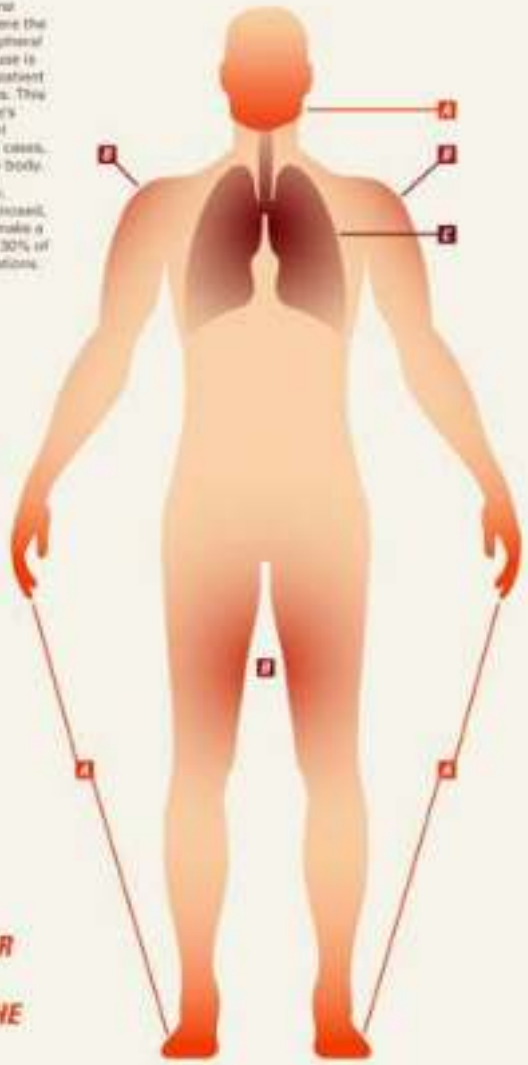
- Autonomic dysfunction - especially heart rhythm disorders
- The course is monophasic - the symptoms last 2-4 weeks, the maximum - up to 4 weeks
- AMAN - (axonal form) faster progression, longer improvement, more often worse outcome
- 9% - atypical course - can also be normal reflexes

GUILLAIN-BARRÉ SYNDROME

WHAT IS IT?

Named in 1916, *Guillain-Barré Syndrome* (GBS) *is an auto- immune disorder* where the body's immune system attacks its peripheral nervous system. Although its exact cause is unknown, GBS often follows after the patient has recovered from an infectious illness. This syndrome most often damages a nerve's Myelin Sheath, causing signals to travel slower throughout the body. In serious cases, GBS may lead to paralysis of the entire body.

GBS is a rare and very serious disorder, affecting 1 in every 100,000. Once diagnosed, proper treatments may help a patient make a complete recovery though as many as 30% of patients will still face residual complications.



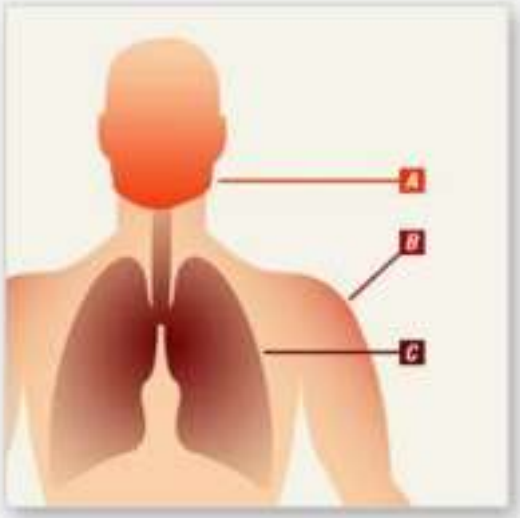
WHAT ARE THE SIGNS AND SYMPTOMS?

A NUMBNESS & TINGLING
Feeling of "pins and needles" that usually begins at the feet, hands, and/or face. The sensation stays in initial areas while spreading through out the body. Numbness and tinging maintains the same level of feeling or becomes more intense as spreading occurs.

B UNCOORDINATED MOVEMENT
Inability to perform any bodily movements such as walking, flexing digits in hands and feet and smiling. Includes blurred vision. May affect one or both sides of the body.

C TROUBLE BREATHING
Shortness of breath, difficulty taking breaths, or not breathing while experiencing other symptoms simultaneously.

CONTACT YOUR DOCTOR IMMEDIATELY IF YOU EXPERIENCE ANY OF THE SIGNS & SYMPTOMS.



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B UNCOORDINATED MOVEMENT
Inability to perform any bodily movements such as walking, flexing digits in hands and feet

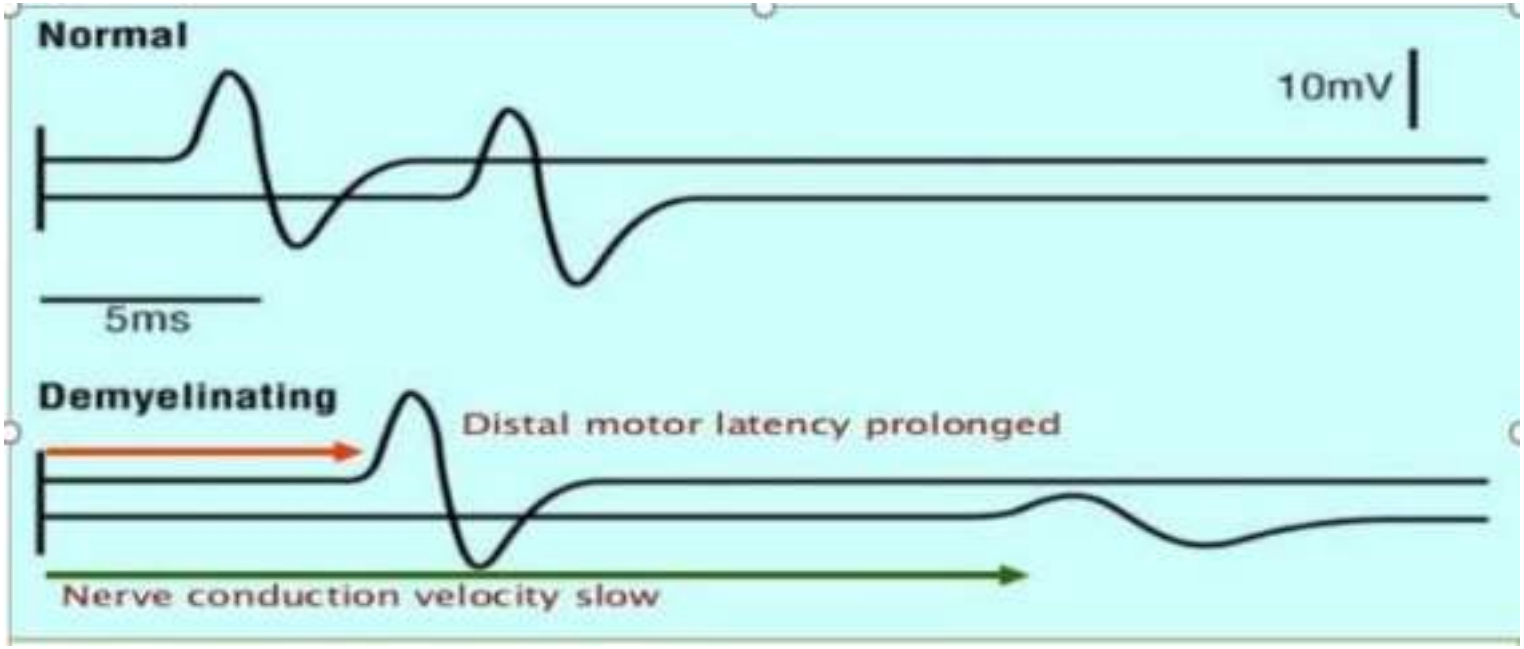
G-B syndrome - diagnostics

- Clinical picture

- Cerebrospinal fluid - increased protein (hyperproteinorrhachia)
- (albumin-cytological dissociation)
  but may not be (present in about 64%)
  50% - during the first 3 days, 80% - within a week
  Sometimes - 10 or more mononuclear cells

- EMG - maximum - after 2 weeks

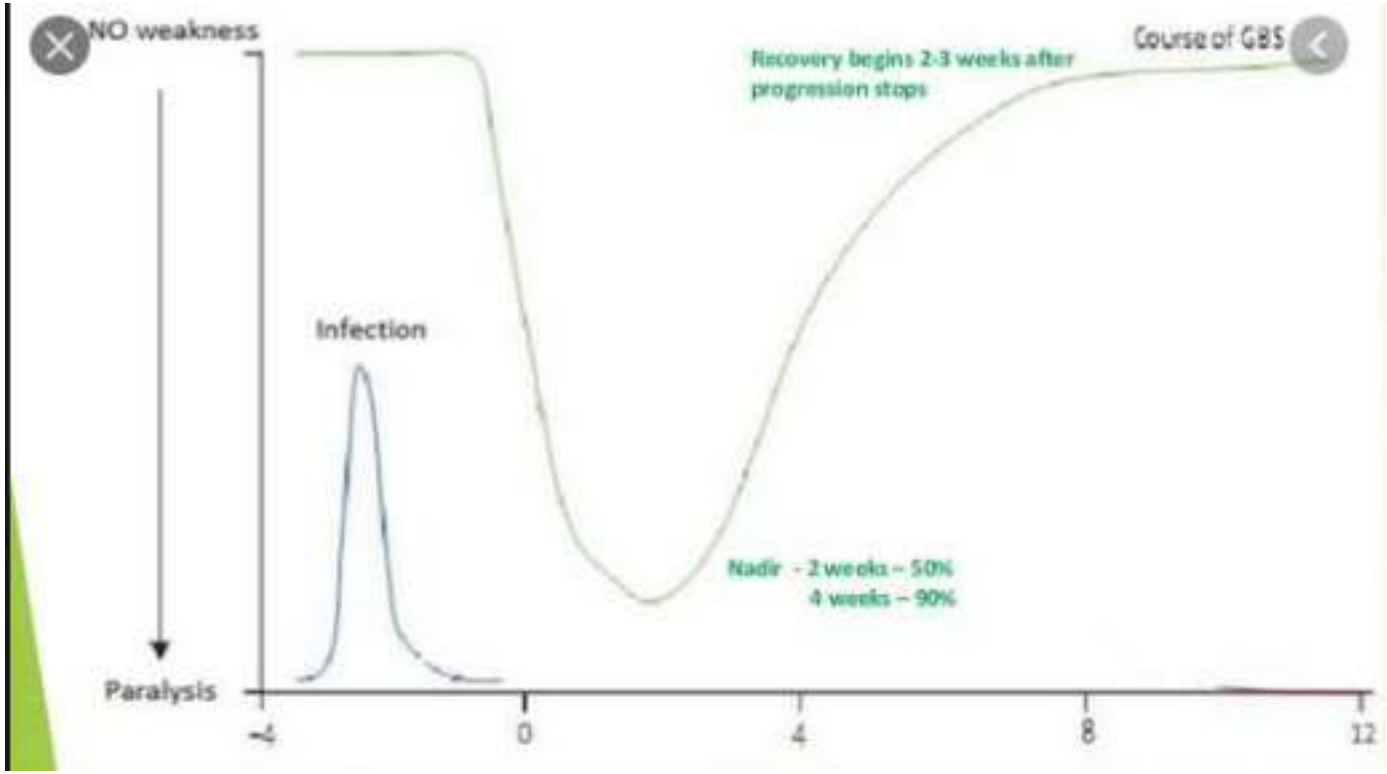
Diagnostics - EMG

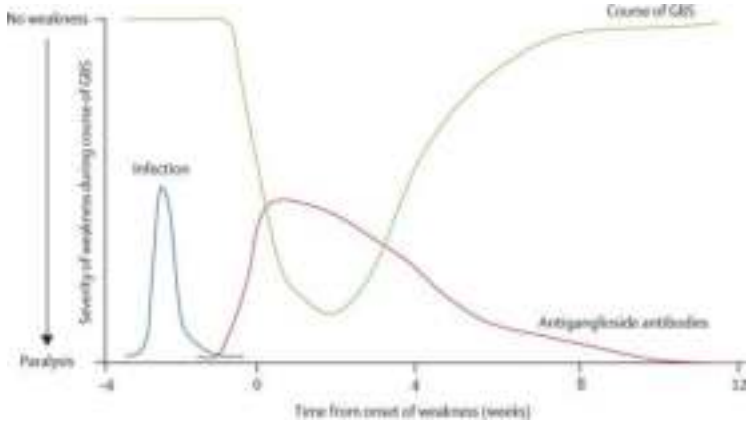


AIDP

- AIDP - prolonged distal motor latency, slowed conduction velocity, prolonged F-wave latency
- AMAN - decrease in amplitude

Course of the disease





Type	Symptoms	Nerve conduction studies	Antiganglioside antibodies
Acute inflammatory demyelinating polyneuropathy (AIDP)	Sensory symptoms and muscle weakness, often with cranial nerve weakness and autonomic involvement	Demyelinating polyneuropathy	No clear association
Acute motor axonal neuropathy (AMAN)	Isolated muscle weakness without sensory symptoms in less than 10%; cranial nerve involvement uncommon	Axonal polyneuropathy, normal sensory action potential	GM1a/b, GD1a & GalNac-GD1a
Acute motor and sensory axonal neuropathy (AMSAN)	Severe muscle weakness similar to AMAN but with sensory loss	Axonal polyneuropathy, reduced or absent sensory action potential	GM1, GD1a
Pharyngeal-cervical-brachial variant	Weakness particularly of the throat muscles, face, neck and shoulder muscles	Generally normal, sometimes axonal neuropathy in arms	Mostly GT1a, occasionally GQ1b, rarely GD1a
Miller Fisher syndrome	Ataxia, eye muscle weakness, areflexia but usually no limb weakness	Generally normal, sometimes discrete changes in sensory conduction or H-reflex detected	GQ1b, GT1a

Therapy

- Plasmapheresis
- to be effective - during the 1st week, usually 5 times during 2 weeks, worse course - 7 times
- IVIg - 0.4 g / kg daily for 5 days
- Corticosteroids - ineffective
- Controlled ventilation
- Rehabilitation

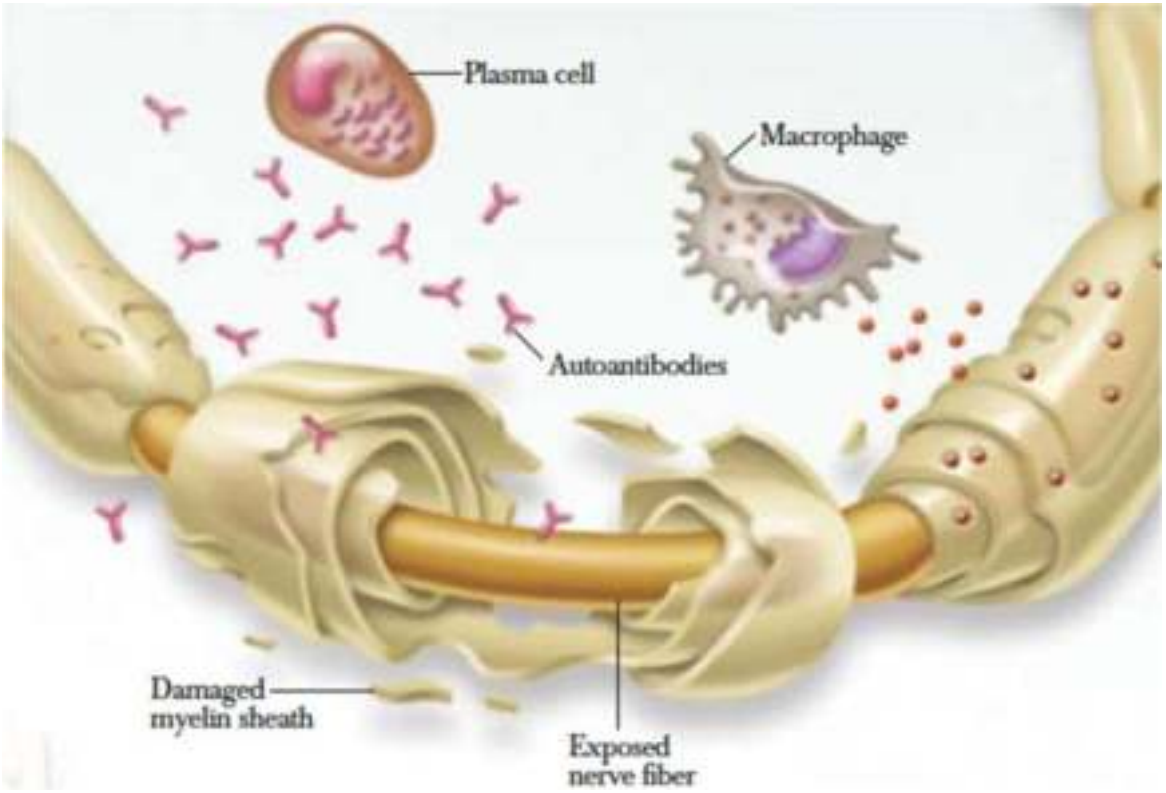
AIDP - prognosis

- 75% - cure without residual finding,

  duration of resumption of function 6-12 months
- 7 - 15% - mild residual finding
- Small % - bed binding
- 5% - exit

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

- pathogenesis



CIDP – clinical picture

- Slower development - even more than 8 T until it reaches its peak
- Weakness usually more pronounced than sensitive symptoms
- Peripheral neuropathy predominantly on lower extremities
- Sensitive symptoms - paraesthesia, pain (20%), - sock and glove distribution
- Hyporeflexia to areflexia
- Cranial nerves

CIDP

- It affects the roots and proximal nerves
- The onset and relapse of the disease is provoked by infection, vaccination
- Good response to corticoids, immunosuppressants, plasmapheresis, IVIg
- Originated at any age
- Both sexes are affected

CIDP vs. Guillain-Barré

	CIDP	Guillain-Barré Syndrome
Onset	Slow onset & progress for a longer period; may return in the future	Rapid onset that progresses quickly & stops progressing within 2-4 weeks
Treatment	Often needs sustained treatment (even with remission)	Once symptoms stabilize there is rarely any further deterioration

CIDP vs G-B syndrome

- It could be also acute onset of CIDP

Characteristic	GBS	GBS-TRF	A-CIDP	CIDP
Time to nadir	<2 weeks (maximum 4 weeks)	<2 weeks (maximum 4 weeks)	4–8 weeks, followed by progression with deteriorations	>8 weeks
Disease course	Monophasic	1–2 deteriorations within 8 weeks	>2 deteriorations or deterioration after 8 weeks	Progressive, stepwise or fluctuating
Severity	Highly variable between patients, ranging from mild symptoms to paralysis	Highly variable between patients, ranging from mild symptoms to paralysis	Mostly moderate	Mostly moderate, distal and proximal weakness
Ventilator dependence	20–30%	20–30%	Almost never	Almost never
Cranial nerve deficits	Often	Often	Sometimes	Sometimes
Response to IVIg	Good	Good, with fluctuations	Variable	Good
EMG/NCS*	Sometimes no classification possible at first EMG/NCS	Sometimes no classification possible at first EMG/NCS	Often demyelinating polyneuropathy at first EMG/NCS	Demyelination
Treatment	IVIg or plasma exchange	Repeat IVIg or plasma exchange	IVIg or plasma exchange, on confirmed diagnosis of CIDP consider also switch to prednisolone maintenance treatment	IVIg, prednisolone or plasma exchange

*AIDP or AMAN. Abbreviations: A-CIDP, acute-onset CIDP; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; EMG, electromyography; GBS, Guillain–Barré syndrome; GBS-TRF, Guillain–Barré syndrome with treatment-related fluctuation; IVIg, intravenous immunoglobulin; NCS, nerve conduction studies.

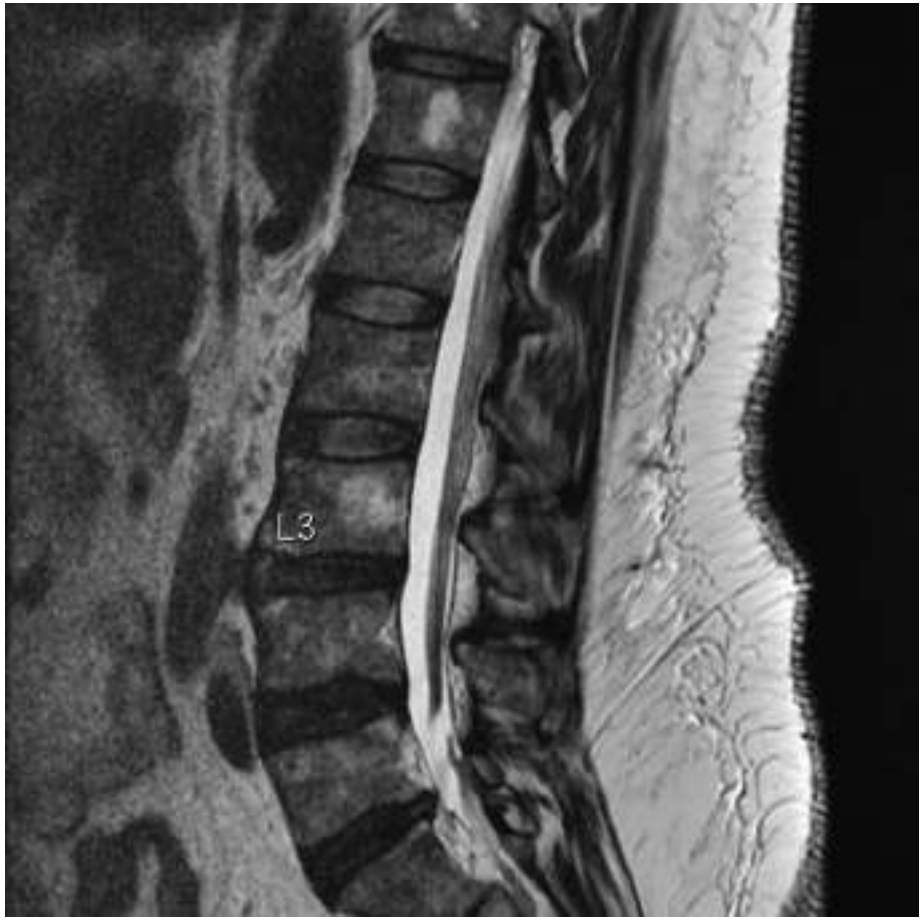
Existing Diagnostic Criteria for CIDP

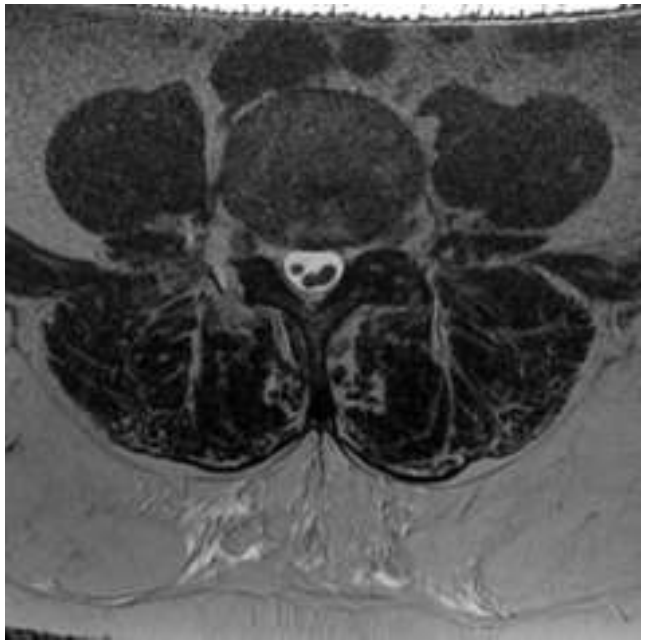
	Baronn et al.. 1988	AAN Ad Hoc Subcommittee 1991	Saperstein, 2001	INCAT, 2001
Mandatory clinical features				
Pattern of clinical involvement	Symmetric proximal + distal weakness	Motor &/or sensory dysfunction for more than 1 limb	Major: Symmetric proximal + distal weakness Minor: exclusively distal weakness or sensory loss	Motor & sensory dysfunction in >1 ectremity; significant disability in arm or leg function
Reflexes	Below normal or absent reflexes	Below normal or absent reflexes	Below normal or absent reflexes	Below normal or absent reflexes
Time course	-	-	At least 2 months	At least 2 months: stable or worsening
Laboratory Features				
EMG	Motor conduction <70% of normal	3 of 4 nerve tests showing low reaction levels (involving the major arm and leg nerves)	2 of the 4 tests	Look for a number of idfferent issues and combinations of issues in a pattern
CSF	Protein >45 mg/dL - high proteins	Mandatory: Cell count <10mm3, Not VD Supportive: elevated protein	Mandatory: protein >45mg/dL Supportive: cell count <10/mm3	Supportive but not mandatory
Nerve biopsy	Main feature of demyelination, inflammation	Unequivical evidence of demyelination & remyelination	Main feature of demyelination, inflammation - not required	Supportive but not mandatory
Requirements for diagnostic categories				
Definite	Clinical, EMG, CDF & Biospy	Clincial, EMG, CSF & Biopsy	Clincial major , EMG & CSF. Biopsy Supportive	Clinical & EMG
Probable	Clinical & 2 of 3 others	Clincial, EMG & CSF	Clincial major , EMG or CSF & Biopsy	-
Possible	Clinical and 1 of 3 others	Clincial & EMG	Clinical major & 1 out of 3 Clinical minor & 2 out of 3	-

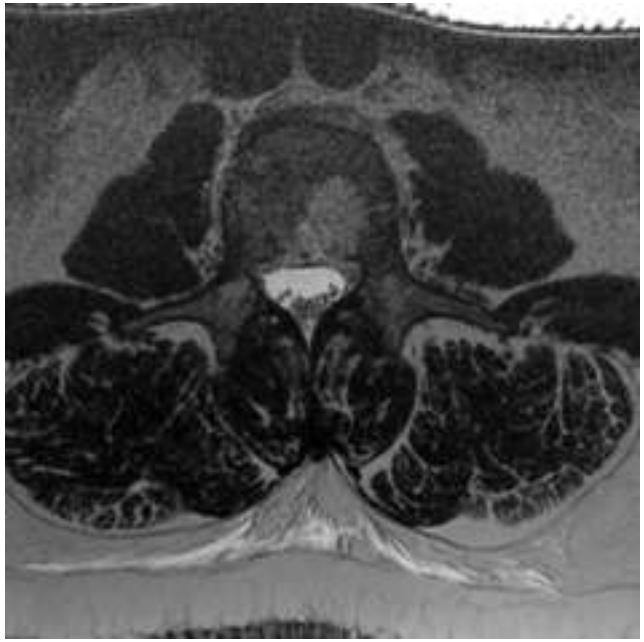
CIDP – diagnostics

- Clinical picture
- Cerebrospinal fluid - increased protein
- MRI - gadolinium enhancement or root hypertrophy
- EMG
- Improvement after immunotherapy

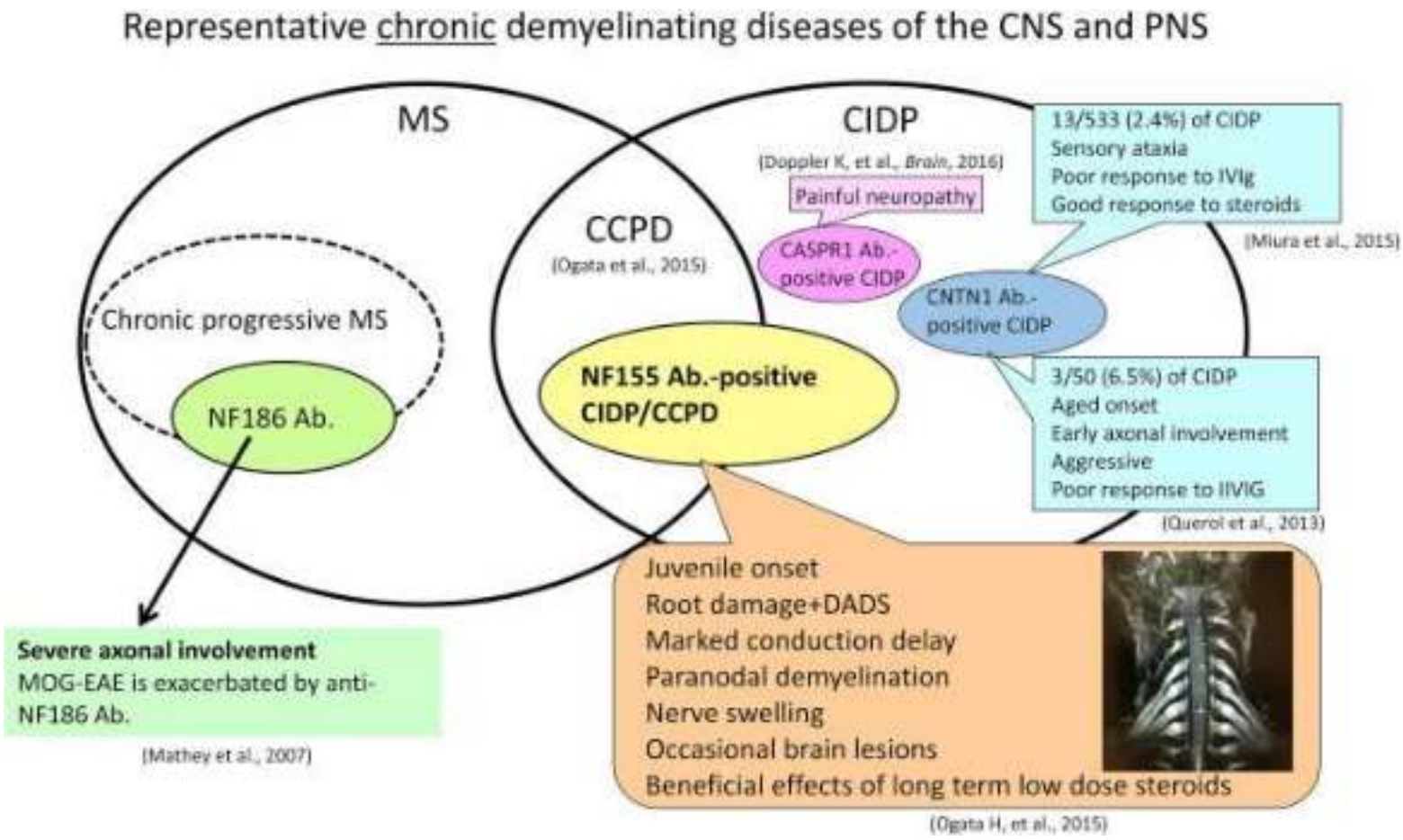
CIDP – diagnostics







CIDP – dif. dg.


Representative chronic demyelinating diseases of the CNS and PNS
MS
CIDP
(Doppler K, et al., Brain, 2016)
Painful neuropathy
13/533 (2.4%) of CIDP
Sensory ataxia
Poor response to IVIg
Good response to steroids
(Miura et al., 2015)
CCPD
(Ogata et al., 2015)
CASPR1 Ab.-positive CIDP
CNTN1 Ab.-positive CIDP
Chronic progressive MS
NF186 Ab.
NF155 Ab.-positive CIDP/CCPD
3/50 (6.5%) of CIDP
Aged onset
Early axonal involvement
Aggressive
Poor response to IIVIG
(Querol et al., 2013)
Juvenile onset
Root damage+DADS
Marked conduction delay
Paranodal demyelination
Nerve swelling
Occasional brain lesions
Beneficial effects of long term low dose steroids
Severe axonal involvement
MOG-EAE is exacerbated by anti-NF186 Ab.
(Mathey et al., 2007)
(Ogata H, et al., 2015)

CIDP – liečba

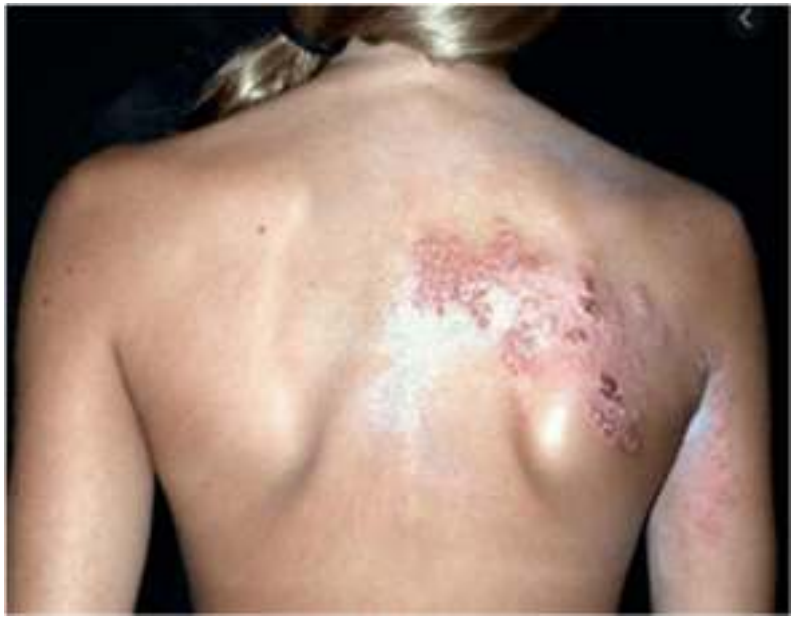
- Good response to corticoids, we start with high doses, gradual reduction (suppression of antibody formation)
- Immunosupresion - azathioprin, cyklofosfamid
- Plazmaferesis
- IVIg – 400 mg/kg/day 4-6 times
- Rehabilitation

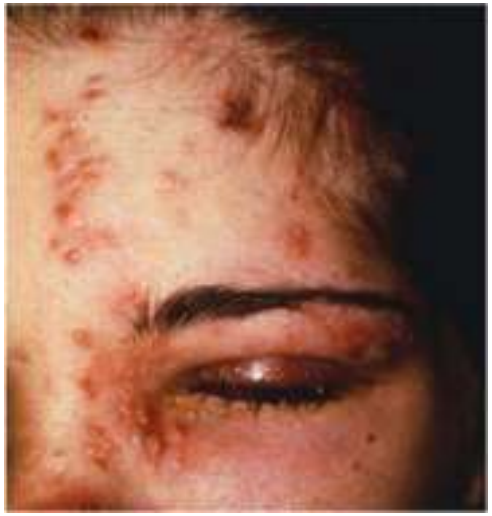
Herpes zoster (shingles)

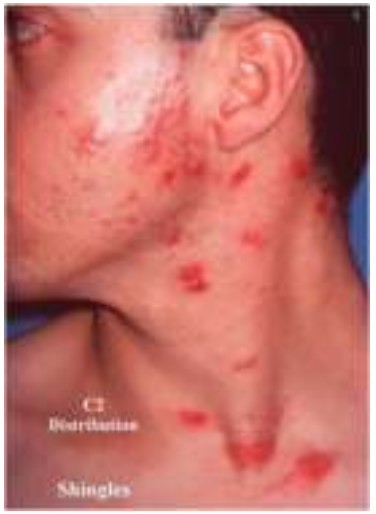
- Varicella zoster virus
- Incidence 3-5 /1000/ year – old people, with malignancies, mainly lymphoma and M. Hodgkin
- Latent varicella virus in senzoric ganglia after the primary infection with chicken post is reactivated

Herpes zoster (shingles)

- Radicular pain – sometimes before erruption
- Vesicular cutaneous erruptions spread ower two or three dermatomes on one side
- Most often - thoracal part
- Ramsay Hunt - n. VII. palsy, vertigo, deafness







Herpes zoster – diagnostics

- Clinical feature - typical
- CSF – ↑ elements and proteins
- Pain 1 – 4 weeks
- Later – postherpetic neuralgia
- Treatment – Acyclovir 800 mg 5x /day, 7 days
  reality – 5 x 200 mg

A patient with acute herpes zoster is contraindicated for rehabilitation - an infectious disease

Postherpetic neuralgia

- Paint in territory of herpes zoster, lasting minimally 3 month after erruptions
- 10 -15% patients
- Treatment

  Gabapentin 3 x 300 – 3 x 1200 mg,

  Pregabalin – 2 x 75 mg to 2 x 150 mg

  Common analgetics are not effective !!!