Other neurological diseases with autoimmune origin

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Autoimmune neurological disorders

- Nervous system disorders caused by aberrant immune system
- Antigen-specific
- May be paraneoplastic or idiopathic
- Often unified by Ab marker detected in serum or CSF

How do patients present?

- Subacute onset symptoms
- Fluctuating course
- Can affect any neurological domain
- Often multifocal
- Think rostro-caudal

Autoimmune disease

- Central nervous system
  - Multiple sclerosis
  - Other demyelinating disease
  - Encephalitis
    - Idiopathic, paraneoplastic
- Peripheral nervous system
- Myasthenia gravis
- LEMS
- AIDP, CIDP
- Sensory neuronopathy
- Autoimmune autonomic neuropathy

How do patients present?

- Central nervous system
- Brain: encephalopathy, dementia, seizures
- Brainstem: rhomboencephalopathy
- Cerebellum: cerebellar degeneration
- Spinal cord: myelopathy

How do patients present?

- Peripheral nervous system:
- Nerve root: radiculopathy
- Nerve plexus: plexopathy
- Peripheral nerve: neuropathy
- Autonomic nerve: autonomic neuropathy
- Neuromuscular junction: myasthenia gravis or Lambert-Eaton syndrome
- Muscle: myopathy

How do patients present?

- autonomic nervous system:
- Impaired pupillary light reflex
- anhidrosis (loss of sweating)
- orthostatic hypotension
- cardiac arrhythmias
- gastrointestinal dysmotility
- sicca manifestations
- bladder dysfunction

Diagnosis

- Neurological + mental examination
- MRI imaging
- Electrophysiology (EEG, ENG, EMG)
- Serum Ab testing: thyroid peroxisase, connective tissue cascade
- Neural Ab testing
- CSF testing: cell, protein, Ig index, OGP, neural Ab
- (cancer predictive values vary)

Demyelinating diseases (CNS)

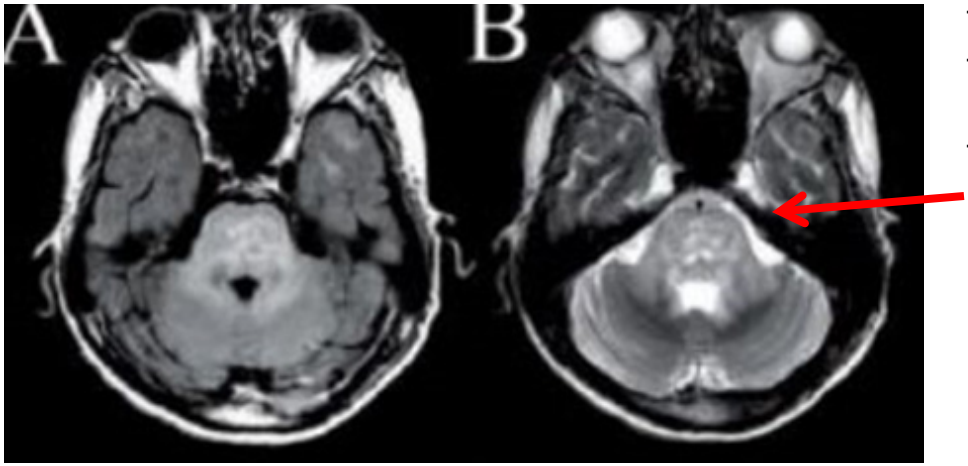
- Multiple sclerosis (MS)
- Neuromyelitis optica (NMO; also referred to as Devic syndrome or disease)
- Acute disseminated encephalomyelitis (ADEM),
- Weston Hurst syndrome (Hurst disease)
- CLIPPERS

Acut Disseminated Encephalomyelitis

- ADEM is monophasic, but it can also be recurrent, relapsing, and multiphasic.
- The hallmark clinical feature is encephalopathy, which can range from simple lethargy to frank coma and seizures
- with polysymptomatic presentation
- MRI of the brain with contrast is the imaging modality of choice, typically showing bilateral, asymmetric, poorly marginated lesions in the deep and subcortical white matter, with relative periventricular sparing on T2-weighted images and FLAIR sequences.
- Once the diagnosis of ADEM is established, steroids—in particular, high-dose intravenous (IV) corticosteroids—are the mainstay of treatment.

Weston Hurst syndrome

- acute hemorrhagic leukoencephalitis
- a very rare form of fulminant form of ADEM.
- The presentation is variable, with acute onset of fever, headache, nausea, vomiting, seizures, and coma.
- MRI of the brain may reveal extensive lesions involving the white matter with punctate hemorrhages



Clippers

- CLIPPERS is a steroid responsive Chronic lymphocytic inflammation with pontine perivascular enhancement
- relapsing-remitting brainstem disorder with punctuate and curvilinear gadolinium-enhancing lesions involving the brainstem
- Similar clinical, radiological, and histological finding can be seen in the early stage of two other diseases
  - i.e. primary angiitis of the CNS
  - and B-cell CNS lymphoma
  - and a CNS lymphomatoid granulomatosis
  - It is unclear if CLIPPERS represents a new entity or rather a disorder overlapping with one of these two diseases.

Devic syndrome

- NMO (Devic syndrome or disease) is an idiopathic inflammatory demyelinating disease
- specific to the spinal cord and optic nerves
- that results in acute attacks of severe myelitis and acute or subacute unilateral or bilateral ON
- MRI of the spine typically reveals longitudinally extensive transverse myelitis with necrotizing and cavitating lesions extending over three or more vertebral segments
- Wingerchuk et al in 2006, require
  - positive serology for NMO-IgG (antibody to aquaporin-4 [AQP4]
- In 2015, the International Panel for NMO Diagnosis updated consensus diagnostic criteria term: NMO spectrum disorder (NMOSD)
- which can be divided serologically into NMOSD with AQP4-IgG and NMOSD without AQP4-IgG
- NMOSD is characterized by clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentations.
- NMOSD without AQP4-IgG or when serologic testing is unavailable, more stringent clinical criteria and additional neuroimaging findings are necessary.

Treatment of Devic syndrome

- Initial treatment of acute attacks of ON or myelitis: mainly of high-dose IV corticosteroid therapy
- Plasmapheresis (1-1.5 L of plasma per exchange) over a period of 2 weeks may be initiated in patients who do not respond to treatment with corticosteroids. Azathioprine, mycophenolate, and methotrexate with or without prednisolone and rituximab are considered the first-line therapies
- Monthly pulse cyclophosphamide, mitoxantrone, cyclosporine, and regular IV immunoglobulin (IVIG)/plasma exchange have been suggested as second-line therapies

Suspected symptoms - AID

- Epilepsy – NMDAR
- FBDS - LGI1
  - hyponatraemia
- Psychosis
- Cognitive
- Chorea
- Myoclonus: cortical, subcortical, brainstem – opsoclonus, spinal
- Cerebellar ataxia (cerebellar atrophy) - mGluR1
- Limbic encephalitis: memory, behaviour changes, seizures
- Brainstem: eye movement disorders, dysphagia, Parkinsonism, sleep disorders – narcolepsy-cataplexy - Iglon5
- Paraneoplastic myelopathy
- Stiff man syndrome – GAD-65

Neuronal nuclear and cytoplasmic antibodies: Classic paraneoplastic disorders

- Adenocc.
  - ANNA-1 (Hu)
- Breast:
  - ANNA-2
- Ovarium
  - PCA-1 (Anti-Yo)

Autoimmune synaptic disorders and chanellopathies of the peripheral nervous system

- Neuromuscular junction disorders
- Myasthenia gravis: involves episodic muscle weakness and easy fatigability caused by autoantibody- and cell-mediated destruction of acetylcholine receptors
- characterized by varying degrees of weakness of the voluntary muscles
- Lambert-Eaton syndrome
- paraneoplastic

Symptoms

- Weakness of the ocular muscles (diplopia): involves only extraocular muscles

- Weakness of the muscles of the face and the throat, and generalized weakness. Weakness of the facial muscles results in bland facial expression.

- Laryngeal irritation causes voice impairment and dysphonias and increases the patient's risk for choking and aspiration.

MG

- Generalized weakness of all the extremities and the intercoastal muscles resulting in decreased respiratory capacity and vital capacity.

- Myasthenia gravis is purely a motor disorder with no effect on the sensation and coordination.

DIAGNOSTIC TEST

- Edrophonium test
- Ice Pack Test
- Blood test: presence of abnormal antibodies
- Repetitive nerve stimulation, SFEMG
- Pulmonary function tests

Treatment of MG

- Anticholinesterase drugs to relieve symptoms
  - Pyridostigmine
- Corticosteroids, immunomodulating treatments (eg, IV immune globulin [IVIG], plasma exchange)
- Immunosuppressant drugs, and thymectomy to lessen the autoimmune reaction
- Supportive care

Peripheral neuropathy

- Generalized term including disorders of any cause affecting PNS
- May involve sensory nerves, motor nerves, or
- both
- May affect one nerve (mononeuropathy),
- several nerves together (polyneuropathy) or
- several nerves not contiguous (Mononeuropathy multiplex)

Further classified

- into those that primarily affect the cell body (e.g., neuronopathy or ganglionopathy), myelin (myelinopathy), and the axon (axonopathy)

The clinical response to motor nerve injury

	Loss of function "- symptoms"	Disturbed function "+ symptoms"
Motor nerves	Wasting	Fasciculation
Large fibre	Hypotonia	Cramps
	Weakness	
	Hyporeflexia	
	Orthopedic deformity	

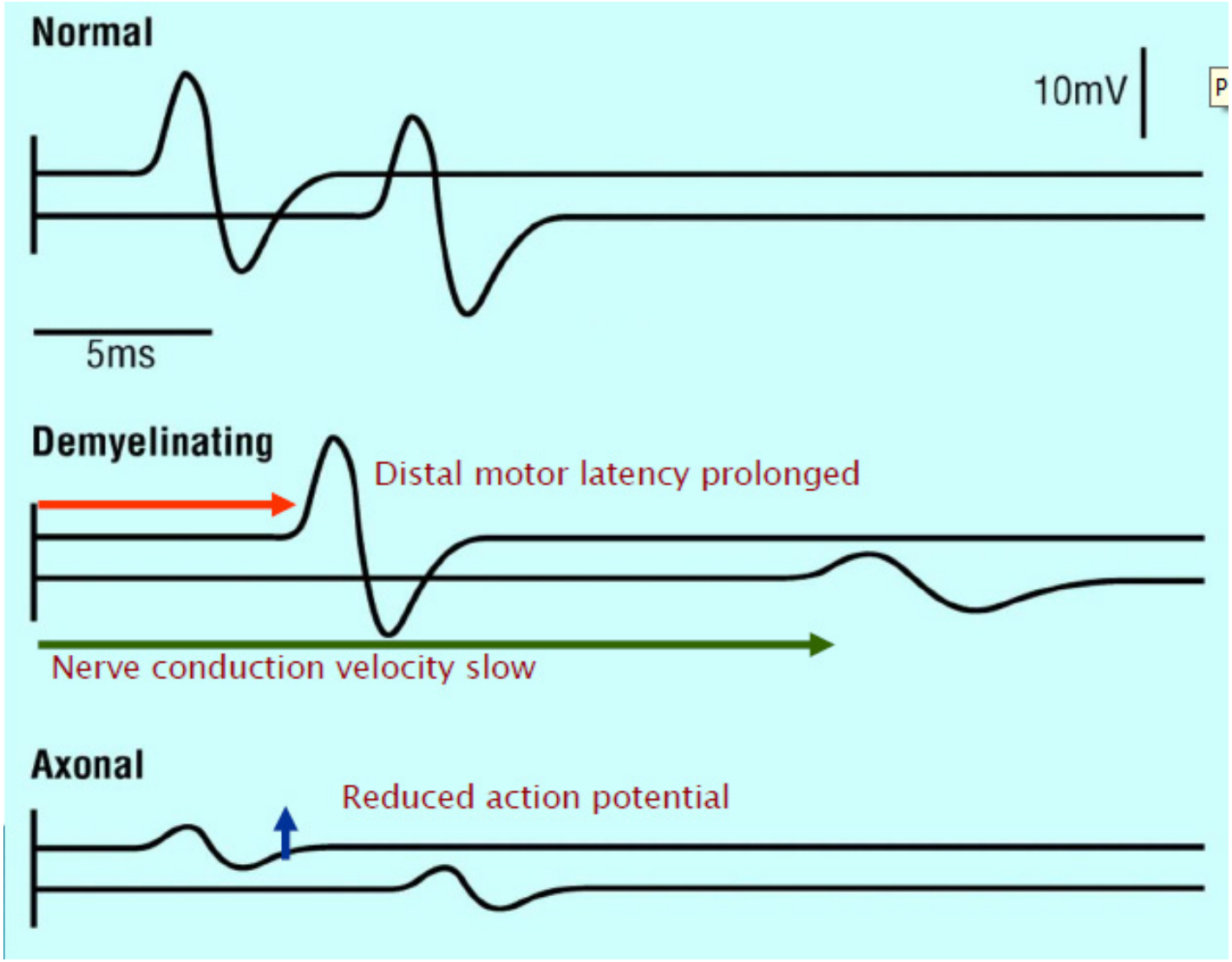
The clinical response to sensory nerve injury

	Loss of function "- symptoms"	Disordered function "+ symptoms"
Sensory	↓ Vibration	Paresthesias
"Large Fiber"	↓ Proprioception	
	Hyporeflexia	
	Sensory ataxia	
Sensory	**↓ Pain**	Dysesthesias
"Small Fiber"	↓ Temperature	Allodynia

ENG: Confirming the presence of neuropathy

Locating focal nerve lesions

Nature of the underlying nerve pathology



Immune-mediated neuropathies can be divided into acute and chronic forms

- The acute immune-mediated polyneuropathies are a heterogeneous condition with several variant forms:
  - Acute inflammatory demyelinating polyradiculoneuropathy (AIDP - GBS)
  - Acute motor axonal neuropathy (AMAN)
  - Acute motor and sensory axonal neuropathy (AMSAN)
  - Miller Fisher syndrome (MFS)

GBS

- Campylobacter jejuni infection is the most commonly identified precipitant of GBS. Cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus (HIV) infection have also been associated with GBS.
- A small percentage of patients develop GBS after another triggering event such as immunization, surgery, trauma, and bone-marrow transplantation.

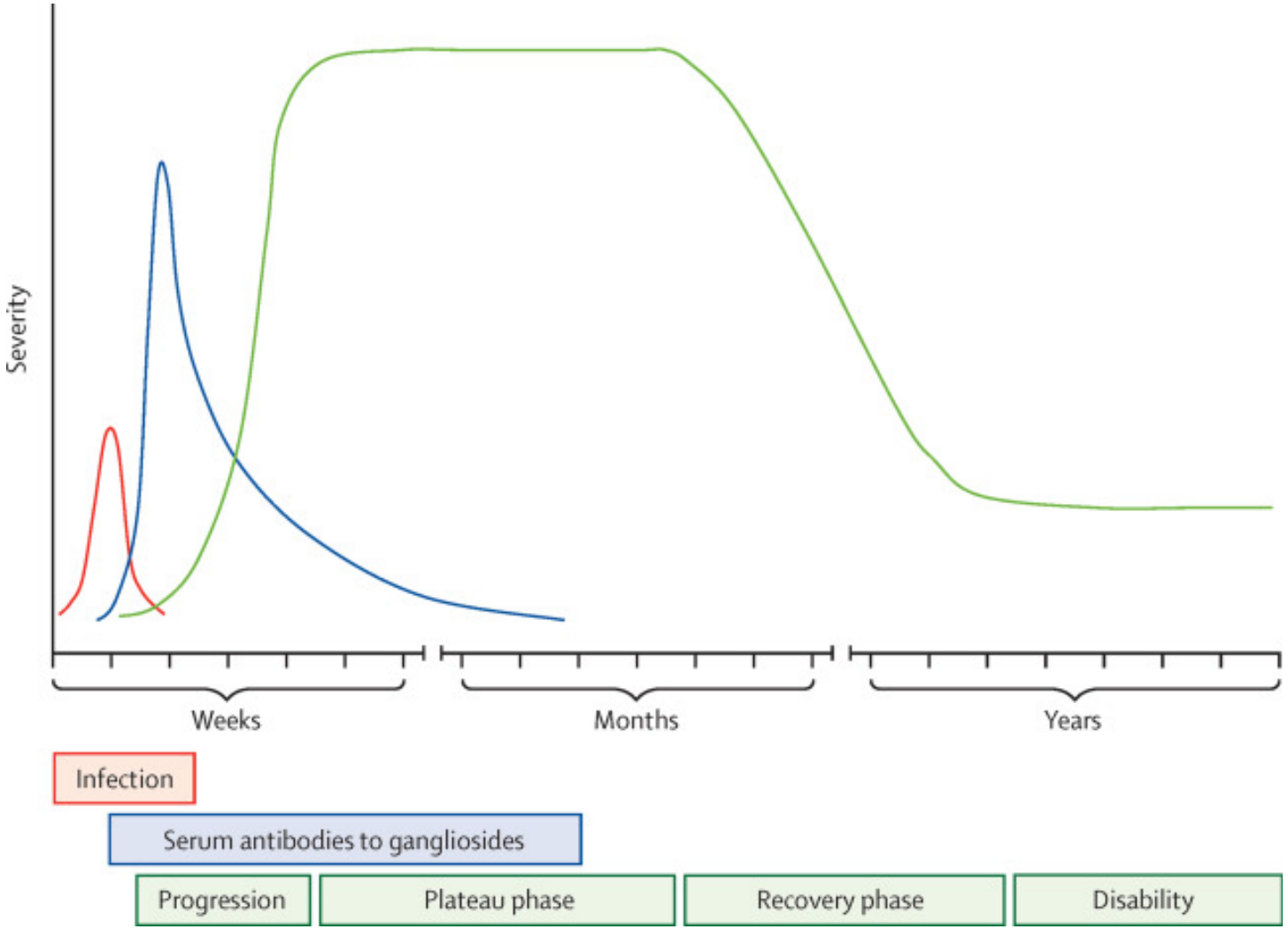
GBS

- The cardinal clinical features:
- progressive, mostly symmetric muscle weakness and absent or depressed deep tendon reflexes
- The weakness can vary from mild to severe, with nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles.
- Severe respiratory muscle weakness necessitating ventilatory support develops in about 30 percent, and dysautonomia occurs in 70 percent of patients.
- GBS usually progresses over a period of about two weeks.

Diagnosis

- Based upon the clinical presentation
- Clinical neurophysiology studies:
  - show evidence of acute polyneuropathy with either predominantly demyelinating or axonal features
- confirmed by cerebrospinal fluid (CSF) analysis
  - albuminocytologic dissociation - found in 50 to 66 percent of patients in the first week after the onset of symptoms and in ≥75 percent of patients in the third week
  - an increased cerebrospinal fluid (CSF) protein with a normal CSF white blood cell count

AIDP


Severity
Weeks
Months
Years
Infection
Serum antibodies to gangliosides
Progression
Plateau phase
Recovery phase
Disability

GBS Treatment

- severe autonomic dysfunction occurs in about 20 percent and warrants intensive care unit (ICU) monitoring.

- plasma exchange or intravenous immune globuline
- the treatments are equivalent and improve outcome

Prognosis

- Even with treatment, approximately 5 to 10 percent of patients have a prolonged course with very delayed and incomplete recovery
- 5 percent die despite intensive care.
- In addition, about 2 percent of patients with GBS will develop the chronic relapsing weakness of chronic inflammatory demyelinating polyradiculoneuropathy

Classis CIDP

- Both the cellular and humoral components of the immune system appear to be involved in the pathogenesis of CIDP and its variants.
- The precise cause is unclear, since specific provoking antigens have not been identified!

Supporting the diagnosis

- Progression over at least two months
- Weakness more than sensory symptoms
- Symmetric involvement of arms and legs
- Proximal muscles involved along with distal muscles
- Reduced deep tendon reflexes throughout
- Increased cerebrospinal fluid protein without pleocytosis
- Nerve conduction evidence of a demyelinating neuropathy
- Nerve biopsy evidence of segmental demyelination with or without inflammation

Treatment

- Primary therapies
  - intravenous immune globulin
  - glucocorticoids
  - plasma exchange
- While the long-term prognosis of CIDP is generally favorable, data are limited, and up to 15 percent of patients are severely disabled despite treatment

Multifocal motor neuropathy

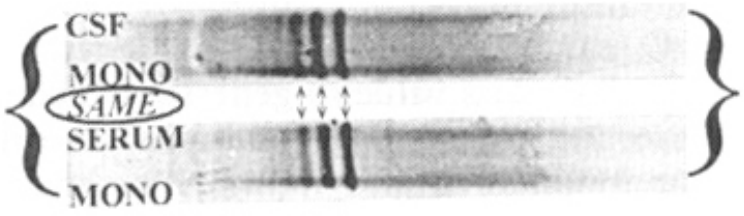
Type of ALS with lower motor neuron impairment

No pain

Therapy: IVIG

SYSTEMIC DISORDERS ASSOCIATED WITH IMMUNE-MEDIATED NEUROPATHIES

- A number of systemic disorders may be associated with one or more of the clinical phenotypes associated with chronic inflammatory demyelinating polyneuropathy (CIDP) or CIDP variants.
- Include
  - monoclonal gammopathy of undetermined significance (MGUS)
  - multiple myeloma
  - Waldenstrom macroglobulinemia
  - mixed cryoglobulinemia
  - other systemic diseases



Summary

- Autoimmune neurological disorder are important to consider
- Potentially treatable
- May be indicative of accult cancer
- Clues max emanate from
  - History
  - Examination
  - Serum & Csf Ab evaluation
  - Response to treatment