AUTOIMMUNE NEUROMUSCULAR DISORDERS

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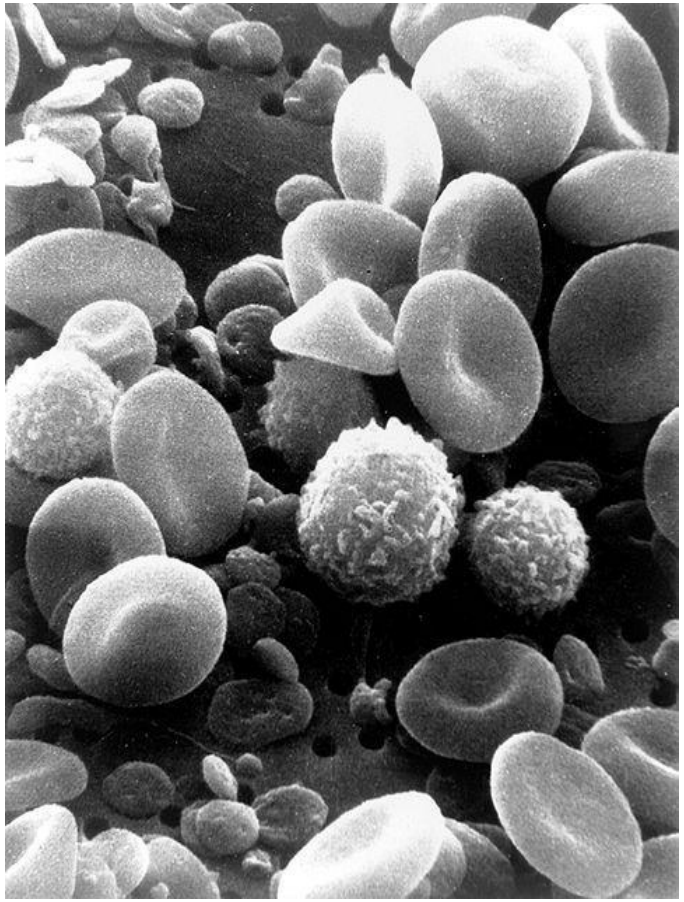
Neuromuscular disorders affect peripheral nerves, neuromuscular junction or muscle and have a wide clinical spectrum. They result as post-infectious immune reaction, paraneoplastic syndromes, but often we do not find any triggering or preceding events. As a part of an abnormal autoimmune response, autoantibodies are frequently found in serum of patients with autoimmune neuromuscular disorders.



MAIN PRINCIPLES ON IMMUNOTHERAPIES IN NMD

- Diagnosis should be well established.
- The risk-to-benefit ratio of the drugs must be considered.
- Comorbidities and concomitant treatments influence drug selection. Periodic liver and kidney function tests are recommended for patients taking most immunosuppressants
- In women, pregnancy planning is very important as many immunosuppressants are teratogenic.
- The lack of response to one drug does not mean the patient will not respond to others, and sequential trials with different drugs may be necessary until the appropriate one is found.
- Time-to-response may be long for some of the drugs, and the treating doctor and patient should be aware of this. Drugs should be given sufficient time to develop their effects and not be withdrawn after a short period of time with the patient considered "resistant" to the drug.
- It should also be taken into account (and the patients informed) that in addition to specific short-term side effects, long-term immunosuppression can increase the risk for development of infections and neoplasms.

- Classic immunosuppressants remain the most beneficial and widely used drugs for immune-mediated neuromuscular diseases.
- The majority (60% to 80%) of patients with immune-mediated neuromuscular diseases improve and have a good quality of life if they receive the appropriate drug, at the appropriate dose, for the appropriate time.
- Several new specific therapies developed recently are potential treatments for the immune-mediated neuromuscular diseases
- Define goals and expectations of therapy (i.e.ocular MG, mild case of GBS, early anti-MAG neuropathy)
- Assess response with objective measurements of strength, sensation, (i.e. INCAT Leg Disability scale), not with a change of a laboratory value (CK, antibody level, EMG/NCV…)
- Consider "add-on" or "combination" therapy, either from the outset when the disease is aggressive, or when response is suboptimal (i.e. IVIg+ Immunosuppressants -AZA, MTX, MF, CY etc in CIDP), (MG, PM/DM; plasmapheresis+IVIg)

TREATMENT OF AUTOIMMUNE NEUROMUSCULAR DISORDERS:

1) **Corticosteroids** (conventional, non-specific): Prednisone 0.75-1.5 mg/kg/day for 2-6 weeks, then taper down (e.g. reduce by 5-10 mg mg/day every 1-4 weeks) or in combination with steroid-sparing agents to reduce corticosteroid dose (e.g. azathioprine, mycophenolate)

   - MG, CIDP, PM/DM, Vasculitic Neuropathies

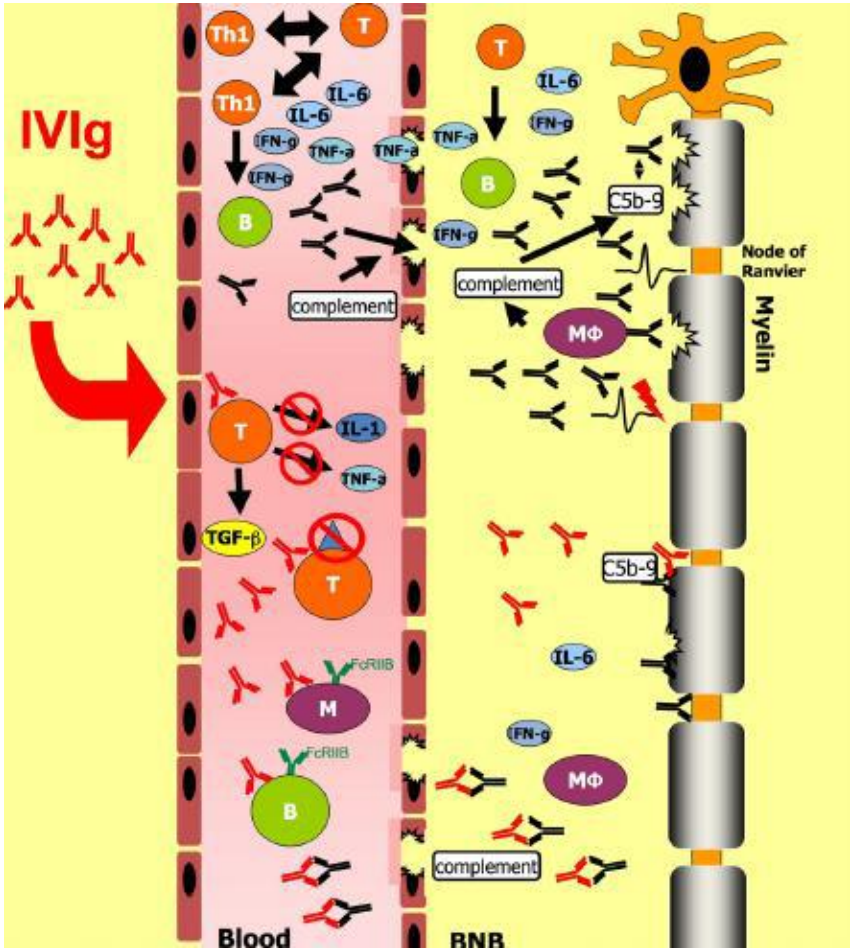
1) **Intravenous immunoglobulins:** 2 g/kg divided over 2-5 days, maintenance protocol may include monthly infusions of IVIG starting at 0.5-1g/kg every 2-4 weeks or 2 g/kg every 1-2 months . Caution renal insufficiency and IgA deficiency.

   Side effects 10%: migraine, aseptic meningitis, TE events, skin reaction, anaphylactic reaction, renal tubular necrosis

   - GBS, CIDP,MMN, MG, DM

3) **Plasmapheresis (2-5x):** Removal of the blood's liquid soluble components including immunoglobulin, immune complexes, complement and cytokines

   - MG,GBS, CIDP



Hartung et al., J Neuroimmunol 2011

Intravenous high dose immunoglobin IVIg

Mechanism of action:

- Anti-idiotypic Ab binding
- Inhibition of T cells, cytokines
- "Sponging" of complement
- Binding to Fc receptors so macrophages can't bind
- Binding neonatal Fc Receptors to increase catabolism of endogenous IgG

4) **Immunosuppressive therapy**

- Cytotoxic agents (Cyclosporine A, Methotrexate, Azathioprine, Cyclophosphamide, Mycophenolate Mofetil)

- MG, Vasculitic Neuropathies; CIDP, PM/DM, MMN

5) **New agents and biologicals**

- Monoclonal antibodies (Rituximab, Alemtuzumab, Ocrelizumab)
- Fusion proteins (Etanercept)

? MMN, CIDP, anti-MAG demyelinating neuropathy, MG

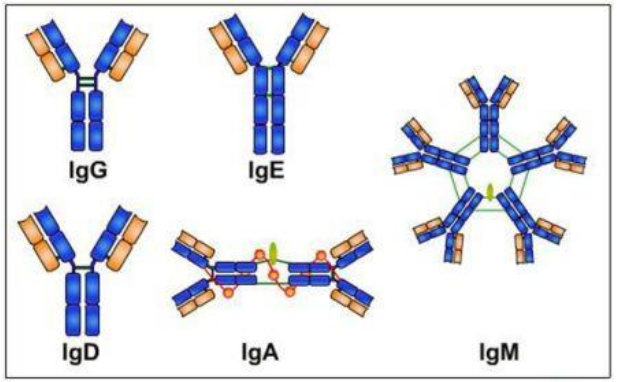
6) **Other treatments:** Anticholinesterase drugs, Thymectomy (early onset, generalised **MG**), diet, antacids, Fosamax

IMMUNE NEUROPATHIES

- Occur as isolated disorders affecting peripheral nerves only or may occur in the context of multisystemic autoimmune conditions (eg. Sjogren's syndrome, sarcoidosis, inflammatory bowel disease, celiac sprue).
- Elevated titers of autoantibodies targeting peripheral nerve glycolipids and myelin are found, but the clinical significance is limited.

ACUTE/SUBACUTE

- ❑ **Guillain Barre Syndrome**
- ❑ **Paraneoplastic sensory neuropathy** (anti-Hu)
- ❑ **Chronic neuropathies with occasional acute onset or relapse**
  - CIDP
  - MMN
- ❑ **Vasculitic Neuropathy**



Guillain Barre Syndrome

- acquired inflammatory polyradiculoneuropathy (*AIDP, ASMAN, AMAN, Miller-Fisher syndrome, sensory GBS, acute dysautonomic neuropathy*) characterized by progressive symmetric ascending muscle weakness, paralysis, and hyporeflexia with or without sensory or autonomic symptoms; variants involving the cranial nerves or pure motor involvement are not uncommon.
- Incidence: 1-2/100,000
- 2/3 flu-like illness or gastroenteritis triggering the immune response
- Humoral immunity mechanisms targeting peripheral nerve antigens
- Infections:

Viral

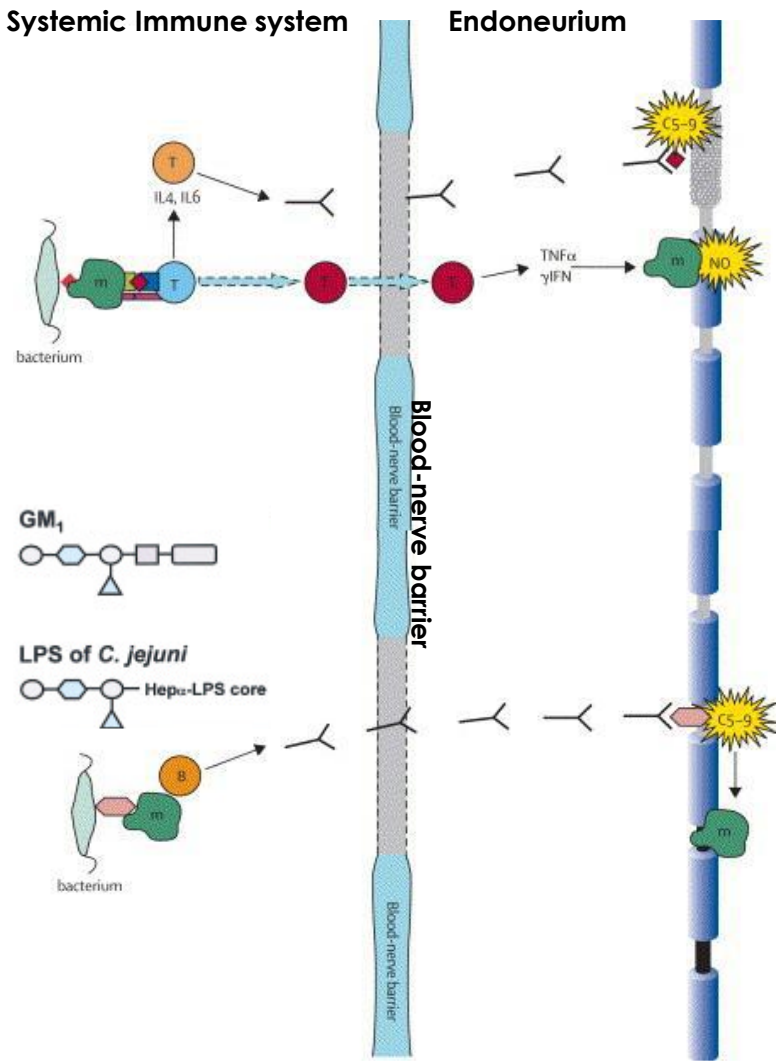
Cytomegalovirus (CMV)
Epstein-Barr virus (EBV) ± Hemophagocytic syndrome
Human immunodeficiency
Influenza (Vaccination)

Bacterial

Campylobacter jejuni
Mycoplasma pneumoniae

- *AMAN* (C. jejuni): IgM vs GM2 ganglioside, IgM vs GalNAc-GD1a ganglioside
- *Miller-Fisher syndrome* (ophthalmoplegia, ataxia, areflexia): elevated titers of GQ1b antibodies
- Th: IVIG, plasmapheresis

IMMUNOPATHOGENESIS OF DEMYELINATING VS. AXONAL GBS

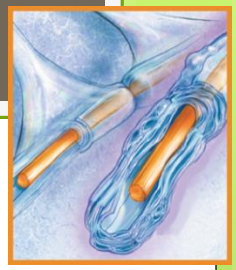


DEMYELINATING - May be responsible for AIDP
- Paranodal myelin
- Internodal myelin

<u>T and B cell mediated</u>
Excessive cytokine release due to profound immune stimulus in presence of danger signals may awaken self tolerant auto-reactive T and B cells and/or may cause expression of MHC complexes in peripheral nerve

AXONAL – May be responsible for:
AMAN/AMSAN/MFS
- Nodal axolemma
- Terminal axons

<u>B cell mediated</u> Molecular mimicry
Microbe cell surface Ag resembles self myelin glycolipids. Abs cross-react with parandoal or terminal ganglioside complexes in the PNS
(Ex C. jejuni mimics GM1, GD1a)

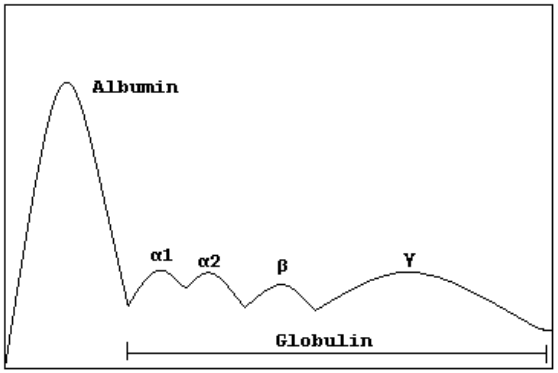


CHRONIC IMMUNE DEMYELINATING NEUROPATHIES- CIDP

- 2- 8/100,000
- CIDP is the chronic counterpart of GBS
- Peak of illness: 4-6 weeks in GBS compared to several months (> 8 weeks) in CIDP
- Course: GBS is monophasic; CIDP is relapsing or slowly progressive
- Infections induce GBS and exacerbate CIDP (16-32% of CIDP patients may have an infection or vaccination the preceding 6 weeks)
- Motor/sensory deficits in>1 limb; weakness in proximal and distal muscles; Progressive more than 2 months
- CSF examination (not mandatory): typically shows increased protein without cells
- EMNG: slow NCV<75%; conduction block/dispersion; prolonged distal latencies>140% and F-waves>120%
- CIDP variants: Predominantly distal weakness (DADS), pure motor CIDP (may worsen with steroids), pure sensory CIDP, asymmetric (Lewis-Sumner syndrome)
- Treatment;
  - Steroids (effective)
  - Plasmapheresis (effective)
  - IVIg (treatment of choice)
  - Immunosuppressants: Azathioprine, Mycophenolate, Methotrexate, Cyclophosphamide, Cyclosporin
  - New therapies (Rituximab?)

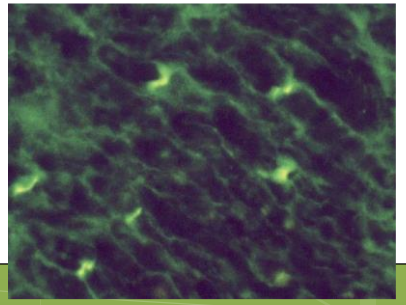
PARAPROTEINEMIC NEUROPATHY

- A clonal proliferation of plasma cells and production of monoclonal M-proteins (paraproteins).
- Monoclonal gammopathy occur in the context of hematologic malignancies or isolated as monoclonal gammopathy of undetermined significance (MGUS)
  - 10% of patients with cryptogenic peripheral neuropathy
- Patients with MGUS up to one third will have peripheral neuropathy
- MGUS-related neuropathy: 50% titers of antibodies against myelin-associated-glycoprotein (MAG):
  - ↑ IgM (often) or
  - ↑ IgA/IgG
- Increased risk of developing hematologic malignancies, especially multiple myeloma, Waldenstrom's macroglobulinemia, osteosclerotic myeloma, primary amyloidosis (light chain), lymphoma or leukemia
- IVIg (IgM anti MAG), plasma exchange (IgA,IgG anti MAG)
- Corticosteroids; Cyclosporine; Azathioprine; Cyclophoshamid
- Rituximab



MULTIFOCAL MOTOR NEUROPATHY

- ✓ Chronic, slowly progressive immune-mediated neuropathy, characterized by progressive, predominantly distal, asymmetric limb weakness mostly affecting upper limbs, minimal or no sensory impairment, and by the presence of multifocal persistent partial conduction blocks on motor but not sensory nerves.
- ✓ 1-2 per 100,000, 80% between 20 - 50 years
- ✓ Serum IgM antibodies to ganglioside GM1 were reported in 22-85% of patients (IgM 43%, IgA 5%, IgG 1%), 9% antibodies to ganglioside GD1a
- ✓ Anti-GM1 antibodies bind to epitopes of the nodal axolemma and paranodal myelin, possibly leading to conduction block (antibody-mediated demyelination or block of the voltage-gated sodium channels at the node of Ranvier), and to epitopes of of spinal-cord motor neurons, possibly leading to axon loss.
- ✓ More severe disability was associated with more axon loss, years untreated, symptom onset in a leg, and presence of IgM anti-GM1 antibodies.
- ✓ More severe weaknes was associated with axon loss and years untreated.
- ✓ The effect of IVIG declines during prolonged treatment
- ✓ Treatment:
  - IVIg, repeated IVIg treatment should be considered in selected patients (1 g/kg every 2-4 weeks, or 2 g/kg every 1-2 months), 16% solution of human normal IgG infused s.c. in the tisssues of the abdominal wall twice or three times weekly;
  - Iv. cyclophosphamide (1 gr/m2)
  - Rituximab
  - Steroids add on therapy



Neuropathy	Clinical Features	Antibody	M-Protein	Treatment
CIDP	Motor > Sensory Weakness: Proximal & Distal Symmetric Onset: 1 to 80 yrs Chronic or Relapsing	Targets β-tubulin Heparan sulfate binding to Schwann cell processes and neurites binding to Neurofascin or Contactin-1 (CNTN1) Class: IgM or IgG Frequency: 20%	15%	T-cell immunosuppression Prednisone Cyclosporine A Methotrexate Azathioprine Mycophenolate Mofetil HIG Plasma Exchange
Multifocal CIDP (Lewis-Sumner neuropathy)	Chronic Motor > Sensory Weakness: Distal > Proximal Asymmetric: Arms > Legs Onset: 15 to 75 yrs	?	?	T-cell immunosuppression Prednisone HIG
MMN	Motor only Distal > Proximal Arms > Legs Asymmetric Onset: 25 to 60 yrs, Slowly progressive	Targets Co-GM1, NP-9 or NS6S Class: IgM Frequency: 80%	20%	HIG B-cell immunosuppression Cyclophosphamide ± Plasma Exchange Rituximab
Anti-MAG	Sensory > Motor Distal; Symmetric Gait disorder, Tremor Onset: > 50 yrs, Slowly progressive	Target: MAG Class: IgM Frequency: 100%	85%	B-cell immunosuppression Cyclophosphamide ± Plasma Exchange Rituximab, ? Fludarabine
GALOP	Gait Disorder Sensory > Motor Distal; Symmetric Onset: > 50 yrs	Target Sulfatide in lipid membrane Class: IgM	80%	HIG Cyclophosphamide ± Plasma Exchange
Anti-Sulfatide	Slowly progressive Sensory > Motor Distal; Symmetric Onset: > 45 yrs	Target Sulfatide Class: IgM	90%	HIG Cyclophosphamide ± Plasma Exchange
Anti-GM2 & GalNAc-GD1a	Sensory > Motor Ataxia: Limb & Gait Distal Symmetric or Asymmetric Onset: Adult, Slowly progressive	Targets GM2 GalNAc-GD1a Class: IgM	Common	HIG
Polyneuropathy **O**rganomegaly **E**ndocrinopathy **M**-protein **S**kin changes	Sensory & Motor Symmetric Onset: 25 to 60 yrs	Target: ? Class: IgA or IgG	90%	

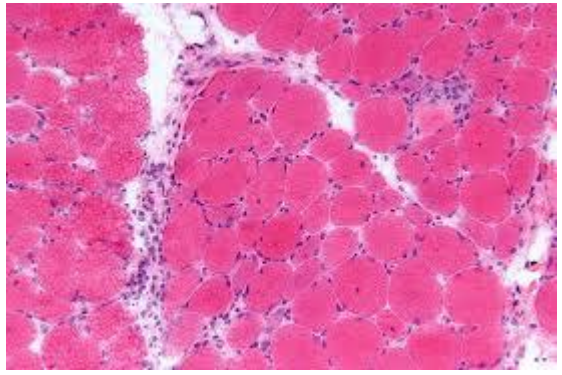
AUTOIMMUNE MYOPATHIES

- Idiopathic inflammatory myopathies are chronic muscle disorders of unknown etiology
- +/- systemic inflammatory disorders, paraneoplastic syndromes

Histopathologic features:

a. **Polymyositis**
b. **Dermatomyositis**
c. **Immune-mediated Necrotizing Myopathy**
    - ♦ Myopathy with Signal Recognition Particle (SRP) antibodies
    - ♦ Malignancy-associated necrotic myopathy (Lung, Stomach, Colon, Prostate, Breast)

a. **Inclusion Body Myositis**



Dermatomyositis

- Clinical features:

  Skin

  Erythematous rash: Heliotrope, Face & Eyelids, Sun-exposed areas, Extensor joint surfaces

  Periorbital edema

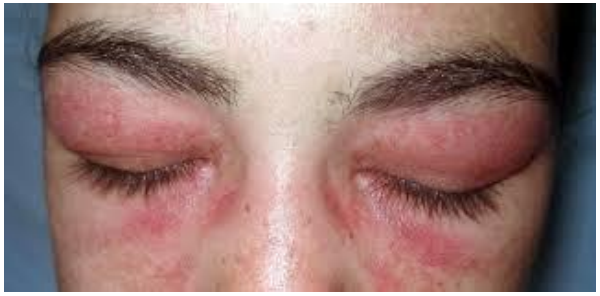
  Muscle weakness: Proximal; Dysphagia

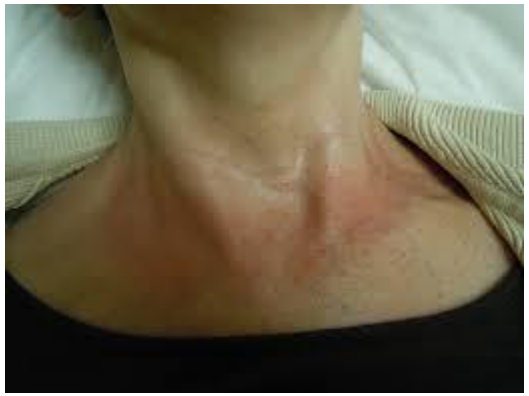
  Joint contractures

  Other occasional systemic features:

  Ocular: Retinopathy; Conjunctivitis; Iritis; Uveitis

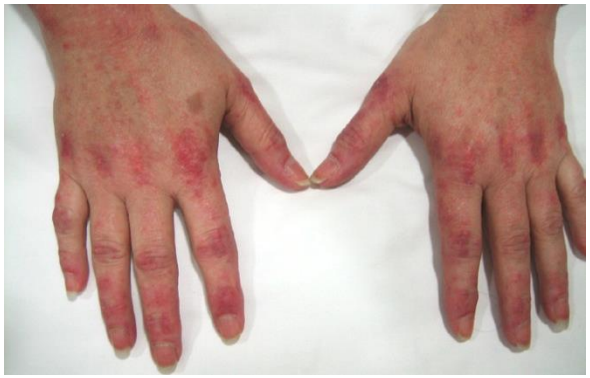
  Cardiac: Small vessel disease, Abnormal vasoconstriction
- Serum CK: Normal or High (up to 30 times normal)
- Antibodies: p155/140, CADM-140, MJ (p140), SAE, Mi-2, Atypical DM (IMPP syndromes): Jo-1





CLASSIFICATION

- ❑ **Childhood (Juvenile) Dermatomyositis** (Mi-2 Antibodies)
- ❑ **Adult DM:** Mi-2 antibody negative
- ❑ **DM: Malignancy associated** (adenocarcinoma: Ovarian, Nasopharyngeal, Breast, Lung, Hematologic: Lymphoma/Leukemia)
- ❑ **Amyopathic DM**
- ❑ **Drug induced DM** (D-penicillamine Hydroxyurea, Atorvastatin, Carticaine, Niflumic acid)

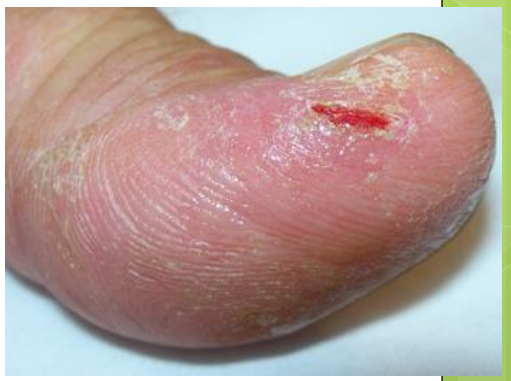


Polymyositis

- Muscle weakness
  - Proximal > Distal, Symmetric
  - Selective regions of weakness: Dysphagia; Posterior neck; Quadriceps
- Onset age: Usually > 20 years
- Progression: Months
- Pain: 30%; Especially with associated connective tissue disease

Associated disorder

- Cardiac: Arhythmias; Inflammatory cardiomyopathy
- Pulmonary
  - Respiratory muscle weakess
  - Interstitial lung disease: HLA class II (anti Jo-1)
  - tRNA-synthetase antibodies
  - Perimysial connective tissue pathology (IMPP)
- Esophageal paresis
  - Upper 1/3 with muscle weakness
  - Lower 2/3 with scleroderma
- Malignancy: Mild increased risk
- Autoimmune: Associated syndromes
  - Lupus
  - Sjögren's
  - Anti-phospholipid antibodies & syndrome: 5% to 8%
- Thyrotoxicosis



- **Laboratory features**

  Serum CK: Normal or High (Up to to 100 times normal)

  Antibodies

  Disease specific (MSA): 25% aminoacyl–transfer ribonucleic acid (tRNA) synthetases (anti-Jo-1), nuclear Mi-2 protein, and components of the signal-recognition particle (SRP).

  Disease associated (MAA): 20-50% of patients, commonly encountered in other connective tissue diseases

  - PM/Scl nucleolar antigen, nuclear Ku antigen, small nuclear ribonucleoproteins (snRNP), cytoplasmic ribonucleoproteins (RoRNP)

  Electromyographic findings are abnormal in almost 90% patients

- **Therapy PM and DM**:

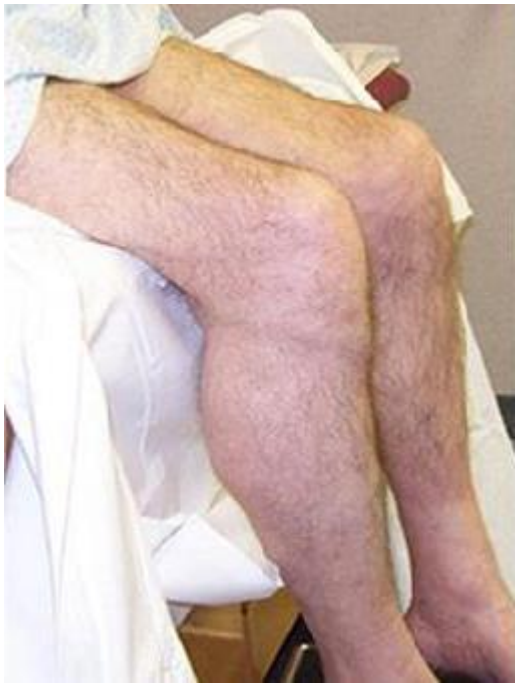
  Corticosteroids;

  Cyclosporine; Azathioprine; Methotrexate; Mycophenolate Mofetil

  Intravenous immunoglobulin (IVIG)

Inclusion Body Myositis (IBM)

- Epidemiology: Male preponderance: 57% to 75%, Sporadic
- Onset age: > 50 years in 80%
  - Weakness
    - Legs: 70%; Difficulty with chairs or stairs
    - Arms, Distal: 15%
    - Swallowing difficulty: 10%
- Clinical features
  - Weakness
    - Proximal & Distal: Distal predominant in 20%
    - Upper & Lower extremities
    - Asymmetric
    - Focal regions with more severe involvement
      - Arms
        - Weakness: Wrist & Finger flexors
      - Legs
        - Weakness: Quadriceps, Foot dorsiflexors
    - Progression
      - Slow over 5 to 20 years



- Serum CK: Mildly elevated 2 to 5 fold; or normal
- Histopathologic studies show: myofibers with rimmed vacuoles and myofibers surrounded by inflammatory cells.
- Often resistant to treatment

Response to Immunotherapies: **DM>PM>NM>IBM**

NEUROMUSCULAR JUNCTION (NMJ) DISORDERS

Autoimmune myasthenia gravis

Myasthenic syndrome (Lambert-Eaton)

- Presynaptic neuromuscular junction disorder associated with elevated titers of anti-VGCC antibodies

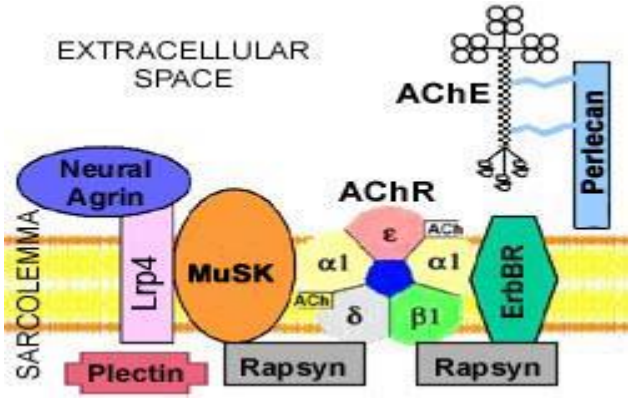
  LEMS subgroups

  1. LEMS without neoplasm
  2. LEMS with neoplasm (SCLC 50-60%, Lymphoproliferative neoplasm: Reticulum- cell sarcoma; T-cell leukemia; Lymphoma; Castleman's disease)
  3. LEMS without anti-(VGCC) antibodies

- Th: diaminopyridine, steroids, azathioprine, IVIg (severe cases)

AUTOIMMUNE MYASTHENIA GRAVIS:

- Incidence: 3-4/1,000,000 population
- Women are affected more than men during childbearing years, and trend reverses after the age of 50.
- Clinical features: fluctuating weakness and muscle fatigue (presenting symptoms are diplopia, ptosis, dysphagia, dysarthria, facial weakness, and shortness of breath). The muscle weakness is usually worse after repeated activity and improves with rest.
- The autoantibodies in MG result in loss and dysfunction of the acetylcholine receptors on the post-synaptic muscle membrane, and eventually transmission failure.
- Associated with thymic hyperplasia and thymoma (10-15%)
- Therapy: thymectomia, anticholinesterase inhibitors, corticosteroids, azathioprine, cyclosporine, plasmapheresis, intravenous immune globulin (IVIg)
- Serum antibodies:
  - IgG vs AChR (generalized MG: 85 to 90%, Childhood MG: 50% Ocular MG: 50-70%)
  - IgG vs MuSK (15%)
  - IgG vs LRP4
  - Anti-Striational (50%)
    Thymoma associations
    Titin (late onset MG: 30%)
    Ryanodine receptor



Treatment Options for Therapy of Autoimmune Neuromuscular Disorders

	Corticosteroids	*IVIG*	*Plasma exchange*	*Azathioprine*	*Cyclophosphamide*	*Mycophenolate*	*Rituximab*
CIDP	1	1	2	2	3	3	3
GBS	-	1	1	-	-	-	-
Multifocal motor neuropathy	NO	1	2 (with CYC)	-	2	-	3
Vasculitic neuropathy	1	2	2	3	1	op	op
Anti-MAG	-	-	-/op	-	-	-	op
Polymyositis	1	2	op	2	op	3	op
Dermatomyositis	1	2	op	2	op	3	op
Inclusion body myositis	-	op	-	-	-	-	-
Myasthenia gravis	1	CR, M	CR, M	M	op	M	op

1 - first option; 2 - second option; 3 - third option; op - may consider in individual cases; CR- treatment of myasthenic crisis; M- maintenance treatment; NO - should avoid.

Thank you!