Paraneoplastic Neuromuscular Disorders

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Paraneoplastic neuromuscular disorders

- Peripheral neuropathy and ganglionopathy
  - Sensory, autonomic, motor
- Peripheral nerve hyperexcitability (PNH)
- Neuromuscular junction disorders
  - Lamber-Eaton myasthenic syndrome
  - Myasthenia associated with thymoma
- Myopathy
  - Inflammatory myositis

Paraneoplastic neuropathies

Phenotype	Antibody	Tumor
Sensory neuronopathy	Anti-Hu, anti-CV2, anti-amphiphysin, seronegative (16%)	SCLC, lymphoma, adenoca, neuroblastoma
Autonomic	Anti-Hu, ganglionic nicotinic AChR Ab (10-20%)	SCLC, adenoca, thymoma
Motor	Anti-Hu (very rare)	SCLC, lymphoma, ovarian cancer
Demyelinating sensorimotor	Anti-CV2 (rarely)	Lymphoma, adenoca SLCL
Axonal sensorimotor	Anti-Hu, anti-CV2	SCLC (Ab+), adenoca (usually Ab-)

MG associated with thymoma

- late-onset (over 40 years), equal sex distribution, generalized form
- AChR seropositive: high levels of AChR-modulating antibodies (> 90%)
- Thymoma is not found in seronegative MG or in patients with MuSK MG.
- All newly diagnosed patients should have chest CT to evaluate for thymoma.
- If negative initial imaging in high risk patients, repeat studies in 3-6 months
- Thymectomy: facilitation of MG treatment, prevention of tumor progression
- Complete MG remission after thymomectomy is unlikely.
- Most patients require long-term immunosuppression and symptomatic therapy.
- After thymoma treatment, prognosis similar to nonthymomatous late-onset MG.

Thymoma

- Thymoma associated with MG: WHO type B histology
- Histologically benign, but 1/3 of cases are considered malignant because of invasion through the capsule or into neighboring tissues.
- Thymic carcinoma: presence of malignant cells and high mitotic rate
- Paraneoplastic syndromes occur in up to 70% of patients with thymoma.
- Other paraneoplastic antibodies: CRMP-5, VGKC, GAD antibodies.
- Other paraneoplastic neurological disorders: myositis, peripheral nerve hyperexcitability (PNH), autonomic neuropathy/ganglionopathy, gastrointestinal dysmotility, encephalitis, stiff-person syndrome.

Peripheral nerve hyperexcitability

- Involuntary muscle fiber activity (muscle cramps, myokymia, rippling, and fasciculations) due to excessive activity in the motor nerve terminal or axon
- Depending on the clinical and electromyographic manifestations,
  - Neuromyotonia (NMT or Isaacs syndrome)
  - Generalized myokymia
  - Cramp-fasciculation syndrome
  - Morvan syndrome (NMT with fluctuating encephalopathy, insomnia, and dysautonomia)
- Idiopathic autoimmune or paraneoplastic SD (20%)
  - Thymoma (MC), SCLC, Hodgkin's disease or plasmocytoma
- Antibodies associated with NMT
  - Antibodies to VGKCs: 50-60% of patients with NMT
  - Antibodies to contactin-associated protein-2 (CASPR2)

Paraneoplastic LEMS

- A malignancy, mostly SCLC, is found at the time of diagnosis or within 2 years in 50% of patients. LEMS occur in 3% of SCLC patients
- Patients with LEMS have a better oncologic outcome than comparable SCLC patients without a paraneoplastic SD.
- Antibodies against P/Q-type VGCCs
  - may be found in paraneoplastic cerebellar degeneration associated with SCLC
- Antibodies to SOX1 (antiglial nuclear antibodies, AGNA)
  - 64% of patients with paraneopatic LEMS but none of the patients without SCLC
  - useful specific marker of SCLC in patients with LEMS
- AChR antibodies can be detected in a minority of LEMS patients.
- Paraneoplastic LEMS typically improves after successful cancer treatment.

Paraneoplastic antibodies to intracellular antigens (nuclear or cytoplasmic antigens)

Antibodies	Tumor	NMD
Anti-Hu (ANNA-1)	SCLC, neuroblastoma	Sensory neuronopathy, autonomic and sensorimotor neuropathy, LEMS
Anti-CV2 (CRMP-5)	SCLC, thymoma	Peripheral neuropathy, sensory neuronopathy, optic neuropathy
Anti-Yo (PCA-1)	Ovarian, breast ca	Motor Neuropathy (rarely)
Anti-Ri (ANNA-2)	Breast, SCLC	Sensorimotor neuropathy (rarely)
Anti-amphiphysin	SCLC, breast ca	Peripheral neuropathy, stiff-person syndrome

Paraneoplastic antibodies to cell surface antigens (ion channel or related proteins)

Antibodies	Tumor	NMD
Anti-AChR	Thymoma	MG
Anti-gAChR (ganglionic nicotinic AChR)	SCLC, thymoma	Autonomic ganglionopathy
Anti-VGCC (P/Q type)	SCLC	LEMS
Anti-VGCC (N type)	Lung, breast ca	Peripheral neuropathy
Anti-VGKC complex (LGI1, CASPR2)	Thymoma, SCLC	Peripheral nerve hyperexcitability (PNH), autonomic neuropathy

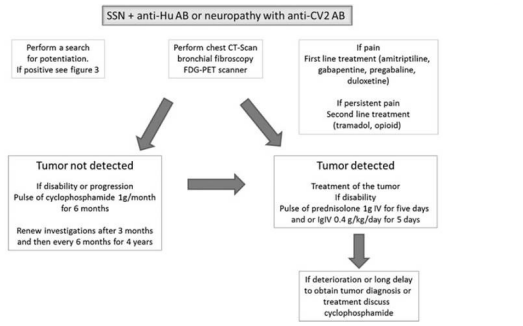
Two categories of immune mechanisms

- Antibodies to intracellular antigens (cell-mediated disorder)
  - HuD, CV2/CRMP5
  - subacute sensory neuronopathy or sensorimotor neuropathy
  - Antibodies have no access to their intracellular target.
  - T cells are the main effectors of the immune process
  - Cancer associations are relatively strong and prognosis is poorer.
  - The degree of recovery depends on the degree of axonal damage.
- Antibodies to cell surface antigens (antibody mediated disorder)
  - Ion channels and related proteins on peripheral nerves or NM junction
  - Antibodies have access to their target: altering the physiology of the targeted systems, direct pathophysiologic effects
  - Better response to immunotherapy than cell mediated paraneoplastic diseases

Treatment

- Treatment recommendation : most class IV studies
- Three categories of treatment
  - Tumor treatment
  - Immunomodulatory: steroids, IVIg, plasma exchanges, rituximab (little evidence, severe refractory cases), cyclophosphamide
  - Symptomatic: 3,4 diaminopyridine (LEMS), carbamazepine (PNH)
- Cancer treatment is crucial in patients with Ab to intracellular antigens and improve patients with Ab to cell membrane antigens.
- In patients with Ab to intracellular antigens and disabling disorder, bolus of methylprednisolone and or IVIg with tumor treatment.

Therapeutic strategy: antibodies to intracellular antigens



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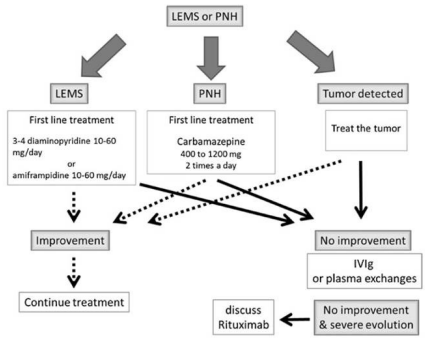
Therapeutic strategy: antibodies to cell surface antigens



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