Neurological Paraneoplastic Syndromes

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NEUROLOGICAL PARANEOPLASTIC SYNDROMES - immunologically mediated* complications ("remote" effects) of systemic cancer affecting nervous system.

*i.e. do not reflect effects of direct invasion / metastatic disease, metabolic / nutritional disorders, infection, stroke, or complications of therapy

- antibodies (in serum and CSF) recognize antigens shared by neurons and tumor cells (i.e. antibodies also confer some degree of antitumor effect).
- occur in 1-3% of cancer patients.
- in 2/3 cases, neurological syndrome precedes diagnosis of cancer (months ÷ years).
- most common cancers - lung (usually oat cell*), breast, ovary.

  *small cell carcinoma of lung (Kulchitsky basal neuroendocrine cells in bronchial epithelium arise from neural crest cells)
- *clinical manifestations differ* even in seemingly homogeneous antibody-positive syndrome - some patients have encephalitis, some have sensory neuropathy or autonomic neuropathy, some are asymptomatic, and some have more than one syndrome.
- some tumor types are associated with multiple types of autoantibodies.
- some patients have easily controlled neoplasms but die of neurologic disorder!

CLASSIFICATION

I. Brain & Cranial Nerves

1. (Subacute) cerebellar degeneration
2. Opsoclonus/myoclonus
3. Limbic encephalitis and other dementias and brain stem encephalitis as part of encephalitis, encephalomyelitis
4. Optic neuritis
5. Retinopathy/photoreceptor degeneration

II. Spinal Cord and Dorsal Root Ganglia

1. Necrotizing myelopathy; myelitis, as part of encephalomyelitis
2. Subacute motor neuronopathy
3. Motor neuron disease (ALS)
4. Myelitis
5. Sensory neuronopathy

III. Peripheral Nerves

1. Subacute or chronic sensorimotor peripheral neuropathy
2. Acute polyradiculoneuropathy (Guillain-Barré syndrome)
3. Mononeuritis multiplex and microvasculitis of peripheral nerve
4. Brachial neuritis
5. Autonomic neuropathy
6. Peripheral neuropathy with islet-cell tumors
7. Peripheral neuropathy associated with paraproteinemia

IV. Neuromuscular Junction & Muscle

1. Lambert-Eaton syndrome
2. Myasthenia gravis
3. Dermatomyositis, polymyositis
4. Acute necrotizing myopathy
5. Carcinoid myopathies
6. Myotonia
7. Cachectic myopathy
8. Stiff-person (Moersch-Woltman) syndrome

INTERNATIONAL EXPERT GROUP classification (2004):

A. Definite paraneoplastic syndromes:

a) classical syndromes (i.e. encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus/myoclonus, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstruction, LEMS, dermatomyositis) + cancer that develops within 5 years of diagnosis of neurological disorder, regardless of presence of paraneoplastic antibodies.
b) nonclassical syndrome that objectively improves or resolves after cancer treatment, provided that syndrome is not susceptible to spontaneous remission.
c) nonclassical syndrome with paraneoplastic antibodies (well characterized or not) and cancer that develops within 5 years of diagnosis of neurological disorder.
d) neurological syndrome (classical or not) with well-characterized paraneoplastic antibodies (i.e. anti-Hu, anti-Yo, anti-Ri, anti-amphiphysin, anti-CV2, anti-Ma2)

B. Possible paraneoplastic syndromes:

a) classical syndrome without paraneoplastic antibodies and no cancer but at high risk to have underlying tumor (e.g. smoking history).
b) neurological syndrome (classical or not) without cancer but with partially characterized paraneoplastic antibodies.
c) nonclassical neurological syndrome, no paraneoplastic antibodies, and cancer that presents within 2 years of neurological syndrome.

DIAGNOSIS

- of exclusion (unless characteristic autoantibodies are found in serum or CSF).

- **CT / MRI** exclude *brain metastasis*.
- **MRI / myelography** exclude *spinal metastasis*.
- **CSF cytology** evaluates for *carcinomatous meningitis*.
- **serum autoantibodies**:

N.B. absence of paraneoplastic antibodies does not rule out paraneoplastic syndrome

anti-Hu*, s. **antineuronal nuclear antibody-1 (ANNA1)** – associated with *small cell lung cancer* (subacute cerebellar degeneration, limbic encephalitis, brain stem encephalitis, subacute sensory neuropathy).

N.B. Hu antigen is expressed by small-cell lung cancer cells and by all neurons (CNS & PNS)!

anti-Ri*, s. **antineuronal nuclear antibody-2 (ANNA2)** – associated with breast, small cell lung cancer (opsoclonus/myoclonus).

anti-Yo*, s. **anti-Purkinje cell antibodies (APCA)** – associated with breast, gynecologic cancer (subacute cerebellar degeneration).

N.B. if no underlying malignancy is found but anti-Yo is present in woman, prophylactic total abdominal hysterectomy/bilateral salpingo-oophorectomy is recommended!

anti-glutamic acid decarboxylase

cancer-associated retinopathy (CAR) antibodies**

antibodies to voltage-gated calcium channels (VGCCs)**

*available in commercial laboratories

**available in research laboratories

Most important DIFFERENTIAL DIAGNOSIS:

1) metabolic brain disease (uremia, hepatic and respiratory failure, hypercalcemia, hyponatremia, hypoglycemia)
2) meningeal carcinomatosis
3) progressive multifocal leukoencephalopathy
4) complications of therapy

MANAGEMENT

1. Treatment of primary cancer - removal of antigen source.
2. Specific treatment (e.g. 3,4-DIAMINOPYRIDINE for Lambert-Eaton syndrome)
3. Immunosuppressive therapy (may be difficult with concurrent chemotherapy) – corticosteroids, plasmapheresis, protein A column therapy, IVIG, AZATHIOPRINE, CYCLOPHOSPHAMIDE.

Paraneoplastic syndromes **responsive** to therapy - "neurochemical or neurophysiological" disorders - characterized by antibodies directed against ***neurotransmitters*** or ***physiological processes***.

e.g. stiff-person syndrome - antibodies to glutamic acid dehydrogenase; Lambert-Eaton myasthenic syndrome - antibodies to gated sodium channels

- less responsive are disorders with profound inflammatory component.

e.g. limbic encephalitis and peripheral microvasculitis of nerve and muscle

Paraneoplastic syndromes **unresponsive** to therapy – cell degenerative processes.

e.g. cerebellar degeneration (with Purkinje cell loss), retinopathy, motor neuronopathy.

BIBLIOGRAPHY for ch. "Neuro-Oncology" → follow this LINK >>