III./11.9.: Neurological consequences of malignant tumors (metastases, meningeal carcinomatosis, paraneoplastic syndromes)

Malignant extraneural tumors may affect the nervous system directly (metastases, meningeal carcinomatosis) or indirectly (paraneoplastic syndromes).

### III./11.9.1 Metastases

**EFNS guideline:**


In adults, CNS metastases are more common than primary brain tumors. Brain metastases may occur in 20-40% of patients with cancer, which become symptomatic in 60-75%. In adults, tumors that are most likely to metastasize to the brain are lung (50%), breast (15-25%), skin (melanoma 5-20%), colorectal, and renal cancer. The primary tumor remains unknown in up to 15% of patients.

Most of the metastases are found in the brain, spinal cord metastases are rare. Bone metastases in the vertebrae cause secondary damage to the spinal cord. The incidence of CNS metastases has increased in recent times, which reflects the improvement of overall survival of cancer patients due to modern oncological treatments. The appearance of CNS metastases affects the quality of life of patients with malignancy, and increases mortality.

**Symptoms:**

- symptoms related to increased intracranial pressure: headache, nausea, vomiting, disorder of consciousness
- focal neurological symptoms
- epileptic seizures

Acute “stroke like” symptom may also occur caused by a sudden intratumoral hemorrhage.

**Diagnosis:**

Contrast-enhanced MRI is more sensitive than contrast-enhanced CT in detecting brain metastases. MRI often detects multiple metastases where CT showed only a solitary brain metastasis. For differential diagnosis or to confirm histopathology of the tumor, biopsy (stereotactic or open surgery) should be done. CSF cytology is needed when meningeal carcinomatosis is suspected. If the primary tumor is unknown, further extensive evaluations are needed (X-ray, ultrasound, CT, bone scan, PET-CT).

**Treatment:**

- Surgical resection (in case of solitary metastasis, or in multiple metastases when the tumor is in accessible location, is large, and its mass effect is considerable).
- Stereotactic radiosurgery
- Radiotherapy (WBRT: whole brain radiotherapy)
- Chemotherapy
- Supportive care:
  - dexamethasone to decrease cerebral edema
  - anticonvulsants should be prescribed after an epileptic seizure has occurred, prophylactic treatment is not indicated
  - thrombosis prophylaxis
**III./11.9.2 Meningeal carcinomatosis**

In addition to forming solid tumors in the CNS, metastatic tumor cells may also cause leptomeningeal infiltration. Meningeal carcinomatosis frequently occurs in breast cancer, lung cancer, GI cancer, melanoma, lymphomas, and in childhood leukemias.

It may be the first sign of the malignancy, but usually the primary tumor is already known.

**Symptoms**

Headache, nausea, loss of consciousness, back pain, polyradiculopathy, cranial nerve palsies, due to the infiltration and compression of spinal roots and cranial nerves. Focal neurological signs and epileptic seizures may occur. Up to 50% of patients have hydrocephalus.

The development of symptoms is subacute, and progression is usually rapid.

**Diagnosis**

Diagnosis is based on CSF examination with cytology and the biochemical analysis of tumor markers. Increased opening pressure during lumbar puncture, elevated CSF protein level, low glucose level, and lymphpocytic pleocytosis (cell count up to 100/mm3) are typical for leptomeningeal carcinomatosis.

Neuroimaging is not sensitive in detecting leptomeningeal carcinomatosis. Gadolinium-enhanced MRI may show typical subarachnoid nodules and sulcal/dural enhancement.

**Treatment**

The prognosis is poor, mean survival is 1-3 months without treatment. Patients with breast cancer, small cell lung cancer, and lymphomas may survive longer after effective therapy.

Radiotherapy: WBRT or radiotherapy of the symptomatic region

Administration of intrathecal methotrexate (through Ommaya reservoir or lumbar puncture)

Frequency of leptomeningeal infiltration in various malignancies:


Diagnostic and therapeutic management of leptomeningeal carcinomatosis:


**III./11.9.3 Paraneoplastic neurological syndromes**

**Definition and epidemiology**

Paraneoplastic neurological syndromes are the remote effects of cancer, not the direct local effect of the tumor and its metastasis. Paraneoplastic syndromes are believed to be immune-mediated disorders, explained by molecular mimicry. Tumor cells express "onconeural" antigens, which are identical or antigenically related to molecules expressed normally in neurons. An autoimmune response initially targeting the tumor antigen(s) "cross-reacts" to neurons expressing the same or similar antigens, leading to a clinical neurologic disease. Both cellular (T-cell mediated) and humoral immune responses play a role in the process. Incidence is 0.1-1% among patients with malignancies.

### Paraneoplastic syndromes

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<thead>
<tr>
<th>Central nervous system</th>
<th>Peripheral nervous system</th>
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<td>Multifocal encephalomyelitis</td>
<td>Sensory neuropathy</td>
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<tr>
<td>Cerebellar degeneration</td>
<td>Motor neuropathy</td>
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<tr>
<td>Limbic encephalitis</td>
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<td>Opsoclonus-myoclonus</td>
<td>Autonomic neuropathy</td>
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<td>Extrapyramidal syndrome</td>
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<td>Brainstem encephalitis</td>
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<td>Stiff-person syndrome</td>
<td>Polymyositis/dermatomyositis</td>
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<td>Optic neuritis</td>
<td>Necrotizing myopathy</td>
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<td>Retinal degeneration</td>
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### Diagnosis:

Clinical symptoms: the development of typical clinical symptoms is rapid, in many cases causing severe disability within days or weeks. Spontaneous improvement is rare. In 60-80% of cases, the paraneoplastic neurological syndrome precedes the diagnosis of the malignancy by several months to years.

Laboratory findings:

- **CSF examination**: in CNS forms: slightly elevated cell count, mildly increased protein level, detection locally synthesized IgG, oligoclonal band; in other cases, CSF is normal.

- **The detection of antibodies** in the serum and CSF is the most important element of diagnosis. Some paraneoplastic antibodies have selective neuronal reactivity and are found only in patients with a particular clinical syndrome, but a clinical syndrome may be associated with several autoantibodies. Some paraneoplastic antibodies indicate the presence of a specific type of malignancy. Most paraneoplastic autoantibodies show a more widespread or pan-neuronal reactivity and are associated with a variety of clinical neurologic syndromes.

  (Anti-VGCC antibody: Lambert-Eaton myasthenia syndrome, small-cell lung tumor)

  Anti-Yo antibody: cerebellar degeneration, breast cancer, ovarian cancer)

- **Tumor markers**: for the identification of the primary tumors

  - Neuroimaging: differential diagnosis, verification of the tumor
  - Electrophysiological examinations
  - Differential diagnosis: infiltrative tumor, metastasis, side effect of therapy, nutritional causes, metabolic causes, infection, vascular compression

### Treatment
Degenerative processes are irreversible.

Resection or removal of the tumor (it does not help in degenerative processes).

Methylprednisolone, IVIG, plasma exchange, immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, tacrolimus)

In patients treated with chemotherapy because of the associated tumor: corticosteroid, IVIG, plasma exchange

Limbic encephalitis and opsoclonus/myoclonus syndromes respond well to immunosuppressive therapy.

Supportive therapy in severe cases

Autoantibody mediated diseases respond well to therapy (especially disorders of the neuromuscular transmission). Degenerative processes are irreversible.

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Recommended references


