Multiple Sclerosis/PGS (VPL)

Differential diagnosis of multiple sclerosis (MS)

Exclude causes that better explain the clinical/paraclinical findings

Clinical and paraclinical findings

- contain warning signs **(red flags) indicative of another diagnosis** - we rule out causes that better explain the symptoms
  - MS is unlikely (it is necessary to look for another disease, especially a treatable one)

or

- they indicate MS but also a **coincidence** with another disease (perform tests and imaging methods to confirm the coexistence of both diseases).

Differentiation of signs of clinically isolated syndrome and other affections

Eye symptoms

- **typical** - unilateral retrobulbar neuritis, pain during eye movements, partial visual impairment, central scotoma, or normal papilla findings
- **less common** - bilateral retrobulbar neuritis, without pain, no perception of light, moderate prominence of the papilla without hemorrhages, posterior uveitis
- **atypical** - progressive optic neuropathy, severe permanent orbital pain, permanent complete vision loss, neuroretinitis, anterior severe uveitis.

Brain stem and cerebellum

- **typically** - bilateral internuclear ophthalmoplegia, ataxia and nystagmus, paresis of the abducens nerve (VI nerve), facial hypoesthesia
- **less often** - unilateral internuclear ophthalmoplegia, deafness, trigeminal neuralgia (nV), paroxysmal tonic spasms
- **atypical** - complete external ophthalmoplegia, vascular territorial syndrome, paresis of the oculomotor nerve (n.III), progressive sensory neuropathy of the trigeminal nerve, focal dystonia, torticollis.

Spinal cord (spinal symptoms)

- **typically** - partial myelopathy, Lhermitt's sign, deafferentation on the upper limbs, impaired tactile sensation (touch), urge incontinence, erectile dysfunction, progressive asymmetric spastic paraparesis
- **less often** - complete transverse myelitis, radiculopathy, areflexia, thermal sensation disorders, Brown-Sequard syndrome, stool incontinence, progressive symmetrical spastic paraplegia;
- atypical - territorial lesion of the anterior spinal artery, cauda syndrome, acute localized segmental pain, acute urinary retention, progressive sensory ataxia.

Supratentorial region

- **typically** - moderate subcortical cognitive impairment, hemiparesis;
- **less often** - epilepsy, hemianopsia
- **atypical** - encephalopathy (hallucinations, confusion, somnolence), cortical blindness.

Procedure in differential diagnosis

1. are symptoms **consistent with inflammatory demyelinating disease** (mono/multifocal)
2. **exclusion of non-myelinating syndrome** - demographic data, specific symptoms, clinical course, radiological and laboratory tests
    1. classification as **idiopathic inflammatory demyelinating disease** (according to specific symptoms, clinical course, radiological and laboratory tests);
        - it is not MS (neuromyelitis optica, acute demyelinating encephalomyelitis,... unclassified);
        - consistent with MS
            - dissemination in time and space according to McDonald's criteria
    2. determining the diagnosis of a non-inflammatory demyelinating disease (if we recognize red flags, we consider an alternative diagnosis).

The most common RED FLAGS - warning findings when we are looking for another diagnosis

- clinical findings:

    - **persistent monofocal symptoms** - consider a structural lesion (Chiari malformation), brain tumor
    - **peripheral neuropathy** - consider vitamin B12 deficiency, adrenoleukodystrophy, metachromatic leukodystrophy, Lyme disease;
    - **Fulminant course** - consider acute demyelinating encephalomyelitis, lymphoma, thrombocytopenic purpura;
    - **Psychological changes in patients treated with natalizumab** - consider progressive multifocal leukoencephalopathy
    - **Kidney involvement** - consider vasculitides, SLE, Fabry disease;
    - **Cardiac disease, arterial hypertension** - rule out cerebral infarctions (multiple), brain abscesses (with endocarditis), right-to-left heart shunt;
    - **Pulmonary involvement** - consider sarcoidosis, lymphomatoid granulomatosis;
    - **Progressive ataxia** (without other symptoms) - consider multisystem atrophy, hereditary spinocerebellar ataxia, paraneoplastic cerebellar syndrome,
- display methods:
    - **simultaneous enhancement of all lesions on MRI** - consider vasculitis, lymphoma, sarcoidosis
    - **persistent gadolinium enhancement + slowly enlarging lesion on MRI** - consider lymphoma, glioma, vasculitis, and sarcoidosis
    - **lacunar infarctions** - consider hypertension, cerebral autosomal dominant arteriopathy (CADASIL), Susac syndrome
- findings of laboratory deviations:
    - **neuromyelitis optica / anti-aquaporin 4 in serum** - consider neuromyelitis optica;
    - **specific IgM in CSF/PCR** - consider neuroborreliosis;
    - **antineuronal antibodies in serum** - consider paraneoplastic syndromes or autoimmune encephalitis.

McDonald's diagnostic criteria for MS (according to the 2010 revision))

Clinical manifestation	Diagnostic Criteria
>/= 2 relapses, objective clinical evidence >/= 2 lesions or 1 lesion and history of previous attack	none
</= 2 relapses, objective clinical evidence of 1 lesion	MRI dissemination in space, or another clinical attack as a result of a lesion in another location in the CNS
1 relapse, objective clinical evidence >/= 2 lesions	MRI dissemination over time, or another clinical relapse
1 relapse, objective clinical evidence 1 lesion (clinically isolated syndrome)	MRI dissemination in space and time, or another clinical relapse
severe neurological progression suggestive of MS (primarily progressive MS)	1 year of progression (retro/prospectively determined) + 2 of 3 seq. criteria (MRI evidence of dissemination in a space in the brain or spinal cord, or a positive finding in the cerebrospinal fluid)

Requirements for auxiliary examinations for the McDonald criteria:

- **DIS** (dissemination in space):
    - on MRI >/= one T2W-weighted lesion in 2 of 4 CNS regions (periventricular, juxtacortical, infratentorial, spinal cord)
    - it is not necessary for the lesion to uptake gadolinium, if the patient has clinical spinal cord/stem syndrome, the symptomatic lesion is not counted in the lesion count.
- **DIT** (dissemination in time):
    - on MRI new T2W and/or gadolinium-enhancing lesions on the next MRI against the previous one, regardless of the timing of the first scan, or the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time.
- finding in the cerebrospinal fluid:
    - positivity for 2 or more oligoclonal bands in the CSF in the alkaline region that are absent in the serum, or an elevated IgG index.

Diagnostic algorithm of multiple sclerosis

1. clinically definite **relapsing-remitting multiple sclerosis**
    - **2/more relapses** (objective evidence of >/=2 lesions, or objectively 1 lesion with acceptable anamnestic evidence of a previous attack)
        - NO => reevaluate the diagnosis!
        - YES => **dissemination in space** (=DIS) ev. **dissemination over time** (=DIT), **positive finding in CSF** (not necessary) = clinically definite MS
    - **2/more relapses, objective evidence of at least 1 lesion**
        - NO => reevaluate the diagnosis!
        - YES => **dissemination in space**, or another clinical attack in another CNS localization = clinically definite MS
2. single clinical episode:
    - **one relapse with objective evidence of >/= 2 lesions => dissemination over time** (clinically isolated syndrome with a high probability of conversion to clinically definite MS), or a **second relapse**
        - NO => reassess the diagnosis (examine cerebrospinal fluid and diff.dg. tests)
        - YES => **conversion** from clinically isolated syndrome to **clinically definite MS**

- **one relapse with objective evidence of one lesion => dissemination in space** (a clinically isolated syndrome with a high probability of a version to clinically definite MS) or **another clinical relapse of a different localization and at the same time dissemination in time, or a second relapse**
  - NO => reassess the diagnosis (examine cerebrospinal fluid and diff.dg. tests)
  - YES => **conversion** from clinically isolated syndrome to **clinically definite MS**

Treatment of multiple sclerosis - managing agent of MS treatment

Therapeutic algorithm of MS

Clinically isolated syndrome with probable development of MS / clinically definite relapse relapsing MS

- first-line drugs:
  - glatimer acetate
  - IFN-beta
  - **in case of imperfect response / intolerance, aggressive MS:**
    - second-line drugs:
      - natalizumab (monitor any psychological changes as stated above)
      - fingolimod
      - **imperfect response / intolerance:**
        - other treatment options: IVIG (off label), mitoxantrone, and other alternative options
        - new drugs - dimethyl fumarate, teriflunomide, and alemtuzumab

When relapses persist and MRI activity or intolerance

- **switch** - change from first-line drugs:
  - IFN-beta => increase frequency / dose
  - IFN-beta => glatimer acetate
  - glatimer acetate => IFN-beta
  - fingolimod => glatimer acetate / IFN-beta
  - natalizumab => glatimer acetate / IFN-beta
- **switch** - change in second-choice drugs:
  - natalizumab => fingolimod
  - fingolimod => natalizumab

Intolerance of first-line drugs

- IVIG in off label use.

Natalizumab/fingolimod intolerance or insufficient therapeutic response

- mitoxantrone.

Significant MS activity without being affected by registered drugs

- rituximab, daclizumab (so far off label), cyclophosphamide, autologous high-dose immunoablation with stem cell support.

Algorithm of managing patients for therapy with drugs affecting the course of the disease

Treated patient (evaluation within 6-12 months):

- **negative MRI** => reduced frequency of monitoring
- **active MRI, positive NAbs on IFN-beta treatment**
  - **relapses and/or progression** (active MRI) => change therapy;
  - **no relapses / no progression** => consideration of treatment change.

Current treatment of MS **reduces the frequency of relapses**, disability as well as activity and atrophy on MRI. **Early initiation of therapy** in clinically isolated syndrome **slows down the risk of developing clinically active multiple sclerosis**. The combination of clinical monitoring and MRI monitoring better reflects the treatment effect. **If the effectiveness of the first-line drugs is reduced , the strategy within the first-line drugs must be changed**, or in the case of a more aggressive course, the **second-line drugs** must be used.

Links

Related articles

- Multiple Sclerosis - article for undergraduate studies

References

- PIŘHA, J, et al. Algorithms of diagnosis and treatment of multiple sclerosis. *Neurol. practice.* 2014, year 2014, vol. Suppl. C, pp. Suppl.C, ISSN 1213-1814.