Movement disorders in multiple sclerosis

MDS Virtual Regional Course: «Movement Disorders in Neurological and Systemic Disorders”

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Disclosure

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Outline

✓ Epidemiology
✓ When and how?

✓ Clinical presentation and phenomenology
✓ Treatment

✓ Movement disorders in other demilinating diseases

✓ Causal or concidential association
✓ A didactic case & conclusive remarks
Epidemiology

• **A rare but still challenging association**: 1.6% of MS patients have a movement disorders

• The most common movement disorder in MS patients is **tremor**: 25.5% - 58%, troublesome in 3 – 15%

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Jankovic et al., J Neurol Sci 2013; Rinker JR et al., BMJ 2015; Candeias da Silva, et al., PRD 2018
Clinical presentation
A pragamatical approach

- **Time/ When?:**
  - Before the diagnosis → in patients who does not have a diagnosis of multiple sclerosis
  - After /during the disease progression → in patients with a known diagnosis of multiple sclerosis

- **HOW?**
  - A rapid/subacute onset
  - The presence of strategically located demyelinating lesions and/or an almost complete/partial resolution of the symptoms after steroid treatments (RR)

- **Phenomenological definition**

Abboud et al., Neurol Clin practice 2019; Jankovic et al., J Neurol Sci 2013
Tremor

**Frequent:** described by Charcot into the triad of characteristic MS symptoms, along with *speech* disturbances and *nystagmus*.

A key feature of MS tremors is the absence of rest tremors (or very uncommon).

<table>
<thead>
<tr>
<th>Tremor Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Cerebellar (intention) tremor</td>
<td>Pure or predominant intention tremor Uni- or bilateral. Frequency below 5 Hz. Postural tremor may occur but no tremor at rest</td>
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<tr>
<td>Titubation</td>
<td>Head or trunk tremor. Usually involves proximal muscles. Occurs only during muscle activity. Frequency mainly below 4 Hz. No tremor at rest</td>
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<tr>
<td>(High) frequency postural hand tremor</td>
<td>Unspecific postural tremor Mild action tremor Frequency variable Lateralization possible</td>
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*Jankovic et al., J Neurol Sci 2013; Deuschl Neurod Dis Manag, 2016*
Tremor

Strategic location
- cerebellum, the lateroventral or centromedian thalamic nuclei, or their connections
- cerebellum, brainstem involvement or both is seen in up to 81.6% cases of MS at some time during the illness

Its severity correlates with the degree of dysarthria, dysmetria and dysdiadochokinesia

Differential diagnosis: severe essential tremor and Holmes tremor

Jankovic et al., J Neurol Sci 2013; Deuschl Neurod Dis Manag, 2016
Cerebellar tremor

Typical clinical pictures of MS tremor

• 54 yrs, Relapsing-remitting (RR) MS since 30 yrs in a secondary progressive pattern

• Titubation (slow frequency anterior–posterior trunk and head tremor), cervical dystonia, postural and intentional tremor

• Benefit from Botulin toxin

By courtesy of Dr M. Carecchio

By courtesy of Dr A. Merola
Task specific tremors

30 yrs
Recurring optic neuritis
Right UL tremor, only during writing

(task-specific tremor when attempting to hold the computer mouse)

Association of tremor and dystonia

Dearbhla et al., Neurology 2016; Van der Walt A et al., Mult Scle 2015
Palatal tremor

✓ Palatal tremor is characterized by rhythmic movement of the soft palate at 0.5 to 5 Hz.
✓ Not limited to the palate: muscles innervated by brainstem nuclei (eye movements, face) or spinal motoneurons (trunk and extremity tremor)
✓ Concomitant nystagmus/ataxia
✓ Lesion in the dentato-olivary pathway

By courtesy of Dr G Rizzo

- 40 yrs, diagnosis of R-R MS
- 2 years before an active lesion (central pons)
- Few month later palatal tremor
Tremor – Oral Treatment

• **Few evidences / many failures**: case reports, uncontrolled open label studies and few small low-power randomized controlled trials

• Primidone, propranolol, carbamazepine, high dose isoniazid....(D9-tetrahydrocannabinol, no effect)

• **Botulinum toxin** if associated focal dystonia
Tremor – Surgical Treatment

No RCT – German guidelines

Selection inclusion criteria
- distal extremities, disabling
- >3Hz
- **no ataxia**
- No response to medication
- (no relapse within the previous 12 months)

Exclusion criteria
- Severe paresis of the trembling extremity
- Significant psychiatric comorbidity
- Immunosuppressive therapy (e.g., mitoxantrone)
- Rapidly progressive MS variant with clinical or MRI evidence of relapse and neurosurgical contraindications

Doubts
- Optimal time to operate
- Availability of objective tests to differentiate tremor and ataxia
- Effects of immunomodulation
- Effects of immunosuppression; and long-term effects

Deuschl Neurod Dis Manag, 2016
Paroxysmal dystonia/tonic spasm

• **Second most frequent** movement disorder related to MS

• **Stereotypical pattern** of **short duration** (30 secs to 5 min), high frequency attacks, up to 200/day.

• Consciousness is unaffected and EEG is normal

• **Most cases have dystonic** pure symptomatology, although pain, sensory, ataxic and akinetic symptoms are also possible

• The **location of the precipitating lesion remains unknown** as they may occur with no new lesion or with lesions in the cervical spinal cord, brainstem, cerebellum, cerebellar peduncles, cerebral peduncles, thalamus, subthalamic nucleus, internal capsule, and basal ganglia

• **Challenge diagnosis**: DD all genetic paroxysmal dyskinesia
Tonic spasms

By courtesy of Dr D. Biotti

Painful, preceded by a sensory aura in either the affected or the contralateral limbs

Provoked by hyperventilation, startling noise, tactile stimulation or voluntary movement
Paroxysmal spasm treatment

• Good response to treatment with low doses of carbamazepine or acetazolamide, or a combination of both

• Other antiepileptic drugs (diphenylhydantoin, valproate, phenobarbital, primidone) may also be effective but the evidence is less well documented
Paroxysmal kinesigenic dyskinesia

- Precipitated by sudden or rapid movements, startle or hyperventilation; few to 100 attacks/day
- MS first cause of secondary PKD – 25%
- Lesion: thalamus, lentiform nuclei, globus pallidus, internal capsule, mesencephalic peduncle and cervical cord
- Improvement with corticosteroid
Dystonia

• Even as presentation symptom – from focal to generalized (CD, sustained hand dystonia, blepharospasm, OMD dystonia, generalized dystonia and hemidystonia)

• Challenging pathogenic relationship

• Possible association with spinal cervical lesion
  ▪ Persistence of dystonia during sleep, improvement with immunotherapy despite discontinuing botulinum toxin injections argues in favor of a causal relation

  ▪ If dystonia persists despite the use of immunosuppressant medication: anti-cholinergics, baclofen, muscle relaxants or botulinium toxin injections

Shiraishi et al., Neurodevelp 2004
Myoclonus

Rare in MS patients
Generalized, multi-focal, focal.....

Putative lesions: spinal cord, brainstem and cerebral cortex

Therapy: MS treatment and a long list of symptomatic treatment......clonazepam, valproic acid, levetiracetam, phenytoin, carbamazepine, gabapentin, acetazolamide, zonisamide .......

2019: Progressive multifocal leukoencephalopathy under natalizumab one year before
NO new lesion
Previous cognitive and motor (hemiparesis) sequela

Epilepsy

R-R MS since 2014

No new MRI lesion
Normal EEG
TP: Clonazepam

By courtesy of Dr Lepine
Facial movements

- **Rare:** hemifacial spasm (synchronous spasm of one side), rarely bilateral alternating HFS, continuous facial myokimia (CFM) unilateral
- HFS: No lesion/ lesion of the ipsilateral facial nucleus
- CFM: brainstem lesion
- **Good response** to methylprednisone iv, BoNT only if persist after immunotherapy

By courtesy of Dr Lepine

Progressive multifocal leukoencephalopathy under natalizumab
Epilepsy, cognitive and motor severe sequela

Eyelid flutter/bleparoclonus, spontaneous remission.....
Search for EEG abnormalities and ipsilateral pontine lesion
Parkinsonism

• **Subacute/acute onset**, even many years after MS diagnosis
• Clinical picture similar to idiopathic PD, but with **additional symptoms**
• **Demylinating lesion** in the thalamus, Gpi and SN, with partial resolution after corticosteroid (not always), **good response to dopaminergic drug is the lesion is in the SN**

• NO DATA on Dat-scan
• Autopsy revealed **Lewy bodies** in locus ceruleus and SN in few cases.... Even without parkinsonism

Folgar et al., MDJ, 2003; Nociti et al., Multiple Sclerosis 2008
Tics

Few case report described

Pathogenesis of TICS: the basal ganglia portions of cortico-striato-thalamo-cortical circuits & thinning of the sensorimotor cortices

30 yrs, secondary-progressive MS
7 years after the onset of the disease: motor and phonic tics, self-injurious behaviour
MRI: increased lesion burden (brainstem, middle cerebellar peduncles and both thalami) and increased atrophy around Sylvian fissures, no active lesion
NO improvement with corticosteroid, not tolerated risperidone, mild improvement with quetiapine

Nociti et al., J Neurol Science 2009; Sowell ER et L., Nat Neurosci 2008
Others movement disorders

Chorea and ballism: rare, spontaneously improved or disappeared in almost half of the reported cases - plaque of demyelination in the contralateral subthalamic nucleus and all the reported imaged patients with chorea had lesions in the basal ganglia, especially the striatum

Lang and Riley MDJ, 1988

Restless leg syndrome/Periodic limb movement disorders: 2 to 5.5 fold increase in the prevalence of RLS in MS patient, more severe, without relation of its severity with the duration of MS, described as very common in early MS patients, usually acutely or subacutely during a spinal relapse

Abboud et al., Neurol Clin practice 2019
Other demilinating diseases

**Neuromielitis optica**

- ranging from unilateral isolated optic neuritis to extensive myelitis with bilateral optic neuritis
- anti-aquaporin-4 antibody, an NMO-IgG biomarker
- **Paroxysmal dystonia in 25% of the NMO**, being myelitis at disease onset a predictor of paroxysmal dystonia in the NMO group
- **Painful tonic spasm**: frequent, lasting few min, preceded by brief paresthesia, no precipitating factors

Kim et al., Arc neurol, 2012; Candeias da Silva, et al., PRD 2018; Wingerchuk et al., Neurology 2015
32 yrs
8-year history of sporadic abdominal muscles movements, aggravated by lying down and impeded falling asleep
Since 18 yrs, recurrent optic neuritis

Spinal MRI: lesions localized at C2 to C7 and D5 to D9
AQP4-specific serum auto-antibody

Vetrugno et al., MDJ 2009;
Other demilinating diseases

- Acute disseminated encephalomyelitis
- Acute ataxia (50%) [132].
- Acute choreoathetosis, hemidystonia, paroxysmal hemidystonia and hemichorea plus dystonia (12%) [132].
- Painless torticollis [134].
- Segmental myoclonus [135].

Central pontine myelinolysis and extrapontine myelinolysis
- Parkinsonism, frequently responsive to levodopa [138,140,141].
- Dystonia. Multifocal, segmental or generalized. Responds well to trihexyphenidyl [138,143,144].
- Truncal ataxia [147].
- Paroxysmal dystonia [137].
- Chorea [138].
- Phenomenology can evolve from one movement to another over time [145].
- These movement disorders can be transient or permanent and can start as early as within a week of the brain insult, or be delayed by up to 5 months [138,139,143–145].
- Parkinsonism responsive to intra venous methyl prednisolone [150].
- Dystonia, ataxia, rigidity, choreoathetosis and tremor [151].

Post bone marrow transplant demyelinating leukoencephalopathy.
Hypomyelination with atrophy of the basal ganglia and cerebellum

Jankovic et al., J Neurol Sci 2013
A didactic case

Outpatient visit

• 50 yrs, subtle balance difficulties since 46 yrs
• Depression/cognitive problems at work, altered coordination, slurred speech
• Doubts on family history (grand-mother)
• Genetic testing for SCA1, 2, 3, 6, 7, 17: Negative
• Neuropsychological tests: cognitive disturbances in the executive/memory domain
• Cerebral MRI: periventricular white matter T2 hyperintense lesions and brain and ponto-cerebellar ATROPHY

In-patients assessment:
Liquor: Ologoclonal band /Altered visual evoked potential
Temporal dissemination at cerebral and spinal MRI
NGS panel SCA: negative

Primary progressive MS – Ocrelizumab treatment

By courtesy of Prof. F. Morgante
Causal or concidential association?

• Movement disorders in MS are **not common**, with the exception of tremor
• May happen with basal ganglia involvement and without
  • **Causal**: abrupt onset, resolution/improvement with immunotherapy
  • **Coincidental**: many years after the diagnosis, typical clinical picture and not strategic new lesion

Plaques can involve all the CNS, and the extrapyramidal pathway could be impaired at multiple levels, with a diffused tissue damage that can impair nervous fibers involved in specific motor pattern that is able to induce a MD or induce an aberrant neuronal plasticity

Nociti et al., J Neurol Science 2009
Conclusive remarks

- Rare but more common than previously thought
- Hyperkinetic>>hypok
- Few months after spinal or brainstem/cerebellar relapses but may occasionally be the presenting symptom of a relapse
- Neglected topic, few study in the last 10 years
- No RCTs

Pt with a known diagnosis of MS who present a new mov dis

- Familiar history
- Phenomenology
- Clinical onset

MRI active lesions/increased lesion buden

1. MS treatment
2. If no response to immunopressant tp, treatment based on disorders phenomenology

Pt with a mov dis onset without a known diagnosis of MS

- Familiar history
- Phenomenology
- Clinical onset

Suggestive MRI?

Oligoclonal band?

MS : not to be missed
Thanks for your attention

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