CMI Clinical Management Issues

Case report

Very Late Onset Multiple Sclerosis associated with Restless Legs Syndrome. A case report

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Abstract

We report the case of a 83-year-old woman suffering from Restless Legs Syndrome (RLS) since 2002 and Multiple Sclerosis (MS) since 2007, when she was 72 and 77, respectively. She had been diagnosed as RLS five years before MS, with the support of a polysomnographic examination. The clinical diagnosis of MS took place at the age of 77, while complaining of walking difficulties and abnormal sensitivity in lower limbs, especially in the evening. Associated symptoms included dysesthesias on the left leg and arm and left hemitrunk, visual acuity reduction, blurred vision, and fatigue. The brain magnetic resonance showed multiple lesions in white matter, inconsistent with vascular disease but suggestive for demyelinating disease. She was admitted to the hospital, where the spinal fluid examination and a second magnetic resonance confirmed the diagnosis. Since that, the patient regularly performed medical examinations and magnetic resonance controls which didn't show any increase of lesions burden nor pathological enhancement, but highlighted a slow worsening of ambulation. Due to the patient's age, a disease modifying therapy for MS was not established, but only symptomatic agents were administered.

Keywords: Late Onset Multiple Sclerosis; Restless Legs Syndrome; Comorbidity

Un caso di sclerosi multipla ad esordio molto tardivo associata alla sindrome delle gambe senza riposo

CMI 2014; 8(1): 19-23

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CASE REPORT

P.R. is a 83-year-old woman who presented since 2002 (when she was 72) walking difficulties and abnormal sensitivity in lower limbs, especially in the evening. Other symptoms included fatigue and dysesthesias on left limbs and left hemitrunk, visual acuity reduction with blurred vision, visual field reduction on left side. In the past history, she underwent a hip joint prosthesis in 2001, had an arterial hypertension and hypercholesterolaemia since 2004, and surgery for grey cataract in left eye in 2006. The patient referred also increased anxiety and insomnia.

In 2002 she performed an electromyography examination and a polysomnographic confirmatory recording. Nocturnal sleep showed a longer sleep onset latency, a shorter total sleep time, a lower sleep efficiency, a higher arousal index, and a longer REM sleep latency as compared with healthy laboratory controls. Furthermore, the patient's fragmentation index, the periodic leg movements index and the periodic leg movements-arousal index were all elevated,

Why we describe this case

Notwithstanding the high prevalence of Restless Legs Syndrome (RLS) in Multiple Sclerosis (MS), the present case report is interesting for a very late onset of MS and the association with a RLS preceding the clinical diagnosis of the demyelinating disease

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Disclosure
Authors declare they have no conflict of interests related to the issues discussed in this paper

Five essential criteria for the diagnosis of Restless Legs Syndrome [1]: all must be met

1. *An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs*
2. *The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting*
3. *The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues*
4. *The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during day*
5. *The occurrence of the above features are not solely accounted for as symptoms primary to another medical or behavioural conditions (e.g. myalgia, venous stasis, leg oedema, arthritis, legs cramp, positional discomfort, habitual foot tapping)*

leading to diagnosis of Restless Legs Syndrome (RLS).

As walking difficulties increased over time, a cranial magnetic resonance (MRI) was performed on 2007. The examination showed multiple white matter lesions whose morphology and localisation were strongly suggestive for a demyelinating disease and inconsistent with vascular lesions or other disorders. An ophthalmological examination detected an atrophy of left eye fund, likely related to a demyelinating disease.

The neurological examination showed an ataxia with muscular spasticity, especially

Clinical Presentation	Additional data
2 attacks; objective clinical evidence of 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	
2 attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: • 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or • Await a further clinical attack implicating a different CNS site
1 attack; objective clinical evidence of 2 lesions	Dissemination in time, demonstrated by: • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or • Await a second clinical attack
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated for DIS by: • 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or • Await a second clinical attack implicating a different CNS site For DIT by: • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or • Await a second clinical attack
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 out of 3 of the following criteria: • Evidence for DIS in the brain based on 1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions; • Evidence for DIS in the spinal cord based on 2 T2 lesions in the cord; • Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Table I. *Diagnostic criteria for Multiple Sclerosis. Modified from [2]*

CNS: Central Nervous System; CSF: Cerebrospinal Fluid; DIS: Dissemination In Space; DIT: Dissemination In Time; IgG: Immunoglobulin G; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; PPMS: Primary Progressive Multiple Sclerosis

on the right side, horizontally and vertically limitation of eyes movements and a pathological plantar-cutaneous reflex on the right foot. Therefore, she was admitted to the hospital, where the following examinations were performed:

- Doppler ultrasound of cerebro-afferent vessels and transcranial vessels doppler: no abnormal findings were detected;
- Visual Evoked Potentials (VEPs): bilateral reduction of amplitude was observed;
- Spinal Evoked Potential of lower limbs (SEPs): abnormal conduction of central motor time was found bilaterally;
- Trigeminal-facial reflex: there was the finding of disorder of the pons on the left side and of the bulb bilaterally;
- Lumbar puncture and spinal fluid examination: there was evidence of 11 oligoclonal bands;
- Cranial MRI: no new intracranial lesions were detected as compared with the previous imaging nor gadolinium enhancement.

The findings allowed a diagnosis of Multiple Sclerosis (MS) (Table I).

A high dose intravenous corticosteroid therapy was performed and paresthesias gradually decreased. Due to her age, a disease modifying therapy for MS was not initiated.

Although the diagnosis of MS was made in 2007, the symptoms were in place earlier, at least when she was 72, but were likely attributed to the RLS. The evidence of an optic atrophy in the left eye at the ophthalmologic assessment at the time of MS diagnosis supports this assumption. Thereby, the diagnosis of a MS was established at the patient's age of 77, but the disease probably initiated years before.

A symptomatic drug treatment was prescribed with pregabalin and zolpidem, although with a low level of patient's compliance.

Since then, the patient continues to perform periodical clinical controls and periodical MRI examinations, so far showing stabilisation of MS lesion burden.

Notwithstanding, the patient complains of progressive increase of gait difficulties and paresthesias on left side of the body.

DISCUSSION

Multiple Sclerosis with onset after 50 years of age is usually described as LOMS, i.e. Late Onset Multiple Sclerosis. Although uncommon, with a prevalence calculated between 4% and 9.6%, this form of MS is usually more aggressive than the juvenile form named YOMS, i.e. Young Onset Multiple Sclerosis. In fact, the time to secondary progression of LOMS is quite shorter and the primary progressive course is more commonly observed in elderly patients.

Main questions a doctor should ask himself in this situation

- *Notwithstanding the patient's age, are neurological symptoms compatible with a demyelinating disease?*
- *Are MRI features really suggestive for a demyelinating disorder?*
- *Are patient's clinical disturbances the real onset of MS or some previous symptoms were neglected?*
- *What therapeutic strategy the late onset MS deserves?*
- *Which level of therapeutic adherence we must expect from the patient?*

At its onset, clinical symptoms usually involve motor (90% vs. 67% of juvenile form) and cerebellar system. No differences are detected between LOMS and YOMS cases for sensory disturbances, ataxia, ocular movements alterations, cognitive symptoms, and fatigue [3,4]. A typical LOMS MRI shows supratentorial and infratentorial lesions, but more frequently spinal cord lesions are detectable. Even though MRI has high sensitivity, specificity is limited because of concomitant presence of age-related microangiopathy in these patients, which limits a precise diagnosis.

de Seze et al. conducted a clinical study in LOMS patients evaluating sensitivity and specificity of Barkhof MRI criteria for MS [5]. Study results showed that in this group of patients Barkhof criteria are less specific. Moreover, gadolinium-enhancing lesions are not frequently detected, likely due to a predominance of a degenerative process instead of inflammation. The Authors suggest to perform a spinal fluid examination and VEPs in LOMS patients, to add specificity to MRI. In fact, oligoclonal bands are present in LOMS in the same percentage of YOMS patients.

A relevant issue emerging from clinical studies is a usually delayed diagnosis in LOMS patients. A differential diagnosis should be always investigated. Common differential diagnoses include:

- Cerebral or spinal vascular syndromes;
- Hypertension-related disorders;
- Compressive myelopathies;
- Primary or secondary vasculitis;

- Metabolic diseases;
- Degenerative syndromes;
- Nutritional deficiencies;
- Chronic infections (i.e. syphilis, Lyme disease, HTLV-1, HIV);
- Paraneoplastic syndromes [6].

Another interesting feature of this case, yet described in the literature, is the comorbidity with Restless Legs Syndrome (RLS). RLS is defined as involuntary movement disorders of legs, with unpleasant sensitivity, starting or worsening during the sleep. Disturbances improve with movement [1]. The RLS pathophysiology is probably related to a dopaminergic system dysfunction, as current evidence suggests. In 2008, a multicenter study [7] showed a higher RLS prevalence in MS patients as compared with healthy controls. In addition, comorbid RLS seems to be more frequent in the elderly subjects, in patients with a long history of

Key points

- *The onset of MS in elderly subjects is unusual and is described as LOMS (Late Onset Multiple Sclerosis) when the onset takes place after the age of 50*
- *LOMS has some typical clinical and neuroradiological features:*
  - *Prevalence of motor and cerebellar symptoms;*
  - *Low frequency of gadolinium-enhancing lesions.*
- *MRI typical features are more frequently represented by multiple degenerative lesions than inflammatory areas*
- *In these Late Onset MS patients the differential diagnosis with other diseases of the white matter is essential, i.e. vascular, infective, paraneoplastic, metabolic disorders or nutritional deficiencies, which could delay the correct diagnosis*
- *The association between Multiple Sclerosis and Restless Legs Syndrome is sometimes observed, and has been already reported, especially in old patients*

THERAPEUTIC ALGORITHM IN MULTIPLE SCLEROSIS

<table>
<tr><th colspan="4">Clinically Isolated Syndrome (CIS)</th></tr>
<tr><td colspan="2">Attending strategy
Clinical and neuroradiological follow-up</td><td colspan="2">First line therapy
Immunomodulatory drugs:
• IFNβ1a
• IFNβ1b
• Copolymer</td></tr>
<tr><th colspan="4">Clinically Definite Multiple Sclerosis (CDMS)</th></tr>
<tr><td colspan="4">• Relapsing Remitting
• Secondary Progressive
• Primary Progressive</td></tr>
<tr><th>Escalating therapy</th><th>Induction therapy</th><th>Immunomodulatory therapy</th><th>Immunosuppressive therapy</th></tr>
<tr><td>First line therapy
Immunomodulatory drugs:
• IFNβ1a
• IFNβ1b
• Copolymer

Second line therapy
Immunosuppressive drugs:
• Natalizumab
• Fingolimod
• Mithoxantrone
• Others (azathioprine, cyclophosphamide)

Third line therapy
Autologous stem cells transplantation</td><td>Immunosuppressive drugs:
• Mitoxantrone
• Natalizumab
• Cyclophosphamide

Maintenance therapy:
Immunomodulatory drugs</td><td>IFNβ1b</td><td>Mitoxantrone</td></tr>
</table>

MS, with relevant disability and an involvement of pyramidal and sensory systems rated by the Expanded Disability Status Scale (EDSS score). Another hypothesis emerging from the same study is the existence of a secondary form of RLS, due to MS itself. This hypothesis is supported by some evidence, as the association with a major level of disability implies a more aggressive course of MS. The onset of RLS usually follows the MS diagnosis (about 5 years later) and symptoms are usually asymmetric. However, in a small subgroup of patients, RLS can come prior to MS diagnosis.

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