Multiple Sclerosis and Related Disorders 37 (2020) 101373

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Editorial

Progressive Multifocal Myelopathy or Multiple Sclerosis?

Spinal cord syndrome is a common feature of progressive Multiple Sclerosis (MS), and most patients presenting with chronic progressive myelopathy turn out to have a spinal form of MS. The clinically definite diagnosis cannot be, however, performed until the spatial dissemination of lesions is demonstrated. (Thompson et al., 2018) The McDonald criteria for the diagnosis of MS in disease with progression from onset require, in addition to one-year clinical worsening, at least two of the three following findings: one or more T2 brain lesions in characteristic area for MS, two or more T2 spinal cord lesions, presence of CSF-specific oligoclonal bands. (Thompson et al., 2018) Previously, we reported on patients affected by chronic progressive spinal cord dysfunction related to solitary spinal lesion. (Lattanzi et al., 2014) Here, we describe three patients with a progressive myelopathy in the presence of multiple demyelinating lesions of the spinal cord not accompanied by any involvement of other CNS sites.

We identified the patients admitted to the Neurological Clinic of the Ospedali Riuniti of Ancona between January 2003 and December 2008 and followed up for at least 5 years, who met the following criteria: signs and symptoms of spinal cord dysfunction, sub-acute or insidious onset, chronic progressive course, focal T2 hyperintense, non-longitudinally extensive, lesions of the spinal cord in absence of definite lesions or history of relapses affecting other CNS locations. Exclusion criteria were infectious or para-infectious, paraneoplastic, primary or metastatic neoplastic, toxic-nutritional, inherited or compressive myelopathy, connective tissue diseases, sarcoidosis, primary or secondary CNS vasculitis, history of spinal cord irradiation. All patients provided written informed consent according to the Declaration of Helsinki.

Three patients, two females and one male, were identified (Table 1). The clinical presentation was characterized by progressive motor deficits and sensory disturbances with impairment of spinothalamic and/or posterior column modalities; all patients had neurogenic bladder dysfunction. In all patients, CSF analysis did not detect elevations in oligoclonal bands or IgG index. Cell-based assays for neuro-myelitis optica (NMO) antibodies were negative, and infectious, immunological and metabolic workup were uniformly unremarkable. Visual evoked potentials, electromyography, and instrumental exams were consistently normal. Details of performed investigations have been reported elsewhere. (Lattanzi et al., 2014) MRI revealed circumscribed, T2 hyperintense lesions, non-longitudinally extensive, in the absence of Gadolinium enhancement or swelling, at level of cervico-medullary junction, cervical and thoracic spinal cord (Fig. 1). Slowly progression of the neurological impairment was observed despite treatment. None of the patients presented symptoms suggestive for relapse or involvement of other CNS sites/locations. During the follow-up, MRI scans of the CNS did not reveal new lesions nor Gadolinium enhancement in two patients. In one case (patient n. 3), a new, non-contrast enhancing, lesion was detected at cervical (C6) cord after two years from onset.

Non-infectious idiopathic inflammatory demyelinating disorders of CNS are monophasic, multiphasic and progressive diseases, with proved or presumed autoimmune pathogenesis, which variably involve in localized, multifocal or diffuse form the brain and spinal cord. They represent a heterogeneous spectrum of diseases with specific characterization but also with considerable overlaps and grey areas. (Lattanzi et al., 2014; Cañellas et al., 2007)

The characteristics of the lesions in the reported cases resemble MS plaques, and clinical phenotype closely remembers primary progressive MS; nonetheless, the lack of characteristic brain involvement and CSF markers did not allow MS diagnosis. (Thompson et al., 2018) Although patients may develop new lesions satisfying the McDonald criteria, the long follow-up suggests that this evolution would be unlikely. The progressive myelopathy, the lack of optic involvement and the characteristics of the lesions, which were not only small but also marginally located rather than longitudinally extensive and centrally located, play against a diagnosis within the NMO spectrum disorder. Despite brain MRI and LCR negativity, the progressive course in absence of recurrences ruled out the diagnosis of chronic recurrent transverse myelitis.

Chronic progressive demyelinating myelopathies occurring without any involvement of the CNS at other sites represent a diagnostic challenge. Recently, progressive neurological impairment from an isolated demyelinating lesion within the spinal cord has been described as *solitary sclerosis*: (Schmalstieg et al., 2012) despite the course clinically indistinguishable from progressive forms of MS and the presence of CSF-specific oligoclonal bands, this condition does not satisfy the criteria for MS and has been identified as a high-priority area for further research by the International Panel on Diagnosis of MS.

The cases are suggestive to be sustained by an inflammatory demyelinating condition, but they did not meet the diagnostic criteria of any currently defined nosological entity. Given the incomplete understanding of the pathogenesis of CNS inflammatory demyelinating diseases, current classification and diagnostic criteria still remain incomplete. New variants or alternative entities should be considered in future revisions to include patients with atypical or uncommon presentation. (Thompson et al., 2018) Focused collaborative studies should be prompted to evaluate whether and which patients may mostly benefit from treatment and predict individual outcome. (Lattanzi et al. 2015; 2017a, b)

https://doi.org/10.1016/j.msard.2019.08.015
Received 8 July 2019; Received in revised form 9 August 2019; Accepted 14 August 2019

Table 1
Characteristics of patients.

Patient	Sex	Age at onset, years	Clinical syndrome	MRI lesion number/site	Initial SNRS	Follow-up, years	Last SNSR	Therapy
1	Female	60	Paresis of right limbs, sensory impairment of lower limbs, bladder dysfunction	3/C4-C5 (antero-median), C7-D1 (right postero-median/ paramedian), D12	82	13	76	Steroid; MTX
2	Female	64	Paresis of right upper arm and lower limbs, sensory impairment of lower limbs, bladder dysfunction	4/Cervico-medullary junction (right), C2, C3 (right postero-lateral), C5 (right lateral)	86	9	76	Steroid + MTX
3	Male	47	Paresis of left upper arm and lower limbs, sensory impairment of lower limbs, bladder dysfunction	5/C1 (anterior), C2-C3 and C3-C4 (left lateral and postero-lateral), C4-C5, C6 (right lateral)	82	15	60	Steroid + MTX; AZT

Abbreviations: AZT: azathioprine; MTX: methotrexate; SNRS: Scripps Neurological Rating Scale.

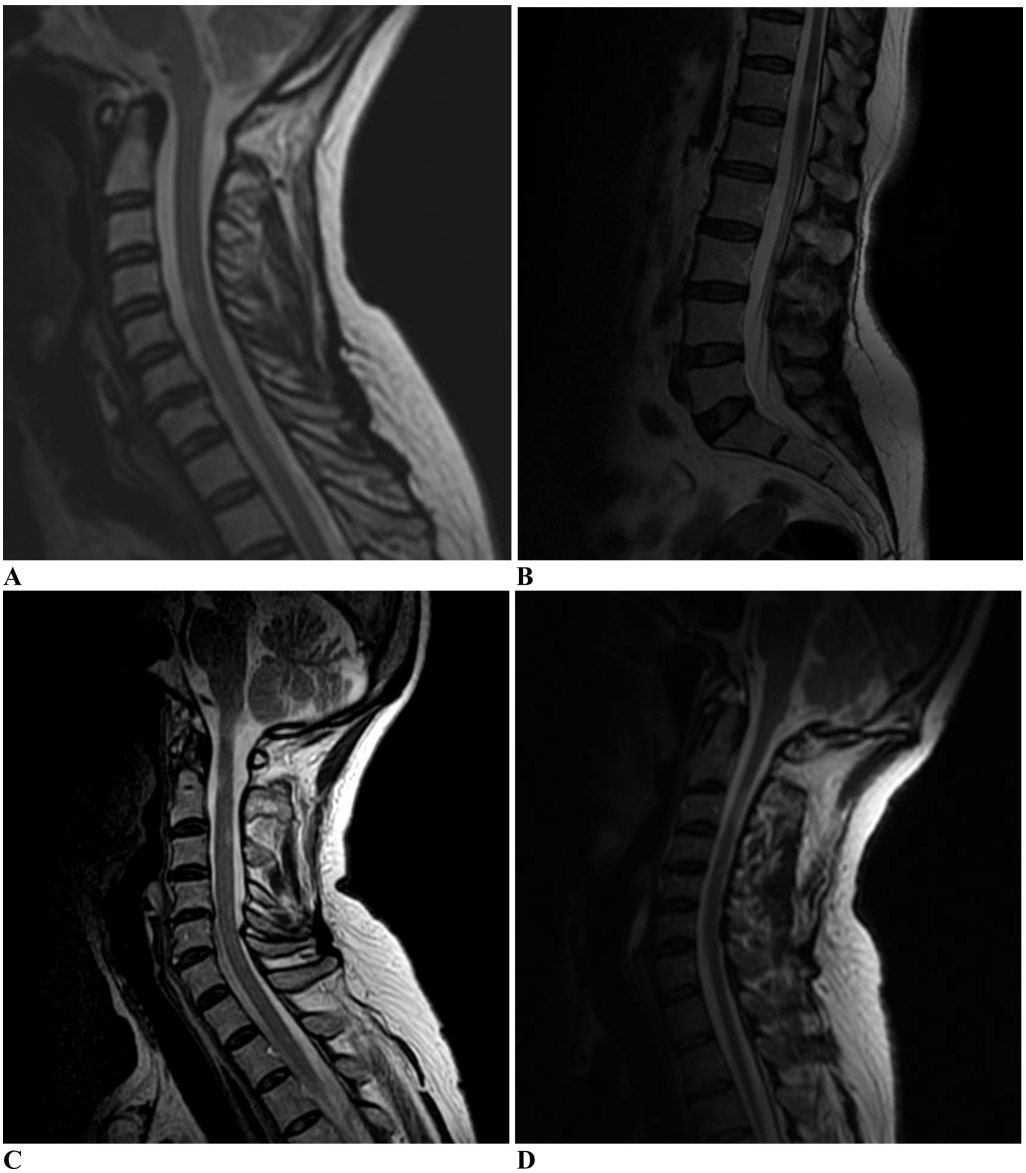

Fig. 1. T2-weighted MRI findings, **A-B** (patient 1): hyperintense lesions of spinal cord at level of C4-C5 (A) and D12 (B). **C** (patient 2): hyperintense lesions at ventral cervico-medullary junction and cervical cord. **D** (patient 3): hypertintense lesions of upper cervical spinal cord.

Study funding

No targeted funding reported.

Declaration of Competing Interest

The authors report no disclosures.

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