Case report

Solitary sclerosis: Progressive neurological deficit from a spatially isolated demyelinating lesion: A further report

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Context: Progressive myelopathy can be a manifestation of a variety of disorders including progressive multiple sclerosis. However it is extremely uncommon for a single lesion to cause a progressive myelopathy in MS. Such a myelopathy, i.e. a progressive neurological deficit from a solitary demyelinating lesion, not fulfilling the International diagnostic criteria for MS or Neuromyelitis Optica was first reported in 2012 and termed 'solitary sclerosis'.

Method: We report 3 further cases of progressive myelopathy fulfilling the diagnostic criteria for solitary sclerosis.

Findings: Two patients had a single demyelinating lesion in the cervical cord and the third patient had it in the brain stem. All patients had serial MRI scans showing no dissemination or progression of lesions. Extensive diagnostic tests including aquaporin 4 antibodies were negative in all. At last follow-up at a median of 3.8 years, all patients continued to clinically progress despite immunosuppressive treatment.

Conclusion/Clinical Relevance: Solitary demyelinating lesions can cause a progressive myelopathy without clinical or radiological evidence of dissemination. Importantly, clinicians, both surgical and medical should be aware of such a diagnosis, to avoid invasive and often harmful tests particularly biopsies.

Keywords: Myelitis, Progressive, Multiple sclerosis, Neuromyelitis optica, Spinal cord tumour, Solitary sclerosis

Introduction

Demyelinating lesions of the central nervous system can be extremely heterogeneous in their clinical presentation.¹ Gradually progressive myelopathies too have clinical courses and causes distinct from acute transverse myelitis.² Progressive myelopathy with MRI evidence of a single intramedullary spinal cord lesion (with normal brain imaging) has an even limited differential diagnosis including but not limited to neoplasms, paraneoplasia, sarcoid, arteriovenous malformations, infections (e.g. HIV, syphilis), Behçet's disease³ or metabolic causes (e.g. deficiency of B12 or copper).

Progressive multiple sclerosis whilst being an extremely common cause of progressive myelopathy rarely presents without additional brain or cord lesions and abnormal cerebrospinal fluid (CSF). In fact current International Panel diagnostic criteria for primary

progressive MS (PPMS) recommends 2 out of 3 of the following for the diagnosis in the presence of progressive myelopathy⁴:

- (1) ≥ 1 T2 brain lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)
- (2) ≥ 2 T2 lesions in the cord
- (3) Positive CSF: isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index.

Recently Schmalsteig *et al.* from the Mayo Clinic⁵ reported 7 cases of a novel clinicoradiological phenotype characterised by progressive neurological deficit—a progressive myelopathy associated with a single lesion in the spinal cord or brain stem and termed it Solitary Sclerosis (SS). Seven further cases have been reported from Italy⁶ and one from France.⁷ Patients did not fulfill international diagnostic criteria for multiple sclerosis (MS)⁸ due to absence of dissemination of lesions in space, nor criteria for Neuromyelitis optica (NMO).⁹ Some patients had oligoclonal bands confined to CSF, suggesting that SS might be a spatially isolated, forme fruste, of MS.

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Here, we describe 3 retrospectively identified (between 2008 and 2013) cases from the Walton Centre, Liverpool, United Kingdom, who fulfilled the criteria for SS⁵:

- (1) MRI evidence of a focal, T2 hyperintense lesion involving the corticospinal tracts in the brainstem or upper cervical spinal cord;
- (2) Progressive motor deficit (duration ≥ 1 year) attributable to the lesion on MRI;
- (3) MRI of the brain and spinal cord that did not fulfil International Panel imaging requirements for dissemination in space;⁴
- (4) No clinical history suggesting relapses affecting other portions of the central nervous system.

Patient 1

A 47-year-old man presented with gait difficulty, progressive heaviness and fatigue in his legs for a few months and urinary urgency in 2010; this was preceded by a 3-year history of brief (usually minutes) transient paraesthesia of all four limbs on neck flexion consistent with Lhermitte's. Examination showed left hemiparesis of Medical Research Council grade 4/5, brisk reflexes and left ankle clonus, reduced vibration and T12 sensory level.

Blood tests including extensive autoantibody testing (particularly antineuronal antibodies and aquaporin-4 antibodies), serum ACE, HIV, VDRL, Lyme disease, viral serology and CSF were normal. MRI Spine showed an intrinsic cord lesion from the lower border of C3 to mid C6 vertebra with edema (Fig. 1A and B). Though there were spondylotic changes at this level, the axial sequences showed only cord swelling but no compression or flattening of the cord. The extent of the swelling and edema was more than that expected by the disc which was thought to be incidental. Neither the radiologists nor spinal surgeons thought that the disc was responsible for the myelopathy. The patient received IV methylprednisolone (IVMP) for 5 days without much benefit. He continued to progress and was treated with multiple courses of oral methylprednisolone. He refused other immunosuppressive therapy. Seven years after onset he uses 2 canes to walk. MRI done 26 months after the first scans (Figs. 1C and D) showed spondylotic changes with reduction in cord signal and swelling.

Patient 2

A 45-year-old woman presented with stiffness and 'jelly-like' feeling in the legs, which progressed over three

Figure 1 (A) Sagittal T2W sequence of the cervical cord with a hyperintense lesion extending from C3 to mid C6 vertebra with cord swelling in patient 1; there is an adjacent disc which is not compressing the cord. (B) Axial section through the disc in patient 1. (C and D) Follow-up sagittal and axial MRI respectively at 26 months in patient 1.

Figure 2 Patient 2- T2 Sagittal MRI showing lesion at cranio-vertebral junction in the anterior two-thirds of upper cervical cord and brain stem.

months to walking difficulty. She also had a corset-like sensation in her trunk and bladder urgency. On examination, she had brisk reflexes, ankle clonus and right extensor plantar. She was given a 5 days of IVMP with transient improvement for a week.

Routine haematological and biochemical tests including B12, folate, serum ACE, ANA, ENA (extractable nuclear antigens), paraneoplastic screen, aquaporin 4 antibodies, Lyme disease, and viral serology were all

Figure 3 Patient 3- T2W axial scan showing lesion on right side of pons.

negative. CSF showed type 3 oligoclonal bands (OCB) and raised CSF IgG index. MRI of the brain and whole spinal cord showed a high signal lesion at the cranio-vertebral junction in the anterior two-thirds of the upper cervical cord and lower brainstem (Fig. 2). Repeat MRI brain and whole spine after 10 months showed no change. Three mitoxantrone infusions (20 mg monthly) did not improve symptoms. Her motor function gradually deteriorated and 32 months after onset she had 3/5 weakness in both lower limbs, and now walks with two canes.

Patient 3

A 48-year-old woman presented with one-month history of episodic left arm and leg weakness and diplopia, each lasting 15–30 minutes. She had bilateral horizontal gaze evoked jerk nystagmus, left hemiparesis (grade 4/5) with brisk reflexes, extensor plantars, dysmetria on the left arm and gait ataxia. She also developed occasional mild oral ulcers (no genital ulcers) more than 5 years later and was reviewed in a specialist Behçet's clinic but was considered to be very unlikely to have Behçet's disease.

Blood tests as in cases 1 and 2 were normal. CSF showed slightly raised protein (0.51 g/l) and IgG index without OCB. Visual evoked responses were normal. MRI of the brain showed an area of increased signal in the right side of the pons (Fig. 3) with an irregular

Table 1 Summary of cases presenting with a progressive neurological deficit from solitary lesion

Patient/ sex/age at onset	Disease course	Duration of progressive neurological (motor) symptoms in years	EDSS at initial visit	EDSS at last follow up	Time from initial assessment to last EDSS in years	MRI lesion location	OCB/IgG Index	VERS	Serum ACE/CSF ACE	Treatment
1/M/44	Progressive gait difficulty, Lhermitte's with left sided weakness which progressed to quadriparesis	7 (7)	4	6.5	3.8	Lower border of C3 to mid C6 vertebrae	Absent/ Normal	NA	Slightly raised/ normal	Steroids
2/F/45	Progressive stiffness and weakness in both legs followed by progressive paraparesis	2.8 (2.8)	2	6	2.2	Cranio-vertebral junction extending into upper cervical cord	Present/ Raised	Normal	Normal/ normal	Steroids Mitoxantrone
3/F/48	Transient left sided weakness followed by progressive left hemiparesis	5.3 (5.3)	3	6.5	4.8	Right side of the pons	Absent/ Raised	Normal	Normal/ normal	Steroids Mitoxantrone

M, male; F, female; NA, not available; MRI, magnetic resonance imaging; EDSS, expanded disability status scale; OCB, oligoclonal bands; VERS, visual evoked responses; CSF, cerebrospinal fluid.

rim of enhancement around the lesion, raising the possibility of an intrinsic tumour or an inflammatory lesion. MR spectroscopy did not yield additional information. A trial of IVMP resulted in resolution of contrast enhancement in 3 weeks without clinical improvement.

Sequential MRI scans at 2 and 7 months showed slight decrease in the size of both the lesion and mass effect, making neoplasia unlikely. Mitoxantrone, 20 mg given monthly for 3 months did not produce any improvement. Her left sided symptoms gradually worsened over the following months and 62 months after onset she has marked left hemiparesis and walks with two 2 crutches; MRI shows atrophy without new lesions.

Discussion

The features of our patients summarised in Table 1 are very similar to those in the Mayo series.⁵ Two out of three patients were female with the age of onset between 44–48 years. Disease course was progressive over a period longer than 12 months in all. The lesions on MRI could be initially mistaken for neoplasm but most likely represent demyelination.

One patient had CSF OCB indicating an intrathecal synthesis. Aquaporin-4 antibodies for NMO, tested by

cell-based assays (the assay with highest sensitivity) at John Radcliffe Hospital, Oxford were negative in all the patients. Though seronegative NMO cases are reported and assay type determines seropositivity to some degree,¹⁰ the clinical phenotype too did not fit with NMO (progressive disease course over several years associated with short solitary lesion and absence of relapses without evidence of optic neuritis). No other alternate diagnoses were identified despite extensive testing and follow up. Only one patient had some transient benefit from steroids. All three patients had worsening of their EDSS over time (Table 1). Our patients did not have clinical or radiological evidence of dissemination in space after a median follow up of 3.8 years and duration of progressive symptoms of 5.3 years. They did not satisfy criteria for diagnosis of PPMS. Patient 3 had positive CSF and oral ulcers and might satisfy the diagnostic criteria for MS or Behçet's disease but did not have evidence of clinical or radiological dissemination in space or time and Behçet's disease felt to be very unlikely by national experts.

We therefore strongly feel these cases represent SS. Although SS is most likely to represent a limited variant of progressive multiple sclerosis, pathological studies on autopsied material are needed.

Conclusion

Solitary demyelinating lesions can produce a progressive myelopathy. SS probably represents an MS variant and should be considered in the differential diagnosis of myelopathies. Clinicians, both surgical and medical should be aware of such a diagnosis. In the right clinical context, this will help to avoid invasive and often harmful tests particularly biopsies for ‘suspected granulomatous disorders or tumours’ and radiotherapy.

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Disclaimer statements

Contributors Conceiving and designing the study: DR and AJ. Collecting the data: DR, LE, AK, CY and AJ. Analysing and interpreting the data: DR, LE, AK, CY, AL and AJ. Writing the article in whole or in part: DR, LE and AJ. Revising the article: LE, AK, CY, AL and AJ. Study supervision: AJ.

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Ethics approval No ethical approval is required.

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