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CASE REPORT

Simultaneous combined central and peripheral demyelination with acute inflammatory demyelinating polyradiculoneuropathy and short segment myelitis

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Abstract

Combined central and peripheral demyelination (CCPD) has been proposed to describe the occurrence of demyelination in both central and peripheral nervous systems. The aetiopathogenesis of combined demyelination is unknown, but the possibility of a shared pathogenic epitope has been suggested. Although it has been described in paediatric patients, reports of simultaneous onset CCPD with short segment myelitis among adults are scarce. We report a case of simultaneous onset monophasic CCPD in an adult who developed both Guillain-Barre syndrome and short segment spinal cord demyelination that responded to immunomodulation with intravenous immunoglobulins and plasmapheresis. The patient also had evidence of chronic thyroiditis which supports an autoimmune aetiopathogenesis of CCPD. Differentiating this diagnosis from multiple sclerosis has therapeutic implications.

KEYWORDS
Demyelination, Guillain-Barre syndrome, myelitis, immunotherapy

INTRODUCTION

Combined central and peripheral demyelination (CCPD) describes demyelination in both central and peripheral nervous systems (PNS). It is a distinct disease rather than co-existence of central and peripheral demyelination. Most CCPD patients respond to immunotherapies, particularly systemic steroids and plasma exchange (PLEX), suggesting an underlying immune-inflammatory mechanism.[1] However, interferon-beta (IFN-β) therapy, used in multiple sclerosis, can at times exacerbate CCPD.[1] Since IFN stimulates antibody production of all subclasses, an autoantibody-mediated mechanism is postulated in the pathogenesis of CCPD. Furthermore, improvement with PLEX and intravenous immunoglobulin (IVIg) favours an antibody-mediated immunepathology. Literature on adult simultaneous onset CCPD with short segment myelitis is scarce and to the best of our knowledge, this is the first case reported from Sri Lanka.

CASE REPORT

A 52-year-old woman presented with four days of back pain and difficulty walking. She had difficulty climbing stairs. There was no recent infection. Examination revealed pallor and a diffuse goitre. Muscle power in the upper limbs were 3/5 proximally and 4/5 distally; and in the lower limbs, were 0/5 proximally and 1/5 distally. Reflexes were absent globally. Plantar responses were flexor. She had a T4 sensory level with sacral sparing. Intravenous methylprednisolone was initiated for presumptive myelitis.

On day 5 of the illness, she developed urine retention requiring catheterization. On day 6, a left lower motor facial nerve palsy was noted, progressing to facial diplegia. The patient progressed to respiratory failure requiring mechanical ventilation. On repeat examination, extensor plantar reflexes were noted with absent joint position sense.

Cerebrospinal fluid (CSF) analysis showed a protein of 60 g/l (20-40g/l), with 10/mm^3 (0-5/mm^3) lymphocytes. CSF and serum did not reveal monoclonal bands. Magnetic resonance imaging (MRI) of the brain was normal, MRI spine showed an intramedullary lesion at C5-C6 level without contrast enhancement (Figure 1). Nerve conduction studies showed features of focal segmental demyelinating motor and sensory polyneuropathy. Presence of uneven conduction slowing, temporal dispersion in compound muscle action potentials and conduction blocks favoured an acquired cause.

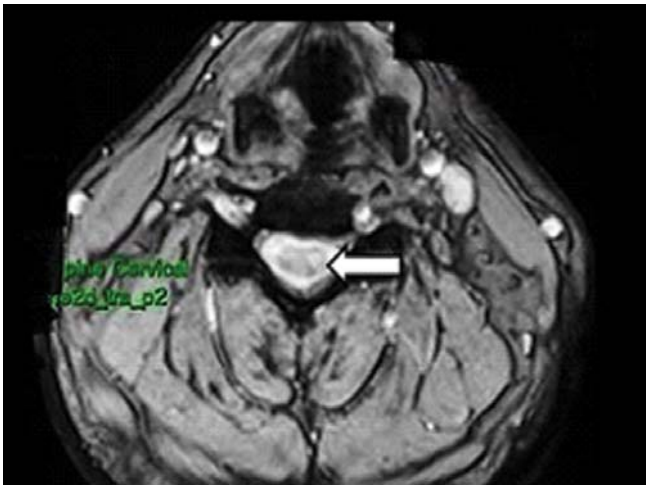

FIGURE 1 T2 weighted MRI axial image of the spine showing an intramedullary lesion within the cervical cord (arrow).

Hematological analysis revealed normochromic normocytic anaemia (haemoglobin – 8.2 g/dL) and normal white cells and platelet counts. Liver and renal profiles were normal. Thyroid stimulating hormone (TSH) was high: 12.2 ug/dl (4.6-12) with a free T4 of 0.9 ng/dl (0.7-1.9). Thyroid ultrasonography showed features of chronic thyroiditis. Thyroid receptor antibodies and anti-thyroid peroxidase antibodies were negative. Fine needle aspiration cytology was reported as a benign smear with follicular nodules (class-Thy2 – features consistent with nodular goitre or thyroiditis). Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies (cANCA, pANCA), Hepatitis B and C serology, human immunodeficiency virus (HIV) screening, and venereal disease research laboratory (VDRL) tests were negative. Cytomegalovirus IgM antibodies was negative. Mycoplasma antibodies (IgM and IgG) were positive with a titre of 1:60 (IgG) without subsequent rise.

Concurrent myelitis and Guillain-Barre syndrome (GBS) were diagnosed on clinical, radiological and neurophysiological evidence. The patient was treated with intravenous methyl-prednisolone 1g/day for 3 days, but did not improve. Subsequently, she was treated with IVIg followed by five cycles of PLEX. By the second week of treatment, she was weaned off artificial ventilation. She regained 5/5 upper limb power, four weeks after immunomodulatory treatment. After five weeks, lower limb power returned to 5/5 with bilateral flexor plantar responses, normal deep tendon reflexes and normal sensory examination. Repeat MRI after five weeks of treatment was normal. The patient went home with a tapering dose of prednisolone. She was asymptomatic at 3-months follow-up.

DISCUSSION

Combined central and peripheral demyelination (CCPD) is predominantly reported in children.[2] In the largest case series involving 40 patients with CCPD, two subtypes, depending on whether symptoms in the central nervous system (CNS) and peripheral nervous system (PNS) appeared simultaneously (within 2 months of one another – simultaneous-onset group) or at different times of disease progression (>2 months – temporally separated-onset group), has been proposed.[3] Simultaneous-onset disease is associated with severe deficits, respiratory failure, and more extensive cerebral and spinal cord lesions. Isolated short segment spinal cord lesions are not observed in the simultaneous-onset group.[3] The temporally separated-onset disease exhibits a more indolent course and is usually associated with optic nerve involvement.[3] This subtype can have a monophasic, relapsing and remitting or a chronic progressive course. The monophasic course is observed more often in the simultaneous onset subtype. Our patient had early bladder involvement, a sensory level with extensor plantar responses and disproportionate lower limb involvement coupled with imaging abnormalities in the cervical cord suggestive of central demyelination. Although the sensory level was keeping with a thoracic cord lesion, this was thought to be a false localizing sign of a cervical cord lesion which has been described previously.[4] The pathophysiology of this phenomenon is poorly understood. Simultaneously, she developed lower motor facial diplegia, upper and lower limb weakness with prominent proximal weakness and global areflexia with demonstrable electrophysiological evidence of peripheral demyelination. Reduced motor nerve conduction velocities, motor conduction blocks and abnormal temporal dispersion with prolonged distal motor latencies, combined with its acute progression was consistent with an acute inflammatory demyelinating polyradiculoneuropathy (AIDP). Thus, she fulfilled criteria described by Ogata et al. for simultaneous onset monophasic CCPD with severe motor impairment and respiratory failure.[3] Although rare, several case reports have described features of AIDP as evidence of PNS demyelination in CCPD (Table 1). In contrast to classical simultaneous CCPD in which longitudinally

extensive myelitis is observed, our patient had short segment spinal cord demyelination. Furthermore, none of the patients in the previously described simultaneous-onset group had PNS involvement and isolated spinal cord involvement, without concurrent cerebral involvement, unlike that seen in our patient.[3]

TABLE 1 Summary of presentation and clinical response to management of CCPD in adults

Study	Diagnosis and time of follow up	Clinical response to treatment	MRI findings
Cohort study **Ogata *et al.*[2]** **N=40**	Simultaneous or temporarily separated CCPD, 4 years.	Clinical improvement (%) IVMP - 88.3% Oral steroids - 75% IVIg - 66.7% PLEX - 87.5% IFN-β -10% (Hughes functional scale scores were significantly lower after immunotherapies compared with pretreatment scores: more prominent in the simultaneous onset group than in the temporarily separated onset group)	Cerebral lesions (75%) ≤3 lesions - 20% 4-8 lesions - 43.3% ≥9 lesions - 36.7% Gd-enhancement -18% Lesions > 3 cm - 25% Cerebellar lesions (15%) Gd-enhancement - 5% Brainstem lesions (32.5%) Gd-enhancement - 7.5% Optic nerve lesions (18%) Gd-enhancement - 2.5% Spinal cord lesions (75%) LESCL - 7.5% Gd-enhancement - 28%
Case Report **Kinoshita A *et al.*[6]**	Simultaneous onset combined acute disseminated encephalo-myelopathy and demyelinating polyradiculoneuritis, 12 days.	Not responded to steroids. Responded to IVIg and PLEX.	T2 weighted MRI of the brain showed extensive multifocal high intensity lesions in the cerebral white matter, with Gd enhancement in the corpus callosum and left internal capsule.
Case Series **Yuceyar *et al.*[7]** **N=4**	Multiple sclerosis and peripheral segmental demyelinating neuropathy.	Satisfactory clinical and radiological responses to high dose IVMP.	75% fulfilled 2010 McDonald criteria for multiple sclerosis for dissemination in space. Specific location of lesions – not reported.
Case Report **Joshi *et al.*[8]**	Simultaneous onset acute, demyelinating type of sensory-motor peripheral neuropathy and transverse myelitis, 2 years, one relapse.	Marked improvement with steroids.	T2 weighted patchy hyper intensities in the cervical cord.
Case Report **Bezerra *et al.*[9]**	Temporarily separated acute demyelinating polyneuropathy and MRI evidence of multiple subcortical and periventricular white matter lesions, 2 years, two relapses.	Immediate improvement with IVIg, 0.4 g/kg/day and oral prednisolone 1 mg/kg/day.	Multiple subcortical and periventricular white matter lesions, hyperintense in T2 weighted images and hypointense in T1, with Gd enhancement. Cervical spinal cord non-enhancing intramedullary signal changes similar to the cerebral lesions.

(Continued)

Study	Diagnosis and time of follow up	Clinical response to treatment	MRI findings
Case Series Zéphir *et al.*[10] N=5	Temporarily separated multiple sclerosis and demyelinating peripheral neuropathy, 1 year, two relapses.	An improvement in clinical status and neurophysiological parameters in three patients after treatment with either IVIg or cyclophosphamide.	Barkhof's criteria on MRI and the McDonald criteria for MS met - 100% Brain lesions - 100% Spinal cord lesions - 60%
Case Report Katchanov *et al.*[11]	Simultaneous onset combination of acute disseminated encephalomyelopathy and demyelinating polyradiculoneuritis, 1 year, no relapses.	Not responded to steroids. Responded to IVIg and PLEX.	Multiple dot-like cortical and subcortical lesions were delineated, predominantly located in the frontoparietal gray and white matter.
Case Report Baheerathan *et al.*[12]	Simultaneous onset bilateral optic neuritis and GBS secondary to *Mycoplasma pneumoniae* infection, 8 months, no relapses. .	Complete recovery following IVMP and PLEX	Enlargement of both optic nerves with Gd enhancement.
Case Report Pfausler *et al.*[13]	Simultaneous onset bilateral optic neuritis and GBS secondary to *Mycoplasma pneumoniae* infection, 1 month, no relapses.	Partial recovery following IVMP and PLEX. Recovery of mobility with minor residual sensory disturbances. Complete recovery of visual acuity of the left eye, grossly impaired vision on the right.	Normal imaging.
Case Report Nadkarni and Lisak.[14]	Simultaneous onset bilateral optic neuritis, acute disseminated encephalomyelitis and GBS secondary to *Mycoplasma pneumoniae* infection, several months, no relapses.	Partial recovery following IVMP and PLEX. Poorly sighted – able only to discern shapes and identify faces. Near normal mobility and activities of daily living.	Cerebral white matter lesions – multiple T2 and proton density-intense lesions that enhanced with Gd.
Case Report Henderson *et al.*[15]	Simultaneous onset bilateral optic neuritis and GBS secondary to *Mycoplasma pneumoniae* infection, 25 days, no relapses.	Partial recovery following IVMP and IVIg. Visual acuity 6/9 in left eye and 6/12 in right. Mild upper and lower limb weakness.	Normal MRI brain and spine.
Case Report Ginestal *et al.*[16]	Simultaneous onset bilateral optic neuritis, myelitis and GBS secondary to *Mycoplasma pneumoniae* infection, 44 days, no relapses.	Partial recovery following IVMP and IVIg. Bilateral visual acuity of 20/30. 4/5 quadriparesis and able to walk unaided.	Normal imaging.

Gd – gadolinium, LESCL – longitudinally extensive spinal cord lesions, IVMP – intravenous methylprednisolone, MS – multiple sclerosis, IVIg – intravenous immunoglobulin, PLEX – plasma exchange sclerosis

The aetiopathogenesis of CCPD remains unknown, but the possibility of a shared pathogenic CNS and PNS epitope has been suggested.[5] It has been proposed that antigenic cross-reactivity with myelin proteins and other antigens may elicit similar immune responses, thereby producing demyelination in immunologically susceptible individuals. Several studies identified anti-ganglioside antibodies (anti-GM1 IgG) and neurofascin antibodies in patients with CCPD and hypothesized that central and peripheral demyelination may have a common pathophysiology.[5] Moreover, identifying such antibodies is important, especially in patients with neurofascin antibodies as they respond well to IVIg or PLEX.[5]

CCPD has been reported to be associated with autoimmune thyroid disease with high titres of thyroid antibodies.[17] It is reported that patients with Hashimoto thyroiditis can have anti-GM1 antibodies. Our patient demonstrated chronic thyroiditis on sonography though autoimmune antibodies were negative. We postulate that our patient was predisposed to CCPD due to sero-negative Hashimoto thyroiditis. However, GM1 antibodies were unavailable to test.

CCPD with long-segment myelitis has been reported to show a greater response to high dose steroids than CCPD with short segment myelitis.[3] Additional IVIg and PLEX are required in CCPD patients with inadequate response to high dose steroids. Since CCPD can worsen with IFN-β, it is important to differentiate it from multiple sclerosis.

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