Combined Central and Peripheral Demyelination

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Abstract
Demyelinating disorders are very common, but remains isolated to the part of nervous system they involve. However, infrequently, combined involvement of central and peripheral nervous system with demyelinating process have been described. We report one such rare case, with possible theories of common etiological basis. We present a middle aged male patient with Chronic Inflammatory Demyelinating Polyneuropathy(CIDP), who responded to immunomodulation. Subsequently, he developed Acute Transverse Myelitis (ATM). Recently a common substrate protein, NF186 has been described as responsible for this rare clinical entity.

Introduction
Demyelinating disorders are very common, but remains isolated to the part of nervous system they involve. However, infrequently, combined involvement of central and peripheral nervous system with demyelinating process have been described.

Case
A 45 years old farmer was presented with history of gradually progressive paresthesia, involving all four limbs, over last 4 months. He also complained of difficulty in walking with history of frequent falls. He had problems combing the hair and also difficulty breaking the chapatti. He denied any visual, bulbar, bowel or bladder symptoms. On examination, he had power MRC grade 4/5 in all group of muscles of both upper and lower limbs. Deep reflexes were sluggish in upper limb and absent in lower limbs. Cognition, cranial nerve and sensory examination did not reveal any abnormality. Nerve conduction study showed evidence of generalized, asymmetrical, demyelinating type of sensory-motor peripheral neuropathy. There was high protein, normal sugar and normal cellular count on cerebrospinal fluid (CSF) examination.

Patient was explained about the diagnosis of CIDP and the need for immunomodulation. With steroids (high dose pulse methylprednisolone followed by oral prednisolone) and regular physiotherapy, he noticed marked improvement and after 4 months, he reported ability to walk independently. Gradually with increasing dose of azathioprine and reducing dose of steroids, he had stable neurological course of almost a year.

After 15 months, he was readmitted, with chief complains of fever and cough. He had leucopenia and pneumoslide panel confirmed legionella infection. Immunosuppressants were stopped. Antibiotics given for 14 days helped him to recover from lower respiratory tract infection.

Only after 3 months of infection, he presented again with sudden onset paraparesis and urinary retention. He also complained of numbness below chest region. He required support of two persons to stand or walk. Examination findings confirmed spastic paraparesis (MRC 3-/5), with D4 sensory level, hyporeflexia and extensor planter. MRI Dorsal spine confirmed patchy, long segment T2 hyperintense lesion (Figure 1). CSF
showed mild increase in protein with normal glucose and cell count. Short course of IV methylprednisolone was given and azathioprine was restarted with counseling.

Patient was on regular immunosuppressive therapy with close monitoring of blood count and liver functions, for next 6 months. He required minimum support for walking with residual urinary symptoms.

Discussion

Generally, inflammatory demyelinating diseases of nervous system selectively affect either brain and spinal cord or peripheral nerves. Here, we report a case of sequential, combined central and peripheral demyelination in the same patient, which contribute to clinical syndrome independently.

Though similar case reports have been noted in literature, the rare occurrence of this type of combined demyelination raises question about occam’s razor. In 1968, Gamstorp and Blennow used the descriptive diagnosis of “encephalo-myelo-radiculoneuropathy” to delineate pediatric cases of Guillaine-Barre syndrome, with presumed CNS involvement. Mendell JR et al in 1987 has also shown asymptomatic MRI lesions in CIDP patients, and questioned about the coincidence.\(^1\)

Kawamura et al described a large group of similar patients, of “combined central and peripheral demyelination” (CCPD).\(^2\) The clinical features of these patients were nonspecific and were indistinguishable from more common diseases. Central and peripheral involvement may occur either simultaneously or sequentially. Clinical presentation, course, CSF and electro-diagnostic findings of peripheral demyelination in CCPD were same and identical as in CIDP. Central involvement is mostly typical for multiple sclerosis, fulfilling McDonald’s criteria. Periventricular white matter and multifocal spinal cord lesions with gadolinium enhancement can develop. CSF oligoclonal bands are negative in most cases, while CSF protein levels show variable degrees of increase. Interestingly, it was noted that response to corticosteroids was variable, while immunoglobulin and plasmapheresis are beneficial for both CNS and PNS lesions.

Recently, Ogata et al described a nation-wide (Japan) survey of 40 patients of CCPD and found distinctive clinical differences between simultaneous and temporarily separated onset of CNS and PNS involvement. They noted that CCPD patients with simultaneous central and peripheral involvement exhibited greater disability, but less recurrence and more frequent extensive cerebral and spinal cord MRI lesions, as compared to temporally separated CCPD patients. Optic nerve affection in temporally separated CCPD patients was more common.\(^6\)

Few other case reports are available in literature, with different presumed etiologies, like inherited predisposition, NMO spectrum and infections.\(^3\) Earlier, experimental Lewis rat model showed elevated titers of antibodies against CNS myelin basic protein induced by peripheral nerve protein P1.\(^4\) Connexin29 is one such protein that is found to be uniquely distributed in intermodal and juxta-paranodal of small myelin sheaths in CNS and large myelinated fibers in PNS, as common substrate for antibody mediated damage.\(^5\)

Neurofascins are also one such transmembrane adhesion molecules, present at the nodes and paranodes of both the CNS and PNS. It is well documented that NF186 is an axonal membrane protein, ubiquitously present at high concentrations at the node of Ranvier; while NF155 is expressed by glial cells at the paranodes.\(^6\) Kawamura group found that autoantibodies against this type of protein were present in patients with CIDP more commonly as compared to MS and CIDP patients. They propose that immune reaction attacks axoglial integrity at the paranodes and nodes, but not compacted myelin, resulting in inflammatory demyelination in both the CNS and PNS.\(^7\) Ogata et al found 5 patients positive for antineurofascin 155 antibodies, out of 11 CCPD patients tested (45.5 %).\(^8\)

Because of unavailability of testing of autoantibodies to NF, for commercial use in India, we wished but could not do the test. Our patient did respond well to steroid and azathioprine initially and later to plasmapheresis during CNS relapse, but it is early to recommend definite management with such small number of patients and no RCT.

Conclusion

Sequential, combined central and peripheral demyelination in the same patient and more studies are required in such cases to formulate diagnostic and management guidelines.

References