A Rare Combination of Amyotrophic Lateral Sclerosis and Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Abstract

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Amyotrophic Lateral Sclerosis (ALS) are two separate disease entities with differing clinical and electrodagnostic features. We report the case of a 56-year-old female who was referred to us with a confusing clinical and electrodagnostic picture of CIDP vs ALS. In spite of immunosuppressive treatments, her condition rapidly turned fatal favoring ALS. Autopsy confirmed coexisting features of CIDP and ALS. Combination of CIDP and ALS are very rare and creates diagnostic dilemma for providers and uncertainty and fear for patients. The etiology of this condition remains unknown. Further studies are necessary to elucidate the underlying neuro-inflammatory process.

Keywords: CIDP; ALS; Combination of CIDP and ALS; ALS Pathology; CIDP Pathology

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired chronic progressive demyelinating disease with symmetric proximal and distal weakness with or without cranial nerve involvement and reduced or absent reflexes. Atypical variants may have predominant distal involvement, asymmetric or focal presentations and pure motor, or pure sensory involvement. Clinical findings of diminished to absent reflexes, albuminocytologic dissociation in CSF, and electrophysiological findings of delayed conduction velocity, conduction block and temporal dispersion all points to a diagnosis of CIDP. Further confirmation to the diagnosis comes from a good response to immune-modulatory agents or a nerve biopsy showing unequivocal evidence of demyelination and/or re-myelination. On the other hand, amyotrophic lateral sclerosis (ALS) involves degeneration of anterior horn cells characterized by lower and upper motor neuron involvement in bulbar, cervical, thoracic or lumbosacral regions with bulbar or peripheral weakness usually asymmetric in onset with minimal or no sensory symptoms and varying degrees of

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progression with almost always a fatal outcome. Electro diagnostic features of active denervation with reduced recruitment, fibrillations and large motor units are seen on needle examination with minimum (<10% reduction in conduction velocity) or no nerve conduction abnormalities. The following case report depicts a patient with mixed findings of ALS and CIDP.

2. Case Report

A 59-year-old female was referred to us by a neurologist for a second opinion on a complex electrodiagnostic finding in the setting of progressive sensorimotor symptoms and signs. The patient first noticed a right-sided foot drop four months prior to our encounter. Incidentally, she had gotten a 'flu' shot and had also done 'flea bombing' of her house a day prior to the onset of the symptoms. She progressively felt her legs getting weak and she had difficulty in climbing stairs, getting out of her car and rising up from her chair. Her past medical history was significant for osteoarthritis and treated vitamin D deficiency. She was of Irish and English descend. There was no family history of neuromuscular disease or peripheral neuropathy. She was a non-smoker, rarely drank alcohol and was working as a nurse before being disabled from this illness. Her primary care physician who saw her initially had obtained a magnetic resonance imaging (MRI) of her lumbosacral without contrast (LS) spine, which was unremarkable.

Over the next several weeks, there was further decline with weakness of proximal upper extremities, sensory symptoms in hands and imbalance on walking. She had no radicular symptoms, bowel or bladder complaints and no breathing or swallowing difficulties. She was seen by the referring neurologist at this point and noted bilateral foot drop as well as shoulder girdle weakness. Blood tests for myopathy, myasthenia gravis and inflammatory markers were negative. Nerve conduction studies that he performed showed significant slowing of both motor and sensory conduction velocities in sural, radial, ulnar, tibial and peroneal nerve with mildly prolonged F waves suggestive of a demyelinating neuropathy. On the other hand, the needle electromyography (EMG) study showed diffuse active denervation in three limbs as well as cervical, thoracic and lumbar para-spinal muscles. A CSF study showed normal protein levels. The clinical dilemma of atypical CIDP vs. atypical ALS led to the referral to us.

On our examination her higher functions were normal, cranial nerves were intact with a normal jaw jerk. Neuromuscular examination showed proximal weakness (4/5) in bilateral upper extremities. There was intrinsic hand muscle weakness on the left side without atrophy. She had hip flexion weakness (4/5) and ankle dorsiflexion weakness (4/5) bilaterally. Deep tendon reflexes were diminished (+1) throughout and was absent at the ankles. Plantar responses were equivocal with withdrawal responses. There was sensory loss in the ulnar distribution on left hand with a positive Tinel's in the left cubital tunnel. In lower extremities there was loss to all modalities of sensation from mid-shins down. Finger-to-nose and heel-to-shin test was intact but rapid alternating movements were slow in the feet and the hands. She had a wide-based unsteady gait and a positive Romberg sign. Electro diagnostic studies were repeated by us around 2 months from the prior study which confirmed a combination of reduced motor nerve conduction velocities, prolonged distal motor latencies, reduced compound muscle action potentials (CMAPs) amplitudes and prolonged F wave latencies in peroneal, tibial and ulnar nerves. Needle EMG study again demonstrated generalized active denervation in upper and lower extremities as well as orbicularis oculi.
We admitted the patient to our institution for completion of workup and a trial of intravenous immunoglobulin (IVIG). Repeat CSF study showed normal protein with no cells. Workup for diabetes mellitus, vitamin deficiencies, paraneoplastic antibodies, autoimmune diseases, infectious and inflammatory diseases, hereditary conditions and vasculitis markers were negative. MRI of the brain showed nonspecific white matter changes and MRIs of the cervical and thoracic spine were normal. At discharge she had minimal improvement in her symptoms with IVIG.

A sural nerve biopsy was performed a month after her initial visit, which showed no evidence of inflammation or demyelination but there was a decrement in large axon, and some evidence of limited axonal regeneration. The process seemed indolent as there was no evidence of active axonal degeneration and the biopsy was non-diagnostic. The patient had progressive worsening of her symptoms with difficulty writing, overhead tasks, walking and activities of daily living. There was no response to a second trial of IVIG and a course of intravenous methylprednisolone. A trial of Rituximab infusion was tried to halt the progression of disease but there was no benefit with worsening of her extremity weakness with an inability to stand or transfer and becoming wheelchair bound.

During subsequent follow up evaluations she was noted to have tongue and biceps fasciculations. Deep tendon reflexes, which were previously diminished, were now found to be pathologically brisk with extensor plantar responses. The patient was seen at another tertiary center where the diagnosis of ALS was favored over CIDP this time. She had SOD1 mutation genetic testing, which was negative. Her condition continued to deteriorate and she was enrolled into hospice care. She died of respiratory failure ten months from the onset of her symptoms. An autopsy was performed.

3. Pathology

No significant abnormalities were noted on macroscopic examination of the brain or spinal cord. Microscopic sections revealed extensive axonal loss and degeneration with myelin digestion in both the anterior and posterior nerve roots, more pronounced in the anterior nerve roots (Fig 1a-g). CD3 staining revealed diffuse T-cell infiltration with occasional clusters of lymphocytes in the nerve roots. CD68 staining revealed macrophage/monocyte populations in both the anterior and posterior nerve roots. LFB/PAS (Luxol Fast Blue and Periodic Acid-Schiff) staining highlighted the numerous digestion chambers and demyelination, which was more pronounced in the anterior nerve roots. Cross sections of the lumbar spinal cord sections showed loss of anterior horn cells and extensive background gliosis (Fig 2 a-c). At the level of the medulla, the pyramidal tracts contained diffuse microglial activation and macrophages consistent with Wallerian degeneration of the corticospinal tracts; the same was noted in the cerebral peduncles. There was no such microglial/macrophage predominance elsewhere in the brainstem. Tibial nerve sections were also obtained and revealed axonal spheroids, lymphocyte-macrophage clusters, sub-perineural edema and ongoing myelin breakdown. In light of these findings, as well as the loss of anterior horn cells, axonal loss of anterior spinal nerve roots and microglial activation of the pyramidal tracts, it was concluded that both Amyotrophic Lateral Sclerosis (ALS) and Chronic Demyelinating Inflammatory Polyneuropathy (CIDP) were present.
Fig. 1a. Example Anterior nerve roots. H&E stain. Axonal loss and degeneration with myelin digestion. There is also lymphocytic infiltration.

Fig. 1b. Anterior nerve roots. LFB/PAS Stain. Numerous digestion chambers, significant axonal loss and demyelination present.
Fig. 1c. Anterior nerve roots. CD68 stain. Chronic inflammatory process with macrophage/monocyte cells (stained brown) infiltrating the anterior nerve roots.

Fig. 1d. Posterior nerve roots. CD68 stain. Chronic inflammatory process with clusters of macrophage/monocytic cells (stained brown) infiltrating posterior nerve roots.
Fig. 1e. Anterior nerve roots. CD 3 stain. T-cell infiltration in anterior nerve roots with focal accumulation of T-cells in several areas.

Fig. 1f. Anterior nerve roots. LFB/PAS Stain. Numerous digestion chambers, significant axonal loss and demyelination present.
**Fig 1g.** Posterior nerve roots. CD3 Stain. T-cells are present in the nerve roots (stained brown) consistent with chronic inflammatory process, as seen in the anterior nerve roots.

**Fig. 2a.** Pyramidal tract at level of mid-medulla. CD68 Stain. Microglial activation and macrophage infiltration indicative of Wallerian degeneration of pyramidal tract.
Fig. 2b. LCA stain (20x magnification) of lumbar spinal cord. There is diffuse activation in the anterior horn areas (TDP 43 and LCA stains are both from adjacent sections of the lumbar spinal cord).

Fig. 2c. CD68 stain (10x magnification). Tract specific macrophage and microglial activation highlighted by CD8 staining.

4. Discussion

This case depicts a complex clinical scenario with overlapping feature of two distinct disease processes - CIDP and ALS. This case was a diagnostic challenge with a non-compartmentalized presentation and mixed clinical and electro diagnostic findings. There was symmetric proximal weakness, prominent sensory symptoms and reduced reflexes, which were suggestive of CIDP. The nerve conduction findings showing slowed conduction velocities, prolonged F waves and motor latencies supported this. However, a unilateral onset, evolution of brisk reflexes, normal CSF protein, unrevealing nerve biopsy and a lack of response to multiple immunomodulation therapies were not
typical of CIDP. Later in her course, ALS became a more likely diagnosis based on the needle EMG findings of multi-level active denervation and fasciculations, progressive weakness and brisk reflexes, but the prominent sensory symptoms and slowing of conduction velocities were conflicting. A dual diagnosis was confirmed when pathology findings revealed anterior horn cell degeneration as seen in ALS and peripheral nerve demyelination consistent with CIDP.

A literature search revealed rare case reports of patients with sensory symptoms of CIDP who failed immunosuppressive therapies and then went on to develop ALS (Rajabally & Varanasi, 2013) (Echaniz-Laguna et al., 2006) (A. P. Venizelos, Brown, & Fisher, 2011) (A. Venizelos, Park, & Fisher, 2011) (Ahdab, Creange, Saint-Val, Farhat, & Lefaucheur, 2013; Isaacs et al., 2007). An interesting feature among these case reports have been the stereotypical nature of presentation where patients presented with a focal sensory or motor finding followed by a rapid progression and deterioration of motor function, which was unresponsive to steroids, IVIG or immunosuppressants leading to quadriparesis in months. The underlying etiology of these distinct disease processes have not yet been identified and it is not clear if this is a separate disease entity or an atypical manifestation of ALS or CIDP. Even though clinically or electrodiagnostically sensory findings are minimal in ALS, it has been shown pathologically to consistently affect the dorsal root ganglion leading to axonal loss, demyelination and demyelination (Heads, Pollock, Robertson, Sutherland, & Allpress, 1991). Patients with familial ALS have higher proportion of sensory symptoms in up to 20% cases compared to 5% in sporadic ALS (Li, Alberman, & Swash, 1988). ALS with sensory neuropathy therefore can also be considered to fall within the wide spectrum of multisystem disorders that ALS represents. In addition to this, sensory symptoms from compressive neuropathies arising from muscle weakness in ALS may also contribute.

Our patient had exposure to insecticide and influenza vaccination a day prior to the onset of her symptoms. Whether it had any causal relation to her condition is debatable. CIDP onset two days following influenza vaccination and motor neuron disease from chronic exposure to pyrethroid compounds (active components of flea bombs) has been reported in the past (Li et al., 1988) (Brostoff, Beitverda, & Birns, 2008).

The question remains as to how these two disease processes, CIDP and ALS could have a common link. Theories on inflammation have been put forth citing an initial insult to dorsal root ganglia followed by progressive sensory axonal atrophy, secondary demyelination, re-myelination and finally axonal loss (Heads et al., 1991). We postulate that this patient initially developed an autoimmune CIDP like illness that created significant neuro-inflammation that progressed to destruction of lower motor neurons and then to upper motor neurons. What signaling or underlying physiological process led to this evolution remains unclear. The observations in this case report highlights the importance and need for further understanding of neuro-inflammation in some cases of ALS/motor neuron disease.

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6. Conflict of interest
None
7. References

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