

Amyotrophic lateral sclerosis with laboratory abnormalities of uncertain significance: A brief review

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Abstract

Amyotrophic lateral sclerosis (ALS), the most common form of motor neuron disease, is a progressive and devastating disease involving both lower and upper motor neurons, typically following a relentless progression towards death. Therefore, all efforts must be made by the clinician to exclude alternative and more treatable entities. ALS with laboratory abnormalities of uncertain significance is a subgroup of ALS that occurs in association with laboratory defined abnormalities that are of uncertain significance to the pathogenesis of ALS. The clinical utility of these abnormalities and what they ultimately mean in patients with ALS is discussed here, along with a review of the literature.

Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, fatal degenerative disorder, involving the first and foremost motor neurons of the cerebral cortex, brainstem and spinal cord. It is one of the most common

neurodegenerative disorders of adulthood. Median age of onset is in the sixth decade. The disease affects men more than women (about 1.5-2:1).¹⁻³

The World Federation of Neurology (WFN) Research Group on Motor Neuron Diseases have developed the 1994 "El Escorial" diagnostic criteria⁴ and the revised 2000 criteria,⁵ to assist in identifying and classifying ALS patients for investigational studies.

There are a number of ALS syndromes⁵ that must be recognized, these include:

Sporadic ALS: Most of the cases are sporadic ALS, occurring alone or present incidentally with other preexisting disease processes.

Familial or hereditary ALS: A minority of patients that ALS manifests in one or more generations, associated with different modes of inheritance.

ALS-plus syndromes: ALS presents in association with other neurological diseases.

ALS-mimic syndromes: This syndromes present as a result of other pathogenic processes and do not represent other forms of ALS.

ALS with laboratory abnormalities of uncertain significance (ALS-LAUS): ALS occurring in association with laboratory defined abnormalities

that are of uncertain significance to the pathogenesis of ALS and since it seems to be untreatable, all efforts must be directed to exclude other diagnoses. Standard inquiries should look for any impending curable cause of the syndrome. In addition, electrodiagnostic investigations typically comprise neuroimaging studies to exclude anatomic structural disorder such as cervical myelopathies, and typical laboratory investigations to search for any latent treatable metabolic abnormality.

ALS with laboratory abnormalities of uncertain significance (ALS-LAUS):

ALS-LAUS includes patients with clinically definite or clinically probable ALS associated with:⁵ autoantibodies (high-titer GM1 ganglioside antibody, etc.), endocrine abnormalities (hyperthyroidism, hyperparathyroidism, etc.), monoclonal gammopathy (monoclonal gammopathy of unknown significance, Waldenstrom's macroglobulinemia, osteosclerotic myeloma, etc.), Infection (HIV-1, HTLV-1, varicella-zoster, brucellosis, etc.), lymphoma (Hodgkin's and non-Hodgkin's lymphoma) and exogenous toxins (e.g. lead, mercury, aluminum).

Monoclonal gammopathy and lymphoma:

There have been various reports of patients with both monoclonal gammopathy and motor neuron disease (MND). Monoclonal antibodies are produced by expanded single B-cell clones and are variously recognized as monoclonal protein, M protein, M component, monoclonal gammopathy, or paraprotein. Monoclonal gammopathy can be allied with non-malignant or malignant lymphoproliferative disorders. The non-malignant monoclonal gammopathies have been identified as "monoclonal gammopathies of undetermined significance". The medical literature suggests that patients with MND may have a higher incidence of lymphoproliferative disorders (LPD). When MND does occur in association with LPD, it appears to have both upper motor neuron (UMN) and lower motor neuron (LMN) involvement compatible with a diagnosis of ALS.⁶ The association between MND and LPD could be accidental, but LPD seems to be unduly common in patients with MND compared to the general population.⁷ Despite an initial report suggesting that major improvements occurred occasionally with reductions in paraprotein levels using immunomodulatory treatments even in some patients who had the clinical appearance of ALS,⁸ most of the subsequent literature disagreed. Gordon et al.⁹ showed that most of the patients with MND with LPD had Hodgkin's or non-Hodgkin's lymphoma, such as myeloma or macroglobulinemia. Among these patients, only some had a favorable neurological response to immunotherapy, and most died of the

neurological disease.⁹

Other reports highlight the association of MND and the presence of a lymphoplasmacytoid infiltration of Waldenstrom's macroglobulinemia in particular, and the lack of neurologic improvement after treatment of the underlying disorder with plasmapheresis and immunosuppressive therapy.⁷

Endocrine dysfunction and MND:

The association of muscle weakness with primary hyperparathyroidism (PHP) dates back to the 1800s,¹⁰ and since then numerous patients have been reported with PHP, muscle weakness, hyper-reflexia, and muscle atrophy. There were even reports of patients with PHP, and signs of ALS who underwent parathyroid adenoma resection and demonstrated improved muscle performance.^{11,12} However, Rodriguez et al.¹³ reported on a series of patients with the diagnosis of ALS and concluded that there was no pathogenic association between thyroid or parathyroid dysfunction and ALS. Jackson et al.¹⁴ reported five patients with ALS and PHP that underwent parathyroid adenoma resection. Each patient subsequently had normal serum calcium and PTH levels, but unfortunately they all had progressive weakness that eventually resulted in death within 3 years.

There are some similarities in the neuromuscular symptoms and signs between PHP and ALS. Patients with PHP often have brisk muscle stretch reflexes with flexor or extensor plantar responses. Muscle cramps have been reported in around half of patients with PHP. Severe respiratory muscle and bulbar involvement resulting in hoarseness and dysphasia, as well as abnormal tongue movements have been reported in PHP.¹⁵ However, there are some important differences between ALS and PHP symptoms. Patients with PHP may develop muscle weakness and atrophy in lower limbs that tends to be symmetric and involves predominately the proximal muscles. They often have stocking-glove sensory loss as well as parathesias.¹⁵ Patients with PHP may also have associated ataxia and abnormal upper limb posturing¹⁵ along with cognitive dysfunction, emotional lability, personality changes, anxiety, and hallucinations.¹⁴ Although there are remarkable correlations between PHP and MND, most of the literature does not indicate a conclusive relationship between ALS and hyperparathyroidism and its treatment does not lead to improvement of MND.

ALS and infections:

By 2002, there had been reports of 19 patients with MND, with no evidence that HIV infection increases the likelihood of developing ALS. Most of them had a disorder that was unlike ALS in one major way, the rapidity of progression. The time from onset of

symptoms to severe disability was in weeks and not months.¹⁶

This HIV-related ALS differed in other ways too. The patients were younger than most cases of ALS. Several of the patients had CSF pleocytosis, contrasting ALS. CSF protein content was increased in most cases, but the most remarkable difference from ALS was the regression of symptoms by the treatment of infection.^{17,18}

Therefore, ALS in HIV-positive people may take either of two forms, one that responds to treatment and another that does not. The responsive form seems to be related to viral infection. Predictors of therapeutic response are young age at onset, progression in days or weeks, and abnormal CSF. The unresponsive form may be sporadic ALS that occurs by chance.

In HTLV-1 infection, ALS syndrome has been described, but in some cases chance could not be excluded.¹⁹ Typically, HTLV-1-infected patients with symptoms and signs suggestive of ALS have a high HTLV viral load and present symptoms and signs suggestive of tropical spastic paraparesis jointly with symptoms and signs typical of ALS. In general, these patients tend to progress more slowly than typical sporadic ALS.^{20,21} Thus, patients from endemic areas

with symptoms and signs suggestive of ALS combined with sensory symptoms or bladder dysfunction should be tested for HTLV infection.

Rheumatologic disorders and MND:

Saadatnia et al.,²² described a 55-year-old Persian man with typical presentation of ALS in whom raised level of antiphospholipid antibodies was found. He was treated with plasma exchange and prednisolone. After 3 months of treatment, the symptoms improved and antiphospholipid antibody titres decreased. Furthermore, a small number of studies have described the association of ALS with systemic lupus erythematosus (SLE)²³⁻²⁵ even with neurolysis.²⁵

Conclusion

ALS-LAUS meets the clinical and electrophysiological criteria for clinically probable or clinically definite ALS but has laboratory-defined features which may be relevant to the development of the ALS phenotype, or may be coincidental finding. Correction of the associated abnormalities may result in improvement of the disease course. Owing to a relentless progression of ALS towards death, all efforts must be made by the clinician to exclude alternative and more treatable entities.

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