Amyotrophic Lateral Sclerosis (ALS) with Laboratory Abnormalities of Unknown Significance (LAUS) -- Where Does It Begin and Where Does It End?

P5

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Objective

Define the prevalence / natural history of ALS-LAUS at an ALS Multi-disciplinary Clinic in the South- eastern USA.

Background

ALS-LAUS

ALS-LAUS, characterized by upper and lower motor neuron signs together with LAUS, was categorized as a diagnostic classification category by the World Federation of Neurology Research Group on Motor Neuron Disease/ALS [1]. Lower motor neuron syndromes (LMNS) with LAUS may be separated out as ALS-Mimics [2,3].

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Consensus Guidelines for Diagnosis

El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis

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APPENDIX 1: ALS-Plus and ALS-Mimic Syndromes

ALS-Plus Syndromes and ALS-Mimic Syndromes must meet the clinical, electrophysiological and neuroimaging criteria for Clinically Possible, Clinically Probable or Clinically Definite ALS. The predominant presentation in ALS-Plus Syndromes and ALS-Mimic Syndromes is that seen in sporadic ALS, but includes one or more features such as:

1. Geographic clustering (including disorders seen in the Western Pacific, Guam, Kii Peninsula, North Africa, Madras, etc).
2. Extrapyramidal signs (bradykinesia; cogwheel rigidity; tremor; familial or sporadic).
3. Cerebellar degeneration (spinocerebellar abnormalities; familial or sporadic).
4. Dementia (familial or sporadic; frontal lobe type; Creutzfeldt-Jacob amyotrophic form).
5. Autonomic nervous system involvement (clinically significant abnormal cardiovascular reflexes; bowel or bladder control problems; familial or sporadic).
6. Objective sensory abnormalities (decreased vibration; sharp/dull discrimination; blunting of cold sensation; familial or sporadic).
7. Ocular movement abnormalities (supranuclear; nuclear; familial or sporadic).
8. ALS mimics (delayed post-poliomyelitis; multifocal motor neuropathy with or without conduction block; endocrinopathies; lead intoxication; infections).

APPENDIX 2: ALS with Laboratory Abnormalities of Uncertain Significance (ALS-LAUS) Syndromes

ALS with Laboratory Abnormalities of Uncertain Significance (ALS-LAUS) must meet the clinical, electrophysiological and neuroimaging criteria for Clinically Probable or Clinically Definite ALS. ALS-LAUS have laboratory-defined features which may be relevant to the development of the ALS phenotype. In some patients correction of the associated abnormality may result in alteration of the disease course. Such patients need special consideration in the context of research studies.

ALS-LAUS includes patients with Clinically Definite or Clinically Probable ALS associated with:

1. Monoclonal gammopathy (monoclonal gammopathy of unknown significance, Waldenstrom's macroglobulinemia, osteosclerotic myeloma, etc).
2. Autoantibodies (high-titer GMI ganglioside antibody; etc).
3. Nonmalignant endocrine abnormalities (hyperthyroidism, hyperparathyroidism, hypogonadism, etc).
4. Lymphoma (Hodgkin's and non-Hodgkin's lymphoma). Cases of sporadic ALS associated with cancer of the lung, colon or thyroid and insulinoma, are currently thought not to be causally related to the neoplasm.
5. Infection (HIV-1, HTLV-1, varicella-zoster, brucellosis, borrelliosis, cat-scratch disease, syphilis etc).
6. Exogenous toxins (e.g. lead, mercury, aluminum).

References

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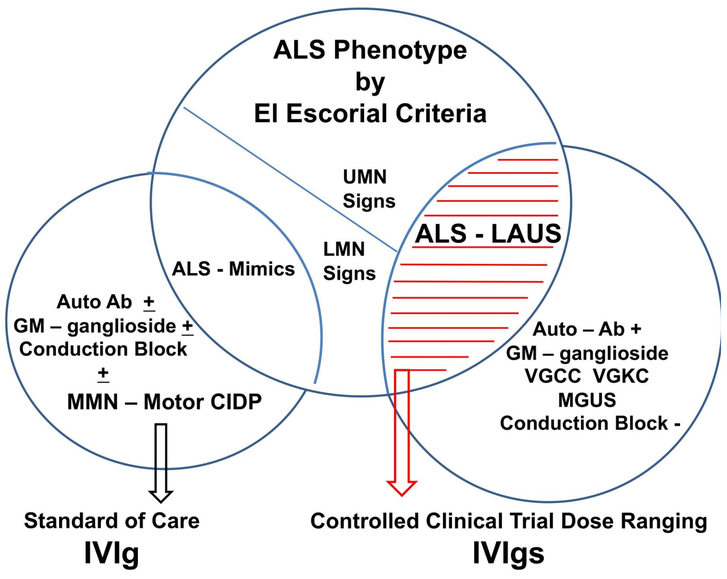
Materials & Methods

ALS-LAUS Definition



ALS - LAUS Prevalence

ALS-LAUS was seen in [79 / 457 = 17.2%] of evaluated patients with probable-laboratory supported, clinically probable and clinically definite ALS by Revised El Escorial criteria [1] .

Auto-Immune

GM1-ganglioside / HS6S / SGPG Antibodies (Abs) [12/79 = 15.2%], Monoclonal Gammopathy of Unknown Signficance (MGUS) / Waldenstrom [16/79 = 20.3%], Voltage-Gated Calcium or Potassium Channel Abs [7/79 = 8.8%], hypo/hyper-gamma-globulinemia / cryo-globulinemia [12/79 = 15.2%], Acetylcholine Receptor/Ganglionic Acetylcholine Receptor / Skeletal muscle Abs [3/79 = 3.8%], Sjogren's Syndrome [2/79 = 2.5%], and Anti-phospholipid Abs [2/79 = 2.5%] comprise a pattern of possibly immune-mediated motor neuron pathogenesis [52/79 = 65.8%].

Post-Infectious

Concurrent infection with Virus [WNV, HCV, HPV, Rubella] [5/79 = 6.3%] and borrelia burgdorferi [1/79 = 1.3%] was identified.

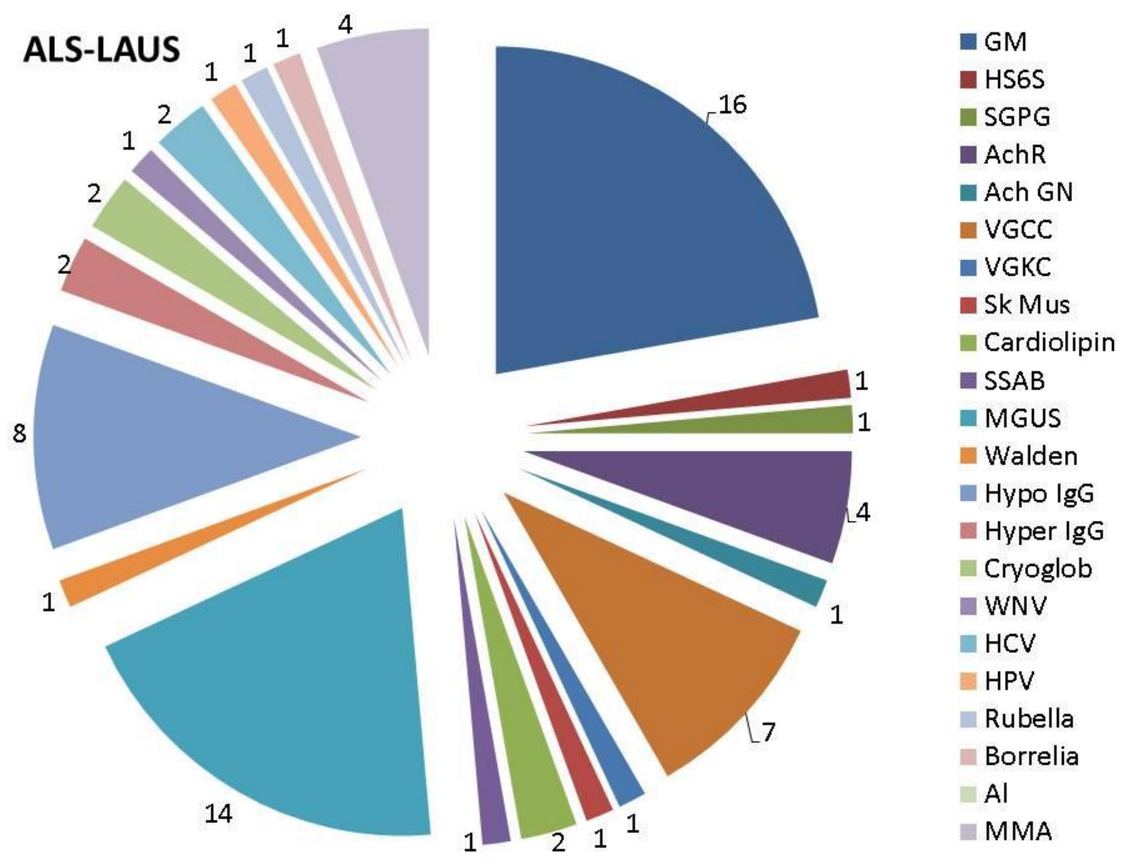
Toxic

Methylmalonic acidemia [4/79 = 5.1%] and aluminum toxicity [4/79 = 5.1%] were identified and treated

Results

ALS-LAUS Prevalence = 1 in 6

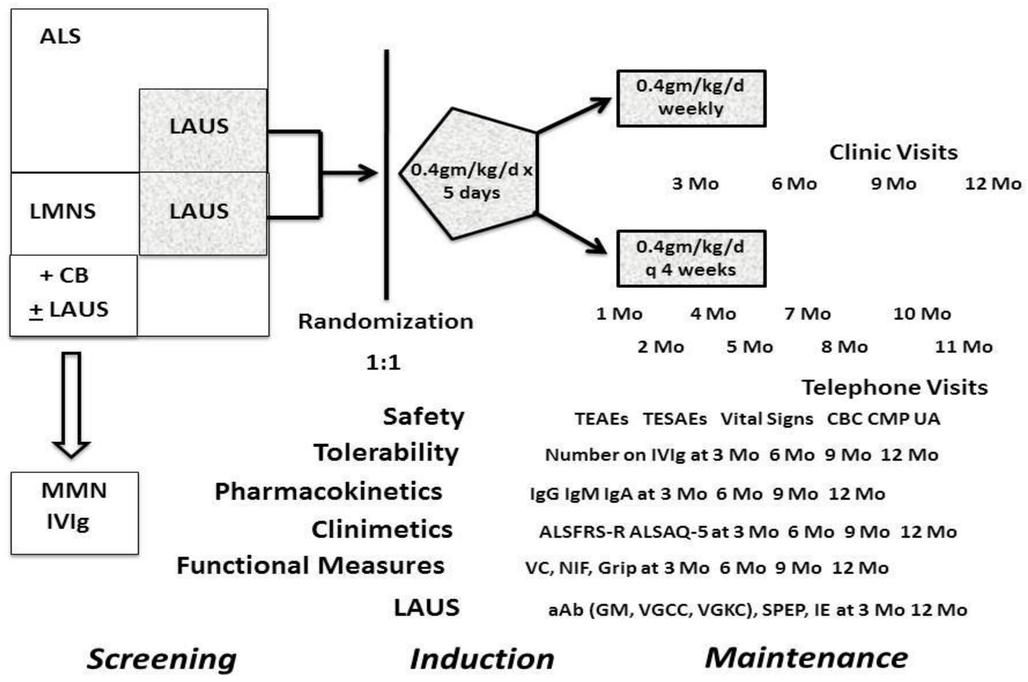
ALS Clinic Evaluations



Immunomodulatory and Immunosuppresive Therapy

In addition to standard riluzole, patients with ganglioside Abs [10/12 = 83.3%], MGUS / Waldenstrom [2/16 = 12.5%], VGCC/ VGKC Abs [4/7 =57.1%], hyper-or hypo-gamma-globulinemia / cryoglobulinemia [1/12 = 4.8%] were treated with IVIg and/or other regimens. Sjogren's syndrome was treated with steroids with improvement confirmed while remaining on steroids but losing that effect if steroids are stopped.

Proposed Auto-Immune ALS-LAUS Clinical Trial



Conclusions

Further detailed analysis of progression rate by site of onset, sex, age, treatment will require assimilation of clinic-based datasets of properly analyzed ALS-LAUS patients from multiple clinic sites.

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