



EI Escorial World Federation of Neurology Criteria For the Diagnosis of ALS

Criteria for the diagnosis of Amyotrophic Lateral Sclerosis

The diagnoses of ALS requires the presence of

- 1) Signs of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination,
- 2) Signs of upper motor neuron (UMN) degeneration by clinical examination, and
- 3) Progressive spread of signs within a region or to other regions, together with the absence of
- 4) Electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degenerations; and
- 5) Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Steps in the diagnosis of Amyotrophic Lateral Sclerosis

The diagnoses of ALS is made possible by

- 1) History, physical and appropriate neurological examinations to ascertain clinical finding which may suggest suspected, possible, probable or definite ALS,
- 2) Electrophysiological examinations to ascertain findings which confirm LMN degeneration in clinically involved regions, identify LMN degeneration in clinically uninvolved regions and exclude other disorders,
- 3) Neuroimaging examinations to ascertain findings which may exclude other disease processes,
- 4) Clinical laboratory examinations, determined by clinical judgment, to ascertain possible ALS-related syndromes,
- 5) Neuropathologic examinations, where appropriate, to ascertain findings which may confirm or exclude sporadic ALS, coexistent sporadic ALS, ALS-related syndromes or ALS variants,
- 6) Repetition of clinical and electrophysiological examinations at least six months apart to ascertain evidence of progression.

Clinical features in the diagnosis of ALS

Patients with signs of LMN degeneration (weakness, atrophy and clinical fasciculation's) and UMN degeneration (spasticity, pathologic reflexes, etc.) may be suspected as having ALS. Careful history, physical and neurological examination must search for further clinical evidence of LMN and UMN signs in four regions of the central nervous system.

Clinical features required for the diagnosis of ALS

- 1) Signs of LMN degeneration (weakness, wasting and fasciculation) in one or more of the four regions (bulbar, cervical, thoracic, lumbosacral). LMN findings in a region are without regard to right or left, but





are indicative of the level of neuraxis involved. Therefore, spread of weakness, wasting and fasciculation's to another region is more important than spread from right to left or vice-versa.

- 2) Signs of UMN degeneration (increased or donic tendon reflexes, spasticity, pseudo bulbar features, Hoffmann reflex and extensor plantar response) in one or more of the four regions. These UMN signs are clinically appreciated best in the bulbar, cervical and lumbosacral regions. UMN findings in a region are also without regard to right or left. Once the physical and neurological examinations provide information on the presence or absence of LMN and UMN signs in the four regions (bulbar, cervical, thoracic, lumbosacral) they must be ordered topographically in the manner to determine the certainty of the diagnosis of ALS.
- 3) The topographical location of certain UMN and LMN signs in four regions of the CNS together with progression of these signs determines the certainty of the diagnoses of ALS. Progression is a cardinal feature of the clinical diagnosis of ALS. Progression of signs within a region and progression of signs to involve other regions are crucial to the diagnosis.

Clinical examinations should be repeated at least every six (6) months to assess progression.

Cases which meet the topographical criteria for probable or definite ALS but which lack progression during the twelve (12) month period diagnosis should be designated as possible ALS.

Definite ALS

is defined on clinical grounds alone by the presence of UMN as well as LMN signs in the bulbar region and at least two of the other spinal regions or the presence of UMN and LMN signs in three spinal regions. The important determinants of diagnosis of definite ALS in the absence of electrophysiological, neuroimaging and laboratory examinations are the presence of UMN and LMN signs together in multiple regions.

Probable ALS

is defined on clinical grounds alone by UMN and LMN signs in at least two regions. While the regions may be different, some UMN signs must be rostral (above) the LMN signs. Multiple different combinations of UMN and LMN signs may be present in patients with probable ALS.

Possible ALS

is defined on clinical grounds alone when the UMN and LMN signs are in only one region or UMN signs alone are present in 2 or more regions or LMN signs are rostral to UMN signs (the latter distribution of signs needs to be differentiated from multiple non-ALS processes). Monomelic ALS, progressive bulbar palsy without spinal UMN and/or LMN signs and progressive primary lateral sclerosis without spinal LMN signs and progressive primary lateral sclerosis without spinal LMN signs constitute special cases which may develop LMN or UMN signs to meet the criteria for probable ALS with time or be subsequently confirmed at autopsy by specific LMN and UMN neuropathologic findings.

Suspected ALS

will manifest only LMN signs in 2 or more regions, although UMN pathology might be demonstrated at autopsy. However, only clinical signs are considered pertinent to this classification at the time of diagnostic evaluation.

Supportive clinical features

Clinical features that support the diagnosis of ALS include one or more of the following:





- 1) abnormal pulmonary function test not explained by other causes,
- 2) abnormal speech studies not explained by other causes,
- 3) abnormal swallowing studies not explained by other causes,
- 4) abnormal larynx function studies not explained by other causes,
- 5) abnormal isokinetic or isometric strength test in clinically uninvolved muscles,
- 6) abnormal muscle biopsy with evidence of denervation.

Inconsistent clinical features

Clinical findings inconsistent with the diagnoses of ALS include one or more of the following not explained by physiological changes associated with aging or other disease processes:

- 1) sensory dysfunction,
- 2) sphincter abnormalities,
- 3) autonomic nervous system dysfunction,
- 4) anterior visual pathway abnormalities,
- 5) movement abnormalities associated with probable Parkinson's disease defined by DATATOP criteria,
- 6) cognitive abnormalities associated with clinical Alzheimer's disease as defined by NINCDS-ADRDA criteria.

If these clinical findings occur, then close attention should be paid to the possible diagnosis of other disease processes.

Lower motor neuron and upper motor neuron signs may occur together with other clinical signs in disease where the pathologic process is not primary motor neuron degeneration.

Types of ALS

The clinical signs of progressive LMN and UMN degeneration seen in ALS may

- a) occur alone (sporadic ALS),
- b) be present incidentally with other pre-existing disease processes that have not developed in parallel with the ALS (coexistent sporadic ALS),
- c) Occur in association with laboratory-defined or epidemiologically defined abnormalities that are time-linked to the ALS (ALS-related syndromes), or
- d) Occur in association with clinical, genetic or epidemiological features which develop in parallel with the ALS (ALS variants).

The physical and neurological examinations will allow for the clinical diagnosis of ALS to a particular degree of certainty as defined above; however, the history of the disease onset, toxic exposures, past medical history, injuries, family history, geographic location, etc., must be incorporated with the clinical examinations in determining whether the patient may have an ALS related syndrome or an ALS variant.

ALS-related syndromes must meet the clinical, electrophysiological and neuroimaging criteria for possible, probable or definite ALS. ALS-related syndromes have unique laboratory-defined or epidemiologically defined features which are time-linked to the development of the ALS phenotype. If correction of the associated laboratory-defined





feature does not result in correction of the ALS phenotype, then the patient with an ALS-related syndrome should be considered in the same way as a patient with sporadic ALS.

ALS-related syndromes include

- 1) Monoclonal gammopathy (monoclonal gammopathy of unknown significance, Waldenstrom's macroglobulinemia, osteosclerotic myeloma, etc.),
- 2) Dysimmune motor system degeneration (autoimmune; 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 insulinoma, lung, colon or thyroid cancer are thought not to be casually related,
- 5) Infection (HIV-1, HTLV-I, encephalitis lethargica, varicella-zoster, brucellosis, cat-scratch disease, Creutzfeldt-Jakob disease, syphilis, delayed post-poliomyelitis, etc.),
- 6) Acquired enzyme defects (detoxification enzymes, etc.),
- 7) Exogenous toxins (lead, mercury, arsenic, thallium, cadmium, manganese, aluminum, organic pesticides, lupin seeds, etc.),
- 8) Physical injury (electric shock, radiation therapy, etc.),
- 9) Vascular (vasculitis; ischemic (Dejerine anterior bulbar artery syndrome, etc.),
- 10) Spondyloitic myelopathy (painless myelopathy with no sensory signs, stabilization or progression post-surgery).

ALS Variants must meet the clinical, electrophysiological and neuroimaging criteria for possible, probable or definite ALS. The predominant presentation is that seen in sporadic ALS, but includes one or more features such as:

- 1) Familial pattern of inheritance (multiple phenol-types characterized by age of onset; site of onset; length of survival; and presumed type of inheritance.)

Familial ALS variants in genetic linkage studies should be characterized by an established genetic mode of inheritance over at least two generations and at least one clinically definite or autopsy confirmed case and compelling evidence excluding other possible causes. Affected sub pairs occurring in one generation alone may not result from a single gene effect.

Examples:

- a) ALS with defined inheritance and known gene product (hexosaminidase A/B deficiency, superoxide dismutase deficiency)
 - b) ALS with defined inheritance and chromosome linkage but no gene product (chromosome 21 associated familial ALS or chromosome 2 associated juvenile familial ALS)
 - c) ALS with defined inheritance and no known linkage or gene product (most cases of familial ALS).
- 2) Geographic clustering (including disorders seen in the Western Pacific, Guam, Kii Peninsula, North Africa, Madras, etc.)
 - 3) Extrapyramidal signs (bradykinesia; cogwheel rigidity; tremor; clinically significant onset of supranuclear eye signs (pursuit abnormalities); familial or sporadic)
 - 4) Cerebellar degeneration (spinocerebellar abnormalities; familial or sporadic)
 - 5) Dementia (progressive cognitive abnormalities; familial or sporadic)





- 6) Autonomic nervous system involvement (clinically significant abnormal cardiovascular reflexes; bowel or bladder control problems; familial or sporadic)
- 7) Objective sensory abnormalities (decreased vibration; sharp-dull discrimination; blunting of cold sensation; familial or sporadic)

Electrophysiological features in the diagnoses of ALS

Patients with suspected, possible, probable or definite ALS on clinical grounds should have electrophysiological studies performed to confirm LMN degeneration in clinically affected regions, find electrophysiological evidence of LMN degeneration in clinically uninvolved regions and to exclude other pathophysiological processes.

ALS may be most reliably identified when the clinical and electrophysiological findings are widespread, involving a sufficient number of regions so that other possible cause of similar EMG abnormalities are highly unlikely. The confirmation of the diagnosis of ALS depends on finding electrophysiological evidence of LMN degeneration in at least two muscles of different root or spinal nerves and different cranial or peripheral nerve innervation in two or more of the four (bulbar, cervical, thoracic, lumbosacral) regions. The features of LMN degeneration in a particular muscle are defined by electromyographic needle examination and nerve conduction studies using standard methods for each measure.

Electrophysiological features required to identify definite primary LMN degeneration include all of the following:

- 1) Reduced recruitment (reduced interference pattern with firing rates over 10 Hz),
- 2) Large motor unit action potentials (large amplitude, long duration), and
- 3) Fibrillation potentials.

Electrophysiological features that support the identification of possible primary LMN degeneration include one or more of the following:

- 1) either reduced recruitment, large motor unit potentials, fibrillation potentials or unstable motor unit potentials alone,
- 2) polyphasic motor unit potentials or increased single fiber density alone,
- 3) low amplitude compound muscle action potentials if the disease duration is over 5 years or if there is associated atrophy,
- 4) low amplitude compound muscle action potentials,
- 5) compound muscle action potential change between proximal and distal sites of stimulation that is uniform along the length of the nerve,
- 6) up to 30% decrement in motor conduction velocity below established normal values if a low amplitude compound muscle action potential greater than 10 percent of normal is present,
- 7) up to 50% decrement in motor conduction velocity below established normal values if the compound muscle action potential is below 10% or normal,,
- 8) up to 20% decrement of the compound muscle action potential on 2 Hz repetitive stimulation,
- 9) up to 10% decrement in sensory nerve conduction velocity and action potential amplitude from established normal values,
- 10) complex repetitive discharges, and
- 11) absence of fasciculations.





Electrophysiological features compatible with UMN degeneration and not excluding ALS include one or more of the following:

- 1) up to 30% increment in central motor conduction velocity,
- 2) up to 10% decrement in somatosensory, evoked potential amplitude and up to 10% increment in somatosensory evoked potential latency,
- 3) mild abnormalities of autonomic function,
- 4) mild abnormalities of polysomnography,
- 5) mild abnormalities of electronystagmography.

Electrophysiological features that are inconsistent with the diagnoses of ALS or suggest the presence of additional other disease processes include one or more of the following:

- 1) focal reduction in compound muscle action potential or more than 10% in a 4-cm segment,
- 2) motor conduction velocities, F wave latencies or H wave amplitudes which are more than 30% above established normal values,
- 3) more than 20% decrement of repetitive stimulation at 2 Hz,
- 4) sensory action potential latencies more than 20% above or sensory action potential amplitudes more than 20% below established normal values,
- 5) unstable motor unit potentials with no other electromyographic changes,
- 6) more than 30% increment of central motor conduction velocity,
- 7) more than 10% increment in sensory evoked potential latency or more than 10% decrement in sensory evoked potential amplitude,
- 8) moderate or greater abnormalities in autonomic function or electronystagmography.

Employing electrophysiological evidence of LMN degeneration to confirm the diagnosis of ALS

The certainty of LMN degeneration is determined by the presence of the above finding for each muscle tested in the region.

At least two muscles of different root or spinal nerve and different cranial or peripheral nerve innervation in each region should show electrophysiological evidence of either definite, probable or possible LMN degeneration for that region to be ranked as showing definite, probable or possible LMN degeneration.

Definite LMN degeneration by EMG has the same significance as clinical LMN degeneration and can upgrade the certainty of the clinical diagnoses of ALS in the same fashion as if the clinical signs of LMN degeneration were present in that region.

Probable or possible LMN degeneration by EMG does not carry the same weight as either clinical signs of definite electrophysiological evidence of LMN degeneration in a particular region.

However, the involvement of the regions with probable electrophysiological evidence of LMN degeneration or one region with probable and one region with possible electrophysiological evidence of LMN degeneration carries the





same weight as one region with definite evidence of LMN degeneration in upgrading the certainty of diagnosis of ALS.

A single region with electrophysiological evidence of probable LMN degeneration or two regions with electrophysiological evidence of possible LMN degeneration can be used to upgrade the certainty of the diagnosis of ALS from possible ALS to probable ALS but not from probable ALS to definite ALS.

Neuroimaging features in the diagnosis of ALS

Neuroimaging studies should be selected in order to exclude other conditions which may cause UMN and/or LMN signs that may stimulate sporadic ALS.

Neuroimaging features required for the diagnosis of ALS:

- There are no neuroimaging tests which confirm the diagnosis of ALS.

Neuroimaging features that support the diagnosis of ALS include one or more of the following:

- 1) minimal bony abnormalities on plain x-ray of skull or spinal canal,
- 2) Minimal abnormalities on head or spinal cord MRI scans without spinal cord and/or root compression,
- 3) Minimal abnormalities on spinal cord myelography with post-myelography CT tomography showing no spinal cord and/or root compression.

Neuroimaging features that are inconsistent with the diagnosis of ALS include one or more of the following:

- 1) significant bony abnormalities on plain x-ray of skull or spinal canal,
- 2) minimal abnormalities on head or spinal cord MRI scans without spinal cord and/or root compression,
- 3) minimal abnormalities on spinal cord myelography with post-myelography CT tomography showing no spinal cord and/or room compression.

Neuroimaging features that are inconsistent with the diagnosis of ALS include one or more of the following:

- 1) significant bony abnormalities on plain x-rays of skull or spinal canal that might explain clinical findings,
- 2) significant abnormalities of head or spinal cord MRI suggesting intraparenchymal processes, arteriovenous malformations or compression of brainstem/spinal cord and/or cranial nerve or spinal nerve roots by bony abnormalities, tumor, etc. MRI of craniocervical junction if bulbar onset and/or MRI of pertinent spinal region if spinal onset,
- 3) significant abnormalities of spinal cord myelography with/without CT tomography or CT tomography alone suggesting lesions as noted above,
- 4) significant abnormalities on spinal cord angiography suggesting arteriovenous malformations.

Employing neuroimaging evidence to confirm the diagnosis of ALS

The absence of abnormalities in appropriately performed neuroimaging studies will raise patients with clinical and/or electrophysiological evidence of probable ALS to definite ALS.





The absence of neuroimaging abnormalities cannot raise possible ALS to probable ALS.

Clinical laboratory features in the diagnosis of ALS

The diagnostic process employed to confirm the diagnosis of sporadic ALS includes repeated clinical examinations, repeated electrophysiological examinations, neuroimaging to exclude other disorders and clinical laboratory examinations or exclude other disorders or support the diagnosis of ALS related syndromes.

Clinical laboratory features required for the diagnoses of ALS

- There are no clinical laboratory tests which confirm the diagnosis of ALS.

Clinical laboratory features that support the diagnosis of ALS include one or more of the following:

- normal complete blood count, platelet count, sedimentation rate, prothrombin time,
- normal electrolyte (Na⁺, K⁺, Cl⁻, CO₂⁻, Mg²⁺, P₀₄) renal (BUN, creatinine) and liver function (bilirubin, SGOT, SGPT, LDH) test,
- creatine kinase (CK) elevation not more than 5 times upper limit of normal,
- normal hexosaminidase A and B activity (if possible of deficiency indicated by suggestive family history or onset under 30 years of age),
- normal cerebrospinal fluid cell count, protein (not more than 65 mg/dl), absence of intrathecal immunoglobulin synthesis, oligoclonal immunoglobulins and evidence of elevated intrathecal antibodies or infectious agents (syphilis, HIV-1, HTLV-I, etc.), if indicated,
- normal parathyroid hormone level if calcium is borderline elevated,
- normal free thyroid hormone concentrations if any thyroid function abnormalities (borderline elevations in T₄, T₃, TSH); normal glycosylated hemoglobin, if indicated,
- Normal serum protein electrophoresis and serum immunoelectrophoresis with immunofixation; normal urine immunoelectrophoresis with immunofixation, if indicated,
- Minimal abnormalities in screening test for collagen vascular diseases (anti-nuclear antibody; anti-DNA antibodies; rheumatoid factor, complement, anti-tissue specific antibodies), if indicated,
- Minimal elevation in screening test for anti-neural antigen (GM1, GM2, GD1b gangliosides, myelin-associated glycoprotein, acetylcholine esterase, etc.) or anti-neuromuscular antigen (acetylcholine receptor, striated muscle, etc.) antibodies, if indicated.

Clinical laboratory features that support the diagnosis of ALS related syndromes

- Abnormalities consistent with monoclonal gammopathy with/without significant elevation in monoclonal anti-neural antigen antibody,
- Significant elevations in polyclonal anti-neural antigen (Gm1, Gm2, GD1b gangliosides, myelin-associated glycoprotein, acetylcholine esterase, etc.) antibody,
- Significant elevation in parathyroid hormone, thyroid hormone or other significant endocrine abnormalities,
- Abnormalities consistent with lymphoma (Hodgkins' or non-Hodgkin's lymphoma),
- Evidence of infection (HIV-1, HTLV-I, borrelia, syphilis, brucellosis, cat-scratch disease, varicella-zoster, influenza, Creutzfeldt-Jakob disease),





- Evidence of intoxication (epidemiological evidence or elevated blood, urine, tissue or cerebrospinal fluid level of lead, mercury, arsenic, cadmium, manganese, aluminum, organic pesticides, lupin seeds, etc.),
- Evidence of physical injury (epidemiological evidence of antecedent electrical or radiation injury or severe trauma),
- Evidence of vasculitis (elevated erythrocyte sedimentation rate and cerebrospinal fluid abnormalities consistent with spinal cord vasculitis, i.e., markedly elevated cerebrospinal fluid protein) or ischemic injury to spinal cord without sensory signs,
- Evidence of pre-existing mild or moderate spinal cord spondylotic compression, not amenable to surgical correction or not responding to surgical correction, which progressed with clinical signs consistent with at least probable ALS.

Clinical laboratory features inconsistent with the diagnosis of ALS:

There is no clinical laboratory finding which, if present with the proper clinical and electrophysiological signs of ALS and appropriate neuroimaging studies, rules out the diagnosis of ALS.

ALS-related syndromes which present with the ALS phenotype as defined have been described with laboratory abnormalities (acquired or genetic), time-linked exposure to chemical, physical or infectious agents and pre-existing structural abnormalities. The correction of laboratory abnormalities, removal of chemical or physical agents, treatment of the associated disease (infection, tumor, structural abnormality) may or may not result in correction or stabilization of the ALS phenotype in ALS-related syndromes.

If correction of the abnormality does not result in improvement, the patient will be considered to have an ALS related syndrome.

If correction of the abnormality does not result in improvement, then the patient will be considered to have an ALS related syndrome.

If correction of the abnormality does not result in improvement then the patient will be considered to have sporadic ALS for the purpose of clinical studies and the therapeutic trials.

Neuropathological features of the diagnosis of ALS:

The clinical diagnosis may be supported or excluded by biopsy studies in the living patient and the pathological diagnosis may be proven or excluded by autopsy examination.

Pathological studies in the living patient with sporadic ALS:

Indications of biopsies:

Biopsies of the skeletal muscle, peripheral nerve and other tissues are not required for the diagnosis of amyotrophic lateral sclerosis, unless the clinical, electrophysiological or laboratory studies have revealed changes that are atypical for ALS. In addition, the muscle biopsy may be used to demonstrate LMN involvement in a body region that had not been shown to be involved by other techniques.





Muscle biopsy:

Features required for the diagnosis:

Disseminated single angulated atrophic muscle fibers, or small or large groups of such fibers.

Features that strongly support the diagnosis:

Angulated atrophic muscle fibers that are strongly positive when stained with oxidative enzyme stains and with non specific esterase or that show immunoreactive surface staining with anti-NCAM antibodies.

Features that are compatible with, and do not exclude the diagnosis:

- 1) Scattered hypertrophied muscle fibers,,
- 2) No more than a moderate number of target or targeted fibers,,
- 3) Fiber type grouping of not more than mild-to-moderate extent,,
- 4) The presence of a small number of necrotic muscle fibers.

Features that rule out the diagnoses or suggest the presence of additional disease:

- 1) Significant infiltration with lymphocytes and other mononuclear inflammatory cells,
- 2) Significant arteritis,
- 3) Significant numbers of muscle fibers involved with the following structural changes: necrosis; rimmed vacuoles; nemaline bodies; central cores; accumulation of mitochondria (ragged red fibers),
- 4) Large fiber type grouping,
- 5) Giant axonal swellings from accumulation of masses of neurofilaments, but not of PAS positive bodies, in intramuscular nerves.

Pathological studies at autopsy, other than in cases surviving for prolonged periods on life support systems

Gross pathological changes

Features required for the diagnosis:

There are positive diagnostic features on gross pathological examination.

Features that support the diagnosis:

There are no positive diagnostic features on gross pathological examination.

Features that support the diagnosis:

- 1) selective atrophy of the motor cortex,
- 2) grayness and atrophy of the anterior spinal nerve roots compared with normal,
- 3) grayness of the lateral columns of the spinal cord,
- 4) atrophy of skeletal muscles.

Features that rule out the diagnosis of ALS or suggest the presence of additional disease:





- 1) Plaques of multiple sclerosis.
- 2) A focal cause of myelopathy.

Light microscopic studies

Features required for the diagnosis:

- 1) Some degree of loss of both of the following neuronal systems. Large motor neurons of the anterior horns of the spinal cord and motor nuclei of the brainstem (V motor, VII motor, I and X somatic motor, and XII); and large pyramidal neurons of the motor cortex and/or large myelinated axons of the corticospinal tracts.
- 2) The following cellular pathological changes in the involved neuronal regions described above; neuronal atrophy with relative increase in lipofuscin and loss of Nissl substance. There should be evidence of different stages of the process of neuronal degeneration, including the presence of normal-appearing neurons, even in the same region.
- 3) Evidence of degeneration of the corticospinal tracts and the same level.

Features that strongly support the diagnosis:

- 1) Lack of pathological change in the motor neurons of cranial nerves III, IV and VI, the intermediolateral column of the spinal cord, and Onuf's nucleus.
- 2) The occurrence of one or more of the following cellular pathological changes in the involved neuronal systems described above:
 - Axonal spheroids with accumulation of masses of neurofilaments,
 - Bunina bodies,
 - Basophilic cytoplasmic inclusions,
 - Non-basophilic hyaline bodies ("Lewy body-like structures") seen in H&E stained sections,
 - Increased immunocytochemical staining for phosphorylated neurofilaments in perikarya of the motor neurons;
 - Atrophy or loss of the arborizations of the dendrites of the motor neurons of the anterior horns of the spinal cord and brainstem motor nuclei.
 - Wallerian degeneration in the anterior roots.

Features that are compatible with, and do not exclude, the diagnoses:

Variable involvement of Clark's nucleus and the spinocerebellar tracts; posterior root ganglia, the posterior columns of the spinal cord and peripheral sensory nerves; the brainstem reticular neurons and the anterolateral columns of the spinal cord; the thalamus; subthalamic nucleus; and the substantia nigra.

Features that rule out the diagnosis or suggest the presence of additional disease:

Major pathological involvement of other parts of the nervous system, including: cerebral cortex other than the motor cortex; basal ganglia; substantia nigra; cerebellum; cranial nerves II and VIII; dorsal root ganglia.

The following cellular pathological changes in the involved neuronal systems described above:

- Extensive central chromatolysis;
- Extensive active neuronophagia;





- Neurofibrillary tangles;
- The presence of abnormal storage material;
- The presence of significant spongiform change;
- The presence of extensive inflammatory cell infiltration.

Electron-microscopic studies

Features required for the diagnosis:

Ultrastructural studies are not required for the diagnosis of ALS

Features that strongly support the diagnosis:

- 1) Accumulation of interwoven bundles of 10 nm neurofilaments in axonal spheroids or motor neuron perikarya, and thicker linear structures associated with dense granules (Hirano et al. 1984 J. Neuropath. Ex. Neurol. 43:461),
- 2) Bunina bodies (Hart et al. 1944 Acta Neuropath. 38:225).

Features that are compatible with, and do not exclude the diagnosis:

The presence of intra-axonal polyglucosan bodies.

Features that rule out the diagnosis or suggest the presence of additional disease;

- 1) The presence of significant numbers of definite viral particles,
- 2) The presence of significant amounts of abnormal storage materials.
- 3) Extensive vacuolation of neuronal perikarya.





Glossary

Definite	specific clinical exclusionary criteria met; no other diagnosis possible on basis of clinical distribution or laboratory findings
Dementia	progressive deterioration of specific cognitive functions
Extrapyramidal	clinical features localizable to basal ganglia and/or midline cerebellum
Hyperreflexia	spread of deep tendon reflex outside stimulated territory
Minor	subjective and objective complaints confirmed by examination (utilization of instrumental sensory testing may increase the detection of sensory abnormalities)
Onset	time of first subjective symptom noticed by patient which later is confirmed by examination
Possible	specific clinical and exclusionary criteria met
Probable	specific clinical and exclusionary criteria
Radicular	distribution conforming to particular nerve root
Region	brainstem, cervical, thoracic or lumbosacral spinal cord level (regional involvement is defined by either right or left sided signs)
Required	necessary or sufficient
Segment	single brainstem or spinal cord level
Spread	involvement of new anatomic segments or regions in the central nervous system
Support	neither necessary nor sufficient, but may suggest
Systemic	non-central nervous system
Weakness	decreased isometric strength
Worsening	increased weakness of muscles in previously affected segment

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