Institute of Genomic Medicine and Rare Disorders
Semmelweis University

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Amyotrophic Lateral Sclerosis Protocol

Amyotrophic Lateral Sclerosis (ALS, G1220) is a rapidly progressive, invariably fatal neurodegenerative disorder. It belongs to the motor neuron diseases where the motor neurons (α motor neurons) degenerate gradually and loss their function. Incidence is around 1-3/100.000/year and prevalence is cc. 4-10/100.000/year. Average time of survival: 2-4 years. Hereditary ALS in 10 percent and SOD1 mutation can be detected in 1-2% of cases.

The appearance of ALS is characterized by muscle weakness, cramps, fasciculation and the loss of ability of voluntary muscle movements. Symptoms begin focally, they become generalized finally. Peripheral and central signs are simultaneously present. Sensory functions, cognitive ability, eye movements and vegetative functions are spared (Hirano criteria).

Diagnostic evaluation (Supplement 2)

Anamnesis:

- Age (usually 55ys<)
- Gender (late onset: female:male 2.5:1; early onset: 1.4:1)
- Familial history
- Various expositions (drugs, chemicals, toxins)
- Laboratory investigation (to rule out other causes of motor neuropathy)

Routine neurological examination

Negative findings

- sensory impairment is absent
- eye movements are intact
- normal vegetative function
- normal cognitive ability

Positive findings

- atrophy and paresis of muscles
- PNS: fasciculation, fibrillation in tounge, dysarthria, dysphagia
- CNS: bris reflexes, pyramidal signs, spasticity

Electrophysiological examination

Sensory functions

- ENG and SEP are normal

Motor functions

- ENG:
  - asymmetric CMAP differences (axonal)
  - increased F wave latency

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EMG:

Most important diagnostic tool in determining diagnostic certainty of ALS
Decreased motor unit recruitment with rapid firing of a reduced number of motor units, and/or large amplitude, long duration MUP with or without evidence of remodeling (increased number of phases) in combination with abnormal spontaneous activity including positive sharp waves (PSWs), fibrillations, and/or fasciculation potentials (FP).The most recent consensus update of the El Escorial Criteria (discussed below) assigned equivalent clinical significance to FP, PSWs, and fibrillation potentials.
Briefly:

- signs of denervation (fibrillation, positive sharp waves)
- signs of degradation of motor neurons (fasciculation) – DDx benign fasciculation
- abnormal single fiber / repetitive stimulation
- Motor unit number estimation – the number of motor units and thus the number of lower motor neurons innervating a muscle; can be followed up
- (El Escorial and Awaji-shima criteria)

- MEP
  - Signs of upper motor neuron degradation

Neuroimaging

- MR – craniospinal
  - hyperintens signal on MR – focal signal in corticospinal tract, cerebral peduncle and internal capsule (present in not all ALS patient)
  - spinal cord – gliosis

Other

- Lumbpal punction

Management:

There is no curative options in ALS. Progression can be slowed down and life quality can be improved.

Medical treatment:

- **riluzol** – anti-glutamate drug and improve the survival in ALS. Modest effect is always present - smallest effect is up to 170 day compared to controls. Dosage: 100 mg/die

- **antisense nucleotide treatment –** in research

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Supportive treatments (Figure 1.):

- Nutrition
  - PEG (! calorie intake should increase cautiously !)
  - Prognostic factors:
    - High calorie diet is better - increase survival time vs. low calorie diet
    - Weight loose of more than 5 kg in 3 month worsen the survival rate
    - Higher LDL/HDL ratio, increased triglyceride increase the survival
- Respiration
  -
  - Non-invasive ventilation - slightly better bulbar function
  - Regardless the type of mask which is used, survival rates are the same (! mask must be used properly !)
  - Diaphragm pacing system is unprofitable for the patient
- Cramps
  - Mexiletine – 300 mg/die is the start dose (900 mg efficient but may become harmful)
- Palliative therapy

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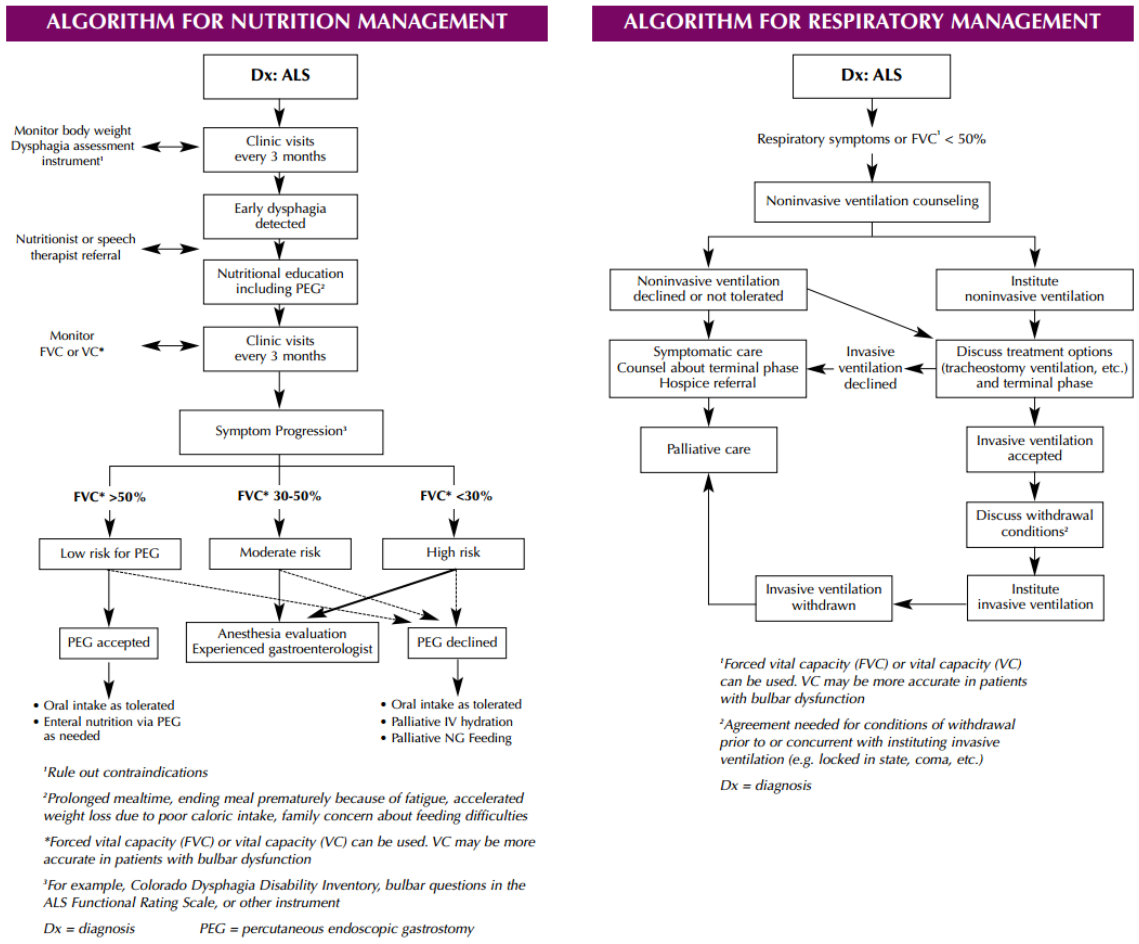

Figure 1. Algorithm for nutrition and respiratory management. (AAN Guideline)

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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:
   - Electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degenerations; and
   - 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:

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

Supplement 1. – Criteria of diagnosis (El Escorial World Federation of Neurology)

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Differential diagnosis

- Adrenoleukodystrophy
- Central nervous system tumors
- Cervical and lumbar myelopathy
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Human Immunodeficiency Virus (HIV)
- Inflammatory myopathies
- Lambert-Eaton Syndrome
- Lyme disease
- Multifocal motor neuropathy with conduction block
- Multiple Sclerosis
- Myasthenia gravis
- Polyradiculopathy
- Syringomyelia

UMN and LMN	**LMN only**	**UMN only**
Sporadic ALS	Progressive muscular atrophy	Primary lateral Sclerosis
Familial ALS	Spinal muscular atrophy	Hereditary spastic paraplegia
	Progressive bulbar palsy	
	Monomelic amyotrophy	
	Bulbar spinal muscular atrophy	
	Poliomyelitis	

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Abbreviations: UMN, upper motor neuron; LMN, lower motor neuron; ALS, amyotrophic lateral sclerosis.

Supplement 2: Differential diagnosis of ALS

References

Joyce NC, Carter GT. Electrodiagnosis in Amyotrophic Lateral Sclerosis. *PM & R : the journal of injury, function, and rehabilitation*. 2013;5(5 0):S89-S95. doi:10.1016/j.pmrj.2013.03.020.

Manage ALS from the beginning (AAN Guideline)