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AMYOTROPHIC LATERAL SCLEROSIS – A PROGRESSIVE MUSCLE WEAKNESS

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a nervous system disease that attacks nerve cells called neurons in your brain and spinal cord. The neurons transmit messages from your brain and spinal cord to your voluntary muscles. At first, this ALS causes mild muscle problems and later people suffering with ALS may find trouble in walking, running, writing and also problems in speech. When muscles in chest fail, people cannot breathe and most of the people die with ALS due to respiratory failure. The disease usually strikes between ages 40 to 60 and there is no cure as medicines relieve symptoms and sometimes prolong survival. In the followed review article, we highlighted the etiology, diagnosis, management and disease modifying treatment in this article and moreover as the reasons for ALS are not exactly confirmed, extensive research is required to find out the causes behind this progressive muscle weakness.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) ALS is a disease that leads to progressivedegeneration of motor system– Hallmark is involvement of both upper and lowermotor neurons. It is characterised by progressive degeneration of upper (UMN) and lower (LMN) motor neurons in the brain and spinal cord. Rare in its own right, ALS is the most common form of motor neuron disease (MND).ALS is almost as mysterious today as it was in the first part of the 20th Century. There are no known causes for most patients and no cures. Genetic mutations account for some of the 5–10 % of cases that are inherited (familial ALS [fALS]), usually in a Mendelian trait. Sporadic ALS (sALS) is thought to have both genetic and environmental influences, but the principle causes await discovery. Once the disease begins, a number of processes transpire in both neurons and surrounding glial cells; how these processes interact is an area of active research.As in otherneurodegenerative diseases, a prominent event in damaged neurons isaggregation of misfolded protein, which might influence nearby wild typeprotein to change conformation and in this way, explain how a diseasethat begins in one area is transmitted widely in the brain. Incidence of ALS is 2-3 people per 100 000 most commondegenerative disorder of the motoneuronal system inadults. Caucasian peoplewere more frequently affected than other ethnicgroups. According to gender men were effected more than women (1.2-1.5:1).Risk of this

condition is peak between the ages of 50-75 years, then declines. Both sporadic and inherited forms of the disease, among them 10% due to inherited gene mutations. The ALS cases can be classified into sporadic,familial, and from the western Pacific(ALS and Parkinsonism-Dementia Complex),the later very common in Chamorro people ofGuam and Marianas island, the Kii peninsulaof Honshu Island, and the Auyu and Jakai peopleof south west New Guinea. In around 5-10%there is evidence of family history (familialALS), and, approximately 20% of these variantsare linked to the gene encoding the enzymecopper-zinc superoxide dismutase (Cu-ZnSOD1), and 2-5% have mutations of TARDBP(TDP-43) gene.

Etiology

Currently unknown that might be geographic and occupationalClusters or environmental factors. It can be also occurs by the following mechanisms such as Mitochondrial dysfunction, Protein aggregation, Free radical generation, Excitotoxicity, Inflammation and apoptosis, Multifactorial and contributions from multiple genes andenvironmental exposures. ALS leads to progressive degeneration of the motor neurons that supplyvoluntary muscles. The disease affects LMNs in the medulla and anteriorhorn of the spinal cord as well as UMNs in the cerebral cortex. The resultfor patients is progressive muscle weakness leading to death, usually fromrespiratory failure. The median survival time after diagnosis is approximately6 months for 25 % of patients, 12 months for 25 % and more than 18months in the remainder.This variability makes anticipating survival timedifficult. Limb-onset symptoms, younger age, better motor function, higherbreathing capacity, stable weight and longer interval between symptomonset and diagnosis are all associated with longer survival. Generally both the upper and lower motor neurons are effected and represents different features such as for upper motor neuron (UMN)disease: Spasticity, Weakness, Increased reflexes, Normal muscle bulk and for lower motor neuron (LMN)disease: Muscle wasting, Weakness, Fasciculations, Dropped reflexes.

Diagnosis

Diagnosis is done after 14 months from onset of symptoms until diagnosis is initial broaddifferential diagnosis: Based primarily on clinical exam:

- No definitive diagnostic test may involve:
- Laboratory testing
- Electromyography (fasciculation, denervation discharges, polyphasic units)
- Genetic testing
- Neuroimaging (MRI)
- El Escorial criteria in 1994 (World Federation of Neurology)
- Multiplerevisions

Definite diagnosis requires:

- LMN degeneration on clinical, electrophysiological, or neuropathological exam
- UMN degeneration on clinical exam
- Progression of motor syndrome within a region or to other regions
- Absence of evidence of other disease processes that may explain the symptoms

There are different criteria for the identification of the type of the ALS, among them El Escorial and Awaji-Shima criteria which improved the diagnostic criteria without false reports. Several investigations are included in diagnosing the ALS:

All patients in whom ALS is suspected

- CBC, Calcium, Phosphate, PTH, TSH, liver enzymes
- Nerve conduction studies/EMG
- MRI of most affected regions

If predominantly UMN pattern

- MRI brain and c-spine +/- other levels
- Copper and zinc levels

If predominantly LMN pattern

- Anti-GM1 antibodies
- Vasculitis/inflammatory serology
- Lead/mercury levels
- West Nile serology
- Kennedy's genetic testing (if bulbar predominant, male)
- Spinal muscular atrophy genetic testing (if shoulder/hip girdle)

The following tumours can lead to aparaneoplastic motor neuron disease

- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- Small cell lung cancer
- Testicular germ cell tumour
- Renal cell carcinoma
- Breast
- Ovarian

Screening

- CT chest/abdo/pelvis
- Testicular U/S, mammography

Management

There is no cure yet for ALS, so care is aimed at maintaining quality oflife and prolonging life as much as possible. The current foundationsare a single neuroprotective medication, multidisciplinary clinics andventilatory support. Some therapies can help relieve symptoms. And also there are some recommendations such as:

1. Multidisciplinary care should be available for peopleaffected by ALS. Attendance at multidisciplinary clinicsmay extend survival, decrease medical complications(level B) and improve quality of life (level C).

2. The following specialists should be part of or readilyavailable to the multidisciplinary clinic team: neurologist,respiratory physician, gastroenterologist, rehabilitationmedicine physician, social counsellor,occupational therapist, speech therapist, respiratorytherapist, specialized nurse, physical therapist, dietitian,psychologist, dentist and palliative care physician(GCPP).

3. Patients should generally be reviewed every2–3 months, although they may require more frequentreview in the months following diagnosis or in the laterstages of disease, and less frequent review if their diseaseis progressing slowly. The patient support teamshould maintain regular contact with the patient andrelatives between visits (GCPP).

4. Ideally, the patient should be followed by the sameneurologist liaising closely with the patient is primarycare physician (family general practitioner) (GCPP).

5. Effective channels of communication and co-ordinationare essential between the hospital-based multidisciplinaryclinic team, the primary healthcare sector,the palliative care team and community services(GCPP).

Neuroprotective treatment/disease-modifying treatment

To date, Riluzole is the only drug that has been shown toslow the course of ALS. Oraladministration of 100 mg riluzole daily improved the1-year survival by 15% and prolonged survival by 3

months after 18 months of treatment. There was aclear dose effect. Eleven people needed to be treatedwith riluzole to delay one death for 12 months.

Symptomatic treatment

Sialorrhoea in ALS was treated with amitriptyline, oral ortransdermal hyoscine, or sublingual atropine drops(GCPP).

1. In patients with refractory sialorrhoea, botulinumtoxin injections into the parotid and/or submandibulargland are effective and generally well tolerated (level Bfor botulinum toxin type B, level C for type A toxin).
2. Irradiation of the salivary glands may be tried whenpharmacological treatment fails (GCPP).
3. Surgical interventions are not recommended (GCPP).

Bronchial Secretions

- Difficulty clearing secretions common complaint
- No controlled trials in ALS

Options to consider

Mucolytic agent: N-acetylcysteine 200-400mg tid and only use if patient is able to cough effectively

Anti cholinergic bronchodilator: Ipratropium

Beta-blocker: Metoprolol or propranolol

Humidifier: Portable suction device

Cramps: Common complaint, can be troublesome at night

• Quinine– Banned by FDA, Cochrane review, No greater AEs compared with placebo

• BeneficialDose 200 mg bid

• Keppra (levetiracetam) may be beneficial– 500mg po bid up to 1000mg po bid

• Cannabinoids ineffective

• Non pharmacologic (no trials)– Exercise, physiotherapy, massage, hydrotherapy

Spasticity: Pharmacologic– Baclofen, Maximum 80 mg daily, in divided doses

• Consider intrathecal pump if intractable– Tizanidine, Maximum 24mg daily, in divided doses

• Non-pharmacologic– Physiotherapy

• Mainstay of treatment

• Shown to be effective– Hydrotherapy, Heat, cold therapy

Venous Thrombosis: Increased risk of DVT – 2.7% annual incidence– Immobility, Impaired respiratory function and No studies to guide management and also Current practice– Insufficient evidence to recommend prophylaxis, Anticoagulate if DVT

Nutritional support: The consequences of malnutrition in patients with ALS are well known. Inadequate dietaryintake can exacerbate catabolism and atrophy of respiratory muscles, weaken the immunesystem and contribute to infection. Weight loss and below-normal body mass index(BMI) resulting from deficient energy intake among ALS patients are correlated with shortened survival. Several more recent studies confirm the observation that weight loss (and / ormalnutrition), defined as BMI ≤ 18.5kg/m2, is an independent, negative, prognostic indicatorfor survival. “Neutraceuticals”, “functional foods” and “dietary supplements” are terms used to describechemical components of foods that may display unique, disease-fighting pharmacokinetics andpharmacodynamics when ingested in amounts above that of one’s typical diet.

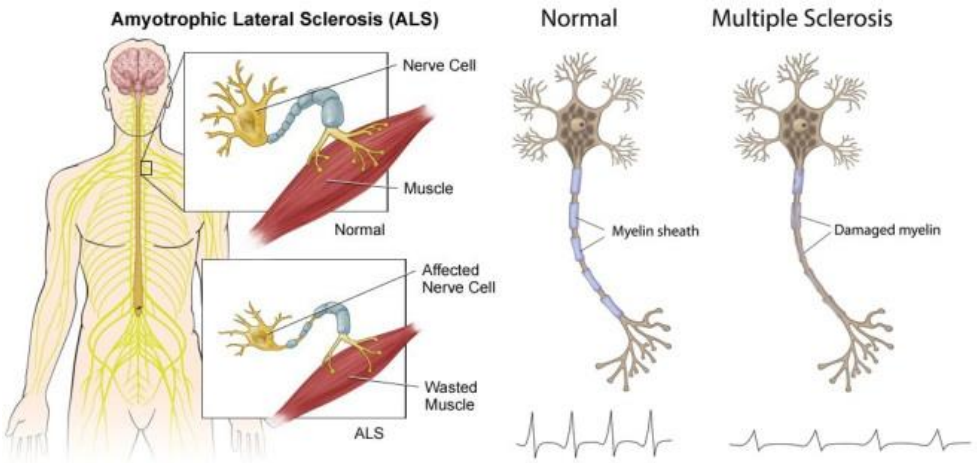

Fig.1 Etiology of Amylotrophic Lateral Sclerosis (ALS)

Criteria	Definite ALS	Probable ALS	Possible ALS	Suspected ALS
El Escorial	Upper and lower motor neuron signs in 3 regions	Upper and lower motor neuron signs in at least 2 regions, with upper motor signs, lower motor neuron signs rostral to lower motor neurons	Upper and lower motor neuron in 1 region, upper motor alone in 2 regions, or lower motor neuron signs rostral to lower motor neurons	Lower motor neuron signs only, in 2 or more regions
Awaji-Shima	Clinical or electrophysiological evidence, demonstrated by the prescence of upper and lower motor neuron signs in the bulbar region and at least 2 spinal regions, or the presence of upper and lower motor neuron signs in 3 spinal regions.	Clinical or electrophysiological evidence, demonstrated by the prescence of upper and lower motor neuron signs in the bulbar region and at least 2 spinal regions, with some upper motor neuron signs necessarily rostral to the lower motor neuron signs.	Clinical or electrophysilogical signs of upper and lower motor neuron dysfunction in only 1 region, or upper motor neuron signs alone in 2 or more regions, or lower motor neuron signs rostral to upper motor neuron signs.	NA

Theemergence of neutraceutical use within the patient population has defined a growing andsubstantial treatment modality. Commonly used dietary supplements are: Vitamin A, Vitamin B6, Zinc, Genistein, Melatonin, Creatinine, Coenzyme Q10, Alpha-Lipoic acid, L-Cartine, Glutathione, Herbs

Functional supports: Red Wine, Epigallocatechin gallate.

REFERENCES

1. Derghazarian, Amyotrophic Lateral Sclerosis A Clinical Overview, 2004, palliative care of neurology.
2. M Andersena, S Abrahamsb, G D Borasioc, M d Carvalhod, A Chioe, P V Dammef et.al; The EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis , 2012, European Journal of Neurology, 19: 360–375.
3. Punter, the Palliation of Amyotrophic Lateral Sclerosis, 2013.
4. C Coupe and P H Gordon, Amyotrophic Lateral Sclerosis – Clinical Features, Pathophysiology and Management, 2013, European neurological review, 8(1):38–44
5. J Rosenfeld and A Ellis, Nutrition and Dietary Supplements in Motor Neuron Disease, Phys Med RehabilClin N Am. 2008 August ; 19(3): 573- 587.