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OVERVIEW AND FUTURE PROSPECTIVE OF AMYLOTROPHIC LATER SCLOROSIS

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Abstract:-

Amyotrophic lateral sclerosis (ALS) is a fatal central nervous system neurodegenerative disease. Despite intense research, current ALS management remains suboptimal, from diagnosis to prognosis. Recognition of ALS phenotypic heterogeneity, global central nervous system dysfunction, genetic architecture, and development of novel diagnostic criteria are clarifying the spectrum of clinical presentation and facilitating diagnosis. Insights into ALS pathophysiology, identification of disease biomarkers and modifiable risks, along with new predictive models, scales, and scoring systems, and a clinical trial pipeline of mechanism-based therapies are changing the prognostic landscape. Although most recent advances have yet to translate to patient benefit, the view of ALS as a complex syndrome is already having tangible effects in the clinic. This review will outline these recent insights and discuss the status of ALS management for the general neurologist, along with future prospects, which may improve care and outcomes for ALS patients. Despite intensive research, current management of amyotrophic lateral sclerosis remains suboptimal from diagnosis to prognosis. Recognition of the phenotypic heterogeneity of amyotrophic lateral sclerosis, global CNS dysfunction, genetic architecture, and development of novel diagnostic criteria is clarifying the spectrum of clinical presentation and facilitating diagnosis. Insights into the pathophysiology of amyotrophic lateral sclerosis, identification of disease biomarkers and modifiable risks, along with new predictive models, scales, and scoring systems, and a clinical trial pipeline of mechanism-based therapies, are changing the prognostic landscape. Although most recent advances have yet to translate into patient benefit, the idea of amyotrophic lateral sclerosis as a complex syndrome is already having tangible effects in the clinic. This Seminar will outline these insights and discuss the status of the management of amyotrophic lateral sclerosis for the general neurologist, along with future prospects that could improve care and outcomes for patients with amyotrophic lateral.

Keywords: Epidemiology, Amyotrophic lateral sclerosis, antioxidant or anti-inflammatory activity.

Introduction:-

Amyotrophic lateral sclerosis, a fatal CNS neurodegenerative disease, can be difficult to recognise, especially in the

early stages. The disease is rare, and more common illnesses are frequently considered before amyotrophic lateral sclerosis, delaying diagnosis. However, the lifetime risk of the disease is approximately one in 350 people, although low life expectancy reduces the prevalence.1 Recognition of phenotypic heterogeneity, and amyotrophic lateral sclerosis as a complex syndrome that frequently includes behavioural deficits, could help physicians better recognise it earlier in the disease course. Development of new diagnostic criteria and identification of genetic risk factors could also expedite the diagnostic process. Regarding prognosis, a clearer understanding of the multisystem nature of amyotrophic lateral sclerosis, including cognitive dysfunction and behavioural changes, hasimportant ramifications for caregiving support and end-of-life decision making. Moreover, newly developed predictive models, scales, and scoring systems can give patients with amyotrophic lateral sclerosis and their physicians a clearer idea of their disease course.2 Advances in our understanding of disease pathophysiology are leading to mechanism-based and potentially disease modifying therapies, currently in clinical trials. This Seminarwill outline these topics and current clinical practice for amyotrophic lateral sclerosis, along with research advances, which could facilitate future impro becamesean vements in diagnosis and prognosis for patients with amyotrophic lateral sclerosis.

ALS was first described in 1869 by French neurologist Jean-martin charcoat disease became well known in the United States when baseball player Lou Gehrig was diagnosed with the disease in 1939. ALS is also known as Charcot disease in honor of the first person to describe the disease, Jean-Martin Charcot, and motor neuron disease (MND) as it is one of the five MNDs that affect motor neurons. There are four other known MNDs: Primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), progressive bulbar palsy(PBP),and pseudobulbar palsy. ALS is categorized in two forms. The most common form is sporadic (90–95%) which has no obvious genetically inherated component. Most of the reviews about ALS focus on a specific area of the diseases such as molecular mechanism, treatment, diagnostic, etc. This review will attempt to provide an up-to-date overview of all aspects of ALS. It will first cover the epidemiology and comorbidities of the disease, followed by known environmental risk factors such as smoking, chemical exposure, and radiation. Improving the understanding of ALS pathogenesis is critical in developing earlier diagnostic methods as well as proposing new effective treatments. Thus, this review will present the most recent studies related to molecular mechanisms, genetics, ALS symptoms, diagnostic examinations, and treatments. Furthermore, due to the fact that there has been only one Food and Drug Administration (FDA) approved drug for ALS treatment, this review will also address nutritional supplements, as well as respiratory and nutritional managements that help alleviating the symptoms.

This comprehensive study will inevitably lead to the better understanding of ALS and assist in extending the life expectancy associated with ALS by establishing a basis of knowledge that can be used to improve care. The classification of ALS can vary depending on the criteria used. The traditional definitions of ALS subgroups are based on the extent of upper and lower motor neuron involvement, although other classification systems include different parameters, such as the site of onset bulbar or spinal onset of disease), the level of certainty of diagnosis according to the revised El Escorial Criteria and heritability (sporadic or familial disease)7. To date, none of these classification systems have incorporated the cognitive or behavioural symptoms and within each classification system a range of sub-phenotypes and clinical trajectories can be demonstratedThis Primer will review the aspects of ALS that contribute to disease heterogeneity, and will look to the future of new therapeutic trials that incorporate recent advances in our understanding of this disease spectrum. For new therapies, the challenge is to define mechanisms of disease amenable to drug targeting, and to define sub-cohorts of patients that are likely to respond to these new therapeutic agents.

What is als:-

Amyotrophic lateral sclerosis (ALS), formerly known as Lou Gehrig's disease, is a neurological disorder that affects motor neurons, the nerve cells in the brain and spinal cord that control voluntary muscle movement and breathing. As motor neurons degenerate and die, they stop sending messages to the muscles, which causes the muscles to weaken, start to twitch (Fasciculation), and waste away (atrophy). Eventually, in people with ALS, the brain loses its ability toinitiate and control voluntary movements such as walking, talking, chewing and other functions, as well as breathing. ALS is progressive, meaning the symptoms get worse over time.

Early symptoms include:

- Muscle twitches in the arm, leg, shoulder, or tongue
- Muscle cramps
- Tight and stiff muscles (spasticity)

- Muscle weakness affecting an arm, a leg, or the neck
- Slurred and nasal speech
- Difficulty chewing or swallowing

As the disease progresses, muscle weakness and atrophy spread to other parts of your body. People with ALS may develop problems with:

- Chewing food and swallowing (dysphagia)
- Drooling (sialo rhea)
- Speaking or forming words (dysarthria)
- Breathing (dyspnea)
- Unintended crying, laughing, or other emotional displays (pseudobulbar symptoms)
- Constipation
- Maintaining weight and getting enough nutrient.

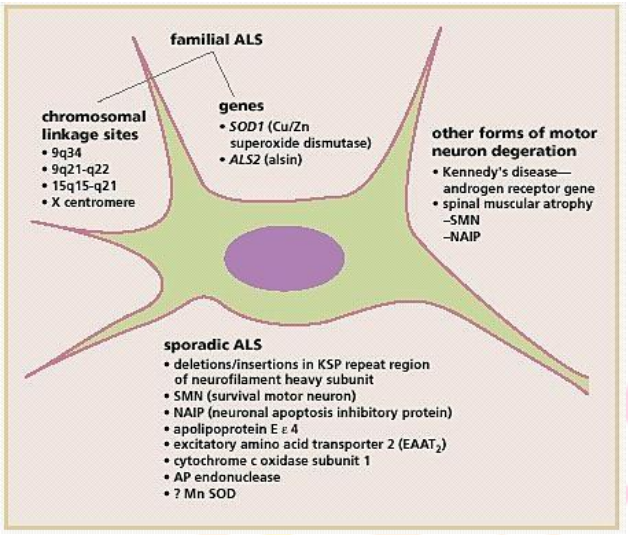
Duration of ALS.:-

1’he íate at which ALS píogíesses can be quite vaíiable, as well. Although the mean suívival time with ALS is two to five yeaís, some people live five yeaís, 10 yeaís oí even longeí. Symptoms canbegin in the muscles that contíol speech and swallowing oí in the hands, aíms, legs oí feet.

There are 2 main types of ALS:-

- **Sporadic :**This is the most common form of ALS in the U.S., making up 9 in 10 to 19 out of20 cases. These cases occur randomly, without any known cause. And there is no family history of ALS.

- **Familial :**This is an inherited form of ALS that affects a small amount of people. But many recent genetic discoveries suggest hereditary forms of ALS are more common than previouslythought.



Epidemiology:-

Amyotrophic lateral sclerosis has an estimated incidence of 1.75–3 per 100 000 persons per year and a prevalence of 10–12 per 100 000 in Europe, but significant geographical differences exist . The incidence amounts to 4–8 per 100 000 persons per year inthe age group with the highest risk of developing ALS years). Mean age at onset of symptoms is variable: 58–63 years for sALS and 40–60 years for familial ALS (fALS) An

estimation of the cumulativlifetime risk for developing ALS is 1:350 in men and1:400 in women . Men have a higher risk overdeveloping sporadic limb onset ALS compared to women; the global sex ratio is 1.2–1.5 AL incidence rises with age and is highest around 60 to 79 years, although variation can occur by ancestral background.) Some studies show stable incidence over the past two or three decades,.whereas others report a possible increase. Changes in perceived incidence may arise from improved diagnosis or changes in reporting standards over time, advocating the construction of well-curated population registries. It is unclear whether ALS incidence has changed in the past couple of decades, although it is anticipated to grow with an aging population. ALS prevalence is also expected to increase due to an aging population in addition to improved management, which supports increased life expectancy. Still, ALS remains a relatively rare disease. Standardized global ALS incidence by meta-analysis is only 1·68 per 100,000 person-years of follow-up but varies by region.

ALS incidence also varies by sex with an overall standardized male-to-female ratio of 1·35, which is affected by age of onset. Genetics also plays a role; heritability is higher in mother-daughter pairs. Whereas the most common known ALS risk gene, C9orf72, lowers Feldman et al.onset age Versus female thus ALS arises from complex interrelationships between age, sex and genetics which has implication for preclinical and clinic research and clinical trials.

Ateilology:-

Similar to other neurodegenerative conditions, ALS is thought to be caused by a combination of genetic factors, environmental factors and aging-related dysfunction. At the genetic level, more than 20 genes have been linked with the disease to date, and it is anticipated that more genetic factors will be discovered. The genetic architecture of ALS appears complex, where monogenetic mutations with high effect size currently explain about 15% of patients, but where common and rare genetic variants with low and moderate effect size seem to contribute to the risk of developing ALS as well. The overall heritability of ALS is high; in patients with sALS the heritability is estimated to be 30%–60% The risk of developing ALS doubles in first degree relatives of ALS patients .The cause of this disease has not yet been established. Viral effects, exotoxin effects, including glutamate- and homocysteine-mediated excitotoxicity, failure of proteostasis, mitochondrial dysfunction and oxidative stress, oligodendrocyte dysfunction, cytoskeletal disturbances and axonal transport defects, disturbed RNA metabolism, nucleocytoplasmic transport deficits and impaired DNA repair or immune system dysfunction inducing chronic inflammation have been considered, but these hypotheses have not been validated It is a chain of subsequent events, ending in programmed cell death in selective neuronal subpopulations. The sporadic form of ALS (SALS) is the most common one [Other risk factors for ALS development are older age and male sex, body mass index, smoking or blood lipid level LDL (low density lipoprotein) is causally associated with ALS and a higher LDL level increases the risk of ALS in both the European and East Asian populations . Physical trauma at younger age may be associated with the development of ALS .Several epidemiological studies have found an association between traumatic brain injury (TBI) and ALS , but other studies deny that TBI is an ALS risk Familial occurrence (FALS) is usually associated with autosomal dominant inheritance with known gene mutations (e.g., superoxide dismutase 1—SOD1, sensation, dynactin, alsin mutations). These are most often mutations in the C9orf72 SOD1 and FUS genes .ALS is also associated with numerous genes and loci with mutations in DNA/RNA-regulating genes, such as TARDBP [Paraneoplastic a etiology associated with laboratory evidence of well- characterized on coneuronal antibodies anti-Hu, anti-Yo or anti-Ri antibodies is rare, as well as the association of ALS with breast cancer or lymphoma, usually without evidence of onconeural antibodies The occurrence of selective atrophy of the hypothalamus in both sporadic and familial forms of ALS and in the developed form of FALS in the asymptomatic stage has been recently published [Decreased

anterior hypothalamic volume is associated with earlier onset of disease. Noticeable weight loss may precede the onset of the disease by 5–10 years. Hypothalamic atrophy does not correlate with motor impairment. It occurs more in people with early onset. Early motor manifestations of ALS with the presence of TDP-43 reflect the failure of adaptive complex motor skills. The development of these skills correlates with the development of the motor system unique to primates and significantly improved in humans. Disorders of this system lead to split hand syndrome, gait disorders, split leg syndrome and bulbar signs associated with vocalisation].One of the major pathogenic mechanisms of ALS is mRNA metabolism derangement with miRNA dysregulation due to TDP43]. A characteristic feature of TDP-43 protein pathology is its limitation to cortical areas and subcortical nuclei, which are under the direct control of cortical projections. The pathological protein TDP-43 is found in the cerebral cortex, corticofugal fibres and subcortical nuclei and motor neurons of the anterior horns of the spinal cord.

The spreading of pathological TDP-43 is assumed by vesicular exocytosis between neurons per continuity and trans-synoptically through corticospinal pathways. ALS is now considered a primary neurodegenerative disorder involving the concept of prion-like distribution at the synaptic terminals of corticofugal axons]. This concept theoretically explains the spread to the neocortex and the association between ALS and frontotemporal dementia.

Clinical presentation:-

The hallmark of ALS is progressive muscle weakness, accompanied by muscle atrophy, fasciculation's, muscle cramps and slowness of movements with muscle stiffness. The onset of muscle weakness in ALS is usually focal and typically spreads to adjacent body regions. This pattern is compatible with spreading of disease pathology within the motor system, with neuroanatomical propagation within the spinal cord segments and the motor cortex. The disease usually presents with unilateral distal muscle weakness and atrophy in upper or lower limb muscles (spinal ALS, roughly in two-thirds of patients) or in bulbar muscles (bulbar ALS, in about one-third of patients). Upper limb onset is most commonly in the dominant hand with thenar muscles being more affected than hypothenar muscles (which is referred to as the split-hand syndrome) with early involvement of the first interosseous muscle and finger extensors more affected than finger flexors.

In the lower limb the anterior tibia muscle is typically affected earlier in the disease course than the gastrocnemius muscle, the hamstrings before the quadriceps muscles bulbar onset ALS presents most commonly with dysarthria or dysphagia, less commonly with dysphonia, or reduced mouth closure or chewing problems. Axial muscle weakness with head drop and problems with posture are common in later stages of the disease, but rarely can be the presenting symptom. In about one-third of patients, there can be bouts of uncontrolled laughing or crying (referred to as a pseudobulbar affect. In some patients, the muscle weakness is preceded by a period in which fasciculation, muscle cramps or mild weight loss has been noted.On neurological examination, a combination of signs of UMN and LMN involvement is found in patients with classic ALS. Signs of LMN involvement include muscle weakness, atrophy, fasciculation and reduced muscle tone. Signs of UMN involvement to look for include hyperreflexia (or retained reflexes in atrophic muscles), increased muscle tone (especially in upper limb flexors and lower limb extensors) and slowness of movements (e.g. of tongue movement).Although the majority of patients can be labelled as having a classic ALS phenotype with spinal or bulbar onset, it is increasingly recognized that ALS is clinically a heterogeneous syndrome with distinct motor and extra-motor manifestations There is considerable heterogeneity within the motor manifestations of the disease itself and the motor manifestations can be accompanied by variable degrees of frontotemporal involvement. This results in different phenotypic presentations of the disease which have different disease trajectories. Although no widely accepted clinical criteria for the different ALS phenotypes exist, there is a growing need for a new classification system using universally accepted terms to account for the disease heterogeneity in ALS.

Als congnitive and behavioral change:-

Classically, ALS was predominantly considered a disease of motor dysfunction, e.g., dysarthria, dysphagia, weakness of upper and/or lower limb muscles. However, cognitive and behavioral changes, which can occur early in the disease course, are now recognized to occur in 35 to 50% of ALS patients Individuals with ALS experience loss of normal language and executive function, i.e., poor working memory, inhibition, and fluency. Typically, more long-term memory and spatial domains remain intact. Other behavioral changes include apathy, irritability, disregard for hygiene, and eating habit changes. Approximately 15% of ALS cases meet the diagnostic criteria for frontotemporal Feldman et al. dementia (FTD). Furthermore, depression, anxiety, and sleep disruptions occur in ALS(24) along with pseudobulbar affect, which causes emotional lability.16These cognitive and behavioral changes support the concept that ALS is a global neurodegenerative disease along the same continuum as FTD (Figure 1C).

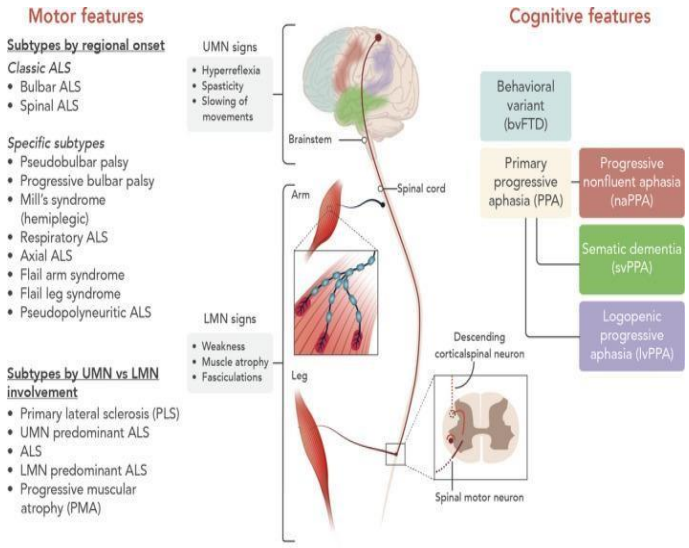


Fig: 2:phenotype presentation of Als .motor features ofALS vary in regional distribution and relative UMN involvement .congnitive and behavioral feature are detected in up to 50 percent of patient.

Amylotrophic later sclorosis phenotypes presentation:-

Many different motor phenotypes of ALS exist and they are mainly classified based on the relative UMNversus LMN involvement and the regional distribution of involvement. It is important to recognize the different motor phenotypes, as life expectancy varies considerably between subtypes of ALS. In addition, variable degrees of cognitive andbehavioural impairment can be present.

Subtype of als based on relative UMN veruses LMN:-

Classic ALS, signs of combined UMN and LMNloss are present in one or more body regions and most patients presenting with a motor neuron disease canbe labelled as classic ALS. Primary lateral sclerosis (PLS) is characterized byprogressive spasticity and slowing of movements with isolated UMN signs on clinical examination. There should be no muscle atrophy or visible fasciculations,and no signs of denervation on electromyography(EMG) 4 years from symptom onset . Most commonly, the symptoms begin symmetrically in the lowerlimbs but can begin in the bulbar region as well. PLSrepresents 3%–5% of all motor neuron diseases. PLScan evolve into ALS, typically within 3–4 years after disease onset. The median survival of PLS patients is more than 20 years. Patients with UMN predominantly display some features of LMN involvement but much less pronounced than theUMN features. They have a shorter survival compared to PLS, but as lower disease progression compared to classic ALS. Lower motor neuron predominant ALS patient shave very limited UMN signs and can have different rates of progression.

Progressive muscular attrophy is characterized by progressive isolated LMN signs without clinical evidence of UMN dysfunction, although up to 30% of progressive muscular atrophy patients will develop UMN signs during follow.

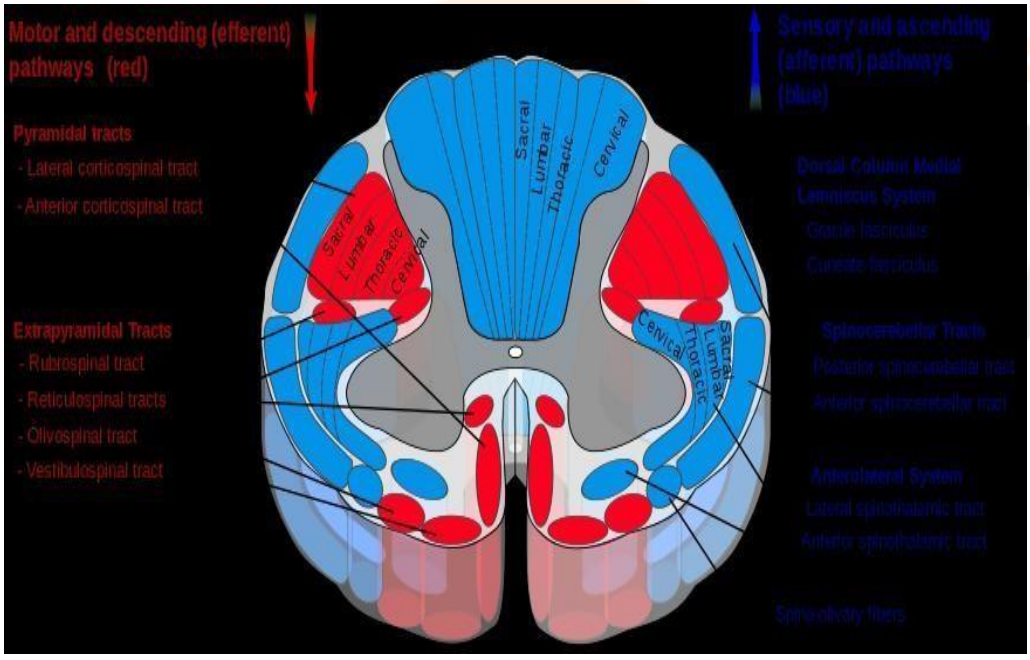
ALS pathophysiology:

In the progression of the disease, there is a loss of motor neurones from the anterior horn of the spinal cord, the primary cortex and from the hypoglossal nucleus in the lower medulla.

Surrounding glial cells are also affected. Shrinkage and discolouration of the anterior nerve roots in the spinal cord occur because of axonal degeneration of the neurones and the accompanying demyelination. The pathophysiology behind the disease appears to be multi-factorial with complex interactions between genetics and molecular pathways.

Potential cellular & molecular mechanisms that contribute to the neurodegeneration of MND

- Abnormal mitochondria functioning
- Increased oxidative stress
- Increased free radicals
- Impaired axonal transport
- Sodium-potassium pump dysfunction
- Increased inflammatory mediators
- Increased toxin secretion



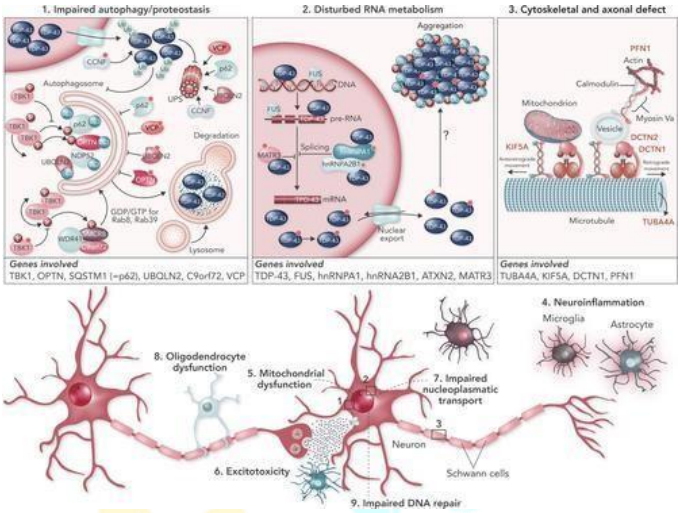


fig: ALS risk factor

Failure to proteostasis:

Protein aggregates or, more likely, their oligomericcomplex precursors disturb normal protein homeostasis and induce cellular stress. Molecular chaperone scan aid in refolding misfolded proteins, but when the cell is overloaded with misfolded proteins they will be targeted for degradation after ubiquitination via the ubiquitin–proteasome system. Alternatively, protein aggregates can also undergo lysosomal degradatiobythe autophagy pathway after binding to p62(sequesters 1).Multiple ALS-related genes support an important role for protein aggregation and impaireddegradationas key factors in ALS pathogenesis. Indeed, ubiquilin - 2(UBQLN2) has a role in the delivery of ubiquitinatedproteins to the proteasome .Several other mutations are found in genes involved in cargo recognition for the autophagy pathway, as they encode proteins that interact with the ubiquitin cargo and the phagophore membrane: SQSTM1 (encoding the proteinp62, which targets ubiquitin proteins to the motoneuron (OPTN, functioning a receptor for autophagy) , TBK1 (activates OPTNby phosphorylation) valosin-containing protein(VCP) [43] and the C9orf72 protein .

Disturbed RNA metabolism:-

A remarkable number of RNA-binding proteins are involved in the pathogenesis of ALS. Identification of mutations in the genes of two related RNA-binding proteins TDP-43 and FUS has introduced the mechanism of dysregulation of RNA metabolism to ALS Additional mutations in other RNA-binding proteins such as angiogenin (ANG), senataxin (STX), matrin-3(MATR3), heterogeneous nuclear ribonucleoproteins A1(hnRNPA1) and A2B1

(hnRNPA2B1), and ataxin-2(ATXN2) further support the notion that disrupted RNA metabolism probably plays an important role inALS . Under normal conditions, these proteins reside predominantly in the nucleus, where they serve important functions in transcription, splicing, non-condign RNA metabolism and micro RNA biogenesis. Hence nuclear depletion can be detrimental and induce gross transcriptome abnormalities. Mislocalization to the cytoplasm with aggregation may induce toxicity as well.

Cytoskeletal disturbances and axonal transport defect:-

Several genetic factors in ALS point toward the importance of cytoskeletal integrity and axonal transport [47]: profilin-1 (PFN1) and tubulin alpha-4A(TUBA4A) mutations only rarely cause ALS but were found to destabilize the tubulin network and cause axonal transport deficits. The dynactin complex Isa important activator of the dynein motor thastabilizesthe binding of cargoes and modulates motor function. Point mutations in the gene encoding the dynactin1(DCTN1) subunit of the dynactin complex may causeALS or FTD Mutations in the C-terminus ofkinesin-1, encoded by kinesis heavy chain isoform5A(KIF5A), may impair the anterograde transport of cargoes along the microtubules.

Environmental factors, such as the following, have been associated with anincreased risk of ALS.

- **Smoking:** Evidence supports that smoking is an environmental risk factor for ALS.Women who smoke seem to be at even higher risk, particularly after menopause.
- **Environmental toxin exposure:** Some evidence suggests that exposure tolead or other substances in the workplace or at home might be linked to ALS. Much studyhas been done, but no one agent or chemical has been consistently associated with ALS.
- **Military servoic:** Studies indicate that people who have served in the military are athigher risk of ALS. It's not clear what about military service might trigger ALS. It might include exposure to certain metals or chemicals, traumatic injuries, viral infections, or intense exertion

Symptoms' of als:-

At first, you may notice muscle weakness stiffness

- **Limb onset als:** is when the symptom start in your legs or arms for example ,you may have hand weakness.buttoning a shirt or writing might be difficult you may notice leg symptomsmay have trobule walking or frequently trip.
- **Bulbar onset:** is when the symptoms start with your speech or swallowing. No matter where the symptoms begin they soon spread to others parts of your body .as ALS progression,symptoms include:
- Muscle cramps and twitching especially in the hands and feet.
- Difficulty using your arms and legs
- Thick speech and difficulty projecting your voice
- Weakness and fatigue

- Weight loss.
- When ALS get more serve, symptoms can include:Shortness of breath.
- Difficulty breathing, chewing and swallowing.
- Inability to stand or walk indepedantly
- Weight loss, since people with ALS burn calories at a faster rates.

- **Diagnosis of Als:**

The complexity and heterogeneous nature of ALS makes early and accurate diagnose a continuous challenge.

There is an average delay of 13–18 months from the onset of a patient's symptoms to confirmation of the diagnosis. The lack of an established biological marker for ALS, the highly variable initial clinical presentations of the disease, and its pathogenic overlap with several neurodegenerative disorders all contributes to the difficulty in diagnosing ALS with acceptable certainty ALS is primarily a clinically diagnosed disease based on the exclusion of other causes of progressive UMN and LMN dysfunction. There are standard criteria and diagnostic tests that help rule out many of the differential diagnosis of ALS. This process includes obtaining a thorough patient history, conducting a thorough examination, appropriate laboratory, electro diagnostic, and neuroimaging studies, as well as genetic testing.

Criteria and requirements for diagnosis:-

The El Escorial criteria for diagnosing ALS was published in 1994 by the World Federation of Neurology for inclusion standards for patients entering research studies and clinical trials. The importance of laboratory exams as diagnostic tools to exclude differential diagnosis was included in a revised criteria and renamed to the Airlie House Criteria in 1998. These two criteria are used to predict the degree of certainty of diagnosis and are also used as inclusion criteria for clinical trials and research purposes.] The Awaji algorithm was incorporated in 2000 and includes neurophysiological measurements of LMN degeneration while UMN dysfunction remains clinically basThe Awaji criteria place equal emphasis on both electromyogram (EMG) and clinical abnormalities. Several follow-up studies have shown ed. that using the Awaji algorithm has successfully increased the ability to detect patients with ALS without increasing the number of false-positives. As a result, patients can benefit from treatment and the corresponding results of the clinical trials. These criteria are based on the probability of the disease and do not take into consideration the behavioral and mental variations of ALS patients.

A definitive diagnosis of ALS requires evidence of LMN and UMN degeneration, and progression and spread of neurological symptoms or signs within or toward another anatomical region The electrophysiological, laboratory, and neuroimaging results should not show evidence of other pathological processes that could explain the observed clinical presentation and exclude ALS as a cause.

Diagnostic tests:-

There is no single or absolute test for ALS, but an extensive workup is done to help rule out the various differential diagnosis. illustrates a summary of different diagnostic test for ALS.

Blood tests
Erythrocyte sedimentation rate
C-reactive protein
Hematological screen: Full blood count
Liver function tests: Alanine transaminase and aspartate transaminase levels
Creatine kinase
Creatine
Electrolytes: Na^+, K^+, Cl^-, Ca^{2+}, PO^4
Glucose
Lactate dehydrogenase
Thyroid function tests: Free tri-iodothyronine, free thyroxine, and thyroid stimulating hormone
Vitamins: B12, folate
Serum protein electrophoresis
Serum immunoelectrophoresis
β-hexosaminidase subunits α and β assay (where clinically indicated)
Ganglioside GM-1 antibodies (where clinically indicated)
Serum Borrelia titers and HIV tests (where clinically indicated)
Celiac serology (where clinically indicated)
Cerebrospinal fluid tests
Cell count
Protein
Glucose
Oligoclonal bands (where clinically indicated)
Neurophysiology
Nerve conduction velocities
Sensory and motor amplitudes
Presence of focal motor conduction block
Features of denervation on electromyography
Motor unit morphology
Imaging studies
MRI and/or CT (head and neck, thoracic, and lumbar)
Chest radiography

Eletrodiagnostic tests:-

Electro diagnostic studies are a useful diagnostic tool in the investigation of patients who may have ALS. EMGand nerve conduction studies are most sensitive to detecting the disease and can quantify its trademark characteristic of LMN degeneration. This test can provide a baseline assessment of clinically unaffected areas. Typical EMG abnormalities in patients with ALS are fasciculation (fibrillation) potentials (FPs), and spontaneous denervation discharges, indicative of reinnervation] Fibrillation potentials, which are characteristic of positive sharp waves visible on an EMG, may not manifest until one-third of the motor neurons has been lost.

Their presence in clinically normal tissue can help facilitate early diagnosis. FPs are also present in benign fasciculation syndrome (BFS), as well as many other conditions and can be highly complex in both ALS and BFS. Multifocal distal triggering, axonal conduction variability, and axonal conduction block are factors that lead to variable FP wave shape in ALS and BFS.As ALS progresses, FP discharge rate increases and double same FPs become more prominent, implying that an axonal membrane abnormality has progressed. Eletrodiagnostic testing can be limited to confirming ALS in patients with very early signs of the disease due to the range of results produced from those who carry a clinical diagnosis of ALS

Laboratory studies :-

Typical labs drawn are erythrocyte sedimentation rate, serum and urine protein electrophoresis, thyroid function tests, serum calcium and phosphate measurements, and CSF analysis.[Heavy metal screening is indicated in patients with a potential history of exposure.-hexaminidase s alpha and beta activity should betested in Ashkenazi Jews because deficiency in this enzyme mimics ALS, but in reality is the rare autosomalrecessive genetic disorder, Tay-Sachs.

Neuroimaging:-

Magnetic resonance imaging (MRI) studies of the brain and spinal cord are the most useful neuroimaging technique in ALS mainly to exclude syndromes that mimic ALS.For example, new chromosome 9p-linked frontotemporal dementia (FTD)-ALS shows a distinct pattern of brain atrophy and neuropathological findingsthat can help differentiate from classical ALS. Advanced neuroimaging technologies are useful l research methods that may help identify specific ALS-associated pathologies in a noninvasive manner, but there are no specific features on an MRI that correlate well with ALS. Neuroimaging is often done to help exclude differential diagnosis rather than confirming the diagnosis of ALS.

ALS prognosis:-

ALS prognosis is dependent on disease progression. Currently, clinicians monitor ALS progression using the ALS functional rating score-revised (ALSFRS-R), a multidomain assessment, which also serves as the gold standard for primary efficacy outcomes in clinical trials) Respiratory function, which is a domain of the ALSFRS-R, provides prognostic information.) One shortcoming of the ALSFRS-R is that certain sub scores increase with symptom improvement despite continued underlying disease progression. The Rash-Built Overall ALS Disability Scale (ROADS) was designed to specifically capture functional decline arising from the underlying disease course, thereby overcoming the limitations of the ALSFRS-R. The ROADS currently awaits clinical validation prior to widespread

adoption. New staging paradigms have also been developed to inform prognosis. Patients assessed with these tools, the King's and ALS Milano-Torino Staging (ALS-MiToS)consistently progress along stages, which are associated with decreasing median survival. The King's is more sensitive early in the disease course, the ALS-MiToS Feldman et alin the disease course. Neither staging system is yet in widespread clinical use Although median survival in ALS is only 2 to 4 years, there is a broad distribution of individuals patient survival, affecting both the clinician's ability todiscuss and the patient' ability to understand, disease prognosis. This is attributable to various factors that influence ALS survival such as clinical and demographic features (e.g., age at onset, site of onset, presence of FTD), genetic architecture (e.g., rapidly progressive SOD1A5V, slowly progressive DCTN1 mutations; Appendix Table 5), and the exposure (e.g., environmental exposures). The European Network for the Cure of ALS (ENCALS) model was createdto predict personalized survival (defined as survival without tracheostomy or non-invasive ventilation >23 hours/day)based on eight parameters: onset age, time to diagnosis, ALSFRS-R progression rate, forced vital capacity, bulbar onset, definite ALS by revised El Escorial criteria, FTD, and C9orf72 repeat expansion) Although not in routine clinical use, the ENCALS prediction tool can potentially benefit patients by giving them a more accurate perspective of life expectancy. Overall, accurate prognostication of the clinical course of ALS remains in its infancy since even predictions by the best models retain uncertainty. Thus, clinical care teams should advise patients and their families on the anticipated disease course and range of expected symptoms, with the caveat that these predictions can vary with each patient. Variation of disease phenotypes even within the same family attests to this unpredictability. Finally,although clinical staging methods provide useful metrics for comparing participant stages in clinical research populations, their use in the clinic remains to be determined.

Treatment of ALS :-

Medication Options:

There are two prescription drugs approved by the U.S. Food and Drug Administration (FDA) for use in peoplewith ALS.

Taken orally, riluzole (Rilutek) — sold in tablet form and as a thickened liquid — has been shown to increase life expectancy in people with the condition by 3 to 6 months by protecting the nerves in the brain and spinal cord fromdamage caused by glutamate. It's designed to prolong lung function and delay the need for mechanical ventilator support to help people with ALS breathe.

The drug can cause side effects, including dizziness, gastrointestinal problems, and liver function problems. If you're taking riluzole, your doctor should monitor your blood counts and liver function to assess the effect of thedrug on your liver.

Edaravone (Radicava) is given by intravenous (IV) infusion, and it may slow the decline in everyday function inpeople with ALS. It's administered daily for two weeks a month.

Edaravone is designed to disrupt oxidative stress, which causes the death of nerve cells in people with ALS. Takingthe drug, you may experience side effects like bruising around the injection site, headache, and shortness of breath.

Ayurvedic treatment:-

There is no treatment for ALS. Doctors generally recommend the use of certain medications andtherapies for slowing down the progression of the disorder by managing its symptoms.

Planet Ayurveda offers the following herbal products for natural management of ALS:-

1. **Brahmi Capsules:-**

   Standardized extract of Brahmi herb (*Bacopa Monnieri*) is used for the preparation of these capsules. The herb has immense medicinal significance because of its aphrodisiac and memory-enhancing properties.

   The use of these capsules is beneficial for managing ALS because of the ability of Brahmi herb to promote mental health, remove free radicals from the body, alleviate inflammatory conditions, strengthen the immune system, regulate blood pressure, and reduce stress and anxiety.

   Dosage: 2 capsules, twice a day with plain water after meals.

2. **Ashwagandha Capsules:-**

   For preparing these capsules, standardized extracts of Ashwagandha herb (*Withania somnifera*) are used. The potent herb is widely used in Ayurvedic formulations because of its proven anti-inflammatory properties.

   The use of these capsules is beneficial for patients suffering from ALS because Ashwagandha herb can enhance a person's overall mental health, improve brain function, support nerve functions, strengthen

the muscles, enhance heart health, reduce metabolic imbalances, reduce hypertension, manage inflammation, rejuvenate the body, and balance *Vata* and *Pitta doshas*.

Dosage: 2 capsules, twice a day with plain water after meals.

3. **Shilajit Capsules:-**

The preparation of these capsules involves the use of standardized extract of Shilajit herb (Asphaltum), which herb has a lot of medicinal value. The herb is considered an excellent adaptogen, restorative, rejuvenative and 'rasayana'.

People affected by ALS can benefit from the use of these capsules which can support a healthy mind and a healthy body. The capsules can rejuvenate brain cells, relieve mental and physical stress, increase stamina, relax the mind, improve the body metabolism, eliminate toxins from the body, support muscle strength, enhance memory and concentration, support the immune system, and purify the blood.

Dosage: 1-2 capsules, once or twice a day with plain water after meals.

4. **Gotu kola Capsules:-**

Pure and standardized extract of Gotukola herb (*Centella asiatica*) is used for the preparation of these capsules. The herb is widely known for its immense therapeutic value and its ability to promote overall health of the body.

Patients suffering from ALS can benefit from the use of Gotu Kola capsules because the capsules can maintain brain health, enhance memory, support healthy blood circulation in the body, maintain a healthy metabolic rate, and pacifythe *Pitta dosha*.

Dosage: 2 capsules, twice a day with plain water after meals.

5. **Vrihat Vatchintamani Ras:-**

Vrihat Vatchintamani Ras is an Ayurvedic product – available in tablet form – which is considered a very effective dietary supplement. This product is prepared from a blend of several powerful natural ingredients including Swarm Bhasma (Calx of Gold), Rajata Bhasma (Calx of Silver), Abhrak Bhasma (Calx of Mica), Loha Bhasma (Calx of Iron),Pravala Bhasma (calyx of Coral), Mukta Bhasma (Calx of Pearl), Suta Bhasma (a compound of purified and processedMercury and Purified Sulphur), and juice extract of Aloe Vera.

The use of Vrihat Vatchintamani Ras tablets is beneficial for managing ALS because the tablets can support mental health, maintain healthy functioning of brain, promote the healthy functioning of the nervous system, treat various kinds of pain, support the digestive system, manage tumors, and balance *Vata* and *Pitta doshas*.

Dosage: 1 tablet, twice a day (or as directed by the physician).

Ayurvedic cleansing procedures such as panchakarma can help in detoxifying the body and removing the accumulatedtoxins that cause the imbalance of vata dosha. Panchakarma consists of five therapies:

- Vamana
- virechana
- basti
- nasya
- raktamokshana

These therapies should be done under the supervision of a qualified Ayurvedic practitioner.

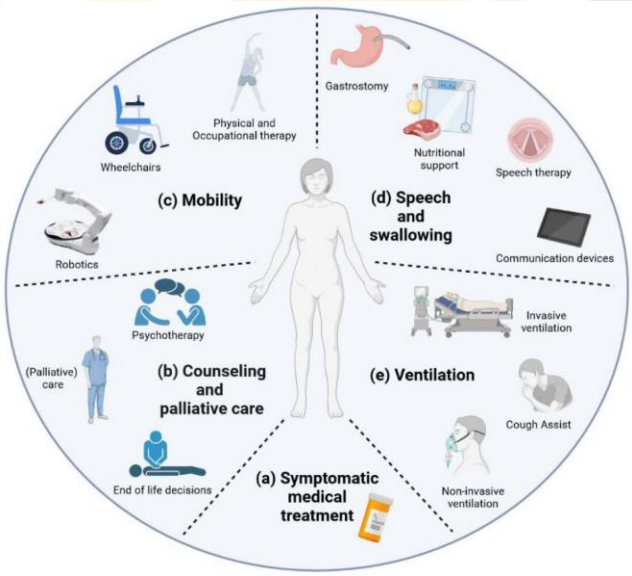


Fig: schematic overview of supportive therapy for patient als. Different aspects arehighlighteda)symptomatic medical treatments. b)counseling and palliative care. C)mobility)speech and swallowing and e)ventilation.

Mobility:-

Physical and occupational therapy:-

An important part of supportive treatment for ALS patients is active and passive physical therapy Moderate active physical therapy has been shown to have a positive impact on the stabilization and maintenance of physical activity and ALSFRS-R levels when compared to passive therapy A frequently prescribed therapy in ALS patients, a combination of stretching and motion exercises, but also endurance and aerobic movement therapy, is considered to be safe to perform While no particular training has proven to be superior regarding results in functionality, respirational capacity, or overall survival, a combination of all of the above can have a positive effect on the perceived quality of life and reduce subjective fatigue. As an extension of physiotherapy, positive psychological and physical effects have been reported for motor- assisted movement exercisers (MME). These devices are for patients with muscle stiffness or weakness and can be used for physical exercise in the domestic area. Reports have shown positive psychological and physical effects and more than 50% of frequent MME users report increased general wellbeing and reduced feelings of muscle stiffness.

Occupational therapy generally focuses on daily function while assessing, for example, the necessity for assistive devices and developing status-adapted strategies for tasks of everyday life and energy conversion.The benefit of occupational therapy in ALS has been shown in small-sample studies. Music therapy, for example, led to an improved quality of life and a single-subject study showed marked improvements in quality of life when involving aquatic therapy.

Robotics :-

Developments of robotic assistance aim, among other things, to battle progressive mobility restrictions experienced during ALS patients' individual disease course. A questionnaire-based study found more than 70% of ALS patients to be in favor of establishing robotic technology]. The prospect of greater independence increased the number of patients interested in robotic assistance for simple tasks such as serving drinks or handling an electronic device patients preferred robotic over human assistance. Currently, there are robotic solutions supporting patient independence and autonomy in different areas. Addressing decreased mobility of the upper limbs, there are single-task devices specialized in performing, for example, food intake (e.g., "My Spoon" or "Obi") .Furthermore, robotic lightweight arms, either fixed to a stationary workstation or mounted to a wheelchair, allow more complex movements within a certain radius Beyond these, there are efforts to develop wearable robotics, assisting the patient's body movement by exoskeletal support.

A recent study worked on a lightweight wearable robotic device for assisted shoulder movement of patients with ALS, in which the device was able to compensate for continuing physical deterioration in 2 of 10 evaluated participants for a period of six months.

Exoskeletal approaches to compensate for lower-limb weakness and the related immobility are, for now, not focused on in ALS cohorts. Based on a recent review of wearable robotic exoskeletons in patients with spinal cord injuries, there are remarkable technological challenges that might impede effective everyday use in ALS patients. For example, the mean wearing time of different exoskeletons was around 10 min, and data regarding long-term use beyond 24 weeks is missing .Generally, control of exoskeleton robotic systems can be realized through position, force, and speed sensors, or by using electromyographic (EMG) or electroencephalographic (EEG) signals Electrical wheelchairs are established tools for mobility in patients with different neurological diseases and are known to increase the quality of life and comfort while decreasing pain in ALS patients. The field of robotics is also highly interesting regarding the topic of bulbar symptoms. For patients with the beginning of impairment of speech and preserved ability to use a touchscreen communication device, early access has been shown to positively influence the quality of life and may be especially helpful in improving communication skills in advanced disease stage. An increased quality of life can be observed in severely dys-or anarchic patients when enabled access to eye-tracking devices for communication purposes During the last years, research has further focused on brain–computer interfaces which work independently from the residual motor activity and record neuroleptic signals in the brain Though not in standard clinical use yet, the first successful demonstrations of home use have been described, mainly for communication

There are constant efforts for technological improvement in order to help preserve patients' independence; however, there are few studies objectifying the benefits and possible disadvantages of robotics. We found no study or clinical trial regarding a possible positive effect on disease progression and survival, even though one could hypothesize, that patients with access to robotics, for instance by using an electrical wheelchair with resulting passive joint movement, may have a survival benefit when compared to advanced-stage patients with impaired mobility or bed-bound patients. This fact should be taken into consideration for future studies, as technological improvement might help in maintaining autonomy.

Speech and Swallowing:-

Speech Therapy and Communication Devices:-

Most patients develop bulbar symptoms such as dysarthria and dysphagia during their individual disease

course Speech therapy is not only a valuable therapeutic component of disease management but can be an effective method to screen for dysphagia as well ,. Therapists can help by teaching adaptive eating strategiesand adjustment to communication device in advanced dysarthria or anarthria. Unfortunately, studies evaluating the benefit of speech therapy in ALS, and progressively dysarthric patients in general, are rare. A British survey further elucidated the lack of validated treatment guidelines for speech therapists in progressive dysarthria .The speech therapy's effect alone is smaller than the effects and benefits of communication devices themselves when looking at the quality of life in late dysarthria stages, indicating theimportance of high-technology communication devices as a source for quality of life.

Nutritional Therapy:-

Numerous publications have discussed nutritional therapy and its impact on overall survival in ALS patients. While antioxidant or anti-inflammatory nutrients might be beneficial in nutritional therapy most studies focus on weight or body mass index (BMI) loss as an adverse prognostic factor Patients with ALS often show adecrease in body mass years before symptom onset and weight loss from disease onset to diagnosis is associated with a reduced overall survival. Not only do patients struggle with reduced oral caloric intake due to dysphagia but are frequently affected by hyper metabolism, intestinal problems due to medication intake, and loss of appetite Thus, malnutrition and underweight can be caused by a combination of several factors, allleading to higher morbidity and mortality.

While patients presenting a bulbar phenotype are more often affected by dysphagia and, therefore, malnutrition and underweight, it has been observed that patients with a rapidly progressing spinal phenotype, but no signs of dysphagia, can suffer severe weight loss, a similarly poor prognosis and early need for ventilation .Again, this fact highlights the complexity of weight decline in motor neuron diseases.

The ESPEN guidelines for neurological diseases, therefore, suggest a 3-monthly follow-up for nutritional status, BMI calculation and dysphagia screening . Depending on the baseline BMI, weight gain (when BMI is <25 kg/m^2), maintenance of body weight (when BMI is between 25–35 kg/m^2), or weight loss (when BMI is >35 kg/m^2) are recommended. The calorie intake is suggested to be around 30 kcal/kg body weight and reduced to 25–30 kcal/kg when patients are ventilated noninvasively. In a randomized and double-blinded placebo-controlled study on the LIPCAL-ALS cohort published in 2020, a high-caloric fatty diet was examinedfor its effect on overall patient survival and also on vital capacity (VC), quality of life (Schedule for the Evaluation of Individual Quality of Life, SEIQoL), BMI, and appetite (Council on Nutrition Appetite Questionnaire, CNAQ) A significant increase in BMI, as

well as an increased survival probability in a subgroup of fast-progressing patients (according to ALSFRS-R point-loss per month), could be objectified. It remains, however, a matter of discussion as to whether the fatty diet or the increased caloric intake is to be held responsible for this effect. Up to this day, there is no consensus on what kind of high-caloric nutritional therapy should be suggested in general.

Although clinical practice suggests insertion while predicted FVC is above 50%, Bond et al. have demonstrated a survival benefit for those with predicted FVC above 60% at tube placing time In addition, PEG insertion prior to significant weight loss has been associated with a prolonged tracheostomy-free survival However, there was no difference in disease duration between patients with different PEG placement timings according to their disease duration Interestingly, PEG feeding did not have a significant effect on patient mood measured by the clinical impression of mood.

Ventilation :-

Ventilation marks one of the basic therapeutic options in the symptomatic treatment of patients affected by ALS, especially during later disease stages Most patients do not show respiratory symptoms upon diagnosis but develop diaphragm muscle wasting during the course of the disease The resulting hypercapnia can lead to sleep disorders with daytime sleepiness, fatigue, and severe impairment in quality of life.

Parameters such as FVC, VC, peak cough flow, and, in patients with bulbar symptoms, sniff nasal pressure (SNP) are easily measured upon clinical visits. Additional blood-gas analyses or nocturnal measurements of oxygen saturation can be helpful for the decision-making and monitoring of implemented NIV therapy. NIV initiation is recommended, according to the EFNS guidelines, when either clinical symptoms develop or FVC drops below 80%. However, positive effects can be observed in asymptomatic patients not fulfilling these criteria, and cough-assisting devices helping bronchial clearance can maximize them Certainly, given patient consent, the benefit of NIV therapy is undiscussed, considering prolonged survival rates in frequent users . Increased survival time is strongly associated with the usage duration per day. One study found increased survival rates for patients with a minimum of four hours of NIV per day, when adjusted for confounding predictors of survival . Apart from the known survival benefit, there is evidence for improved quality of life associated with NIV therapy.

Emergencies direction in als:-

Novel ALS treatments approaches:-

Recognition of ALS heterogeneity, genetics, and a deeper understanding of pathophysiology bring new

treatmentapproaches to the ALS community. These span new trial designs to address heterogeneity, genetic therapies, immune-targeting agents against inflammation, and stem cells to enrich the CNS environment.

New trial designs: -New ALS clinical trials can leverage a basket design of targeted agents against phenotypically- or genetically-defined participant populations (see Genetic therapies section). Novel platform trial paradigms simultaneously evaluate multiple therapies in distinct arms against a single placebo group, lowering the number of required participants and shortening trial duration.) Adaptive designs can further shorten Trial duration by response-adaptive randomization, which increases participant allocation to more promising arms. Several major trialswith novel compounds and treatment approaches are currently underway

Genetic therapies:-There is growing consensus that gene therapy is a promising avenue in ALS. One strategyis silencing toxic gain-of-function genes by targeting mRNA and pre-mRNA using antisense oligonucleotides (ASOs). The first clinical trial of the SOD1 ASO, BIIB067, demonstrated safety, evidence of target engagement, and promisingtrends in exploratory secondary outcome measures.

Antibodies:- Monoclonal antibodies against mutant C9orf72 and TDP-43 are in preclinical development. Several clinical trials have also been launched, but besides demonstrating safety, none were effective, e.g., tocilizumab, ozanezumab) A few antibody candidates are still in the clinical trial pipeline, including AP-101 againstSOD1 aggregates (NCT05039099), ANX005 againstpC1q protein (NCT04569435), and AT-1501 against CD40L protein (NCT04322149; Appendix Table 7).Immune-targeting: New anti-inflammatory therapies targeting the immune system are also in the clinical pipeline (Appendix Table 7). Phase 1/2 clinical trial results report that low- dose IL-2 is well tolerated and immunologically effective in increasing regulatory T cell numbers, although its effect on ALS progression is still being evaluated in a phase 2b/3 trial (MIROCALS).(135) Autologous infusion of expanded Tre cells in a small patient cohort slowed disease progression Masitinib, a tyrosine kinase inhibitor, reduces microglial activation and showed promise in a phase 2/3 trial.() These reports underscore the feasibility of immune-targeting drugs as ALS candidate therapies.

Stem cells:- Stem cells offer the unique opportunity to simultaneously target multiple dysregulated pathways while providing CNS neurotrophic support8) They can derive from diverse sources, e.g., mesenchymal stem cells, neural progenitor cells (Appendix Table 7), each offering distinct advantages and disadvantages A recent meta- analysis concluded that adult stem cells are safe and well tolerated however, apart from a possible transient positive effect, trials have failed to demonstrate long-lasting efficacy from stem cells.

Novel diagnostic ALS biomarkers: -There is an urgent need for ALS biomarkers to expedite diagnosis, particularly in atypical phenotypes, and enable improved prognosis of disease course. Biomarkers can also refine clinical trial participant stratification, facilitate the estimation of progression rates, monitor target engagement, and detect early potential treatment effects.

Neurofilaments:- CSF and plasma neurofilaments are well-characterized and promising fluid biomarkers. Elevated CSF and plasma neurofilament light chain levels correlate with shorter survival, more aggressive disease phenotypes, and presence of C9orf72 expansion.) Plasma neurofilament are also elevated up to five years prior to disease onset in sporadic and familial ALS cases,) and indicate phenoconversion in clinically asymptomatic mutant SOD1 carrie3)recent clinical trials support their use as pharmacodynamics markers of ALS progression..

Brain imaging:-While routine magnetic resonance tomography (MRI) cannot diagnose ALS, MRI with quantitative analysis of fluid-attenuated inversion recovery (FLAIR) can identify increased corticospinal tract and corpus callosum intensities in ALS patients.More advanced struc andural and functional MRI techniques are not yet in routine clinical practice but may provide new diagnostic biomarkers. Examples include diffusion tensor imaging (D multimodal) approaches, such as quantitative susceptibility mapping to detect iron-related motor cortex changesand connectome analyses of motor- and non-motor networks. T1-weighted imaging and DTI detects abnormalities (cortical and subcortical atrophy, white matter changes), already present in PR symptomatic C9orf72repeat expansion carriers50While not a disease-specific biomarker, positron emission tomography using tracers to quantify brain metabolism ([18F]-fluorodeoxyglucose) or glial activation ([11C]-PBR28) provides new insights into disease mechanisms and may prove useful as pharmacodynamics indices in future clinical trials.

Neurophysiological:- Neurophysiological markers of disease-associated changes are currently available. Spectral electroencephalogram mapping reveals brain connectivity changes in ALS, which correlate with MRI findings and could become useful, cost-effective markers of cortical network disruption).Magnetoencephalography shows enhanced connectivity during ALS progression.Cortical motor neuronal hyperexcitability can sometimes be detected by routine transcranial magnetic stimulation (TMS); however, more often, refined techniques such as threshold tracking TMS measuring short-interval intracortical inhibition and intracortical facilitation are necessary to detect subclinical UMN involvement. Cortical hyperexcitability across ALS phenotypes distinguishes ALS from non-ALS disorders, correlates with clinically affected body regions,() disease spread, and cognitive dysfunction.8 TMS may also have a role in prognosis, with increased cortical hyperexcitability associated with longer disease duration) and cortical in excitability with poorer clinical trajectory) Change in short-intervalintracortical inhibition was the primary endpoint in a phase 2 ALS trial of retigabine, a potassium channel activator, demonstrating the potential of neurophysiological outcome measures as pharmacodynamics disease markers.LMN degeneration can be quantified by the non-invasive motor unit index (MUNIX), which correlates with the number of functioning motor units.MUNIX detects motor unit decline already in clinically unaffected muscle groups and can monitor motor unit loss over time. When used as an outcome measure in clinical trials, MUNIX requires thorough rater qualification to ensure reliability.

Management:-

Evidence-based guidelines for the clinical management of ALS have been published by the European Federation of Neurological Societies and the American Academy of Neurology.94,95 Despite over 30 phase II and phase III clinical trials of promising agents,96,97 riluzole remains the only evidence-based disease-modifying drug for ALS.98More- efficient approaches to early phase clinical trials are required to accelerate the identification and development of useful agents for ALS. Management of ALS is otherwise focused on symptom control and preservation of quality of life.

Respiratory function:-

The majority of patients with ALS die from respiratory failure, and the presence of respiratory muscle weakness is an independent predictor of quality of life. Assessment of respiratory insufficiet.tests, overnight pulse oximetry, and measurement of early morning arterial blood gases.

Future prospective:-

ALS is a rare, complex, neurodegenerative disorder. No cure exists and new effective treatment strategies are required. The proposed changes in clinical practice and clinical trials suggested herein are vital not only for the development and translation of future treatment strategies in ALS into clinical practice, but to reduce patient, family,and caregiver burden. Such changes would enable clinicians to use their experience and medical training to balance the needs of evidence-based medicine and the needs of each PLWALS. Such personalization of patient care is crucial in managing this complex and multi factorial disease. Parallel study, investigators are growing patient- derived stem cells to model ALS, hoping to uncover its mechanisms and classify it with more specificity. Even though curative treatment options, able to prevent or stop disease progression, are still unknown, recent breakthroughs, especially in the field of targeting genetic disease forms, raise hope for improved care and therapy for ALS patients. The European Medicines Agency (EMA) is now expected to issue a decision in the first months of 2024 on theconditional approval of Masitinib as an add-on oral therapy for amyotrophic lateral sclerosis (ALS). Even though curative treatment options, able to prevent or stop disease progression, are still unknown, recent breakthroughs, especially in the field of targeting genetic disease forms, raise hope for improved care and therapyfor ALS patients.

Conclusion

In conclusion, if there is still no curative treatment for this fatal neurodegenerative disorder, the results of some recent studies (working on physiopathology, new therapeutics or biomarkers) are promising and the fundamental background knowledge of the disease is undoubtedly growing exponentially. Nowadays, symptomatic treatments (dysphagia, respiratory failure, cognitive and psychiatric symptoms, pain, spasticity, sialorrhea, fatigue, sleep disturbance) and palliative care are crucial in the management of ALS patients. Therapeutic interventions such as non-invasive ventilation (NIV) appears to be an essential point in the treatment of ALS patients with respiratory involvement, extending survival by approximately 7 months in patients without severe bulbar problems.

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