Amyotrophic Lateral Sclerosis: New Suggestions of Pathophysiology and Treatments

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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that specifically affects motor neurons and leads to a progressive and ultimately fatal loss of function, resulting in death typically within 3 to 5 years of diagnosis. The disease starts with a focal centre of weakness, such as one limb, and usually spreads to other extremities, the brain, and muscular involving respiratory. Recent studies reveal a trend towards an increase in the ALS mortality rate, but the significance of this trend remains unclear. Recent ALS incidence studies have given new insight into ALS epidemiology. ALS seems to be distributed uniformly in different countries, with age-specific incidence rates showing a progressive increase up to the 60–79 age group.\(^1\) The pathophysiological mechanisms underlying the development of familial ALS seem multifactorial with emerging evidence of a complex interaction between genetic and molecular pathways.\(^2\) This review provides new insights into the two different form of ALS which primarily highlights epidemiology, clinical manifestations, pathophysiological, current state of ALS therapy and what the best directions are regarding future ALS research. Future directions to treat and manage ALS via stem cell therapy, possibly new drug discoveries, and diet are given.

Keyword: Amyotrophic lateral sclerosis (ALS), neurodegenerative, genetics, stem cell.
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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a human disease resulting from the degeneration of motor neurons in the brain, spinal cord, and peripheral nervous system. ALS is a progressive and fatal neurodegenerative disorder associated with survival ranging from a few months to decades. Known prognostic factors include age at onset, site of onset, duration of weakness, and degree of clinical disability or respiratory function. 3, 4, 5

The majority of patients diagnosed with ALS have no family history of disease and are therefore classified as sporadic cases (sALS). However, it is increasingly clear that sALS in these individuals likely results from complex interactions between their specific genetic makeup and their past and current risk factors. A number of strategies and approaches are being tested around the world, both in the laboratory in human clinical trials and in our clinic. One of the most significant breakthroughs since 1993 has been the discovery that there are two type of ALS, A sporadic form of unknown etiology (sALS) and a familial inherited genetic mutation type (fALS), with the number of mutated genes involved of 200 at last count some of the genes identified in fALS also having been found to be involved in sporadic ALS. Identification of these genes maybe crucial to understanding the epidemiology, clinical manifestations, and pathogenesis of sALS which should help of design therapies for the future. 4, 6

2. ALS Epidemiology

Significant changes in the epidemiology of ALS have been observed over the last few years. During the last few years convincing evidence has been presented that the incidence and
mortality of ALS has been increasing. Sporadic ALS (sALS) seems to be distributed uniform in
different countries, with age-specific incidence rates showing a progressive increase up to the
60–79 age group. 4, 7, 8 The resultant clinical features include weakness of the arms, legs, and
face and difficulties with speech, swallowing, and breathing. sALS affects more men than
women (1.5 to 1), regardless of ancestry, and the risk of disease increases with age. Its clinical
progression is one of the fastest of the neurodegenerative diseases, with death (often from
respiratory failure) typically occurring within 3 to 5 years after onset. The incidence is
approximately 4 to 6 per 100,000 persons per year, and the prevalence is around 400,000
people in the world. 1, 9, 10

Some scientists have reported the increasing incidence as being due to the generally
increasing age of the population as a whole, but this seems unlikely to be the whole
explanation and indeed environmental factors may be contributing to this observed increase in
ALS incidence. 9, 10

Environmental factors that may contribute to the increased incidence include exposure
to heavy metals, electric magnetic fields and spinal trauma. 11, 12 Overall it can be shown that
there is increasing incidence of ALS and whilst this is in part explained by the increasing age of
the general population, it may also be related to more exposures to different environmental
factors that affect the propensity to develop the condition. 13, 14, 15, 16, 17 Sports for example, have
become increasingly popular from grade school to college and finally professional sport
encouraged by the television fan base.
ALS is a progressive and fatal neuromuscular disease. Until now, there is no known definitive cause of ALS, but a hereditary form of the disease, familial ALS, occurs in 5%–10% of cases. Unfortunately, no cure has been identified for either the fALS or the sALS and Riluzole has been the only drug that has been approved by the U.S. Food and Drug Administration (FDA) to treat either type. Riluzole has been demonstrated to slow ALS progression; however, it does not demonstrate marked improvement in ALS symptoms and increases survival time only minimally.\textsuperscript{15, 17, 18, 19, 20}

Recently, Radicut (Edoravone) an antioxidant has been approved for clinical trial in the USA and has already been approved for use in Japan for ALS by their FDA. Multiple clues as to the etiology of sALS are suggested by the mechanisms of action purported to be active in the ALS patient that receive this antioxidant and on October 11, 2016 MediciNova, Inc. announced that the U.S. Food and Drug Administration (FDA) has granted orphan-drug designation to MN-166 (ibudilast) for treatment of Amyotrophic Lateral Sclerosis (ALS).\textsuperscript{21, 17, 18, 19, 20}

Although there is no specific diagnostic blood test for ALS, there are often unusual blood test results such as high levels of immunoglobulin E, low levels of Immunoglobulin M, high ferritin (but with normal irons) and finally positive heavy metal challenge tests that demonstrate high level of mercury and/or lead. Frequent positive blood antibody test for crohns inflammatory bowel disease and positive antibodies to candida, and/or Saccharomyces cerevisiae and elevated chitotriosidase levels in macrophages and sera.\textsuperscript{12, 19, 20} More established diagnostic tests for ALS have been based on signs and symptoms as well as on neurophysiologic tests, primarily electromyograms. A set of clinical and diagnostic features that aim to rule out nonmotor neuron diseases and other motor neuron diseases with restricted
presentations are used to classify ALS patients for research studies. Most persons who receive an initial diagnosis of these other motor neuron diseases ultimately will progress to include both upper and lower motor neurons and thus will receive an ALS diagnosis. \cite{21,22,23,24}

ALS affects persons of all races and ethnicities. Many potential risk factors for ALS have been identified. Whites, males, participation in sports, those aged >60 years, and those with a family history of the disease are more likely to develop ALS. Previous exposure to heavy metals also has been associated with an increased risk for ALS. Certain occupations and sports have been identified as possible risk factors. Nutritional intake, exposure to infectious agents, physical activity, and trauma also have been identified as possible risk factors. However, most risk-factor studies have had small sample sizes or have been conducted in limited geographic areas in populations that might not be representative of the U.S. population. \cite{25,26,27,28}

A new concept of ALS has recently been proposed. In a retrospective case series of 54 ALS patients, 52 had neural foraminal stenosis of long duration, and also had a recent re-injury of these an areas of nerve constriction. Neuro foraminal stenosis is generally considered to be due to a gradual accumulation of calcium associated with degeneration joint disease after an initial injury to the spine (Such as a cervical whiplash). The suggestion is that this re-injury produces a blood CSF barrier break that allow toxic aggregate to enter into the spine at this injury site for most cases of sALS a long standing intestinal. Gastrointestinal (GI) tract dysbiosis is thought to induces or actually produce enteric wall oxidized aggregates. There aggregates then one transported via the blood monocyte to the CSF recent traumatic opening of the Blood-CSF barrier. The aggregates are engulfed by the spinal cord microglia-astroglia and injure
the motor neurons. Secondary to free radicals such as superoxide and peroxynitrate, if true then the treatments necessary for cure will involve removing the noxious GI tract bacteria and yeast biofilms and deposited aggregates including biofilms from the CSF perhaps even the gut walk. In addition, repairs of the recent re-Injury of the spine of the area of neural foraminal stenosis to seal off the blood CSF barrier leak will need to be done.

3. Clinical Manifestation

Since this century, there has been growing scientific and clinical interest in ALS. Advances in our understanding of the glutamate neurotransmitter system and the discovery of causal genes linked to the development of familial ALS have stimulated research interest, problems associated with clinical heterogeneity have been identified, and survival in ALS is now understood to be dependent on several factors, including clinical presentation (phenotype), rate of disease progression, early presence of respiratory failure, and the nutritional status of patients. If the gut-blood CSF barrier breach theory is correct then factors such as diet (no-sugar nor simple carbohydrates) since both bacteria and yeast grow rapidly in their presence.

ALS leads to progressive degeneration of the motor neurons that supply voluntary muscles, including LMNs in the medulla and anterior horn of the spinal cord as well as UMN in the cerebral cortex. The effect clinically is progressive muscle weakness leading to death, usually from respiratory failure. Median survival ranges from months to decades but is 19 months from diagnosis and 30 months from onset on average. The variability and overall rapid progression make it difficult to predict survival time or the timing of interventions. In general,
limb-onset, younger age, better motor function, higher breathing capacity, stable weight, and longer interval between symptom onset and diagnosis are associated with longer survival. \cite{11,29,30,31} Our early positive results of our clinical work with our hypothesis of CFS aggregates being the fundamental etiology would point toward the use of anti-fungal, antibiotic, probiotics and aggregate clearing agents such us trehalose and arginine.

Extending life expectancy in ALS seems to be dependent on improving our understanding of its pathogenesis, which will lead to the development of early and specific diagnostic and therapeutic methods. There is a crucial need to formulate therapies that not only slow disease progression, but also deal with the secondary consequences of malnutrition and respiratory failure. At present, no definitive diagnostic test or biomarker for ALS exists, and neurologists rely on only clinical criteria for diagnosis. An interesting finding is the increase in tumor necrosis factor alpha TNF-alfa, an increase in endotoxin levels in the blood of ALS patients. \cite{19} TNF-alpha was originally named Cachectin and responsible for the weight loss in cancer patients suggesting that treatment with TNF alpha antagonists be tried with patients contending with loss of weight or used as part of a clinical trial for the overall treatment of ALS. \cite{30,31,32} The development of novel biomarkers to objectively assess disease progression holds the promise of greatly refining therapeutic trial design and reducing trial costs. Furthermore, the power of population registries is being increasingly recognized as an essential adjunct to improved clinical assessment techniques. These collaborative endeavors will inevitably lead to a better understanding of ALS and its often unpredictable progression, and will lead to the development of guidelines for improved care of patients. \cite{27,33}
Degeneration of LMNs causes fasciculation, cramps, muscle atrophy and marked weakness, which is often more problematic for patients than the spasticity, hyper-reflexia and modest weakness associated with loss of UMN. Babinski and Hoffmann signs, along with emotional lability are also typical of UMN degeneration. 34, 35

ALS begins in the limbs in about two-thirds of patients, most often in one arm. The first symptoms are usually unilateral and focal and usually on the same side (unilateral) as where the spinal neuro foraminal stenosis has formed.12, 35 The first suggestion indicating the mechanisms causing a lower motor neuron affection in a disease process was given by the description of retrograde exoplasmic transport in peripheral motor axon of foreign macro molecules which had been injected in muscle (Kristensson K; 1979). Transport of fluorescent protein tracer in peripheral nerves (Acta Neuropathol; 16:293-300). This retrograde transportation short circuits the blood-brain-barrier at motor end-plate and allows macromolecules in the plasma to be transported into the CNS (ibid). This has been called “The Trojan horse” route. Both polio and rabies viral particle have been shown to be transported into the CNS by this manner (Bodion D, Hoea HA 1941). The rate of progression of poliomyelitis virus in nerves. Bull John Hosp 69:79-85, Wunner, WH 1982, Is the acetyl cholin receptor a rabies virus receptor? Trends in Neurosciences 5:413-415. Alpha motor neurons are more vulnerable than other neuron to toxic substance mediated by retrograde exoplasmic flow mechanisms in the peripheral neuron system. S. Conradi: Functional Implications of structure and synaptology of motor Neurons in motor Neuron Diseases. Clinical Aspects of Sensory Motor Integration (Springen Verlog;1987). Early findings include clumsiness, weakness of one arm, hand or foot,
difficulty walking, loss of hand dexterity or difficulty lifting the arms over the head. Eventually, limb function can be lost, leading to dependence on caregivers. Patients may fall or lose the ability to walk all-together. Bulbar-onset disease, often occurring in older women, appears to have worse prognosis. On these far advanced cases only high doses of stem cells have been shown to be of help in our experience.

Dysarthria usually begins before dysphagia; symptoms may progress to anarthria, drooling and malnutrition. An atrophied fasciculation tongue is so characteristic of bulbar ALS that it is virtually diagnostic of the condition. Axial weakness can cause dropped head (the dropped head syndrome) and kyphosis, features associated with pain and poor balance. The kyphosis is predictable for cervical spinal nerve foraminal stenosis in our experience and if present should prompt a request for cervical CT exam to demonstrate presence of neuro foraminal stenosis/osteophyte spine CT exam. Sphincter and sensory functions are usually spared. Eye movements are preserved until advanced stages. 36, 37

Cognitive impairment in ALS as an association was considered uncommon until recently. Nocturnal hypoxia is often related to cognitive dysfunction and nocturnal oximetry testing should be routinely ordered and nocturnal Oxygen and/or C-PAP prescribed or needed.

Overt frontotemporal dementia formally called Picks Disease occurs in approximately 15 % of patients, but as many as 50 % are impaired by neuropsychological tests. Changes involve language (Semantic variant of primary progressive aphasia), judgment, personality, affect and executive function. Patients with ALS and dementia have shorter survival, possibly as a result of poor decision-making ability. Depression and anxiety can occur during any stage, from diagnosis
to the time of respiratory failure, though patients suffering from ALS often approach the
disease philosophically and rates of depression may be lower than expected. When present,
emotional symptoms impair quality of life through poor appetite and sleep, and feelings of
hopelessness. Pain can sometimes result from degeneration of sensory neurons, and more
commonly from contractures, loss of mobility, inability to turn in bed osteoporosis or bedsores.
The suffering from being unable to move can be extreme. Morning headache, weakened
cough, orthopnea and exertional dyspnea are early respiratory symptoms. Later, shortness of
breath develops, first during simple tasks such as dressing and eating, and eventually at rest.
Supplemental nasal (Hypoxia inviable Factor-I) oxygen for 2 hours on and 2 hours off during the
day could be tried to increase HIF-I to stimulate motor neuron regeneration and to help reverse
the chronic spinal cord and intestinal hypoxia that present in ALS patients. 9, 37 Nocturnal
oximetry and correction of nocturnal hypoxia in of vital importance.

The El Escorial criteria help standardize the diagnosis for clinical research studies.
Progressive LMN disease by clinical and electromyography examination, and clinical UMN signs
are the core. Patients are classified by the number of involved body regions: bulbar, cervical,
thoracic or lumbosacral. 37

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muscles, including LMNs in the medulla and anterior horn of the spinal cord as well as UMN in
the cerebral cortex. The effect clinically is progressive muscle weakness leading to death,
usually from respiratory failure. Median survival ranges from months to decades but is 19
months from diagnosis and 30 months from onset on average. The variability and overall rapid
progression make it difficult to predict survival time or the timing of interventions. In general, limb-onset, younger age, better motor function, higher breathing capacity, stable weight, and longer interval between symptom onset and diagnosis are associated with longer survival. 7, 8, 38

Loss of LMNs causes fasciculation, cramps, muscle atrophy and marked weakness, which is often more disabling for patients than the spasticity, hyperreflexia and modest weakness associated with UMN disease. Babinski and Hoffmann signs, along with emotional lability are also characteristic findings of UMN degeneration. 11, 13

Familial ALS is clinically heterogeneous even among family members harboring the same gene mutation; a single etiology can lead to numerous clinical syndromes. In addition to variable progression rate, UMN and LMNs are differentially affected, onset occurs in different body regions, and cognitive as well as behavioral disturbances vary. At times fALS patients present in similar fashion as the sALS patients with: 1). Post spinal injury DJD with neuroforaminal stenosis, 2). Chronic infections 3). Recent (within the past 9 months) repeat injury of that same spinal foraminal stenosis area. 35 The heterogeneity found in fALS patients could be explained by this new theory of the etiology of ALS since the type degree of infections spinal nerve damage and gut inflammation would be responsible.

Cognitive impairment in ALS was described by Pierre Marie in the 19th century but was considered uncommon until recently. Overt frontotemporal dementia (FTD) occurs in approximately 15% of people with ALS, but up to 50% are classified as impaired if measured by neuropsychological tests. Primary progressive aphasia, semantic dementia and the behavioral variant are subtypes of FTD that affect executive function, language, judgment, personality, and
behavior. Patients with ALS and dementia have shorter survival, possibly as a result of indecisiveness about care. Depression and anxiety can occur during any stage of the disease, from time of diagnosis to respiratory failure, but patients with ALS often approach the disease philosophically and rates of depression seem to be lower than expected. When present, emotional symptoms impair quality of life through poor sleep and appetite, as well as feelings of hopelessness. 33, 36, 37, 38

Pain can occasionally result from involvement of the spine from degeneration joint disease, sensory neurons, and frequently from contractures, immobility, associated osteoporosis, inability to turn in bed, or bedsores. The suffering that arises from being unable to move can be intense. 39 Morning headache, weak cough, orthopnea, and exertional dyspnea are early respiratory symptoms. As the disease advances, shortness of breath occurs during simple tasks such as dressing and eating, and eventually at rest. Sweating episode should not be considered as part of the disease and the cause of occult infections should be sought and aggressively treated especial basilar bronchopneumonia. 33, 36

The diagnosis, which depends on progressive UNM and LMN findings by history and examination, is accurate 95% of the time when made by an experienced clinician. Electromyography confirms widespread LMN disease and excludes other diseases such as multifocal motor neuropathy with conduction block. Brain and spinal MRI rule out conditions that affect the UMN, including cervical spondylisis but will indicate the presence of neuro foraminal stenosis which may be related to its etiology. 37 Occasionally the brain MRI shows bilateral signal changes within the corticospinal tracts, a finding that is pathognomonic of ALS. 5,
Diffusion tensor imaging (DTI) and magnetic resonances spectroscopy detect these change of ALS in early case diseases.39

4. Pathophysiological Mechanisms

The pathophysiological mechanisms underlying the development of ALS seem multifactorial with emerging evidence of a complex interaction between genetic and molecular pathways. 1, 2, 8 The pathogenic mechanisms that underlie ALS remain largely unclear, but a large spectrum of etiological factors has been considered including genetics, autoimmune responses, environment factors, oxidative stress, glutamate excitotoxicity, mitochondrial damage, defective axonal transport, glial cell pathology, aberrant DNA, and RNA metabolism, aggregation in the CSF, toxic effect of heavy metals, viral infections, paraneuroplastic syndrome, lymphomas, paraprotein, and the present of a blood-CSF barrier leak secondary to trauma within the previous few months in combination with chronic resistant biofilms of bacteria and yeast. 12, 40

Regarding the etiology, approximately 5–10 % of ALS are familial (fALS), mostly autosomal dominant and are due to one of more than 200 mutations identified, beside SOD1 gene mutations, there are three other genes linked to fALS: TAR DNA-binding protein 43 (TARDBP), fused in sarcoma (FUS/TLS) and C9ORF72. 11, 15, 17

The first mutation discovered was in the SOD1 gene on chromosome 21. The SOD1 mutation was used to create a transgenic animal model that has been used to screen new drugs and study disease physiology. SOD1 appears to trigger disease in motor neurons of fALS patients, but astrocytes and microglia promote disease progression, perhaps through
mishandling of glutamate or their reaction to Amyloid-like aggregates of SOD, plus ubiquitin, neurofilaments, etc. Clinical characteristics of families harboring SOD1 mutations include young age-of-onset, onset in the leg with predominance of LMN features, and low frequency of cognitive disturbances. Disease duration spans an average of 9 months (A4V mutation) to decades (D90A mutation). 11, 15, 40, 41

Mutations have been identified in some forms, but the mechanisms by which gene alterations cause fALS await elucidation. The investigators noted that the selective diminution of the mutant SOD1 protein aggregate in microglia greatly delayed the progression of the late-stage disease period characterized by axonal degeneration and a loss of motor neurons. This finding implies that an activity of mutant SOD1 in microglia (phagocytosis of CSF aggregates) initiates events that hasten the demise of motor neurons. Activation of microglia is accompanied by increased expression of surface-membrane proteins that form gap junctions between cells. Moreover, infiltrating macrophages, which replenish microglial populations, may become fusogenic when activated. 41, 42 Close apposition of microglia with motor neurons has been observed in neurodegenerative conditions, but whether actual connections are made, allowing for the passage of molecules through a cytoplasmic bridge, is uncertain. Another possibility and one that is much more interesting with regard to the disease mechanism is that activated circulating monocytes that are attracted to spinal neuro foraminal stenosis re-injury sites supply toxins such as aggregates of TAR43, ubiquitin, oxidized enzyme (SOD1) to the astroglia, and the microglia and these interact with motor neurons by production of free radicals. Activated microglia, which are present in the murine models of ALS and are typically
found in patients with the disease, have been shown to have both neurotoxic and neuroprotective properties in other disease settings. There is much more evidence that oxidized damaged SOD1 molecules form aggregates and these activate microglia to produce free radical like peroxynitrate.\textsuperscript{11, 14, 15, 43}

Recent studies show that a fatal familial ALS-like disease develops in mice expressing particularly unstable mutants of SOD1; but evidence provides compelling evidence that even a modest reduction in the level of expression of mutant SOD1 in motor neurons, and perhaps in other non-neuronal cells, substantially alters the course of disease for the better. The therapeutic implications for an approach that lowers the level of expression of mutant or oxidized proteins might extend to other autosomal dominant neurodegenerative diseases, such as Huntington’s disease. Current studies suggest that the expression of mutant SOD1 in microglia accelerates the death of motor neurons in mouse models of SOD1-linked ALS.

Current understanding links genetic mutations to an increase in toxicity of the SOD1 enzyme with generation of free radicals within the spinal microglia and astrocyte that eventually leads to cell injury and death. SOD1 mutations induce conformational instability and misfolding of the SOD1 peptide, resulting in formation of intracellular SOD1 aggregates, disrupting axonal transport systems and vital cellular functions. \textsuperscript{44, 45, 46} Based on the above report, many investigators believed that the cause may be toxin production via free radicals or the transfer of toxins to nearby motor neurons by astrocytes and/or microglia, or the mutant SOD1 protein may damage the microglia and prevent them from producing yet-to-be-identified
protective factors. A recent paper has focus that SOD1 peptide inhibits amyloid aggregation of fALS SOD1 mutants.

Glutamate-induced excitotoxicity has been implicated in ALS pathogenesis. Glutamate is the main excitatory neurotransmitter in the CNS, and binds to ionotropic N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the postsynaptic membrane. Excessive activation of these postsynaptic receptors by glutamate, known as glutamate-induced excitotoxicity, can incite neurodegeneration through activation of Glutamate-induced excitotoxicity has been implicated in ALS pathogenesis. Glutamate is the main excitatory neurotransmitter in the CNS, and binds to ionotropic N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the postsynaptic membrane. Excessive activation of these postsynaptic receptors by glutamate, known as glutamate-induced excitotoxicity, can incite neurodegeneration through activation of calcium-dependent enzymatic pathways. Since calcium entry into damaged cells disrupts oxidative phosphorylation to cause loss of ATP production and death of the cell-therapies directed toward removing soft tissue calcium, may be of therapeutic use. These therapies could include Calcium channel blockers bisphosphonates, vitamin K2, magnesium, etc. Calcium ions promotes SOD1 aggregation into non-fibrillar amyloid which may be another link to Calcium induced neurotoxicity.

Glutamate-induced excitotoxicity can also result in generation of free radicals, which in turn can cause neurodegeneration by damaging intracellular organelles and upregulating proinflammatory mediators. The mechanism by which glutamate-induced excitotoxicity
mediates motor neuron degeneration in human beings remains unclear. A so-called “dying-forward” process has been proposed, whereby UMN mediate anterograde degeneration of LMN by glutamate-induced excitotoxicity processes. Non-neuronal cells, such as astrocytes and microglia, might also directly contribute to neurodegeneration through mechanisms including insufficient release of neurotrophic factors, secretion of neurotoxic mediators, and modulation of glutamate receptor expression (known as non-cell autonomous neurodegeneration).  

Of further relevance, trans-activating response region DNA-binding protein with a molecular mass of 43 KDa (TDP-43) was recognized as a major component of Ubiquitinated cytoplasmic protein aggregates in almost all patients with sporadic ALS, but not in the nucleus, as in normal neurons. Although there were questions about whether such aggregates triggered neurodegeneration in ALS, mutations in the gene encoding TDP-43 (TARDBP) were reported in 3% of familial ALS and 1.5% of patients with sporadic ALS, suggesting that TDP-43 aggregates have a role in triggering ALS. Evidence for the pathogenicity of TARDBP mutations was suggested when mutations identified in highly conserved regions of DNA were not evident in controls, and segregated with the disease. Given that TDP-43 binds both DNA and RNA, mutations in the TARDBP could result in dysregulation of RNA processing. Fused in sarcomere is a protein that in humans is encoded by the FUS gene and binds to RNA or DNA. Identification of FUS mutations on chromosome 16 associated with familial forms of ALS lends further support to this theory. FUS aggregates were not evident in patients with pathological changes in TDP-43 or SOD1, indicating a novel disease pathway. Although the identification of a causative effect
between mutations in the \textit{TARDBP} and \textit{FUS} genes and ALS was a major leap in understanding familial ALS pathogenesis. \footnote{9,11,15,55}

Advancing age and exposure to tobacco smoke are associated with ALS. A pooled analysis of five large cohorts found modest but significant associations with active smoking, former smoking, duration of smoking and quantity of cigarettes. Recent studies have pointed out endothelial cell damage of spinal anterior arteries in ALS. Cigarette smoke, high cholesterol and PMN’s NAD oxidase (PHox) produce endothelial cell damage via superoxide over-production. Endothelial damage of spinal arterial has been reported in numerous papers by different groups all point to neurovascular dysfunction of spinal arteries in ALS (perhaps at the site of re-injury). Other possible associations include athleticism, particularly professional sports, pesticide exposure and service in the first Gulf war. \footnote{46,47,50,51}

Another possibility in that there is a combination of chronic excess overproduction of superoxide by the body’s defenses of the Gut wall causing subclinical colitis and over production of SOD by white blood cells and by the bacteria and yeast contained in the GUT. The prolonged interaction of superoxide with SOD in the bowel mucosa may well be the initial needed feature for SOD aggregates to form absorbed and carried by WBC in the blood to the CSF. In other words, both blood spinal barrier breach host and invading organisms may well be responsible since both produce superoxide and SOD in excess at the gut-interfaces. \footnote{44} A viral hypothesis, based on the analogy to the enterovirus poliomyelitis, has existed unproven for decades; neuropathological studies and viral cultures have not shown evidence of viral attack but retroviruses and prions are port of yeasts germ. Associations with electrical fields and
various toxins are also uncorroborated but occasional patients will present that have had electrical current shock from one arm to the other, that develop ALS of the arms indicating that a blood-CSF barrier branch could well be very important in the manifestation of these cases of ALS.\textsuperscript{55}

Despite the absence of well proven known causes, more is known about the physiology after disease-onset. Mechanisms that contribute to cell death include mitochondrial dysfunction, protein aggregation, generation of free radicals, excitotoxicity, disrupted axonal transport, inflammation and apoptosis that inhibits regrowth of axons, is increased in the muscle of patients and in the murine model of ALS. Cell-to-cell transmission of aggregated misfolded protein, common to all neurodegenerative disorders, may be responsible for the spread of the disease in the brain.\textsuperscript{51, 52, 53}

5. Progress and Current Therapy for ALS

There is no cure yet for ALS, so, while research continues, the objective of clinical care is to maintain quality of life and prolonging life as much as possible. Management is centered on a combination of a neuroprotective medication, multidisciplinary clinics and respiratory support. Controlled trials are needed to define the best timing and role for gastrostomy, stem cells of neurodrugs, diet, supplements. Many therapies can help relieve symptoms, including anxiolytics and analgesics, which bring comfort in the advanced stages.\textsuperscript{18, 19, 20} A neurologist often oversees clinical evaluations, which are usually done every 3 months to ensure that problems are identified and treated expeditiously. Patients and families see professionals from different disciplines in one sitting, preserving energy and time. The level of experience is high
because the teams see many patients with ALS, a rare disease but frustrating for patients and their family looking for a new therapy since these teams often conventional, insurance caused care and as new of experimental therapy. Patients receive information about advanced directives, treatments for nutritional and respiratory insufficiency, and research. The education and support help patients decide ahead of time whether to choose life support and help guide the multidisciplinary team in setting goals for care. 21,22,52

The recommendations are conveyed to the patient’s primary physician so that care continues in tandem. Bulbar muscle weakness and dysphagia, arm weakness that limits the ability to lift the arm to carry food to the mouth, muscle contractions, gastrointestinal problems, fasciculations, hyper metabolism, and chronic unrecognized GI tract infections all contribute to negative calorie balance. Reduced lean body mass and less physical activity accentuate muscle wasting. The end result is weight loss, which can be rapid and lead to accelerated clinical deterioration. The rate of weight loss may be a more important predictor of disease progression than being under or overweight at diagnosis. 22,53,54 Unfortunately, multidiscipline groups have to present only these therapies that have been well established and are often doubtful of any other type of alternative therapies. Patient and family members cannot rely on these specialty clinics to give all of even some of the latest research findings that can be possibly lifesaving. Monitoring weight in the clinic is the simplest way to assess caloric balance. Calculation of body mass index (BMI) using height and weight is also used. Recommendations vary according to symptom severity: Adaptations in food texture and postural changes such as the chin tuck are sufficient for mild dysphagia. Nutritional high
protein, low carbohydrate supplements can be tried once oral intake of adequate calories becomes difficult. When positive caloric balance is no longer possible by mouth, a gastrostomy is indicated. In our experiences all forms of sugar must be avoided and the most effective diet we have found to date is one which include green vegetables, ground nuts and organic, free range fed animal meats. Avoidance of all toxins is course if necessary. While gastrostomy ensures ample nutrition, beneficial effects on quality of life and life expectancy have not yet been demonstrated and there are no randomized controlled trials that examine the effect of gastrostomy in ALS. Some patients may agree to the procedure too late in the disease to receive meaningful benefits. The ideal timing for gastrostomy awaits definition, but practice guidelines suggest that placement is safer while the vital capacity is above 50% predicted. Parenteral supplementation can be tried for those too ill to withstand a procedure.

When respiratory muscles become weak, symptoms of dyspnea, orthopnea, sleep fragmentation, daytime fatigue, and morning headaches develop. A forceless cough due to diaphragm and bulbar muscle weakness can lead to excessive secretions, poor airway clearance, and aspiration. Assessment of respiratory function includes history, physical examination, overnight pulse oximetry and vital capacity (VC). The maximal inspiratory and expiratory pressures (MIP and MEP) correlate with respiratory muscle weakness. A MIP of <60 cm H2O is a predictor of reduced survival. Sniff nasal inspiratory pressure (SNIP), a noninvasive measure of inspiratory force, estimates intrathoracic pressure, is sensitive to respiratory muscle weakness, declines predictably over time, and predicts survival.
A transcutaneous carbon dioxide sensor can detect elevated carbon dioxide levels due to muscle weakness. 25, 26

Listening to breath sounds and their lack of at the base of the lungs and/or the presence of increasing shortness of breath and sweats would all call for a chest X-Ray at use of antibiotics for treatment of pneumococcal pneumonia. The cause of death in ALS and commonly respiratory failure and often will be due to a chronic unrecognized infection at the base of the lungs. Approximately 60 % of patients have a predictable decline in function and the remainder die suddenly, from concurrent infections, pulmonary edema, and acute CHF while sometimes from other causes. Patients with ALS that have or develop sweats need to be treated aggressively with antibiotics and antifungal agents. Anti-fungal should be rotated every few day fragment drug since resistance is fragment frequent and cures frequently creating solution. If the fever or sweats persist, hospitalization should be considered for IV antibiotic therapies or the lung infection that is causing the sweats may well kill the patient. Non-invasive ventilation (NIV) is an established treatment for patients with respiratory insufficiency. The bi-level intermittent positive-pressure ventilator, which is triggered by a patient’s inspiratory effort and shuts off during exhalation, facilitates physiological breathing. When used at least four hours per day, NIV reduces the work of breathing, improves gas exchange, enhances sleep quality extends survival, and may improve cognition, as well as help stabilize weight. In the advances cases, oxygen is usually prescribed only in conjunction with NIV to prevent inhibiting respiratory drive in the setting of elevated serum carbon dioxide levels (Guidelines for prescription of NIV). 28, 32, 58
Up to now all of ALS care has been palliative because of the relentlessly progressive course. Even if we are optimistic, we have to keep open communication since it is the key to preparing patients for end-of-life decisions, and even though discussions have become more matter-of-fact, the topic is still sensitive. Hospice can be especially helpful in providing a framework for conversations about life support. The goal of ALS care in the terminal phases is to avoid suffering. Hospice teams provide symptom management through the use of medications, as well as emotional support for patients and families. Medications to relieve suffering such as anxiolytics and opioids, can be prescribed under the direction of a physician with knowledge of treating terminal diseases or a hospice team. Narcotic medications are sometime helpful for treating pain, dyspnea and nocturnal discomfort long before the final phase of the illness, but often will end the patient’s life prematurely. End-of-life palliation is usually done at home, but inpatient hospice wards can be used for patients who do not wish to die at home. 34, 51 Given the emerging new concepts ALS of pathophysiology presented here inland new methods of treating diseases, optimism should not be discouraged since hope and determination by all of us may well see these patients stabilize and even recover.

6. Future Directions

Future direction to extend life expectancy in ALS seems to be dependent on improving our understanding of its pathogenic mechanisms, which should lead to the development of earlier and specific methods to treat and manage ALS patients. The use of spinal CT exams looking for spinal nerve impingements, the testing for heavy metals, the analyses of the stool microbiome and urine organic acid testing all help identify the problems that patients with sALS
almost always have. Correction of the identified problem is very important and to be done as soon as possible and the correction of the blood-CSF barrier breech (Break), by stem cells, platelet-rich plasma and autologous conditioned serum is needed. There is a crucial need to formulate therapies that not only slow disease progression, but also deal with the secondary consequences of malnutrition and respiratory failure. A number of strategies and approaches are being tested around the world, both in the laboratory and in human clinical trials, will be important adjunct to improved clinical assessment techniques.

A. Developing stem cell therapies

A new study in the current issue of Stem Cell Translational Medicine demonstrates how human stem cells can successfully engraft, survive and differentiate into mature neurons in the spinal cord of a rat with amyotrophic lateral sclerosis (ALS). The results offer new hope for those suffering from this disease. 19, 20, 63, 64, 67

Stem cell based-therapies have emerged as a potential “stop-gap” therapy used in combination with addressing the fundamental etiologies of the spontaneous forms.

The transplantation of stem-cell derived neural progenitors may have beneficial effect not only for the replacement of motor neurons already lost, but also in counteracting degeneration and death of motor neurons. Spinal motor neurons have been successfully generated from various sources such as embryonic stem cells (ESCs) and neural stem cells (NSCs). Studies also have evaluated the therapeutic potential of bone marrow-derived human mesenchymal stem cells (MSCs) and human umbilical cord blood cells (UCBCs), but modest or
no therapeutic benefit was obtained when transplanted in ALS patients. 21, 22, 61 Our experience with stem cells have been encouraging but still not proven positive for most cases.

Stem cell therapy for incurable central nervous system disorders including ALS has long been viewed as a promising therapeutic option. Based on our experiences approaches on stem cells therapy, focusing on those of mesenchymal origin as easily accessible and well-studied. Mesenchymal stromal cells (MSCs) are a heterogeneous cell population with a remarkable therapeutic plasticity, demonstrated by their ability to dampen inflammation, inhibit pathogenic immune responses and secrete neuroprotective factors. To demonstrate and discuss the broad therapeutic potential of MSCs, this review focuses on our experiences to treat the neurological conditions: amyotrophic lateral sclerosis. 11, 15, 67

Considering the problems of new drug present development. In sum, since no in vitro or in vivo system can guarantee success in humans ALS, consistency of preclinical data, identification of a credible mechanism, evidence of CNS penetration and efficacy in a well-designed animal trial are the foundation of sufficient scientific rationale to study a new drug in people. Adequate toxicology studies in animals also are needed before the US Food and Drug Administration will allow human trials. 61, 62

These statements reflect the past scientific thoughts that have wasted untold amounts of time, energy, and money. Since no explanation of the cause of sALS have been proposed that provide even a modicum of factual support up to the time of our suggestion of sALS being a multi factorial disease consisting of neurovascular spinal artery damage, a spinal cord barrier breach and some kind of chronic infection that induces production of superoxide at the
intestinal mucosa and with subsequent oxidation and aggregation of SOD, ubiquition, FUS, etc. The question of when the SOD1 is bring produced is debatable since yeast and bacteria both produce high amounts of SOD. When SOD1 in being a hacked by superoxide produced by PMN’s. SOD1 aggregates are thought to form and to be carried into the CSF at the site of recent Blood-CSF barrier breach.

Autologous bone marrow-derived MNC transplantation represents an alternative therapy for ALS for which there is either no treatment available or conventional treatments have failed to work. The MNCs obtained from bone marrow are comprised of a variety of cells like hematopoietic stem cells, tissue-specific progenitor cells, stromal cells, and specialized blood cells in different stages of development. 37,38

Our experiences and studies have indicated that stem cells migrate to the site of injury from the site of injection or they produce positive results by secretion of cytokine of growth factors. Bone-marrow stem cells work by enhancing angiogenesis and contributing to neovascularization by producing signaling molecules such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF2). Along with an increase in angiogenesis they also promote tissue remodeling, prevent apoptosis, decrease inflammation, and activate satellite cells. 40,41,42

Administration of autologous bone marrow-derived stem cells in patients with subacute and chronic spinal cord injuries has resulted in improvements like changes in ASIA scale as well as electrophysiological changes. In the case of ALS, published data have revealed that cell
transplantation in patients suffering from ALS is safe and shows apparent neurological improvements. 37, 61

**B. Improvement of the clinical Management**

Symptomatic treatments remain the cornerstone of management for patients with ALS. For some patients, these treatments not only alleviate symptoms but also improve survival and quality of life. Optimum care for patients with ALS is provided by coordinating care with a team multidisciplinary where physiotherapists, occupational therapists, speech therapists, respiratory physicians, gastroenterologists, and social workers collaborate to guide symptomatic management through the course of disease. Multidisciplinary models of care have developed as a predictor of survival, reducing the risk of death by 45% at 5 years. Compared with patients managed in a general neurology clinic, patients managed in a specialized clinic had a better quality of life, possibly attributable to more effective use of resources, with benefits derived after a single visit. Respiratory function and nutrition are crucial symptomatic concerns for patients with ALS, with respiratory failure being the main cause of death. Expert consensus guideline recommendations have been developed for key care concerns in ALS, including respiratory management, nutrition, and palliative care. 9, 39, 61, 65, 66

These guidelines, may now need to be revamped in light of autopsy studies that demonstrate that 100% of ALS patients brain and spinal cords contain yeast antigens. In addition are some reports of spontaneous remissions appearing from patients who have eliminated all forms of carbohydrates and lived on green vegetables and meat in order to decreases their yeast infections. The new concept of the existence of a CSF-Blood barrier
breach in combination with a chronic smoldering infection process that provide toxic aggregate
to the spinal cord given at least same medicine of hope to those as by their terrible conditions.

Declaration of interest:

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