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Review on Motor Neuron Disease: Pathogenesis, Biomarkers, Diagnostics, and Current Therapeutic Approaches.

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Keywords

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Abstract:

Motor neuron disease (MND) is a severe adult-onset neurodegenerative disorder that most commonly presents as amyotrophic lateral sclerosis (ALS). It is the third most prevalent neurodegenerative disease after Alzheimer's disease and Parkinson's disease. Over the past ten years, there have been significant improvements in patient treatment as well as a rapid growth in scientific research. Consequently, it now seems possible to develop sensible medications based on significant pathogenic pathways. ALS shows significant variation in both its presentation and subsequent course of clinical development, with an average one-year delay between the beginning of symptoms and diagnosis. A significant percentage of patients survive into their second decade, even though 50% of them die within 3–4 years after the onset of symptoms, mainly from respiratory failure.

Although motor neuron disease is typically sporadic, 10% of cases have a genetic component. According to recent studies, new genes linked to motor neuron diseases have been found. It has been challenging to identify targets for neuroprotection, rehabilitation, and pathological motor neuron disease. The study of pathophysiological pathways through biomarker research increases our understanding of disease and identifies targets for new therapeutic approaches. Males are more likely than females to suffer from motor neuron disorders. The medication used to treat the disease was the riluzole, a disorder modification agent. These medications have the ability to enhance life's cycle. In the treatment of motor neuron disorders, multimodal intensive care is essential This review describes the most important findings and highlights the developments in the pathophysiology, diagnostics, and biomarkers of the disease, as well as the state of motor neuron disease treatment at the moment.

Abbreviations: MND: Motor Neuron Disease; ALS: Amyotrophic Lateral Sclerosis; UMNs: Upper Motor Neurons; LMNs: Lower Motor Neurons; FTD: Fronto-Temporal Dementia; EMG: Electromyography; Progressive muscular atrophy (PMA).

Conclusion:

Several biomarkers and recently released medications with strong pharmacological effect are used in this investigation. Every neurological condition, including ALS, UMND, LMND, FTD and other, affects the neurons that regulate signal progression and provide the muscular system strength. One of the primary contributions to the development of neuronal abnormalities and the promotion of neurological illnesses is the ubiquitinated protein TDP-43. Previous studies have shown that mutation in the TARDBP and FUS genes also cause neuronal degeneration and muscular atrophy.

1. Introduction

Motor neuron diseases (MNDs) are a group of neurodegenerative disorders associated with the degeneration of motor neurons in the upper and lower extremities [1] It is characterized by selective degeneration of both the upper motor neurons (UMN) and lower motor neurons (LMN), which results in progressive weakening and wasting of the limb, bulbar, and respiratory muscles. Most of the cases are rare and impact older adults who are in their sixth or seventh decade of life. [2] Some MNDs are inherited, however most causes of most MNDs are not known. In sporadic or non-inherited MNDs, environmental, toxic, viral, or genetic factors may be implicated. Based on the region of origin and the degree of neurological involvement, there are four primary phenotypes of motor neuron disease: Amyotrophic lateral sclerosis, Primary lateral

Journal of Chemical Health Risks

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sclerosis, progressive bulbar palsy, and progressive muscle atrophy[3]. It is the third most prevalent neurodegenerative disease after Alzheimer's disease and Parkinson's disease.[4] The most frequent clinical manifestation of motor neuron disease (MND), also referred to as Lou Gehrig's disease, is ALS. MND is a neuromuscular disease that progresses and ultimately results in death. After an of cial diagnosis of ALS, the majority of individuals die within two to ve years. Familial ALS (ALSf), a genetic type of the illness, affects 5–10% of sufferers. People of many races are affected by ALS, and there is currently no national treatment for the disease. The second most common cause of dementia in the elderly is front temporal dementia, which can occasionally be clinically, pathologically, and genetically linked to ALS. [5,6] The most prevalent motor neuron disease, amyotrophic lateral sclerosis, is characterized clinically by widespread paralysis that usually results in respiratory failure and death. Fifty percent of patients pass away within 15 to 20 months after diagnosis. [7, 8] The number of MND patients will rise due to 4 3 5 population aging and advancements in supportive care. The male-to-female ratio is 3:2, indicating a little male predominance. The usual life expectancy for people with motor neuron disease (MND) is three to ve years; however, approximately 5% of patients have been observed to survive up to ten years. Even though the pace at which the disease advances varies, ALS always leads to death, and in most cases, respiratory muscle weakening and subsequent respiratory failure are the cause of this.[9]

2. Classification of motor neuron disease

1. Amyotrophic lateral sclerosis (ALS)

ALS is characterised by mixed picture and is primarily caused by decline in upper motor neurons (UMN) and lower efferent neurons (LMN). [10] Typical symptoms include trembling, cramping, and weakness in the muscles, which eventually result in a loss of power. Typically, during this period, symptoms such as dysphagia and dyspnea are experienced by the patient. Signi cant patient fatality in the event that the respiratory system malfunctions. [11]

2. Progressive muscular atrophy (PMA) is an illness that mostly affects the lower motor neurons. Although there are some upper motor neuron indications, the disorder is primarily characterized by the death of the lower motor neurons. The progressive atrophy of muscles is necessary for the degeneration of the spine's bottom efferent neuron, which is absent along with the superior efferent neuron and bulbar characteristics. Previously, however, such as the undeniable truth of progressive muscular atrophy due to variations in motor neuron disease caused by amyotrophic lateral sclerosis, there was contestation along with doubt regarding the logic of the condition. Additionally, a veritably slow progression has been described by some in cases of progressive muscle atrophy; however, this is not always the case in cases when the condition lasts 4 3 5 for 20 to 30 years. [12, 13]

3. Primary lateral sclerosis (PLS) is an extremely uncommon kind of motor neuron disease. These often include the stylish prognostic along with the upper motor neuron. In the end, only a few numbers of lower motor neuron elements may be generated. It should come as no surprise that efferent nerves survive in large-optical strength and that the vaginal wall is unaffected in all forms of motor neuron disease. Genetic variants that encourage defense are through the domestication of amyotrophic lateral sclerosis.[14]

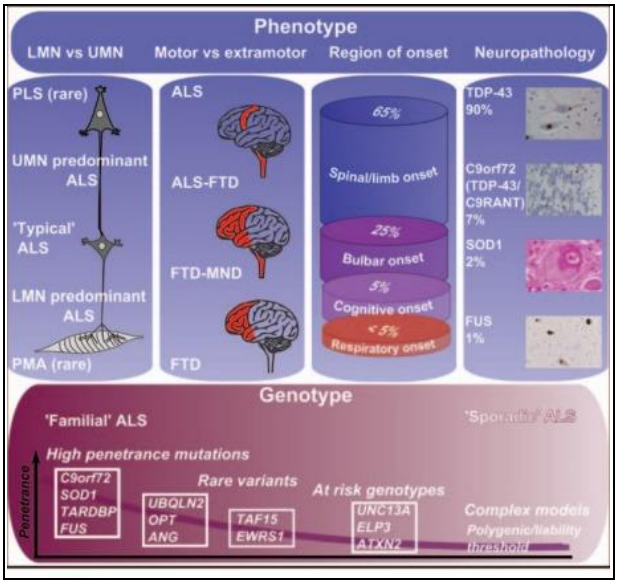

Figure 1. Classification and nomenclature of MND. Note: Clinical, neuropathological, and genetic characteristics can all be used to categorize MND. Crucially, a discrete clinical phenotype is not predicted by a particular genetic or neuropathological group. PLS, or primary lateral sclerosis; PMA, or progressive muscular atrophy; LMN, or lower motor neuron; UMN, or upper motor neuron.

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JCHR (2024) 14(3), 3020-3029 | ISSN:2251-6727

3. Epidemiology:

Though research is insufficient, ALS is thought to occur globally, particularly in China, India, and Africa, where rigorous epidemiology has not yet been conducted.[15] Eight hotspots for the ALS-Parkinsonism-Dementia complex have been identified; they are pathologically unique and exceptional, and the etiology of the condition is still poorly understood. The hotspots are located on the Pacific island of Guam and the Japanese Kii Peninsula. According to a UK population-based study, the annual incidence of ALS is 2.6 per 100,000 people for women and 3.9 per 100,000 people for males. These figures translate into lifetime risks of 1 in 472 and 1 in 350, respectively. [16] According to a UK population-based study, the annual incidence of ALS is 2.6 per 100,000 people for women and 3.9 per 100,000 people for males. These figures translate into lifetime risks of 1 in 472 and 1 in 350, respectively. [17]. Even though minors can occasionally be diagnosed with ALS caused by genetic anomalies in FUS, the disease is highly rare in people under 30 years old, and cases often proceed aggressively. After 40, there is an increase in the risk of having ALS, which peaks in the early 1970s and then mysteriously declines in frequency. A lower age at symptom onset is a positive prognostic factor. ALS patients have a large 4 3 5 prognostic variance even though population-based studies have indicated a median survival of roughly 3-5 years from the beginning of symptoms. Several medical professionals strongly believe that patients with ALS have lower BMIs and higher-than-average levels of pre-morbid physical fitness, even though no consistent environmental risk factor has been identified. One plausible explanation for this correlation is that there may be a genetic profile that predisposes to athleticism but may also be more tolerant of motor system degeneration in later life. [18 19] The estimated number of motor neuron disease cases and fatalities in India in 2019 was 25000 (95% UI 19900–31500) and 1600 (95% UI 1220–1990), respectively. The crude DALY rate of motor neuron disorders varied by 1·7 times between the states, with Goa, Uttarakhand, Punjab, and Himachal Pradesh having the highest rates. The SDI of the states showed a highly significant positive association with the crude and age-standardized prevalence and crude DALY rate of motor neuron disorders, while the age-standardized DALY rate showed a moderately favorable link. From 1990 to, there was an increase in the DALY rates and crude and age-standardized prevalence of motor neuron disorders.[20]

4. Pathogenesis:

The hallmark of motor neuron illnesses is the specific degeneration of motor neurons, encompassing the cranial motor neurons, motor neurons in ventral horn cells, and pyramidal fibers in the cerebral cortex. Ninety percent of MND cases are sporadic; no family history or recognized cause is known for them. 10% of instances remain, and these are classified as familial if they exhibit a family history or test positive for a known genetic mutation that is linked to the condition. As a result, SOD1 gene mutations are present in roughly 20% of 4 3 5 people with inherited forms of amyotrophic lateral sclerosis (ALS). [21] Superoxide dismutase, an enzyme that scavenges free radicals and lowers cellular oxidative stress throughout the body, is encoded by the SOD1 gene. ALS is the most prevalent kind of MND, and individuals with it show signs of both anterior horn cell and corticospinal tract dysfunction. One kind is progressive muscle atrophy (PMA), which only involves a reduced amount of motor neurons. Compared to ALS, it has a better prognosis, an earlier mean age of start, and is slightly more frequent in men. Primary lateral sclerosis (PLS), which only affects the top motor neurons, is another kind of motor neuron disease. It appears that PMA and PLS contribute to about 4 and 2% of instances of MND, respectively [22]. However, over time, many of these people develop ALS.[23] SOD1 is a significant type of motor neuron illness that results in suffering individuals demonstrating evidence of corticospinal tract failure as well as anterior cornucopia cell dysfunction. PMA is a variant found in the lower efferent nerves. These are less common in men with better prognoses and earlier mean onset ages than in those with amyotrophic lateral sclerosis. Additionally, PLS (primary lateral sclerosis) at most efferent nerve deformation are other forms of motor neuron disease. About 2 and 4% of patients with motor neuron disease have progressive muscular atrophy and primary lateral sclerosis, respectively [22]. Nevertheless, many of these instances

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progress to amyotrophic lateral sclerosis over time[23]

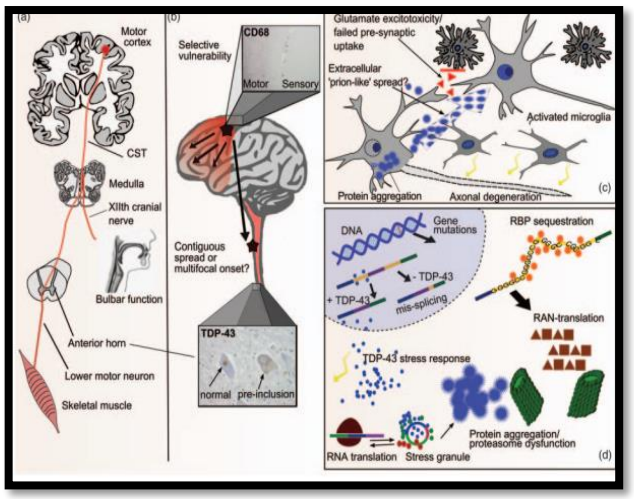

Fig 2: Overview of the pathogenic mechanisms of ALS, ranging from neural systems to tissues to molecules.

(a) Motor neurons in the corticospinal tract (CST), anterior horn of the spinal cord (LMN), and motor cortex (UMN) are affected by ALS. Brainstem LMN loss and corticobulbar tract involvement sometimes coexist to cause bulgar dysfunction.

(b) The disease mostly affects the frontal lobe of the brain, sparing areas like the sensory cortex (see the inset for a CD-68 stain of a section that 4 3 5 includes the primary motor cortex (labeled "M") and primary sensory cortex (labeled "S"). The disease can spread over functional linkages or neighbouring anatomical regions. A possibility is a multifocal onset (lower inset: TDP-43 stain of spinal motor neurons reveals cells with diseased and normal nuclear TDP-43 in some neurons inclusions logical cytoplasmic).

(c) Affected motor neurons show signs of protein aggregation, primarily of TDP-43. It is speculative that prion-like protein clumps can move from one cell to another. Another possible method of cell-to-cell transmission is glutamate excitotoxicity, which is partially caused by astrocytes' inability to absorb glutamate at the synaptic pore. Disease progression could be influenced by activated microglia that have pro-inflammatory characteristics.

(d) It is believed that TDP-43 exits the nucleus as a result of a physiological stress reaction. Stress granules momentarily halt specific mRNAs' translation, but the translating polysomes eventually resume it once the stress has subsided. Stress granule-derived TDP 43 could be the first stage of pathogenic TDP-43 aggregates, which urothelial DP-43 then removes. This could then result in abnormal pre-mRNA splicing. The hexanucleotide repeat expansion in C9orf72 is one example of a "toxic" RNA species that can trap other RNA-binding proteins (RBP). Additionally, this results in accumulating dipeptide repetitions that the machinery responsible for protein breakdown must remove [24].

5. Biomarkers:

Biomarkers that could improve prognostic classification, expedite diagnosis, and track therapy response are necessary. At the moment, trials use the less sensitive modified ALS Functional Rating Score (ALSFRS-R) change in slope or survival as the main endpoint. Neuro inflammatory chemicals, TDP-43, and CSF neuro laments may reject features of the onset and course of illness, but they need to be controlled in large cohorts. In neurophysiology, techniques like 4 3 6 electrical impedance myography and Motor Unit Number Estimation (MUNE) offer quantitative LMN biomarker opportunities [25]. Cortical hyperexcitability determined by transcranial magnetic stimulation exhibits encouraging special city for ALS.23 Even though routine clinical MRI is frequently used to out structural lesions in the differential diagnosis of ALS, more advanced quantitative applications have developed that are establishing the bar for defining a systems-level biomarker signature. Diffusion tensor imaging assessments of white matter tract integrity and surface- and vector-based rule cortical morphometry have demonstrated potential across pathologies [26]. The loss of corpus callosum integrity, weakening of the corticospinal tract, and 7 5 primary motor brain atrophy are consistent results. [27] Functional magnetic resonance imaging (fMRI) can be used to evaluate the networks known as resting states in order to detect alterations in functional connectivity that might be pathologically linked to structural alterations. Even while no single neuroimaging finding has yet made it feasible to distinguish between illness states at the individual level, it is believed that a combination of markers would be effective [28]

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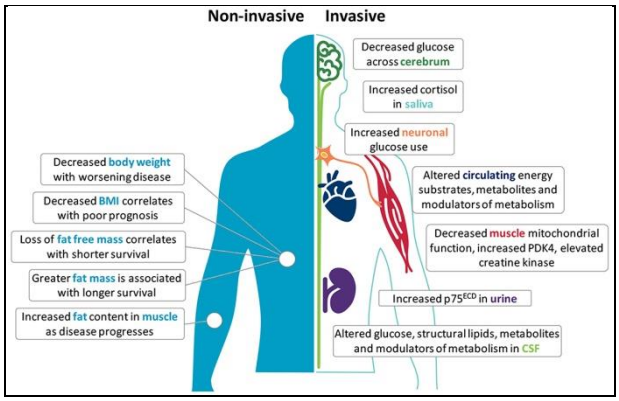

Figure 3: Potential metabolism biomarkers in amyotrophic lateral sclerosis (ALS). The metabolic changes associated with ALS present an opportunity to apply metabolic biomarkers for illness classification, diagnosis, and monitoring. Non-invasive anthropometric measures include body weight, body mass index (BMI), fat-free mass, fat mass, and fat distribution. Invasive procedures include the collection of samples of urine, saliva, blood, cerebrospinal fluid (CSF), muscle tissue, and the use of F18-PET to evaluate glucose metabolism in the central nervous system. When combined with complementary biomarkers (such as neurophysiology and imaging), these 4 3 6 7 5 markers may offer deeper insights into metabolic perturbations that may be responsible for the onset and progression of the disease, even though there aren't many independent markers that are specific, repeatable, or able to track disease in ALS.[29]

6. Clinical feature and diagnosis:

A comprehensive approach that includes a clinical history and symptom evolution, a thorough neurological and neuromuscular examination that includes strength testing, deep tendon and pathological reflexes, and confirmatory neurophysiological studies like nerve conduction studies and needle electromyography is necessary to diagnose ALS in any given patient. Genetic testing is becoming more popular, but there are limitations. The diagnostic process at the bedside or office is still not ideal, but the toolkit of existing techniques and emerging biomarkers is growing. [30] Progressive motor weakening without sensory disruption is ALS's clinical characteristic. UMN and LMN involvement are typically combined to cause loss of motor function, and few plausible mimic illnesses exist where both are clearly seen on examination. [31]

The most difficult instances to diagnose are rare, "pure," LMN or UMN cases, which are usually also more slowly progressing. However, it is rare for a treatable condition to go unnoticed in this situation. Patients experience significant distress when they are not provided with the necessary support due to postponing diagnosis.[32] One prominent feature of ALS is the sign of fatality onset. Patients initially present with dysarthria (30%) or a weak leg (60%) as a result of bulbar dysfunction. FTD and respiratory weakness are also frequent manifestations (both 5%). Two distinct spatially isolated forms of ALS can be 4 3 6 7 5 identified: the ail arm or "man-in-a-barrel" condition, which involves bilateral proximal and often LMN-predominant arm weakness, and the ail leg or "pseudopolyneuritic" syndrome, which typically advances significantly more slowly [33]. While bulbar-onset ALS is usually associated with a faster onset of symptoms, a subgroup of patients, usually older women, may develop severe emotional symptoms along with rapid cortico-bulbar involvement (UMN predominant) that remains isolated for months or even years before the limbs weaken. Bulgaronset patients are frequently misreferred to TIA or ENT clinics, and overinterpreting incidental spondylotic disease in patients who have weakness in one or more limbs can result in unnecessary spine surgery [34]. Weakness progressively extends to additional body parts as ALS worsens. If cognitive impairment manifests at all, it usually does so early in the disease process, sometimes with associated behavioral abnormalities and a faster rate of progressive muscle weakness. A milder form of dysexecutive disorder, which does not obviously deteriorate as quickly as motor weakness, affects up to 50% of patients [35]. In ALS, progressive ventilation failure is typically the cause of death. Patients should be particularly reassured that choking is not a common cause of death, even in cases of severe bulbar weakness. The clinical diagnosis of ALS is based on the presence of a combination of UML and LMN symptoms, as well as a history of progressive motor dysfunction, including weakness and loss of talent. UMN signals can be difficult to elicit at times. LmN enervation can be demonstrated using the electromyography (EMG) technique [36]. However, because EMG is only 60% sensitive, it shouldn't be utilized as a necessary diagnostic test. The diagnostic procedure for ALS in a research setting has been codified by the El Escorial criteria, which classify the disease as

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JCHR (2024) 14(3), 3020-3029 | ISSN:2251-6727

"possible" or "probable" and correlate diagnostic certainty with the number 4 3 6 7 5 of body regions of cited clinically or neurophysiologically [32] Although the neurophysiological aspects of the El Escorial criteria have been enhanced by the Awaji criteria, likely increasing their sensitivity, they remain exceedingly stringent when applied in clinical settings. Planning the timing of therapies such as non-invasive ventilation or gastrectomy requires a reliable diagnosis and an understanding of how each patient's disease will progress. These goals are achieved through clinical evaluation. Initiatives aimed at sickness "staging" that may be helpful in treatment trials have their roots in these accomplishments [37]

7. Treatment

Unfortunately, riluzole, which is believed to have a generally anti-glutamatergic mode of action the only medication to show a survival advantage in human ALS patients. Its effects are quite small; in the context of clinical trials, it extended mean survival from 12 to 15 months. New treatment approaches include those targeted at enhancing muscular function. Antibody NOGO-A, for instance, is believed to promote axonal development based on models of spinal cord injury. The creation of a multidisciplinary team approach within specialized clinics, headed by neurologists with a focus on ALS and supported by a specialized nurse, occupational therapist, speech and language therapist, dietician, physiotherapist, and connections to respiratory and gastroenterology teams, has had a significantly higher impact on patient's quality of life.25 Nutritional management, which includes prompt gastrostomy to preserve the quality of life in dysphagic patients, is a critical intervention to take into account. Non-invasive ventilation is linked to notable increases in survival and quality of life. Patients rarely opt for invasive tracheostomies since they do not lessen the chance of cognitive impairment or the inevitable loss of limb function. Palliative 4 3 6 7 5 care services are usually used to provide close support during the end of life in individuals with ALS. Boost individuality and improve the standard of living. In general, medications are beneficial for treating autonomic disorders based on limited research and personal experiences.[38] Table No.2. Symptomatic treatment of motor neuron disease [39]

Motor dysfunction Symptoms Pharmacological management (treatment) Dyspnea Morphine, Lorazepam Excess saliva Amitriptyline, atropine Spasticity Baclofen, clonazepam Cramps/ fasciculation Carbamazepine, magnesium Thickened saliva Nebulized mucolytics, normal saline nebulizers Laryngospasm/ paroxysmal choking Lorazepam, morphine Nonmotor dysfunction Symptoms Pharmacological management Pain Paracetamol, ibuprofen neuropathic, gabapentin, pregabalin, musculoskeletal Constipation Aperients, suppositories Sleep disturbance Amitriptyline, benzodiazepines Emotional Amitriptyline, citalopram, lability/depression Mirtazapine Cognitive dysfunction Memantine, antidepressant Recent research indicates that the role that medication plays in helping patients with motor neuron disease survive by providing them with a specific, limited treatment is a crucial aspect of how the disease functions. A productive operation could also optimize the working [.40]

Table No.2. Symptomatic treatment of motor neuron disease[39]

Motor dysfunction Symptoms	**Pharmacological management (treatment)**
Dyspnea	Morphine, Lorazepam
Excess saliva	Amitriptyline, atropine
Spasticity	Baclofen, clonazepam
Cramps/ fasciculation	Carbamazepine, magnesium
Thickened saliva	Nebulized mucolytics, normal saline nebulizers
Laryngospasm/ paroxysmal choking	Lorazepam, morphine
Non motor dysfunction Symptoms	Pharmacological management
Pain	Paracetamol, ibuprofen neuropathic, gabapentin, pregabalin, musculoskeletal
Constipation	Aperients, suppositories

Journal of Chemical Health Risks

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JCHR (2024) 14(3), 3020-3029 | ISSN:2251-6727

Sleep disturbance	Amitriptyline, benzodiazepines
Emotional	Amitriptyline, citalopram,
lability/depression	Mirtazapine
Cognitive dysfunction	Memantine, antidepressant

New Therapy:

An increasing number of exploratory drugs are being developed as a result of the meager results of the FDA-approved treatments now available for such a severe illness. With a common master protocol and central infrastructure, the ALS platform trial's development enables the testing of several agents at the same time.[41] Research is being done on a minimum of fifty small compounds with different processes. Growing interest in the use of antisense oligonucleotides, a treatment that targets pathogenic gene expression in hereditary variants of ALS, has been spurred by its efficacy. The FDA's expedited approval of towers for the treatment of SOD1-ALS in April 2023 is evidence of this. Numerous phase 1-2 trials investigating the efficaciousness of various antisense oligonucleotides targeting FUS and C9ORF72 are underway. A phase 1 trial is also investigating vectors for gene therapy utilizing adeno-associated virus to lower SOD1 concentrations. Phase 2 clinical studies are being conducted to assess monoclonal antibodies that target misfolded proteins. [42]

8. Future Scope:

Acknowledging cognition as the "third space" in addition to the conventional UMN and LMN pathology in ALS is yielding new pathogenic insights. Since ALS and FTD are now recognized as spectrum disorders, the idea of selective susceptibility has expanded to include neural networks as opposed to specific cell types.[43] The idea that poisonous prion-like proteins could aid in the spread of disease in adjacent areas is being actively explored at the systems level. This theory states that important ALS proteins, such as SOD1, TDP-43, and FUS, 4 3 6 7 5 initiate foci of aggregation that can spread by permissive templating from one cell to another or via glial cells.[44] The concept of "spread" of disease is strongly tied to the puzzle of selective vulnerability in ALS. This explanation is an appealing t to the clinical observation that disease appears to spread from a primary place of onset to a neighbouring area. [45] It is still unclear why certain subpopulations of motor neurons—such as those feeding the extraocular muscles—are noticeably resistant. These kinds of motor neurons are known to differ physiologically, and now that variations in their transcriptomes have started to show up, we may be able to understand the molecular basis of neuronal vulnerability better.[46] It is increasingly evident that ALS is a condition with a diverse etiology. By making use of the capabilities of current sequencing technologies, the complete genetic contribution to this could be clarified over the next 10 years. This should lead to the development of improved disease models. Currently, TDP-43-based rodent models, as opposed to SOD1-based ones, might more accurately represent the majority of cases of human ALS; however, simulating the wider impacts of pathophysiological. Gene therapy for ALS may be possible if a harmful mutation is present. Antisense oligonucleotides may potentially target the C9orf72 hexanucleotide expansion in order to reduce RNA toxicity; this strategy is already being used to treat myotonic dystrophy. However, only a small percentage of patients would bene t from such highly individualized therapies. As a result, strategies that focus on common pathways will need to take advantage of our growing understanding of the intricate molecular and physiological changes that occur downstream of the genetic defect. Techniques to improve or restore cortical inhibitory intraneuronal functioning could be one example.[47]

Since pathological events most likely happen years, if not decades, before 4 3 6 7 5 symptoms appear, studying pre-symptomatic people with high-risk ALS mutations presents a special opportunity to identify the very rst alterations and possibly start thinking about primary prevention.[48] In a far shorter amount of time, than could have been predicted ten years ago, an approaching therapeutic era for ALS appears assured if the rate of molecular, cellular, and systems-level neuroscientific discovery continues its exponential climb.[49] More research on the pathophysiological rami cations of recent genetic discoveries, such as the C9orf72 mutation, may shed light on the onset, progression, and susceptibility to disease. Patients with motor neuron disease (MND) will live better lives while they wait for these advancements in care.[50]

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9. Conclusion

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