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Review article

A short clinical perspective on the disease amyotrophic lateral sclerosis

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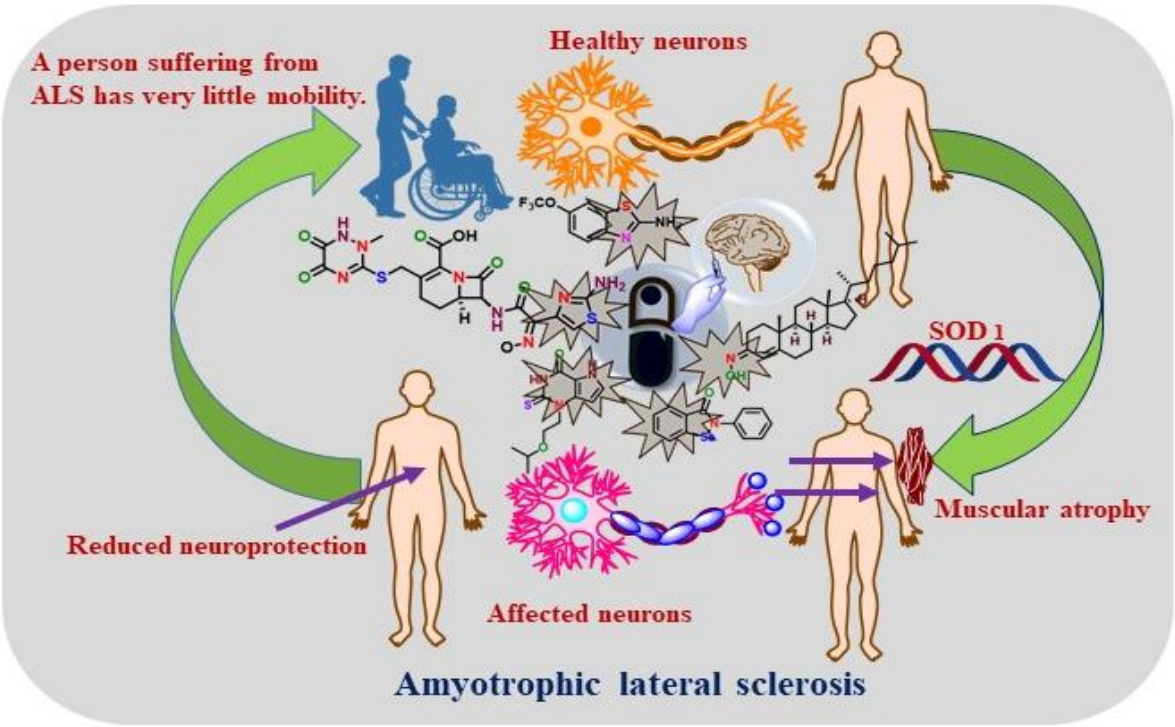
ABSTRACT

There are sporadic and inherited variants of the motor neuron disease amyotrophic lateral sclerosis (ALS). Young and middle-aged persons are more likely to get ALS, and there aren't many therapies for it. Even though frontotemporal dementia mostly affects the nervous system and the fact that cognitive and behavioral symptoms have been documented for more than a decade, there are signs that ALS and frontotemporal degeneration coincide medically, radiologically, and pathologically, in addition to genetically. Cognitive decline in ALS is characterized by personality changes, irritability, obsessions, a lack of comprehension, and extensive abnormalities in frontal executive functions.



The alterations in personality, social behavior, and executive function seen in frontotemporal dementia are consistent with this presentation. We also provide guidelines for the clinical assessment of frontotemporal dysfunction in patients with ALS. Improved protection for victims and their households as well as useful insights into the biology of neurodegeneration will result from knowledge of cognitive damage in ALS.

Keywords: Amyotrophic lateral sclerosis, Nervous system, Cognitive diseases, Cell mutation, Neurodegeneration.

INTRODUCTION

ALS, also referred to as Lou Gehrig's illness or Charcot's disease, is the most prevalent type of motor neuron disease. The condition manifests in life and is brought on by the death of motor neurons, which leads to a progressive atrophy of related connective tissue and supporting cells. In contrast to similar motor neuron illnesses that typically affect just one group of nerves (Primary Muscular Atrophy and Primary Lateral Sclerosis), people who have ALS often notice the inclusion of both the smaller motor neuron (LMN) and upper motor neuron (UMN). Muscle wastage and weakness, particularly in the limbs, cramping, twitching, and speech difficulty aretypical ALS symptoms [1]**.** About 25–30% of patients experience a bulbar outset of the illness, which can present as disabilities, difficulty swallowing, dysphonia, or, in the case more rarely, masseter paralysis. In ALS, there is a wide range in the generation at the beginning, the site of development, and the speed of disease development.

Most individuals with the condition experience unrelenting progression, with an intermediary survival time of roughly 3 years following the onset ofsymptoms, with the primary cause of death being respiratory failure**.** While 35–40% of patientswill experience modest behavioral and/or cognitive abnormalities, front temporal dementia (FTD) can be further diagnosed in 10–15% of instances [2]. Clinical manifestations of FTD include social defects executive functioning limitations and/or linguistic difficulties. FTD can be defined by temporal and anterior temporal lobe atrophy. [3]. the rate at which muscular function deteriorates is positively impacted by riluzole. Even though the drug's exact mechanism of action is yet unknown, this suggests that it may interfere with the disease process [4].

Alteration to the Superoxide Dismutase 1 (SOD1) Gene

Some of the proteins responsible for neurodegenerative diseases may have properties in common with prions, including the ability to capture wild-type proteins, trigger their miss folding or aggregation, and serve as cell-to-cell carriers. The individual's SOD1 gene, which is found on chromosome 21 [5], codes for the homo dimer metallo protein known as human SOD1, which is composed of 153 amino acids and comprises the ions zinc and copper. To reduce oxidative stress, SOD1, a free radical capture, uses Cu and Zn ions to dismutase free superoxide radicals ($O_2^{\bullet-}$) into molecular oxygen (O_2) and hydrogen peroxide (H_2O_2). Human catalase [6] then converts these molecules into water and oxygen. Changes within $SOD1^{WT}$ (wild-type SOD1) in the spinal cord of sporadic ALS persons, participating in endogenously modified SOD1 to protein aggregation that was suggested by Gruzman et al [7] in 2007. Further, Forsberg supported Gruzman's evidence by identifying small aggregates of miss folded SOD1 [8].

Epidemiology

Two to three cases of ALS per 100,000 people have been reported in communities in Europe and those of European origin [9-11]. In the age group with the highest probability of acquiring ALS (50-70 years), the incidence ranges from 4 to 8 per one Lakh in a year. The mean Life time at which symptoms first appear is between 58 and 63 years for random ALS and between 40 and 60 years for hereditary ALS [12]. For men, the risk is approximately 1:350, while for women, it is 1:400 [13-14]. Most community-based studies have shown that men are more likely than women to develop ALS, with 1–2 men developing the disease for every woman [15].

Etiology

ALS is accepted to be conducted by a confluence of genetic, habitat, and abnormal ageing factors, similar to additional neurodegenerative diseases. Beyond 20 genes have been affiliated with the condition genetically to date, and it is proposed that further genetic components will be found. While monogenetic mutations with elevated effect sizes now account for 15% of ALS cases, the genetic architecture of the disease appears to be complicated, and both ordinary and occasional genetic variants with low and tolerable outcome sizes tend to increasethe chance of developing ALS [14, 16]**.**

Cognitive Deterioration Tendencies in ALS

Whereas there is a proven link connecting some types of ALS and front temporal memory disorder, it is yet unknown how frequently, severely, and over time classic ALS patients have Alzheimer's disease. While impairments in memory and language are less well understood, anomalies in the executive system, including spoken proficiency and consideration, are the cognitive alterations in ALS that are most frequently described.

Executive Function

Traditionally, executive functions have been seen as more advanced thought processesthat coordinate and direct other aspects of cognition act. Nearly every investigation of cognitive damage in ALS has revealed impaired verbal fluency, an indication of injury to frontal or striatofrontal areas responsible for the intrinsic beginning of answers. A proportionatedrop in category fluency would indicate a more general semantic impairment, whereas concurrent effects on both forms of dexterity reflect dysfunction in executive system components. However, adjustments to account for response time can enable individuals with upper limb difficulties, and as a result, writing

ailments, to be examined in a meaningful manner.For instance, Abrahams and colleagues [17] created a verbal fluency index using the time it took clients to copy words they had written before in fluency tests. (The typical period it utilized to process the thought of every phrase was estimated as the total amount of time givenfor the exam, minus the years it took to replicate every single word produced allocated by the overall number of words generated.

Reminiscence

Memory issues with ALS remain up for dispute. Intelligence research has revealed individuals with ALS often suffer memory difficulties that lead to acute recall issues. The wide range of weaknesses in postponed recall suggests that the problem lies in the storing of data, and not in how quickly it is forgotten [18]. These findings are in line with hypotheses now held to be true, according to which encoding is an executive ability to remember as it includes a neural loop that originates in the left frontal lobe [19].

Visuoperceptual Function

The several processes that make up visual perception include object identification, object recognition, and attention. Many ALS patients' visual perception mechanisms are still mostly intact [19, 20], but Strong and colleagues [21] have identified several visual shortages. Victims with ALS who also have front temporal mental illness frequently have minimal trouble finding their way around their own homes, finding objects, mimicking non-representational hand gestures, and recognizing their hometown on a map [22].

Language

Language networks appear to be impaired based on Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) tests of ALS patients [23].This validates the previous results that extra motor pathways are affected by ALS. Rakowicz and Hodges [24]. Reported that significant language impairments were observed in patients with ALS and damage, especially on assessments of vocabulary and syntactic comprehension. Individuals with ALS who did not also have mental disease showed a deficiency in language output characterized by trouble finding and identifying words and a tendency to employ semantic errors or circumlocutions. Both groups performed well on tests of conceptual comprehension and grammatical structure. Another possibility is that language impairments are a distinct category of dementia caused by ALS and develop independently of cognitive impairment. Studies relating GRN mutations to ALS, classic front temporal dementia, and a non-fluent progressive aphasia within a single family lend credence to the notion that some forms of ALS and front temporal Alzheimer's disease constitute a continuous process [25].

Social Cognition and Emotional Processing

Several studies have reported a decline in the ability of front temporal dementia patients to socially engage, which is crucial [2]. People with frontal-variant front temporal dementia (fvFTD) have difficulty recognizing all emotions, but particularly fury and disgust, as shown by Lough and colleagues [26]. This may assist in explaining why these individuals had difficulty identifying social transgressions. According to their caregivers, these people also demonstrated unusual empathy. Lule et al. [27]. Showed 52 moving picture slides to 12 patients with sporadic ALS. Functional magnetic resonance imaging (fMRI) was used to measure the brain responses to effective photographs, and the researchers also collected subjective measures of activity and satisfaction. In the extra striate and upper isolated visual regions, ALS patients showed a lower level of response compared to other participants. This demonstrates how brain and behavioral alertness decline with the progression of ALS [28].

Behaviour

The identification of behavior deficiency as a symptom of ALS is spreading. As per assessment instruments such as the Frontal Behavior Inventory, Frontal Systems Behavior Scale, and Neuropsychiatry Assessment, a percentage of up to sixty-three (ALS patients) display symptoms of apathy, irritability, stiffness, restlessness, and dis inhibition. Victims of ALS with a bulbar onset begin in the motor neurons of the head, neck, and face. When ALS begins in one part of the body and spreads to the bulbar region, it is referred to as ALS with bulbar involvement. Compared to people with non-bulbar onset ALS, those with bulbar onset ALS seem to be more likely to show signs of ennui and run into social criticism [29, 30]. The most common symptom, apathy, should be differentiated from fatigue, respiratory issues, and depressive disorders by carefully examining medical history and utilizing established measures. As opposed to indifference, depression, for example, is marked by pervasive exhaustion, grief, crying, loss of hope, thoughts of death, and worry and can be linked to certain stressors [2].

Treatment of ALS

The prevention of maladies progression is the main objective of ALS treatment, however healing already-done damage is a crucial secondary factor. The treatment plan for an ALS patient continues to place a large emphasis on palliative care, including home care and hospice. For instance, ventilator therapy can increase longevity and standard of life [31]. With the help of an assistance group and hospice care near their last days of life, an ALS patient can prepare nourishing meals that are simple to chew, receive drugs for depression, fatigue, and muscle spasms, and have their ventilators adjusted so they can adapt to their new lifestyle restrictions.

Better therapies will be developed as an outcome of biochemical and pharmacological Advancements, even though domestic modifications can significantly relieve current patients. A panel of ALS biomarkers from simple tests would be a big help in diagnosing the disease, tracking its development, and figuring out

which molecular pathways in ALS need to be targeted for treatment [32]. PPX, often referred to as benzothiazolamine (-) - pramipexole (S-configuration), is a medication that is typically prescribed to treat restless legs syndrome and Parkinson's disease. Dexpramipexole, which is also referred to as BIIB 050 or RPPX, is a PPX enantiomer that has demonstrated significant neuro protective effects in numerous animal trials and laboratory experiments. It might therefore be advantageous in the treatment of ALS [33].and Figure 1 displays the compounds' chemical structures.

Treatment options for ALS brought on by patho-genetic variations in SOD1

Based on how they work, the chemical compounds used to treat the SOD1-ALS disease depicted in Figure 2 can be categorized, as will be covered in the section that follows.

Lessen of Excitotoxicity

The cephalosporin antibiotic ceftriaxone (I), increases the activity of the EAAT2 gene promoter and elevates EAAT2 expression, hence reducing glutamate excitotoxicity [34]. markedly improved the ALS phenotype and increased the lifetime of Tg-SOD1G93A mice by 10 days [35].

Mitochondria Targeting

Decreases neuronal cell death in Tg-SOD1G93A mice [36] by Olesoxime (II), a mitochondrial pore modulator. However, these beneficial effects in non-stratified ALS patients were not validated by a Phase II/III clinical trial [37].

Focusing SOD1 Aggregation

The establishment of the intramolecular disulfide bond and proper folding of SOD1 are facilitated by Ebselen (III), an organoselenium cysteine reactive chemical [38]. Instead of the harmful aggregates, it promotes the production of the functioning SOD1 dimer.

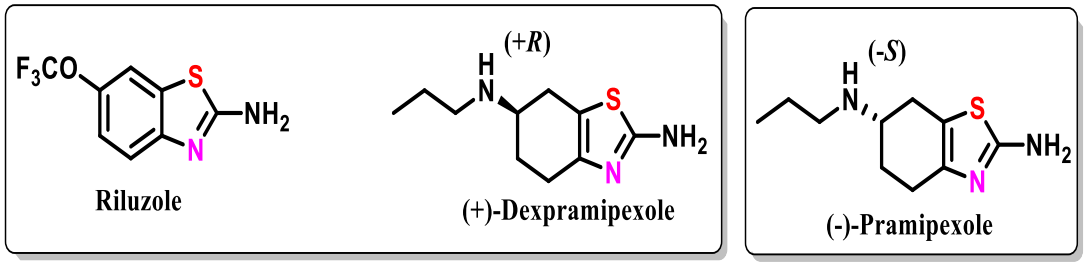


Figure 1: Chemical structure of Riluzole, (+)-Dexpramipexole, (-)-Pramipexole

Figure 2: Chemical formulas of compounds used to treat SOD1-ALS in disease models

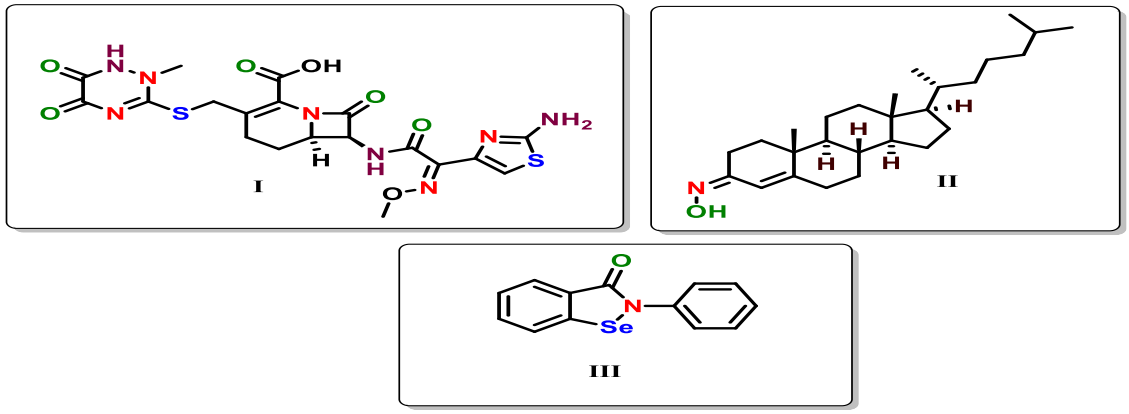
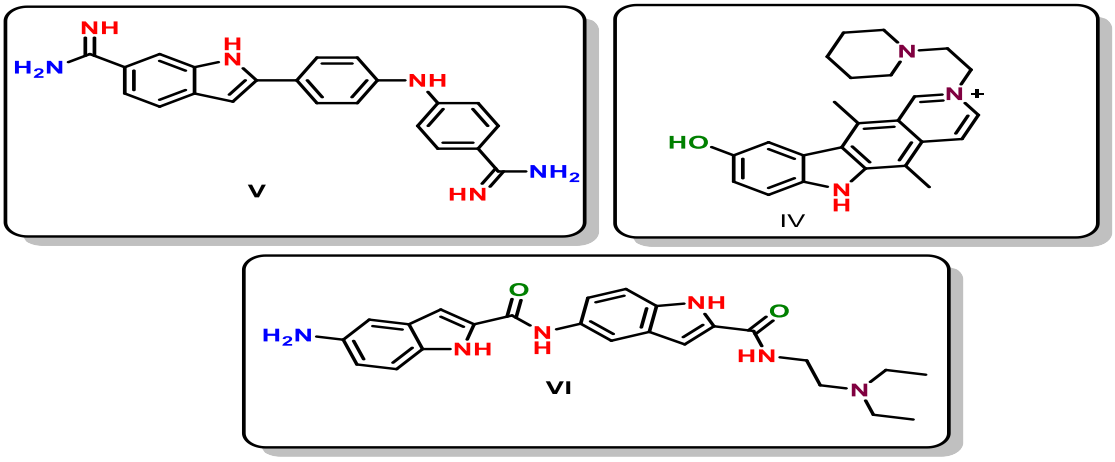


Figure 3: Chemical formulas of compounds utilized to ailment C9ORF72 gene in ALS



G4C2 Pathogenetic Modifications in C9ORF72 Are Intended

The first large repeated expansions inside the C9ORF72 gene are GGGGCC; these expansions code for poly-dipeptides [poly (GA), poly (GP), poly (GR), poly (PR), and poly (PA)]. Both ALS patients and those without frontal lobe dementia (FTD) have been shown to exhibit these enlargements [39, 40].Another group produced the trio of chemicals (IV, V, and VI; see Figure 3) that target the hexanucleotide repetitive region of RNAs. The compounds were tested for their capacity to bind to hairpin RNA and inhibit RAN translation in a system devoid of cells. IV and V significantly reduced RAN translation and RNA foci in neurons expressing the GGGGCC repeat [41].

Furthermore, in Tg-TDP-43wt mice, two tyro kinase inhibitors, such as bosutinib (VIII) and nilotinib (VII), altered glutamate synaptic signaling and showed neuroprotective benefits [42].Anacardic acid (IX), on the other hand, inhibits histone acetyltransferase and reduces TDP-43 mRNA in ALS patients. For the compound's chemical formula, see figure 4.

Clinical Therapies

A summary of numerous therapy-focused clinical trials is provided. Mesenchymal stem cell (MSC)-NTF cell treatment (NurOwn), Tofersen, AMX0035 (Relyvrio, a mixture of taurursodiol and sodium phenylbutyrate), Aldesleukin, Ravulizumab, Verdiperstat, and so on are a few of them; figure 5 shows the chemical structure of these compounds. One of the possible explanations for the high failure rate in ALS clinical trials is that, in the past, ALS patients were often included in research studies with the idea that the disease was homogeneous rather than heterogeneous [43].

Figure 4: Chemical formulas of compounds used to treat TDP-43-ALS in disease models

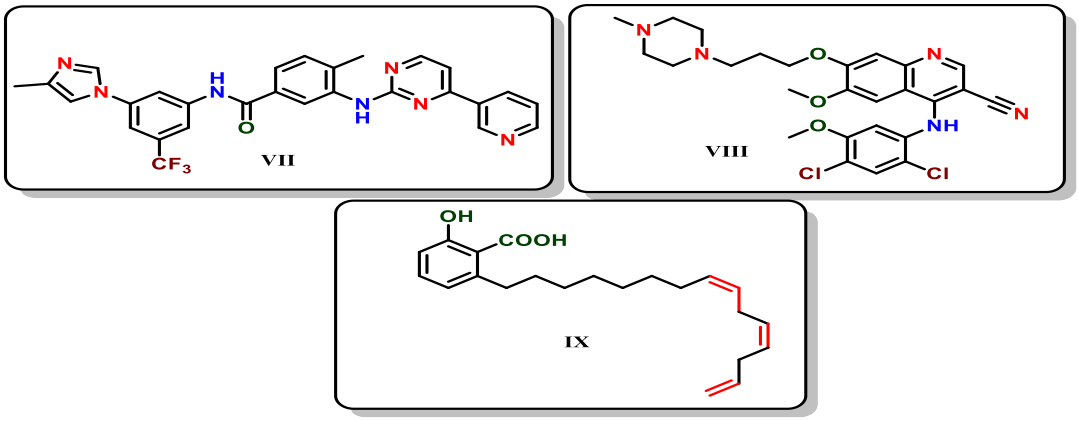
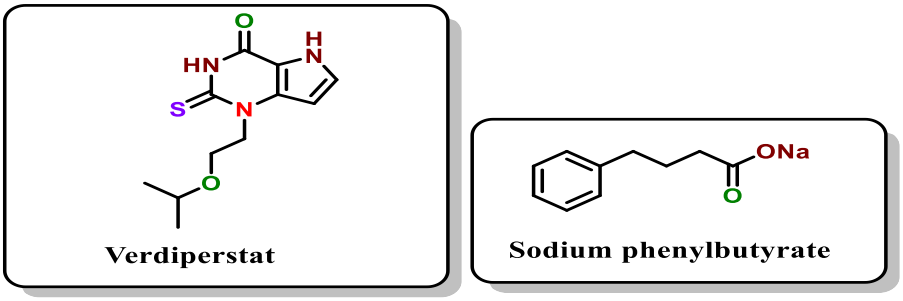


Figure 5: Chemical formulas of compounds used in clinical therapies



Clinical Demonstration

The characteristic of ALS is chronic skeletal muscle weakness which leads to muscle atrophy, cramping, and delay of movement. The development of muscular weakness in ALS patients is typically localized and progresses to nearby body parts [44]. The most common symptoms of ALS in the first phase are dysphagia or dysarthria; chewing difficulties, restricted mouth closure, and dysphonia are less common. In the later stages of the sickness, axial muscular Weakness with body loss and posture issues is prevalent, but it seldom occurs as the initial symptom. Some victims are suffered from unconstrained laughing or crying. [45]. Stereotype behavior includes basic repetitive actions like hand clapping and rubbing hands together, chanting loudly, humming a tune, giggling, and dancing, along with complicated behavioral patterns like following a set path, gathering and accumulating goods, and rituals for dressing and using the restroom. [46]. Patients display an unusual obsession with money or the financial system. This may be shown by patients hoarding money or calculating it constantly, refrainingfrom using their own money, buying the cheapest goods regardless of the quality, or attemptingto limit the use of domestic amenities by those closest to them [47].

CONCLUSION

In conclusion, this review shows how ALS disease negatively affects social interaction and the human brain. It has also included a few clinical treatments and chemically beneficial medications for the ALS illness. Currently, the treatment support may

slow the progression of the illness. Future studies will, therefore, focus on limiting the first circumstances that result in neuronal death.

Declaration of Competing Interest

The authors declare that they have no known competing interests or relationships that could have appeared to influence the work reported in this manuscript.

Authors Contribution

Contributions included an inquiry, validation, data analysis, and final paper drafting from SK, BR, SS, and RK. GK managed the crew and oversaw the job. The manuscript was completed and modified by all contributors.

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Abbreviation

ALS- Amyotrophic Lateral Sclerosis

SOD1- Superoxide Dismutase 1

MRI- Magnetic Resonance Imaging

PET- Positron Emission Tomography

fvFTD- frontal-variant Frontotemporal Dementia

REFERENCE

1. Pratt AJ, Getzoff ED, Perry JJP, 2012. Amyotrophic lateral sclerosis: update and new developments. Degenerative neurological and neuromuscular disease. 12(2), Pages1-14. Doi: 10.2147/DNND.S19803.

2. Phukan J, Pender NP, Hardiman O, 2007. Cognitive impairment in amyotrophic lateral sclerosis. Lancet Neurol., 6(11), Pages 994-1003. Doi: 10.1016/S1474-4422(07)70265-X.

3. Neary D, Snowden JS, Gustafson L, et al, 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 51(6), Pages 1546-1554. Doi: 10.1212 /wnl.51.6.1546.

4. Lacomblez L, Bensimon G, Leigh PN, 1996. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II 347(9013), Pages 1425-1431. Doi: 10.1016/s0140-6736(96)91680-3.

5. Doucette PA, Whitson LJ, Cao X, et al, 2004. Dissociation of human copper-zinc superoxide dismutase dimers using chaotrope and reductant. J Biol Chem. 279(52), Pages 54558-66. Doi: 10.1074/jbc.M409744200.

6. Alfonso-Prieto M, Biarnés X, Vidossich P, et at, 2009. The molecular mechanism of the catalase reaction. J Am Chem Soc, 131(33), Pages 11751-11761. doi: 10.1021/ja9018572.

7. Gruzman A, Wood WL, Alpert E, et al, 2007. Common molecular signature in SOD1 for both sporadic and familial amyotrophic lateral sclerosis. Proc Natl Acad Sci USA; 104(30), Pages 12524-12529. Doi: 10.1073/pnas.0705044104.

8. Forsberg K, Andersen PM, et al, 2011. Glial nuclear aggregates of superoxide dismutase -1 are regularly present in patients with amyotrophic lateral sclerosis. Acta Neuropathol. 121(5), Pages 623-634. Doi: 10.1007/s00401-011-0805-3.

9. Huisman MHB, De Jong SW, van Doormaal PTC, et al, 2011. Population-based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. J Neurol Neurosurg Psychiatr. 82(10), Pages 1165-1170. doi: 10.1136/ nnp.2011.244939.

10. O'Toole O, Traynor BJ, Brennan P, et al, 2008. Epidemiology and clinical features of amyotrophic lateral sclerosis in Ireland between 1995 and 2004. J Neurol Neurosurg Psychiatr. 79(1), Pages 30-42. doi: 10.1136/jnnp.2007.117788.

11. Wittie M, Nelson LM, Usher S, et al, 2013. Utility of capture-recapture methodology to assess completeness of amyotrophic lateral sclerosis case ascertainment. Neuroepidemiology. 40(2), Pages 133-41. Doi: 10.1159/000342156.

12. Logroscino G, Traynor BJ, Hardiman O, et al, 2010. Incidence of amyotrophic lateral sclerosis in Europe. J Neurol Neurosurg Psychiatry. 81(4), Pages 385-90. Doi: 10.1136 /jnnp.2009.183525.

13. Johnston CA, Stanton BR, Turner MR, et al, 2006. Amyotrophic lateral sclerosis in an urban setting: a population-based study of inner city London. J Neurol. 253(12), Pages 1642-1653. Doi: 10.1007/s00415-006-0195-y.

14. Ryan M, Heverin M, McLaughlin RL, et al, 2019. Lifetime Risk and Heritability of Amyotrophic Lateral Sclerosis. JAMA Neurol. 76(11), Pages 1367–1374. Doi: 10.1001/jamaneurol.2019.2044.

15. Manjaly ZR, Scott KM, Abhinav K, et al, 2010. The sex ratio in amyotrophic lateral sclerosis: A population-based study. Amyotroph Lateral Scler. 11(5), Pages 439-342. Doi: 10.3109/17482961003610853.

16. Al-Chalabi A, Fang F, Hanby MF, et al, 2010. An estimate of amyotrophic lateral sclerosis heritability using twin data.Journal of Neurology, Neurosurgery & Psychiatry. 81(12), Pages 1324-1326. Doi: 10.1136/jnnp.2010.207464.

17. Abrahams S, Goldstein LH, Kew JJM, et al, 1996. Frontal lobe dysfunction in amyotrophic lateral sclerosis: a PET study. Brain, 119(6), Pages 2105- 2120 Doi: 10.1093/brain/119.6.2105

18. Bak TH, Hodges JR, 2001. Motor neuron disease, dementia, and aphasia: coincidence, co-occurrence or continuum? Journal of Neurology. 248(4), Pages 260-70. Doi: 10.1007/s004150170199.

19. Kew JJM, Goldstein LH, Leigh PN, et al, 1993. The relationship between abnormalities of cognitive function and cerebral activation in amyotrophic lateral sclerosis: a neuropsychological and positron emission tomography study. Brain, 116(6), Pages 1399-1423. Doi: 10.1093/brain/116.6.1399.

20. Robinson KM, Lacey SC, Grugan P, et al, 2006. Cognitive functioning in sporadic amyotrophic lateral sclerosis: a six-month longitudinal study. Journal of Neurology, Neurosurgery & Psychiatry. 77(5), Pages 668-670. Doi: 10.1073/ pnas.0705044104.

21. Strong MJ, Grace GM, Orange JB, et al, 1999. A prospective study of cognitive impairment in ALS. Neurology, 53(8), Pages 1665-1665. Doi: 10.1073/pnas.0705044104.

22. Barber R, Snowden JS, Craufurd D, 1995. Front temporal dementia and Alzheimer's disease: retrospective differentiation using information from informants. Journal of Neurology, Neurosurgery & Psychiatry. 59(1), Pages 61-70. Doi: 10.1136/jnnp.59.1.61.

23. Abrahams S, Goldstein LH, Kew JJM, et al, 1996. Frontal lobe dysfunction in amyotrophic lateral sclerosis: a PET study. Brain. 119(6), Pages 2105-2120. Doi: 10.1093/brain/119.6.2105.

24. Rakowicz WP, Hodges JR, 1998. Dementia and aphasia in motor neuron disease: an under recognised association? Journal of Neurology, Neurosurgery & Psychiatry. 65(6), 881-889. Doi: 10.1136/jnnp.65.6.881.

25. Snowden JS, Pickering-Brown SM, Mackenzie IR, et al, 2006. Progranulin gene mutations associated with front temporal dementia and progressive non-fluent aphasia. Brain. 129(11), Pages 3091– 102. Doi: 10.1093/brain/awl267.

26. Lough S, Kipps CM, Treise C, et al, 2006. Social reasoning, emotion and empathy in front temporal dementia. Neuro psychologia. 44(6), Pages 950-958. Doi: 10.1016/j.neuropsychologia.2005.08.009.

27. Lule D, Kurt A, Jurgens R, et al, 2005. Emotional responding in amyotrophic lateral sclerosis. J Neurol. 252(12), Pages 1517-1524. Doi: 10.1007/s00415-005-0907-8

28. Lomen-Hoerth C, Murphy J, Langmore S, et al, 2003. Are amyotrophic lateral sclerosis patients cognitively normal? Neurology. 60(7), Pages 1094-1097. Doi: 10.1212/01.wnl.0000055861.95202.8d.

29. Grossman AB, Woolley-Levine S, Bradley WG, et al, 2007. Detecting neurobehavioral changes in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 8(2), Pages 56–61. Doi: 10.1080/17482960601044106.

30. Flaherty-Craig C, Eslinger P, Stephens B, et al, 2006. A rapid screening battery to identify frontal dysfunction in patients with ALS. Neurology. 67(11), Pages 2070-2072 Doi: https://doi.org/10.1212/01.wnl.0000247667.89251.43

31. Bourke SC, Tomlinson M, Williams TL, et al, 2006. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomized controlled trial. Lancet Neurol. 5(2), Pages 140–147. Doi: 10.1016/S1474-4422(05)70326-4.

32. Bowser R, Turner MR, Shefner J, 2011. Biomarkers in amyotrophic lateral sclerosis: opportunities and limitations. Nat Rev Neurol. 7(11), Pages 631–638. Doi: 10.1038/nrneurol.2011.151.

33. Gribko VK, Bozik ME, 2008. KNS-760704 [(6R)-4, 5, 6, 7-tetrahydro-N6-propyl-2, 6- benzothiazole - diamine dihydrochloride monohydrate] for the treatment of amyotrophic lateral sclerosis. CNS Neurosci. Ther. 14(6), 215–226. Doi:10.1038/nm.2579.

34. Cudkowicz ME, Titus S, Kearney M, et al, 2014. Efficacy and safety of ceftriaxone for amyotrophic lateral sclerosis: results of a multistage, randomized, double-blind, placebo-controlled. Lancet Neurol. 13(11), Pages 1083-1091. Doi: 10.1016/S1474-4422(14)70222-4.

35. Rothstein JD, Patel S, Regan MR, et al, 2005. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature. 433(7021), Pages 73-77. Doi: 10.1038/nature03180.

36. Sunyach C, Michaud M, Arnoux T, et al, 2012. Olesoxime delays muscle denervation, astrogliosis, microglial activation, and motoneuron death in an ALS mouse model. Neuropharmacology. 62 (7), Pages 2346-2352. Doi: 10.1016/j. neuropharm.2012.02.013.

37. Lenglet T, Lacomblez L, Abitbol JL, et al, 2014. Mitotarget study group. A phase II-III trial of olesoxime in subjects with amyotrophic lateral sclerosis. Eur J Neurol; 21(3), Pages 529-536. Doi: 10.1111/ene.12344.

38. Capper MJ, Wright GSA, Barbieri L, et al, 2018. The cysteine-reactive small molecule ebselen facilitates effective SOD1 maturation. Nat Commun. 9(1), 1693. Doi: 10.1038/s41467-018-04114-x.

39. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al, 2011. Expanded GGGGCC hexanucleotide repeat in the noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 72(2), Pages 245-256. Doi: 10.1016/j.neuron.2011.09.011.

40. Renton AE, Majounie E, Waite A, et al, 2011. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 72(2), Pages 257-268. Doi: 10.1016/j.neuron.2011.09.010.

41. Su Z, Zhang Y, Gendron TF, et al, 2014. Discovery of a biomarker and lead small molecules to target r (GGGGCC)-associated defects in c9FTD/ALS. Neuron; 83(5), Pages 1043-1050. Doi: https://doi.org/10.1038/s41392-023-01482-9.

42. Heyburn L, Hebron ML, Smith J, et al, 2016. Tyrosine kinase inhibition reverses TDP-43 effects on synaptic protein expression, astrocytic function, and amino acid dis-homeostasis. J Neurochem. 139(4), Pages 610-623. Doi: 10.1111/jnc.13763.

43. Egawa N, Kitaoka S, Tsukita K, et al, 2012. Drug screening for ALS using patient-specific induced pluripotent stem cells. Sci Transl Med, 4(145), Pages 145-150. Doi: 10.1126/scitranslmed.3004052.

44. Mead RJ, Shan N, Reiser HJ, et al, 2023. Amyotrophic lateral sclerosis: A neurodegenerative disorder poised for successful therapeutic translation. Nature Reviews Drug Discovery. 22(3):185-212. Doi: 10.1038/s41573-022-00612-2.

45. Ravits JM, La Spada AR, 2009. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. Neurology. 73(10), Pages 805-11. Doi: 10.1212/WNL.0b013e3181b6bbbd.

46. Parvizi J, Anderson SW, Martin C O, et al, 2001. Pathological laughter and crying: a link to the cerebellum. Brain. 124(9), Pages 1708-1719. Doi: 10.1093/brain/124.9.1708.

47. Neary D, Snowden JS, Gustafson L, et al, 1998. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology, 51(6) Pages 1546-1554. Doi: 10.1212/wnl.51.6.1546.