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Original Article

Neurodegenerative Disorder

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ABSTRACT

"Amyotrophic lateral sclerosis (ALS) is a serious disease that happens when the nerve cells that control movement (called motor neurons) slowly die or stop working."Around the world, there is a big need for better treatments for neurodegenerative diseases. These diseases are hard to treat because the processes that damage brain cells are very complex, and patients can have very different symptoms and causes. This makes it difficult to develop tools to diagnose the diseases early and to find effective treatments.

Keywords: Neurodegenerative Disorder

INTRODUCTION

Key points:

- Amyotrophic Lateral Sclerosis (ALS) is a serious brain and nerve disease that affects about 1 in 350 people during their lifetime. It causes the muscles that control movement to become weaker over time, often in a short period.
- ALS is especially important to study because it gives researchers a good way to understand how nerve cells break down. In the past 10 years, scientists have made big progress in learning what causes ALS, especially how genes are involved and what happens in the body during the disease. They have also created better models in the lab to study ALS and test new treatments. This progress gives hope for finding better ways to treat and understand ALS in the future.
- **New biomarkers found:** Scientists have found signs in the blood and spinal fluid (called neurofilament proteins) that could help track how a disease changes, how well a treatment is working, and who is likely to benefit. These could make future clinical trials faster and more effective.
- **New treatment ideas:** Researchers have discovered several biological processes involved in the disease that could be targeted with new treatments. This has led to a growing number of lab studies and clinical trials testing these ideas

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is a serious condition that affects the nerves controlling muscles. In ALS, the nerve cells in the brain and spinal cord that control movement gradually die, leading to weakness and loss of muscle control. ALS happens worldwide. Each year, about 2 out of every 100,000 people are diagnosed, and at any given time, around 6 to 9 out of every 100,000 people have the condition. The lifetime risk is about 1 in 350. The number of ALS cases seems to be going up, possibly because people are living longer and doctors are getting better at diagnosing it. Around 5–10% of people with ALS have a family history of the disease, often passed down in families. However, with modern genetic testing, doctors can now find a genetic cause in even more people—even in those without a known family history. As ALS progresses, it causes increasing weakness in the arms, legs, and muscles used for speaking, swallowing, and breathing. The speed of disease progression varies, but most people live only 2–3 years after symptoms start, usually due to breathing failure. ALS sometimes overlaps with a type of dementia called frontotemporal dementia (FTD). About 5% of people with ALS develop clear signs of FTD, but more detailed testing shows that up to 50% may have mild changes in thinking and behavior

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related to the brain's frontal and temporal lobes. There is no single test that can confirm ALS. Instead, doctors rule out other conditions that can look similar. This process usually involves blood tests, brain and spine scans, and tests that check how the nerves and muscles are working (called neurophysiological tests). Doctors use special guidelines to help diagnose ALS, including the **revised El Escorial criteria**, the **Awaji Shima criteria**, and the newer **Gold Coast criteria**, which is simpler and more widely used now. There are many treatments being tested for ALS—over 60 different drugs have been studied in clinical trials. However, only **three drugs** have been officially approved for use so far:

1. **Riluzole**
2. **Edaravone**
3. **AMX0035**

Riluzole was the first drug approved. It works by reducing the release of a chemical called glutamate, which can damage nerve cells when there's too much of it. This may help slow down nerve cell damage (a process called excitotoxicity). Although the early studies showed that riluzole added about 3 months to a patient's life on average, later research showed that people who took riluzole lived 6 to 19 months longer than those who didn't.

Advances in preclinical disease modelling in ALS

Historical approach

In 1993, scientists discovered that mutations in a gene called SOD1 could cause ALS. This led to the development of the first SOD1-mutant mouse models, where mice were genetically altered to carry this mutation. These mice developed symptoms similar to ALS, especially affecting their spinal motor neurons, which made them useful for studying the disease. Although these mice were widely used in research, later studies showed that many treatments that seemed to work in these mice didn't actually help people with ALS. This raised concerns about how reliable the mouse model really was.

New and more accurate mouse models for ALS:

As scientists discovered more ALS-related genes, they were able to create better mouse models to study the disease. The most important ones are based on changes (mutations) in TDP-43, FUS, and C9orf72—genes that are more commonly involved in ALS. Most people with ALS—especially those with no family history—have abnormal buildup of the TDP-43 protein in their nerve cells. This makes TDP-43 especially important in understanding the disease.

- When scientists made mice that produce too much TDP-43 (either the normal or mutated version), the mice's nerve cells started to die.
- If the levels of TDP-43 were very high, the damage happened faster.
- Even losing TDP-43 from cells could lead to nerve damage, showing how important the right balance is.

Some mice were made with a specific mutation (called Q331K) at normal levels, and they showed only mild symptoms. These mice didn't have the typical TDP-43 buildup, which suggests this buildup might happen later in the disease. Interestingly, in another model with the same mutation, there was more TDP-43 in the nucleus of cells (where it normally belongs), and not in the wrong place—this was unexpected. These newer models are helping scientists better understand how ALS develops over time. For example, MRI scans of these mice showed they were losing certain types of brain cells (interneurons), which also happens in human ALS.

Using patient cells to study ALS:

Scientists have found ways to take cells from ALS patients (like skin cells called fibroblasts) and turn them into brain or nerve cells. This has become a powerful new tool for studying ALS and testing new drugs. There are two main ways to do this. One popular method uses induced pluripotent stem cells (iPSCs). These are patient cells that are "reprogrammed" to become stem cells, which can then be turned into motor neurons—the nerve cells that die in ALS.

Mitochondria problems in ALS:

Mitochondria are parts of the cell that produce energy. In ALS, these mitochondria don't work properly, and this may play a big role in the disease.

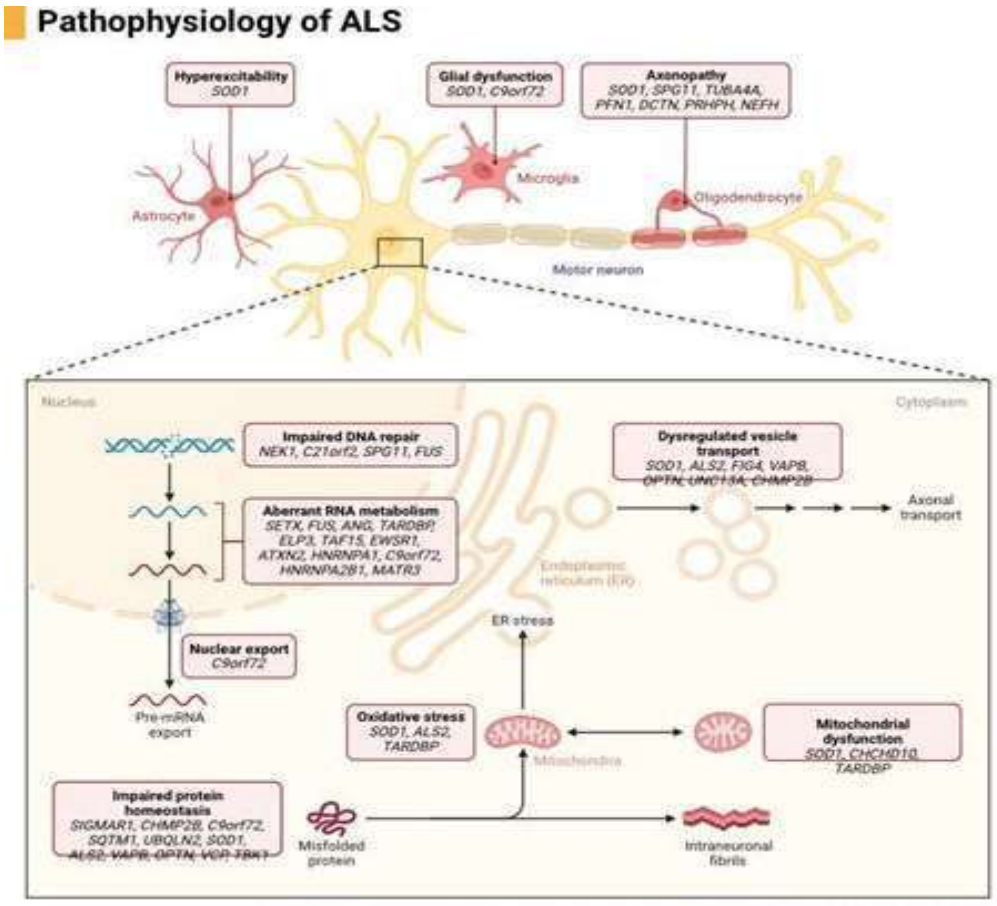
Researchers have found several problems with mitochondria in ALS, including:

- Poor energy production
- Too many harmful molecules called ROS (reactive oxygen species)
- Problems moving mitochondria along nerve cells
- Changes in their shape and function
- Trouble clearing out damaged mitochondria (mitophagy)
- Problems handling calcium
- Activation of cell death (apoptosis)

There are also issues with areas where mitochondria and another part of the cell, the endoplasmic reticulum (ER), interact. When these areas don't work right, it can cause:

- Calcium imbalance
- Mitochondria damage
- ER problems
- Trouble clearing waste in cells

All of this can lead to damage and death of nerve fibers (axons), which is a key feature of ALS.



1. Mitochondria and ALS treatments:

Scientists have tried several drugs to fix mitochondria problems in ALS, since damaged mitochondria are thought to play a big role in the disease. Some drugs, like coenzyme Q10, dexpramipexole, olesoxime, and creatine, worked well in lab tests, but did not help patients in clinical trials.

One drug, **TUDCA**, helps protect nerve cells by:

- Reducing harmful molecules called **ROS**
- Blocking signals that tell cells to die
- Helping mitochondria work better

A clinical trial tested TUDCA combined with sodium phenylbutyrate in 137 ALS patients for 6 months. The results showed it slowed the disease down and helped patients live longer. Another trial in Europe is now testing TUDCA alone. A newer lab study using mice with ALS-related gene mutations (SOD1 and TARDBP) found that blocking a certain protein (protein phosphatase 1) helped stop:

- Mitochondria from breaking apart
- Energy problems in cells
- Damage to nerve fibers
- Nerve cell death

This approach may be worth studying further. Scientists also use a special type of scan called **31P-MRS** to see how well cells in the brain and muscles are making energy. This scan might help track how well treatments are working in future ALS trials.

2. Problems with protein balance in ALS:

Our cells constantly make and remove proteins to stay healthy. This process is called protein homeostasis (proteostasis). It includes:

- Making proteins
- Folding them into the right shape
- Moving them to where they're needed
- Breaking down damaged or unneeded proteins

When this balance is lost, proteins can build up and form harmful clumps, which is a common problem in aging and diseases like ALS.

In ALS:

- Many of the genes linked to the disease affect how cells handle proteins
- Key ALS proteins like SOD1 and TDP-43 are often found in these clumps
- Several other ALS-related proteins help control autophagy (the cell's clean-up system), such as:
    - C9ORF72, P62 (sequestosome 1), optineurin, and ubiquilin 2
- Others are involved in later steps of the process, like:
    - alsin, FIG4, VCP, and CHMP2B

When this protein clean-up system doesn't work properly, it may lead to the damage and death of nerve cells, as seen in ALS.

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