ALS: the fall to the frozen

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MacMillan Group
Princeton University
Nov. 14th, 2023
1. Facts about ALS
2. Symptoms and phenotypes
3. What do we know about the cause?
4. Clinical practices and social impacts
1. Facts about ALS
Facts about ALS

Name

“No” “muscle” “nourishment”

From the spinal cord to the side

An abnormal hardening…

A progressive neurodegenerative disease that causes loss of muscle control
Facts about ALS

Current knowledge

5,000+ People are diagnosed per year

2-5 years Is the average life expectancy

Every 90 mins someone is diagnosed and someone passes away from ALS

90 percent of cases occur without family history

10 percent of cases are linked with family history

$250,000 is the estimated out-of-pocket cost for caring an ALS patient

$2 billion is the estimated cost to develop a drug to slow or stop the progression of ALS

There is NO CURE for ALS

https://www.als.org/understanding-als/what-is-als
Facts about ALS

History

French neurologist Jean-Martin Charcot identified and named the disease as ALS.

1874

ALS gains mainstream attention

1939

https://www.pharmaceutical-technology.com/features/history-of-als
Facts about ALS

Lou Gehrig drew public attention

- Gehrig was diagnosed with ALS on his 36th birthday during a visit to the Mayo Clinic on June 19, 1939.

- Prior to his diagnosis, Gehrig noticed a loss of strength, slipping, and loss of coordination while playing on the field.

“I might have been given a bad break, but I’ve got an awful lot to live for.”

Iconic 1939 “Luckiest Man on the Face of the Earth” speech at Yankee Stadium
Facts about ALS

History

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1993

2006

2011

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Lou Gehrig’s disease

SOD1
First ALS gene identified

ALS genes weighted by number of publications


TDP43
C9orf72

https://www.pharmaceutical-technology.com/features/history-of-als
Facts about ALS

History

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1995

2006

2011

2017

2021

Research into environmental factors became another core focus for ALS cause

ALS genes weighted by number of publications


TDP43
C9orf72
FUS

1995

First ALS gene identified

Riluzole
First ALS drug FDA approved

2011

Second ALS drug FDA approved and alternative dosages

Radicava (edaravone)

50 mg

50 mg

QALSODY (tofersen)

Biogen offers compassionate-use access

https://www.pharmaceutical-technology.com/features/history-of-als
**Facts about ALS**

*Risk factors*

**Male**
gender is consistently detected as a factor associated with a 1.5 times increased risk of developing ALS compared with female gender.

**Smoking**
increases ALS risk, possibly caused by nicotine, oxidative stress, or one of the many other known toxic substances.

**Military**
veterans are more likely to be diagnosed with the disease than the general public.

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**Occupation**  
**Toxin**  
**Trauma**  
**Athletics**  
**Cognitive performance**
2. Symptoms and phenotypes
ALS symptoms and phenotypes
Symptoms along disease progression

2/3 of the patients disease onset in the **limbs**
- Difficulty in gripping objects
- Balance issues…

1/3 of the patients disease onset in the **bulbar muscle**
- Poor articulation and slurring speech
- An unusually hoarse or quiet voice…

https://alsnewstoday.com/stages-of-als/
ALS symptoms and phenotypes

Symptoms along disease progression

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- Difficulty in gripping objects
- Balance issues…

1/3 of the patients disease onset in the **bulbar muscle**
- Poor articulation and slurring speech
- An unusually hoarse or quiet voice…

- Muscles become completely paralyzed and others are weakened
- Rely on aids like walkers or wheelchairs
- Speaking and breathing problem

- Mobility is extremely limited
- Inability to communicate without assistance
- Aids in feeding and breathing are required

**Respiratory failure**
is the most common cause of death in ALS.
Others including malnutrition, pulmonary embolism…

https://alsnewstoday.com/stages-of-als/
**ALS symptoms and phenotypes**

**Varied timelines of disease progression**

*The average survival time is three years, about 20% of people with ALS live five years, 10% survive 10 years and 5% live 20 years or longer.*

*Patients with bulbar-onset suffers worse prognosis, respiratory-onset worst*
ALS symptoms and phenotypes
Aging-related disease and juvenile onset

The majority of ALS starts in fifth or sixth decade of life

The older the onset, the more impacted bulbar system and poorer prognosis

Juvenile onset (<25ys) usually show slower progression

https://www.scientificamerican.com/article/stephen-hawking-als/
ALS symptoms and phenotypes
Juvenile onset and Stephen Hawking’s case

Stephen Hawking 1942-2018
Theoretical physicist, cosmologist and author

- Disease onset at the age of 21, 1962
- Starting speaking through computer in 1985

Active mind, psychological well-being, excellent care…
An extreme outlier

https://www.scientificamerican.com/article/stephen-hawking-als/
3. What do we know about the cause?

Pathophysiology and genetics
ALS pathophysiology and genetics

Motor neurons’ disease

Degeneration of motor neurons

Schweingruber, C., & Hedlund, E. Biology, 2021, 11(8)
ALS pathophysiology and genetics

Motor neurons’ disease

Degeneration of motor neurons
Neurons shrink and accumulate inclusions

Thoracic spinal cord of ALS patient (left) compared with age matched control (right).

SOD1 aggregates in SOD1-related familial ALS

TDP-43 cytoplasmic inclusions in sporadic ALS

How does this happen?

https://www.pathologyoutlines.com/topic/cnsals.html
ALS pathophysiology and genetics

Main theories

ALS pathophysiology and genetics

Mystery of SOD1

SOD1 dimer
First ALS gene discovered in 1993

Cu–Zn superoxide dismutase

Is it due to the reduced activity and subsequent ROS damage?

ALS pathophysiology and genetics

Mystery of SOD1

Counterargument 1

170 ALS-causing SOD1 mutations in its 153 aa peptide

Counterargument 2

Native dismutase activity has no effect on SOD1-ALS disease progression

In many years since the discovery of mutations in SOD1, no consensus on the main toxicity of mutant SOD1 has emerged

Turner, B. J., & Talbot, K. Progress in neurobiology, 2008, 85(1)

ALS pathophysiology and genetics

A prominent finding: SOD1 aggregates

Misfolded SOD1 forms ubiquitinated cytoplasmic inclusions that can occur early in ALS and that escalate as the disease progresses.

ALS pathophysiology and genetics

Main theories
ALS pathophysiology and genetics

Disturbance of PQC

Mutation of autophagy adaptors found to cause ALS
VCP, SQSTM1, UBQLN2, OPTN, TBK1……

ALS pathophysiology and genetics

TDP43 condensations

ALS-causing mutations mostly in C-term...

Ubiquitinated TDP-43 aggregates in >90% ALS patients’ motor neurons and glial cells

ALS pathophysiology and genetics

TDP43 condensations

<table>
<thead>
<tr>
<th></th>
<th>TDP-43 Monomer</th>
<th>TDP-43 Pan</th>
<th>DAPI</th>
<th>Merged with ChAT</th>
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<tbody>
<tr>
<td>Control 1</td>
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<tr>
<td>ALS 7</td>
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</tbody>
</table>

*TDP-43 mislocalization and aggregation is now recognized widely as the hallmark of all forms of ALS*

Oiwa, K., Watanabe, S., Science advances, 2023, 9(31)
**ALS pathophysiology and genetics**

**TDP43 condensations**

*A recent model accounting for TDP43 mislocation*

Oiwa, K., Watanabe, S., Science advances, 2023, 9(31)
ALS pathophysiology and genetics

Main theories

ALS pathophysiology and genetics

ALS-causing RBP disturbances

ALS mutations are found in members of the hnRNP family of proteins that regulates RNA metabolism at every stage of the RNA life cycle

They bind to thousands of RNA targets

ALS pathophysiology and genetics

RBP-RNA pathogenic phase separation

Accumulation of RBPs + mRNAs influx = LLPS persistent condensates

Mutations, misregulations, impaired transportation

ALS pathophysiology and genetics

RBP-RNA pathogenic phase separation

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Mutations, misregulations, impaired transportation

Hyperassembly of stress granules

ALS pathophysiology and genetics
RBP-RNA pathogenic phase separation

Accumulation of RBPs + mRNAs influx = LLPS persistent condensates
Hyperassembly of stress granules

Mutations, misregulations, impaired transportation

ALS pathophysiology and genetics

C9orf72

First discovered through sequencing of non-coding region of chromosome 9p21

\[ n = 2 - 23 \text{ in healthy individuals} \]

\[ n > 60 \text{ in affected individuals} \]

ALS pathophysiology and genetics

C9orf72 loss of function

Decreasing of transcripts level

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frontal Cortex</th>
<th>Lymphoblast Cells</th>
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</thead>
<tbody>
<tr>
<td>Expanded repeat: +</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>(%) of controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C9orf72 KO mice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ALS/FTD features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aged normally</td>
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</tr>
</tbody>
</table>

Non-cell-autonomous inflammatory

Loss of function not considered as the essential cause

ALS pathophysiology and genetics

C9orf72 gain of function

Abnormal RNA foci

C9 ALS patient

Dipeptide repeat DPR cytosolic inclusions

Toxic peptides

ALS pathophysiology and genetics

C9orf72 gain of function

ALS pathophysiology and genetics

Main theories

a Disturbances in protein quality control

b Cytoskeletal defects and altered axonal transport

c Hypertension of microglia

Oligodendrocyte

Glutamate

Spinal motor neuron

Schwann cell

Muscle

Endosome–lysosome

Autophagosome

Proteasome

ER

Descending corticospinal neuron

O_{2}

Oligodendrocyte

EAAT2

Toxic signal

Astrocyte

f Disturbances in RNA metabolism

Alternative splicing

miRNA biogenesis

Sequestration of RNA-binding proteins

Translation

To quickly respond to synaptic signals, neurons must transport all necessary components for translation (mRNA, ribosomes and translation factors) to distal sites for **local protein synthesis**

ALS-causing mutation: KIF5A, DCTN1, NEFH, TUBA4A……
ALS pathophysiology and genetics

Main theories

a Disturbances in protein quality control

b Cytoskeletal defects and altered axonal transport

Dynein
Dynactin
Profilin1

f Disturbances in RNA metabolism

Alternative splicing
Sequestration of RNA-binding proteins
miRNA biogenesis
Translation

Descending corticospinal neuron
Oligodendrocyte
Glutamate
Spinal motor neuron
EAAT2
O2

Toxic signal

Endosome–lysosome
Autophagosome

Muscle
Schwann cell
Astrocyte

ALS pathophysiology and genetics

The crucial role of glia cells

ALS pathophysiology and genetics

Neuroinflammation in ALS

Hyperactivated in all types of ALS

Oxygen radicals, nitric oxide, and cytokines...

Release of cytotoxic and inflammatory mediators

Activation of microglia — faster rate of disease progression

Inhibited activation — delayed onset and prolonged survival

**ALS pathophysiology and genetics**

**Glutamate excitotoxicity**

- Provides motor neurons with nutrients, ion buffering, and **recycling of the neurotransmitter glutamate**

  - One of the earliest proposed mechanisms

  - Glutamate recycled through EAAT2 transporter into astrocyte to **prevent excessive firing** of lower motor neurons

  - **Repetitive firing** caused by accumulated synaptic glutamate

  - Calcium influx, endoplasmic reticulum (ER) and mitochondrial stress

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Although **sporadic ALS** should refer strictly to disease that presents without a family history of ALS, this term is sometimes mistakenly used to refer to ALS that occurs without a genetic basis.
ALS pathophysiology and genetics

Treasure hunting in ALS genetics

Great demand of whole-genome sequencing in ALS research
to identify known pathogenic mutations in up to 70% of familial and 15% of sporadic cases

Sequencing technology development to enable easier whole genome sequencing
4. Clinical practices and social impacts

There is no cure, but there is hope
Clinical practices against ALS

Diagnosis

Revised ALS Functional Rating Scale (ALSFRS-R)

A questionnaire-based scale as the gold standard measure of disability progression

ALSFRS development begins due to need for easily administered clinical rating instrument.

ALSFRS revised to ALSFRS-R to balance respiratory with limb and bulbar categories.

Proposed clinical relevance to be a 20% to 25% change in decline of the ALSFRS-R scale.

ALSFRS-R widely accepted measure of ALS progression by clinical trialists and regulatory bodies.

Speech, salivation, swallowing

Handwriting, cutting food, dressing and hygiene

Turning in bed, walking, climbing stairs

Dyspnea, orthopnea, respiratory insufficiency

Administered by a healthcare provider

https://www.alspathways.com/assessing-function/
Clinical practices against ALS

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Speech, salivation, swallowing

Handwriting, cutting food, dressing and hygiene

Turning in bed, walking, climbing stairs

Dyspnea, orthopnea, respiratory insufficiency

Speech
4 Normal
3 Detectable speech disturbance
2 Intelligible with repeating
1 Speech combined with nonvocal communication
0 Loss of useful speech

BULBAR
FINE MOTOR
GROSS MOTOR
RESPIRATORY

https://www.alspathways.com/assessing-function/
Clinical practices against ALS

Gene testing

- High penetrance
  - C9orf72
  - SOD1
  - FUS
  - TARDBP

- High risk, strongly associated
  - ALS2, CHMP2B, KIF5A, NEK1, UBQLN2
  ... ...

Gene targeted by FDA-approved therapy

Whole-genome sequencing

Free Genetic Testing with **ALS Identified**

sponsored by Biogen

1) A diagnosis of ALS
or
2) A family history of ALS. This includes patients both familial ALS as well as patients with seemingly sporadic ALS

https://www.als.org/understanding-als/symptoms-diagnosis
Clinical practices against ALS
FDA-approved therapies

1995 Riluzole (oral pill formulation)

Inhibits glutamate release by blocking voltage-sensitive Ca\textsuperscript{2+} channel

2018 Tiglutik (thickened liquid formulation)

2019 Exservan (oral film formulation)

for patients with severe swallowing difficulties

2-3 months expansion of lifespan

https://www.als.org/navigating-als/living-with-als/fda-approved-drugs
Clinical practices against ALS

FDA-approved therapies

2017 Radicava (IV infusion)

Radicava®
(edaravone)
IV infusion
30mg/100mL

Radical scavenger, protects neurons from oxidative damage

2022 Radicava (oral suspension)

Radicava ORS®
(edaravone)
Oral Suspension
105mg/5mL

6 months expansion of lifespan

https://www.als.org/navigating-als/living-with-als/fda-approved-drugs
Clinical practices against ALS
FDA-approved therapies

2022 RELYVRIOD (AMX0035)

Act to prevent nerve cell death by blocking stress signals in cells

6-10 months expansion of lifespan

https://www.als.org/navigating-als/living-with-als/fda-approved-drugs
Clinical practices against ALS

**FDA-approved therapies**

2023 Accelerated Approval
QALSODY (monthly injection)

**Antisense therapy** against SOD1

Open-label extension

**Compassionate use access**
Enable patients access to investigational medical products for treatment outside of a traditional clinical trial

**Pre-symptomatic prevention (till 2027)**
To determine whether tofersen can delay the onset of signs or slow declines in function once signs or symptoms appear

**Delayed disease progression**

https://www.qalsody.com/
https://www.als.org/navigating-als/living-with-als/fda-approved-drugs
Clinical practices against ALS

Ongoing clinical trials

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Therapy Type</th>
<th>Target</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-363 (jacifusen)</td>
<td>ASO</td>
<td>FUS mRNA</td>
<td>Phase 3</td>
</tr>
<tr>
<td><strong>AP-101</strong></td>
<td><strong>Monoclonal antibody</strong></td>
<td><strong>Misfolded and aggregated SOD1</strong></td>
<td><strong>Phase 2</strong>*</td>
</tr>
<tr>
<td>BIIIB105 / ION-541</td>
<td>ASO</td>
<td>ATXN2 mRNA</td>
<td>Phase 1/2***</td>
</tr>
<tr>
<td>WVE-004</td>
<td>ASO</td>
<td>C9orf72 mRNA</td>
<td>Phase 1/2**</td>
</tr>
<tr>
<td>APB-102 / AMT-162</td>
<td>miRNA</td>
<td>SOD1 mRNA</td>
<td>Phase 1/2</td>
</tr>
</tbody>
</table>

74 clinical trials ongoing

https://iamals.clicdata.com/v/eKU04ajTv7TA
Clinical practices against ALS
Supportive care

Speech Therapy

Respiratory Therapy

Physical therapy

Psychotherapy
Clinical practices against ALS

ALS reversal

“To gather and study rare reversal cases and replicate them in other patients”

https://alsreversals.com/
https://www.als.org/blog/als-reversals-what-are-they-and-how-can-we-make-them-happen-more-often
Bringing attention to ALS

ice-bucket challenge
Bringing attention to ALS

ice-bucket challenge
Dave MacMillan did ice-bucket challenge another kind...
Bringing attention to ALS

ice-bucket challenge
5,000+ People are diagnosed per year

2-5 years is the average life expectancy

90 percent of cases occur without family history

Every 90 mins someone is diagnosed and someone passes away from ALS

10 percent of cases are linked to gene mutation

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There is no cure but there is HOPE

Thank you!