Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease)

Zach Antonick
Anatomy and Physiology II – Spring 2019
Helena College University of Montana

Background

- Amyotrophic lateral sclerosis (ALS) is a selective degeneration of motor neurons from the brain to the spinal cord and from the spinal cord to skeletal muscles (Julien, 2001).
  - Mentions of ALS began to appear in British and French medical texts in the 1830s and one of the first cases of ALS was documented in great detail in 1853 (Mitsumoto, 2009).
- As motor neurons are lost, muscles become weaker and weaker due to non-use.
- This progressive decline in muscle function eventually results in paralysis, speech deficits and death due to respiratory failure.
- Typically, once a person is diagnosed they only live for 2 to 5 years.

(Julien, 2001).

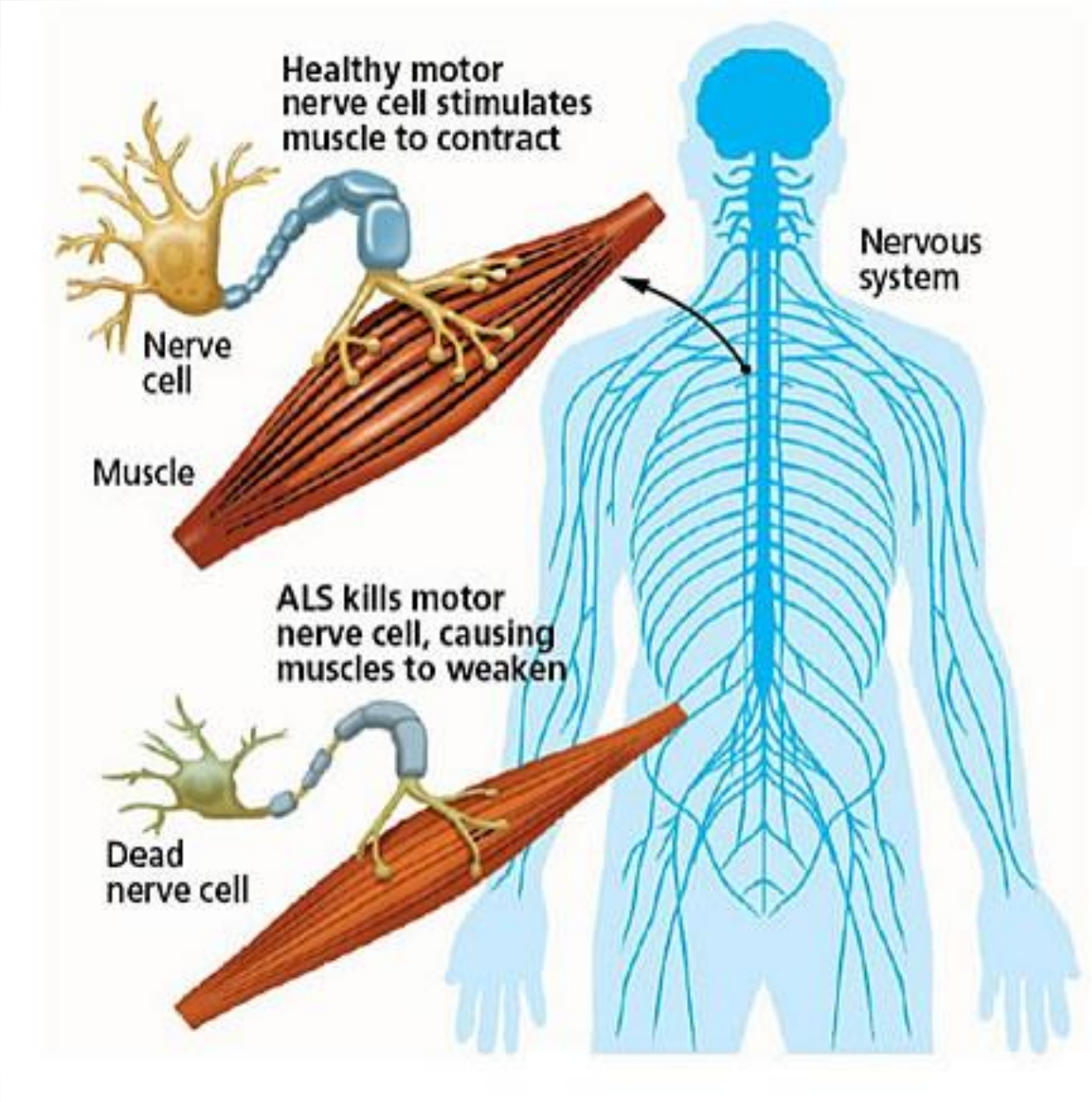

Figure 1: Graphic representation of ALS progression (What Is ALS?, n.d.).

Figure 2: Graphical overview of ALS in the United States (ALS, 2018).

Etiology – Genetic Variant

- Generally speaking, about 10% of ALS cases are genetic while 90% occur sporadically without a known genetic cause (Julien, 2001).
- Mutations in the enzyme superoxide dismutase 1 (SOD1) are the main cause for about 20% of genetic ALS cases (Cleveland, 1999).
  - SOD1 normally functions as an antioxidant but the mutated version becomes toxic and damages motor neurons and associated cells in the nervous system (Mitsumoto, 2009).
- In rare cases, mutations in genes for different proteins such as alsin, spastin, senataxin, dynactin and vesicle-associated membrane protein B have also been suspected to cause the genetic variant of ALS (Mitsumoto, 2009).
- Unfortunately for most with this inherited form of ALS, the exact genetic reason is unknown (Mitsumoto, 2009).

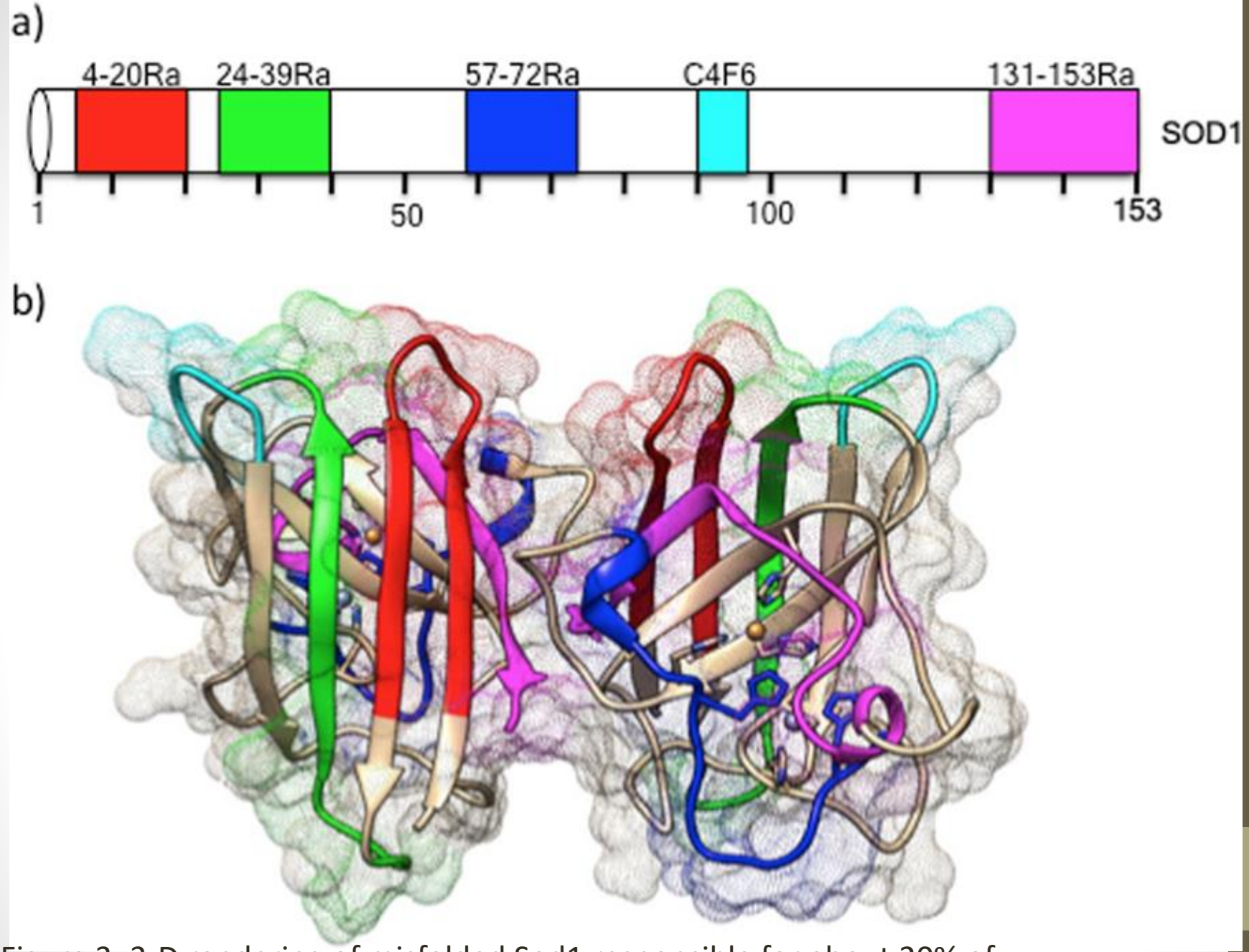

Figure 3: 3-D rendering of misfolded Sod1 responsible for about 20% of genetic cases of ALS (Pare et al., 2018).

Etiology – Non-Genetic Variant

- Finding the true cause of this version of ALS (often called sporadic ALS) remains a question in scientific research.
- Lately, many scientists and researchers suspect the sporadic variant is caused by a multitude of factors including genetic, environmental and yet unknown causes (Mitsumoto, 2009).
- As recently as 2017, Van Es et al. classified ALS as a multidomain neurodegenerative syndrome of motor and extra-motor systems with multiple underlying pathophysiological mechanisms.

Table 1.1 Putative Causes and Etiologic Factors for Amyotrophic Lateral Sclerosis

Altered immunity
Antibodies to calcium channels
Antineuronal antibodies
Antisprouting antibodies

Disordered neuronal metabolism or function
Abnormal neurotransmitter function
Abnormal thyrotropin-releasing hormone
Altered axonal transport
Defects in neuronal membrane structure or function
Defects in the urea cycle
Disordered calcium, phosphate, and bone metabolism
Hyperparathyroidism
Loss of cholinergic receptors
Loss/dysfunction of androgen receptors

Excitotoxicity
Alterations in serum and spinal fluid amino acids
Glutamate transporter protein deficiency
Seed of *Cycas circinalis*

Genetic disorders and abnormalities
Defects in alsin gene
Defects in dynactin gene
Defects in senataxin gene
Defects in superoxide dismutase gene
Defects in VAPB gene
DNA and RNA abnormalities
Genetic markers/HLA antigen
Hexosaminidase deficiency
Single-nucleotide polymorphisms (SNPs)

Heavy metals and trace minerals
Aluminum
Copper
Lead
Manganese
Mercury
Selenium

Infectious or inflammatory factors
Activated astrocytes
Activated microglia
Severe upper respiratory infection
Syphylis
Viruses, especially poliovirus

Nutritional disorders
Dietary deficiencies
Gastrointestinal dysfunction
Vitamin deficiencies

Physical injury
Pneumatic tools
Prior surgery
Prior trauma

Toxic agents or exposures
Animal carcasses and hides
Endogenous "toxins"
Gasoline
Household pets
Spinal anesthesia

Other
Abiotrophy (premature aging)
Malignancy
Neurotrophic factor deficiencies
Paraproteinemia
Vascular disorders

Figure 4: Suspected factors causing ALS (Mitsumoto, 2009).

Body Systems Affected

- Motor neurons in the brain, brain stem, and spinal cord begin to lose function and die (Mitsumoto, 2009).
  - As discussed in earlier slides, the exact reason why these motor neurons begin to lose function is still unknown.
- Once these motor neurons cease functioning, the skeletal muscles they control cease working and atrophy due to disuse (Pare et al., 2018).
  - Interestingly, oculomotor and Onuf's nucleus neurons are resistant so the patient can still control their eyes and sphincters (Van Es et al., 2017).
- The disease usually starts in one part of the body but eventually spreads to other body regions as well (Van Es et al., 2017).

Symptoms

- Many of the symptoms are a direct result of losing motor muscle control in some or most of the body.
- The most common symptoms observed are:
  - Excess saliva and drooling
  - Thick phlegm
  - Laryngospasm
  - Jaw quivering and clenching
  - Anxiety and depression
  - Pain, cramps, and spasms
  - Swelling of hands and feet
  - Sleep disturbances
  - Slurred or impaired speech
  - Difficulty breathing

(Mitsumoto, 2009).

Figure 5: The physicist Stephen Hawking who suffered from ALS for many years (Barr, 2018).

Treatments

- Rulizole is the only widely available drug that prolongs the life expectancy of ALS patients.
  - A drug called Edaravone has been approve for treatment of ALS in Japan but no other countries.
- Due to limited numbers and efficacy of drugs, treating symptoms of ALS is still the most effective way to manage ALS.
- Managing ALS is done by a large team of physiotherapists, occupational therapists, speech therapists, respiratory therapists, dietitians, gastroenterologists, social workers, family doctors, neurologists, and rehabilitation specialists.
  - Weight loss is very common in ALS so maintaining adequate nutritional intake improves ALS patients' survival and quality of life.
  - To assist with breathing, the use of non-invasive ventilation can increase median survival rate by 7 months and makes patients' quality of life better.

(Van Es et al., 2017)

Mission of the ALSA Center Program

To define, establish, and support a national standard of care in the management of amyotrophic lateral sclerosis (ALS), sponsored by the Amyotrophic Lateral Sclerosis Association (ALSA).

Objectives of the ALSA Center Program

To encourage and provide state-of-the-art, multidisciplinary, and interdisciplinary care and clinical management of ALS through

- The involvement of all necessary health care disciplines in the care of the ALS patient and family;
- The offering of multidisciplinary and interdisciplinary care regardless of the ability to pay;
- Collaborative work among centers to enhance ALS patient care techniques.

To select, certify, and support distinguished regional institutions recognized as the best in the field with regard to knowledge of and experience with ALS; and which have neurologic diagnostics and imaging and available on-site licensed and certified ancillary services on clinic days including (but not limited to the following):

- Physical therapy
- Occupational therapy
- Respiratory therapy
- Nursing
- Registered dietitian services
- Doctor of psychology or psychiatry
- Speech and language pathology
- MSW social work services

Figure 6: The Amyotrophic Lateral Sclerosis Association ALS care plan (Mitsumoto, 2009).

Prevention

- Due to the still unknown cause or causes there is no known way of preventing the onset of ALS (Amyotrophic Lateral Sclerosis, 2018).
- Instead, caregivers focus on treatment such as flexibility or stretching, strengthening, and aerobic exercises to slow or prevent the onset of disability.
  - Caregivers also focus on the prevention of other complications such as pressure sores, choking, and pneumonia. (Mitsumoto, 2009).
- One study in 2013 by Fitzgerald et al. concluded that eating food high in carotenoids (yellow, orange, and red pigments produced by plants) may help prevent or delay the onset of ALS.

References

ALS (amyotrophic lateral sclerosis). (2018). Retrieved from MyBioSource.com website https://www.mybiosource.com/als_amyotrophic_lateral_sclerosis

Amyotrophic lateral sclerosis: what is it? (2018). Retrieved from Harvard Health Publishing website https://www.health.harvard.edu/a_to_z/amyotrophic-lateral-sclerosis-als-a-to-z

Barr, R. (2018). Physicist Stephen Hawking dies after living with ALS for 50-plus years. Retrieved from SF Gate website https://www.sfgate.com/world/article/Physicist-Stephen-Hawking-dies-after-living-with-12751523.php

Cleveland, D. (1999). From Charcot to SOD1: Mechanisms of selective motor neuron death in ALS. *Neuron, 24*, 515-520. https://doi.org/10.1016/S0896-6273(00)81108-3

Fitzgerald, KC., O'Reilly, EJ., Fondell, E., Falcone, GJ., McCullough, ML., Park, Y., Kolonel, LN., & Ascherio, A. (2013). Intakes of vitamin C and carotenoids and risk of amyotrophic lateral sclerosis: pooled results from 5 cohort studies. *Annals of Neurology, 73*(2), 236-245. https://doi.org/10.1002/ana.23820

Julien, J.-P. (2001). Amyotrophic lateral sclerosis: Unfolding the toxicity of the misfolded. *Cell, 104*(4), 581. https://doi.org/10.1016/S0092-8674(01)00244-6

Mitsumoto, H. (2009). *Amyotrophic lateral sclerosis: A guide for patients and families.* Retrieved from https://ebookcentral.proquest.com

Pare, B., Lehmann, M., Beaudin, M., Nordstrom, U., Saikali, S., Julien, J.-P., Gilthorpe, J., Marklund, S., Cashman, N., Andersen, P., Forsberg, K., Dupre, N., Gould, P., Brannstrom, T., & Gros-Louis, F. (2018). Misfolded SOD1 pathology in sporadic Amyotrophic Lateral Sclerosis. *Scientific Reports, 8*(14223).

Van Es, M., Hardiman, O,. Chio, A., Al-Chalabi, A., Pasterkamp, J., Veldink, J., & Van Den Berg, L. (2017). Amyotrophic lateral sclerosis. *The Lancet, 390*(10107), 2084-2098. https://doi.org/10.1016/S0140-6736(17)31287-4

What is ALS? (n.d.). Retrieved from ALS Foundation website http://www.alsfoundation.org/learn/