ALS: The Disease behind the Ice Bucket Challenge

By Arthur Serkov

Most of us remember the ALS ice bucket challenge that happened last year when people were dumping buckets of ice water onto themselves "for science". Although a lot of it was people just getting wet, this national trend did help get the word out about ALS, and ended up raising almost $100 million dollars within the month of August alone (Munk 2014). Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive disease that attacks brain cells called neurons, which are responsible for voluntary muscle control. ALS has an incidence of 3.9 cases per 100,000 people, and in 90% of the cases there is no known cause for this disease. Understanding ALS is important to further develop public sentiment about this neurological disease which kills within 3-4 years of onset.

What is ALS?

In a healthy person, neurons within the brain and spinal cord regulate human muscular activity; if you want to move somewhere, it is these motor neurons that tell the feet where to go. In patients with ALS, the neurons within the motor cortex, brainstem, and spinal cord (Meyer et al., 2014) that are responsible for our muscle activity slowly begin to deteriorate and eventually die out. As a result of this, these patients lose the ability to control their muscles, and eventually become paralyzed and unable to move. Don Moire is a person with ALS who had an article published about him in the New York Times in February 2015. In his case most motor muscle ability ceased, and he only has the ability to communicate via eye movements. Special software must be used in order to essentially teach a person how to talk by moving

their eyes, and this eye twitching is how people with ALS communicate with those around them (Brenson 2015). The case of Don Moir is actually a form of ALS that is not as severely progressive as others which are fatal within 3-4 years of onset (Ferraiuolo et al., 2011). In most cases motor muscles responsible for eating and drinking are the initial symptoms for the patients, and death results most often due to respiratory failure (Muscular Distrophy Association 2015).

What are the causes of ALS?

In 1887 a prominent French neurologist named Jean-Martin Charcot wrote (Turner & Swash 2014) about "la sclerose amyotrophique":

> The diagnosis as well as the anatomy and physiology of the condition amyotrophic lateral sclerosis is one of the most completely understood conditions in the realm of clinical neurology.

Charcot might have been slightly wrong because even to this day there has been no definitive understanding of the exact causes of ALS, and it seems to be random in a majority of the cases. ALS is caused by familial or genetic factors in 5-10% and is called fALS, whereas the remaining 90-95% of cases it is sporadic or just random, and is called sALS (Meyer et al., 2014). Cells that normally support neurons called glial cells have also been found to play an important role in the progression of the disease, and make degeneration of motor neurons occur at a faster rate.

The current understanding of ALS is that it occurs due to many different factors all coming together for a perfect molecular storm that results in ALS. The glial cell type that seems to have the most effect on the cell death of motor neurons (MN's) is called an astrocyte. These

supporting cells induce toxicity in MN's and eventually cause them to die, a process called non-autonomous toxicity. One of the molecules that have been found to be linked to ALS is called super-oxide dismutase 1 (SOD1). A mutant form of SOD1 is produced by astrocytes in 20% of fALS and although the mutation itself does not cause ALS, it seems to play a role in the rapid death of MN's (Ferraiuolo et al., 2011). Another molecule that is familiar to bodybuilders is called lactic acid, or lactate, this is the molecule that is causes that "sore" feeling in muscles after a workout. Lactate release is also controlled by motor neurons, and there is evidence (Ferraiuolo et al., 2011) that this release mechanism is impaired in patients with ALS. Lastly a signaling molecule called Nerve Growth Factor (NGF) is important in regulating how neurons develop, as well as determining whether or not a cell will undergo cell death, also known as apoptosis. A specific receptor called p75 that binds only to NGF is overexpressed in people with ALS, and this is also thought to be a significant contributor to MN apoptosis in ALS patients (Ferraiuolo et al., 2011). A receptor is normally a part of the neuronal cell that receives messages from around the neuron, and is regulated in the amount of times it is created by the neurons to receive outside messages, and in the ALS case, the neurons create a lot of these receptors.

What is some of the current treatment for ALS?

Unfortunately, scientists do not have a good understanding of the cause of ALS, the current treatment focuses more on treating the symptoms instead of curing the disease. One medicine available today is known as Rilutek (Riluzole), which works by slowing the disease progression by inhibiting glutamate release (Beghi et al., 2011). Glutamate is a molecule that is used for cell communication in the nervous system and Riluzole acts by slowing this

communication to kill the MN's. However this treatment is not very effective (Beghi et al., 2011), and there is currently a lot of work being done specifically in the area of replacing the neurons with stem cells that then make more neurons to replace them (Meyer et al., 2014). Stem cells are cells that are not specialized yet, and can become different kinds of cells based on the environment that they are exposed to. This treatment works by taking fibroblasts from the skin of a patient, which are cells important in wound healing, and using them to make Neuron Progenitor Cells, or NPC's, which are a type of stem cell that can generate neurons, and astrocytes. Although this path of treatment seems to be rather straightforward, just remaking more neurons and putting them into the areas where the MN's are dying, the issue is that it's only worked on mouse fibroblasts, in a lab, and is very far from human application. Treatments that are in place today to help patients with ALS include physical therapy, respiratory management, as well as nutritional supplementation (NINDS – ALS Fact Sheet 2013).

What is the future of ALS research?

There are a lot of factors causing ALS and they all seem to work together to destroy motor neurons in ALS patients. The future of ALS research is primarily to understand more about the cause of ALS, in other words, figuring out the causes of the disease (Ferraiuolo et al., 2011, Mayer et al., 2014, Turner & Swash 2014). Another direction of research is to treat the symptoms more effectively, perhaps figuring out a drug that could slow the progression of the disease a lot better than Riluzole does currently, or use it in combination with other drugs (NINDS – ALS Fact Sheet 2013). Finally research has already focused, and will continue to focus on the genetic component of what is happening in neurons and astrocytes of people with ALS (Ferraiuolo et al., 2011, Mayer et al., 2014). The genetic component of ALS is the causes of fALS

that were talked about earlier, and is measured by what genes are being expressed in motor neurons of people with ALS. An understanding of a genetic mechanism will hopefully provide insight into some causes of ALS, and provide hope for the 90% or so sALS patients who seem to get this disease at random.

Why is ALS still around?

ALS has been well known and documented as a clinical disease since the late 1880s, however to this day, we really don't know how or why it occurs. As a society it took millions of people dumping buckets of ice water on their head in order for people to care enough that they considered donating their resources to help people with this debilitating disease. A disease which might have been cured a long time ago if people were more informed about it, and did something about the process of legislation, and research funding for ALS.

References

Amyotrophic Lateral Sclerosis (ALS) Fact Sheet*: National Institute of Neurological Disorders and Stroke (NINDS)*. Publication date June 2013. NIH Publication No. 13-916 Web 11 Feb. 2015. http://www.ninds.nih.gov/disorders/amyotrophiclateralsclerosis/detail_ALS.htm

Beghi, E., Chiò, A., Couratier, P., Esteban, J., Hardiman, O., Logroscino, G., … Zoccolella, S. (2011). The epidemiology and treatment of ALS: Focus on the heterogeneity of the disease and critical appraisal of therapeutic trials. *Amyotrophic Lateral Sclerosis : Official Publication of the World Federation of Neurology Research Group on Motor Neuron Diseases*, *12*(1), 1–10. doi:10.3109/17482968.2010.502940

Brenson T. (2015) Watch a Man with ALS Say 'I Love You' for the First Time in 16 Years. *Time* Web. Feb. 18 2015. http://time.com/3712484/als-speak-eye-tracking-love/

Ferraiuolo L., Higginbottom A., Heath P.R., Barber S., Greenald D., Kirby J., Shaw P.J. (2011) Dysregulation of astrocyte-motoneuron cross-talk in mutant superoxide dismutase 1-related amyotrophic lateral sclerosis. *Brain* 2011: 134; 2627-2641 doi:10.1093/brain/awr193

Meyer K., Ferraiuolo L., Miranda C.J., Likhite S., McElroy S., Renusch S., Ditsworth D., Lagier-Tourenne C., Smith R.A., Ravits J., Burghes A.H., Shaw P.J., Cleveland D.W., Kolb S.J., Kaspar B.K. (2014) Direct conversion of patient fibroblasts demonstrates non-cell autonomous toxicity of astrocytes to motor neurons in familial and sporadic ALS. *PNAS* January 14, 2014 Vol. 111 No. 2 829-832 www.pnas.org/cgi/doi/10.1073/pnas.1314085111

Munk C. 2015 Ice Bucket Donations Continue to Rise: $94.3 Million Since July 29. *The ALS Association*. Web. Feb 18 2015. http://www.alsa.org/news/media/press-releases/ice-bucket-challenge-082714.html

Stages of ALS Amyotrophic Lateral Sclerosis. *Muscular Dystrophy Association*. Web. 12 Feb. 2015.http://mda.org/disease/amyotrophic-lateral-sclerosis/signs-and-symptoms/stages-of-als

Turner M.R., Swash M. (2014) The expanding syndrome of amyotrophic lateral sclerosis: a clinical and molecular odyssey. *J Neurol Neurosurg Psychiatry* 2014;0:1-7. doi:10.1136/jnnp-2014-308946