

GENETICS AT THE END

Examining ALS Patients' End-of-Life Decisions

BY SELENA PASADYN

My family received horrific news in November 2011. The muscle weakness that had progressively worsened in my uncle could not be summed up by the typical diagnosis of “old age.” My uncle had amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig’s disease.

ALS is a rapidly progressive neurodegenerative disease that affects motor neurons in the central nervous system. There are many genes already linked to the death of these neurons, and much speculation on the failure of signals to reach the muscles. Patients can have muscle cramping, head drop, speech problems, difficulty breathing, and inability to swallow (1). Typically, two to five years of life remain until the individual dies from neuromuscular respiratory failure (1). Throughout this process, decisions regarding various life-sustaining treatments become very difficult. Patients must use long-term ventilation and enteral feeding to continue living, and sometimes wrestle with the idea of continuing to live with a compromised quality of life.

GENETIC FACTORS IN ALS

A great deal of research has focused on elucidating the possible genetic factors that contribute to both familial and non-familial, or sporadic, ALS in order to develop targeted screening and therapeutics. However, complications underlying ALS are not confined to one chromosome or one method of

inheritance. ALS has been linked to damaged genes on chromosomes 2, 9, 12, 15, 18, 21, and the X chromosome (2).

Specifically, the degenerative nature of the motor neurons has been linked to CAG repeats in ataxin 2 (ATXN2) on chromosome 12, the causative

gene of spinocerebellar ataxia type 2 (SCA2) (Figure 2, 3). Spinocerebellar ataxia type 2 affects the central nervous system and is a hereditary disease. The primary symptom is ataxia, or difficulty with balance and hand coordination (4). However, neuropathy, a degeneration of the peripheral nervous system,

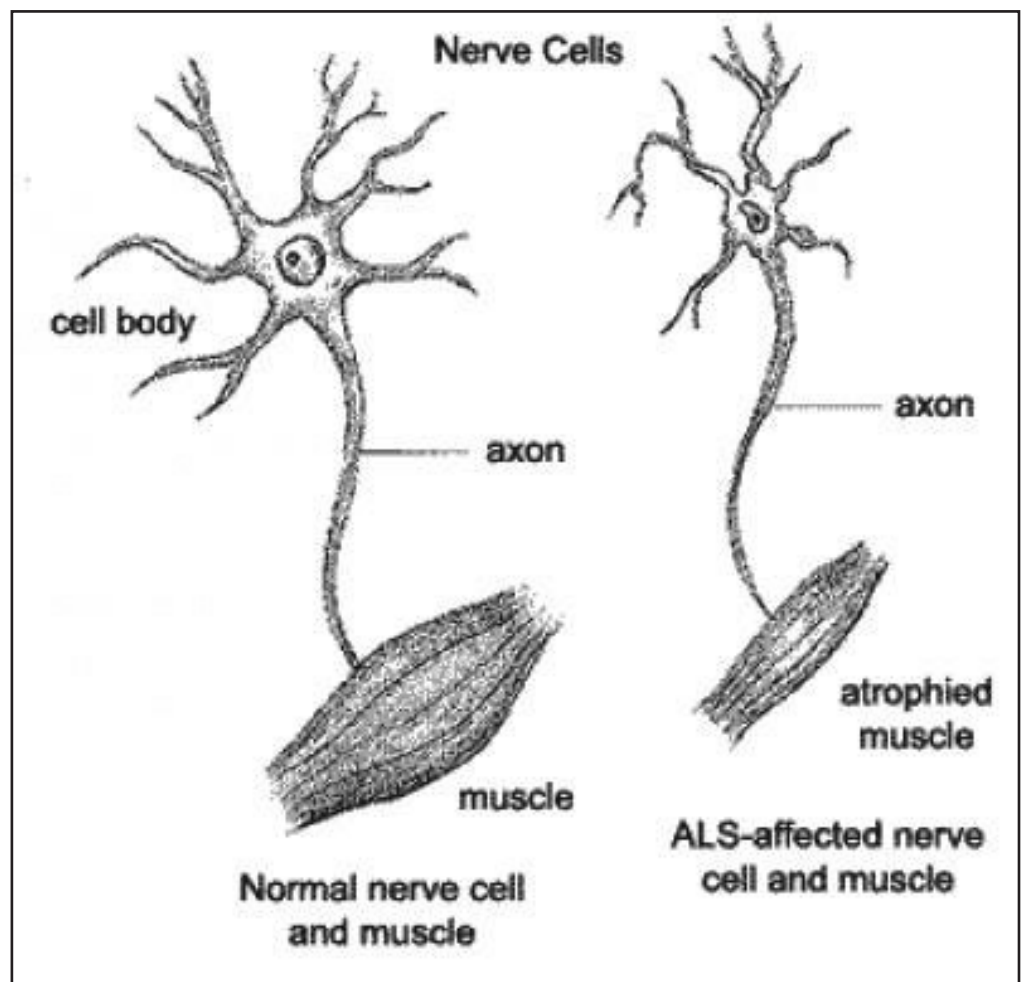


Figure 1: Comparison of normal nerve cells with those of an ALS patient. *Photo courtesy of NCSU Wiki.*

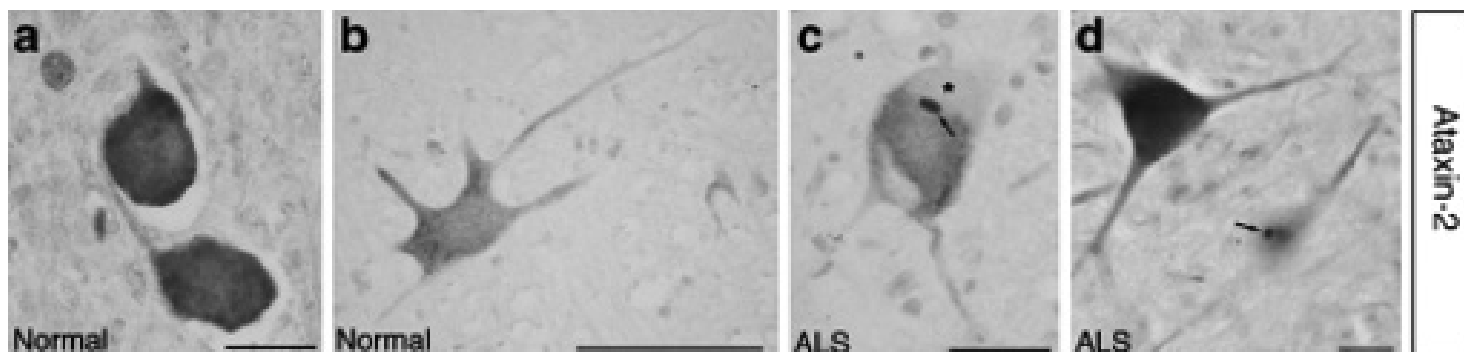


Figure 2: The CAG repeat expansion present in ATXN2 causes aggregation of the Ataxin-2 protein in ALS patients' spinal cord motor neurons (c, d), rather than the diffuse pattern seen in normal neurons (a, b). *Photo courtesy of the National Institutes of Health.*

and slow eye movements can occur and as the disease worsens, difficulty swallowing, spasticity, weakness or memory troubles can occur (5). These striking similarities to ALS correspond to the discovery of the ATXN2 CAG repeat sequence in patients of sporadic ALS. It has been demonstrated in animal models that these repeats lead to a detrimental accumulation of a DNA binding protein followed by neuronal complications (3).

Furthermore, mutations present in the C-terminal of neurofilaments, components of the neuron cytoskeleton that provide structure for the neuron, have been observed in ALS patients (6). Orwell and Figlewicz have shown that mouse models with mutations in the genes that code for this neurofilament also have neurodegenerative symptoms (6).

In addition to the variety of genetic factors that could contribute to sporadic ALS, many genetic mutations have been identified that specifically lead to familial ALS. Approximately 5-10% of ALS cases are inherited (7). Sometimes the inheritance pattern is autosomal dominant, meaning the affected person has a parent with the condition and that just one copy of the altered gene will cause the disorder (7). Although less common, ALS can also be inherited through a recessive pattern or an X-linked dominant pattern (7). By conducting research through linkage studies in families with ALS, chromosome 21

was found to possess a mutation in the gene SOD1 (6). Orwell and Figlewicz demonstrated that transgenic mice over-expressing this mutated gene form developed a deadly, late onset motor neuron disease (6). More than 80 different types of mutations to this gene have been documented (6). Although this genetic mutation does not account for all familial cases, 20% of families with ALS were found to have a mutation in this gene (1). This is an important screening measure for families, and something to consider for pre-natal diagnosis, although some people with the mutated gene do not develop the disease.

It is unclear how all of these genetic mutations exactly affect motor neuron death (1). Many of the known mutations lead to protein aggregates. However, the role of these clumps is not clear, as they could be a byproduct of a dying cell and not actually the underlying cause of ALS (2). Mutations in a variety of genes like SOD1 have been shown to lead to the production of misfolded proteins that form these aggregates (2). Other research has cited the disruption in the development of axons, or the extensions of nerve cells responsible for transmitting nerve impulses, leading to a failure to send essential signals to muscles (2). Other mutations can kill motor neurons by slowing the transport of necessary materials to the axons and failing to break down toxic substances accumulating in the nerve

cells (6).

Due to the variety of locations where genetic abnormalities are found, and then linked to the disease, genetic understanding of the disease has progressed at a slow rate. The continual discovery of these genes is pushing the field forward, despite the difficulty in understanding the pathogenic mechanisms (1). For example, targeting misfolded proteins may be key to developing therapeutics in the future. Gene therapy can be used for SOD1 defects, and also for the genes surrounding SOD1, that are also responsible for damage in the nervous system (1). Finally, through the study of these mutations, scientists are working to find a biomarker for ALS. This chemical indicator of the disease can lead to earlier detection and potentially the development of clinical trials for new drugs (1).

SPECIFIC CHALLENGES

With the need for more research before a cure is developed, the symptoms are wreaking havoc on the lives of those with the condition. Generally, the signs and symptoms of sporadic ALS appear in a person's late fifties or early sixties. At first, symptoms such as cramping, stiffness and muscle twitching arise (1). It seems possible that a hard workout at the gym or a day of yard work could provoke similar irritation; however, when difficulty chewing and swallowing begins, ALS becomes more evident. Malnu-

trition can quickly complicate the situation, especially because the body needs fuel to continue combating the condition (1). Strength begins to deteriorate quickly, making walking impossible and resulting in a loss of function in the hands and arms. The muscles will appear thin and begin to atrophy (8). Finally, 20% of individuals will develop a condition called frontotemporal dementia, which can further impact personality, language and behavior (8). This is difficult when coupled with the emotional impact on an individual and his or her family as they cope with the progression.

Patients with ALS face numerous challenges as a result of their inability to move a sufficient amount of air in and out of their lungs as the disease progresses. Death can occur within

two to ten years after diagnosis from respiratory failure due to respiratory muscle weakness. Non-invasive ventilation systems can be used to a point in the progression, and then dependence on an invasive ventilator becomes necessary. Patients who do not opt for an invasive ventilator will not live as long (1). This decision is very personal and is not governed by law, but by numerous other factors including motivation, symptom progression and available assistance (8).

Currently ALS patients have the right to accept, discontinue, or refuse treatments and therapy (8). Medication therapy, nutritional support, communication devices, and palliative care are all examples of decisions patients face. They have the right to prepare an advanced directive to provide healthcare workers with the

information they need to follow the patient's wishes during emergency and end-of-life treatment choices. The overall purpose is to ensure that patients are treated with dignity.

Genetics can play a role in not only treatment development, but also in the disease severity and age of onset.

Individuals with familial ALS, and the SOD1 mutation, can experience particularly rapid disease progression (6). This may alter life-sustaining treatment options, as patients may quickly progress to using mobility and breathing assistance devices. Additionally, although there is a wide range in the age of onset, on average individuals with familial ALS are diagnosed about 10 years earlier than individuals with sporadic ALS (6). It is especially important for patients diagnosed at a younger age to seek



Figure 3: Patients, under the guidance of healthcare professionals, must make critical decisions about their life-sustaining care. *Photo courtesy of Wikimedia Commons.*

therapy that allows mobility. In general, a patient diagnosed younger experiences a more substantial difference between the activities they were able to do before ALS, and what they can do as their disease worsens (1). If they can maintain an active lifestyle, this disparity will not be as emotionally detrimental.

PHYSICIAN-ASSISTED SUICIDE

Despite relative freedom in choosing care, legal assisted suicide presents an interesting option for some ALS patients and has been labeled the right-to-die movement (9). In a sample of 203 patients with ALS, about one in five patients chose to die as a result of euthanasia (17%) or physician-assisted suicide (3%). Additionally, a study conducted in Switzerland revealed that 54% of ALS patients could imagine asking a physician to prescribe a fatal drug that they could take in the future (9).

The right to die movement began in 1976 and progressed to the establishment of an individual's right to refuse life-sustaining medical treatment (10). The Quinlan court decision was a turning point in the debate as it employed the constitutional right to privacy as the basis for the refusal of treatment, allowing a woman in the vegetative state to be removed from her respirator based on her guardian's wishes (10). Ultimately, this was a step in the direction of placing less power in the hands of medical professionals when it comes to life-ending medical decisions. Another milestone for the right-to-die movement came in 1990 when the Supreme Court deemed it a fourteenth amendment right to refuse medical treatment in extreme situations (8).

The "right to die" encompasses many subsets of end-of-life decisions including the termination of medical intervention (passive euthanasia), or providing the patient with the means to end their life (assisted suicide). Pa-

tients have the right to end their life-sustaining treatment; however, physician-assisted suicide is not included in that right. Several countries, including the Netherlands and Belgium, allow physician-assisted suicide (11). In the United States, Oregon is the only state where doctor-assisted suicide is legal. The patient must be terminally ill and confirmed to be likely to die within six months. They must have sufficient mental capacity to give informed consent (8). If the conditions are met, physicians are permitted to write prescriptions for lethal drugs that can be used by the patient to bring their life to a peaceful and painless end. This Death with Dignity Act has been a source of national debate as Washington instituted a similar act, and twenty other states have had ballots on the issue (10). Since 5-10% of individuals with ALS have familial ALS and tend to experience more rapid progression, many individuals and families must face such tough decisions each year (12).

LOOKING FORWARDS

In a hospital setting, it is easy to imagine the staff making a valiant effort to save a patient, fighting off death at all costs. However, for those living with terminal illnesses, such as ALS, the decisions they face are extremely difficult. Precedent in court rulings has shown that patients do have a right to end their life-sustaining treatments. However, is it morally acceptable for physicians to assist in the process of dying? Is hastening the death of a terminally ill patient prompted by mercy and respect for the individual's wishes, or is it an act of murder?

As my uncle undergoes some personal and intensely difficult decisions, such as continuing his life-sustaining treatments in the future, I will be a loving and supportive family member regardless. However, if the medical community can continue to

work to combat ALS through genetic research and targeted therapies, fewer individuals would have to face these heart-wrenching decisions.

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