Amyotrophic lateral sclerosis (als): physiology and treatment

Amyotrophic lateral sclerosis: Physiological traits

Amyotrophic lateral sclerosis (ALS) more commonly referred to as Lou Gehrig’s disease, is a progressive and deadly disease. Many with ALS experience grief and many families of those affected endure the same. At present medical science has demonstrated great potential in finding a workable cure or efficacious therapy. However, at present no such cure or efficacious therapy exists. A number of treatments can prolong the fatal course of ALS but none can stop it and ALS continues to significantly shorten the sufferer’s lifespan. 3. 9 in every 100, 000 individuals will develop ALS in America, so while the prevalence is relatively low, ALS has generated a great deal of attention due in part to its severity, to numerous movements to raise funding for the disorder and for its generalized physiological symptoms and theoretical relation to other dementing illnesses such as Alzheimer’s. Definitive answers as to the causes of ALS are currently not known. Numerous theories have emerged and research has pinpointed causes which partially explain occurrence or have been found in rat studies but have yet to reach human testing. Promising treatments for the disease have been found however none have made it beyond the research stage. Exposure to different toxins has been suggested as a potential cause, ranging from occupational exposure and physical activity to military exposure and trauma. Males have a higher prevalence rate than females. Particularly, white males ages 60+ are at highest risk for the development of ALS.

ALS is characterized by muscle spasticity, which rapidly progresses to muscle wasting and difficulty breathing, speaking, and swallowing. Most individuals with ALS live for 3 to 4 years. About 5% live longer than 10 years

and a very select few live still longer. The disease's symptoms are due to a result of the loss of upper and lower motor neurons. Present research effort include stage II testing in Israel and soon, the United States at the Mayo Clinic.

Physiological Pathology

A_{2A} Adenosine receptors

A_{2A} Adenosine receptors have been thought to be a potential therapeutic objective but until a recent study (14) the neuromodulatory role of the aforementioned receptors has remained in question. A selective A_{2A} agonist was applied known only as CGS 21680 at present. (Poff et al., 2014) The A_{2A} agonist significantly enhanced average amplitude of endplate potentials (EPP's) and enhanced frequency of miniature endplate potentials (MEPP's) and giant end plate potentials (GMEPP's). The A_{2A} adenosine receptor is now under scrutiny for its potential therapeutic role for presenting symptoms of ALS (Poff et al., 2014).

Cortical atrophy

Cortical atrophy in patients suffering from ALS was linked to neuropsychiatric and cognitive changes. Acidotoxicity has been implicated as a potential cause or contributor to this phenomenon (Behan et al., 2013). With regard to patients with ALS-plus; cortical atrophy presented significantly across motor and somatosensory areas. Additional cortical atrophy was found in frontal and parietal areas of the brain. In patients with ALS no significant cortical atrophy was shown, only brainstem atrophy. In patients with ALS-FTD;

atrophy also affected greater frontal area atrophy and temporal area atrophy in comparison with ALS-plus. Atrophy of the cortexes is implicated as a contributor to the presenting deficits of ALS (Mioshi, 2013).

Genetic links

The vast majority of ALS cases are sporadic and unrelated to genetics. However; 5-10% of ALS cases are thought to be hereditary. Mutations in TAR DNA-binding protein, fused in sarcoma (FUS), and superoxide dismutase 1 (SOD1) comprise the causes for about 30% of classic inherited ALS. A gene known as UBQLN2 which is responsible for the encoding of the protein “ ubiquilin? 2” can cause dominantly inherited, ALS and ALS/dementia. So although the majority of ALS cases occur from causes unknown, a select few cases can be explained by genetic mutation. Suggested from this data is the potential for retracing the steps of the gene and specifying the mechanism of action most exploitable in treatment for the disease. While genetically link ALS is rare the basic mechanism of action is widespread, thus insights into causes for the physiological outcome are valuable in treatment of ALS as a whole (Deng, 2011).

White matter aberrations

White matter has been examined for its aberrations in shape in patients with ALS. What has been found is a link between symptoms indicative of the disease however, not the physiological changes typical in the disease itself (Rajagopalan et al., 2013). Scientists suspect that the unidentified physiological link between white matter changes and physiological changes caused by ALS may play a large role in the disorder. White matter changes

specifically have been correlated with the ALS-FTD-Q, a screening tool for behavioral disturbances in ALS. So while the behaviors correlate, the physiological changes beyond white matter shape change have not yet been linked specifically, leaving room for additional research in this area (Rajagopalan et al., 2013).

Cervical roots and peripheral nerves

A sonogram study found that in patients with ALS, cervical roots and peripheral nerves exhibit reductions in size in comparison to their former size and those in patients without ALS. The study found that the aforementioned both reduced in size and became physically thinner although more significantly the latter (Nodera et al., 2014). Although this phenomenon was measurable in patients with and without ALS it was not related to gender, progression of the disease, and severity of disease symptoms. Despite these setbacks it is suggested that peripheral root atrophy may present a viable marker for detection of the presence of the disease and thus increase progress made on treatment due to decreased false positive diagnoses (Nodera et al., 2014).

Treatment

Metabolic therapy (Deanna Protocol)

Aside from motor neuron degeneration ALS is associated with metabolic dysfunction. A mouse study found that mice given the Deanna Protocol (DP); a metabolic therapy reported to result in some symptom alleviation in patients with ALS. The study found that mice given the treatment had

significant extensions in survival time in ALS mice 7. 5% (p <. 001) and control 4. 5% (p <. 006). Given such findings it appears that metabolic rate may be implicated in ALS but perhaps there is some common benefit to the intervention as well. Future research should focus upon parsing out the benefit exclusively to those with ALS vs. the benefit to unaffected populations as well as whether or not these findings apply to humans as well as mice (Poff et al., 2014).

Human stem cells

Human stem cells have long been considered for their curative abilities toward various diseases. ALS is one such disease. The degeneration of motor neurons can theoretically be counteracted using motor neurons created from stem cells. (Lee et al., 2014; Morgan & Srivastava, 2014). Stem cells present what seems to be a highly promising treatment for ALS. In one study, patients were injected with stem cells and followed up upon 12 months later and not acceleration of the disease was detected (Kim, Lee, Kim, 2013). A large proportion of future research will center upon investigation of this.

Guanabenz

Guanabenz is now under scrutiny for its therapeutic benefits to those suffering from ALS. Guanabenz was found to have an impact on post-apoptic protein synthesis such that scientists conducting the experiment hypothesized that its introduction would have therapeutic effects on ALS patients. In a mouse model female mice were given Guanabenz and were found to have delayed symptom onset, prolonged life span and increased motor ability (Jiang et. Al 2014).

Thalidomide

Inflammation from the cytokine tumor necrosis factor alpha TNFα is believed to be a critical factor in the development and pathology of ALS. TNFα is reduced by thalidomide. Thus the rationale for research surrounding the efficacy of the use of thalidomide in ALS patients. The study found no results suggesting that this theorized mechanism may need revision (Stommel et al, 2009).

Discussion

ALS as aforementioned is a neurodegenerative disease which causes the motor neurons to atrophy and die. Victims of ALS typically suffer from motor impairments which eventually exacerbate to impairments in breathing, swallowing and speaking. Sufferers experience many psychological symptoms as secondary effects from the physiological damage which occurs. Physiologically, impairments typically relate to motor movement. In some cases movement changes but in most cases it becomes more difficult. Numerous treatments are emerging in the research phase due in part to massive donations to the research of a cure or treatment for this disorder. While ALS is unique to other neurodegenerative disorders scientists suspect that some aspects of the treatments used and developed will translate due to the similarities ALS shares.

Evidence has suggested that certain cases of ALS are inherited while others are developed due to toxins which has helped scientists narrow down the possible mechanisms of action which facilitate this disease. While some are known, the cause of most cases is yet to be determined the outcomes have

been more apparent. ALS outcomes include changes in shape of the white matter in the brain, cortical atrophy and thinning of cortical and peripheral nerves. The treatment has made relative progress. Perhaps most promising is the use of stem cells as replacements for motor neurons. Stem cell research has had difficulty using stem cells in large quantities as a corrective measure however motor neuron use requires the use of less cells than most treatments making it especially promising. Other theoretical treatments such as metabolic therapy and Guanabenz have shown some potential in improving the lives of ALS sufferers and perhaps prolonging them somewhat. Guanabenz, an intervention targeted specifically at cell apoptosis has demonstrated an effect on symptoms, speed of progression, and lifespan. Metabolic therapy has demonstrated an effect on symptoms and lifespan. Together therapeutic treatments have a supplementary benefit until a more lasting solution is found.

Future research

Future research implications include additional research on stem cells. Stems cells are highly promising and may be an effective treatment and perhaps eventually have curative effects. Studies at present have found a link between symptom stabilization and treatment in human studies. As with all medical research clinical trials must be completed before anything is open to the public. Additional concerns for this treatment include the political implications of this treatment as some political groups disagree with stem cell research as a whole. Future research should also continue to focus upon the clinical implications of therapeutic treatments such as Guanabenz and Deanna Protocol metabolic therapy.

Conclusion

At present ALS presents future challenges to scientists, doctors, and the people who suffer from it. While promising research and clinical trial have received unprecedented support; the reality is that ALS continues to shorten and end lives. Researchers are far from finding the multiple causes of ALS however, researchers are rapidly gaining ground on how to treat the effects of the disorder. Aside from stem cells, therapeutic treatments have emerged such as Gaunabenz and metabolic therapies such as the Deanna protocol.

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