Exploring Interactions Between Caregivers' and Patients' Stress and Mental Health in Amyotrophic Lateral Sclerosis (ALS)

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disorder that is characterized by progressive muscle weakness leading to loss of mobility, speech, and ultimately death. While the disease's impact on patients is well-studied, there is a significant burden placed on caregivers that is often overlooked. This research paper explores the relationship between ALS patients' and caregivers' mental health, highlighting the psychological burden that caregiving takes over time, which often intensifies as the disease progresses. The paper begins by presenting an overview of ALS, including its genetic basis and molecular structure, as well as the fundamentals of ALS. The paper then discusses the disease's relentless and progressive nature and the limited scope of research, especially regarding diverse populations and ethnic groups. The paper also examines how ALS patients experience significant mental health challenges, such as depression, anxiety, and a reduced quality of life, which are often directly related to the disease's worsening stages. Caregivers are tasked with managing numerous complex emotional, physical, and financial responsibilities, leading to chronic stress, depression, anxiety, and caregiver burnout. Current treatment options for ALS, such as Qalsody (Tofersen), Riluzole, and Edaravone, alongside multidisciplinary care for symptom management, offer some relief. Yet, there remains a significant lack of attention to caregiver stress and trauma, which have long-term detrimental effects on their health. The paper concludes by emphasizing the urgent need for more research into caregiving stress, improved caregiver support systems, and continued advancements in treatment options for ALS patients to enhance the quality of life for patients and their caregivers.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a rare neurological condition where the muscles slowly start to weaken over time, limiting muscle function and movement and leading to death. However, ALS patients are not the only ones who experience negative consequences; the caregivers of the patients do as well. Many overlooked caregivers spend their time worrying about the patients, leading to their health declining. This paper explores the interactions between caregiver and patient stress and mental health related to ALS.

ALS Fundamentals

ALS is a scarce condition that is clinically heterogeneous and only affects 40,000 citizens in the United States each year (Total et al., 2021). Out of these numbers, 1/400 or 1/500 people in the United States and Europe die from ALS each year as well (Total et al., 2021). The average prognosis of patients with ALS is around 3-5 years (Total et al., 2021). Understanding ALS's genetic and molecular fundamentals is crucial because it can help identify potential therapeutic targets and ways to improve patient outcomes. 10% of the cases are inherited. The TDP43 mutation is common in familial ALS (Total et al., 2021). 90% of cases of ALS are sporadic (Total et al., 2021).

ALS is a focal-onset disease that relentlessly spreads throughout the body (Total et al., 2021). ALS also spares the sensory neurons, showing that motor neurons are not the only affected neurons. The average prognosis of patients with ALS is around 3-5 years (Total et al., 2021). ALS has the largest impact on the nervous system, as motor neurons degenerate in the spinal cord and brain, losing the ability to control different muscles (Total et al., 2021). ALS affects the proteins in an individual's body, getting clumped and ubiquitinated together. The proteins involved in ALS are TDP43 proteins, a nuclear protein, a transcription repressor, and a splicing apparatus. This protein is cleaved, hyperphosphorylated, and ubiquitinated in the cytoplasm. This process happens in early ALS and frontotemporal dementia (FTD). Understanding the molecular changes is critical to potentially developing therapies that target the affected proteins.

The survival of the patients depends on the different motor neurons involved in ALS. Mutations in various types of proteins in the human body can lead to ALS, including a *SOD1* mutation (Total et al., 2021). Proteins could also be misfolded (Total et al., 2021), meaning their correct structure and function still need to be achieved. This may lead to cellular stress and further progression of ALS. ALS genes can trigger toxicity through different pathways, such as protein quality control (superoxide dismutase 1; *SOD1*), process extension (PFN1), and RNA metabolism (*C9orf72*), which result in progressive loss of muscle control. *SOD1* is an enzyme that prevents oxidative damage. When it is mutated, toxic protein aggregates and the enzyme's loss of function contribute to the disease pathology. High levels of NfL, a cylindrical neurofilament in the cytoplasm of neurons, contribute to fast disease progression, leading to earlier death. When an individual experiences neuronal damage, NfL is released from the CSF and plasma.

There are several disparities in ALS research. Most of the research on ALS patients is based on European and American White men, who make up a small minority of people with the disease (Total et al., 2021). Limiting the research population prevents the generalization of research. There are also disparities in clinical trials: certain racial/ethnic groups are overrepresented in the study population, and more diverse populations need to be included in ALS intervention studies. There are also environmental risk factors disparities: exposure to

environmental risk factors for ALS may differ based on socioeconomic or geographic characteristics (Total Health, Oncology, 2021).

Mental Health: What We Know

ALS affects the mental health of patients and their ability to adapt to living with the disease. Quality of life for patients decreases as the disease progresses (Stephens et al., 2016). Many pain symptoms come with ALS, resulting in a severe impact on daily activities (Albert et al., 2007). In a study of 197 ALS patients, researchers found moderate pain levels, pain interference with daily activities, and suboptimal pain relief from treatments on average (Albert et al., 2007). The quality of life in ALS patients has varied: many ALS patients can maintain a quality of life in different aspects despite their physical health decline (Albert et al., 2007). As death approached, family involvement, engagement with friends, and leisure activities became even more critical. Furthermore, the amount of satisfaction with these aspects of life was largely independent of their physical functioning (Albert et al., 2007).

Depression and anxiety were both widespread in ALS patients across multiple studies (Albert et al., 2007; Averill et al., 2007; Stephens et al., 2016). Higher pain self-efficacy scores predicted lower pain severity (Albert et al., 2007), indicating they are more aware of their bodies. The prevalence of depression among ALS patients at the end of life was around 9% (Averill et al., 2007). Overall, ALS patients did not have an increase in depression as they were getting closer to death (Albert et al., 2007). However, about 19% of ALS patients have expressed that they wished to die; they have reported higher levels of depressive symptoms, pessimism, and hopelessness (Averill et al., 2007). Those who could plan and “control” their approaching death reported to have less suffering and a greater sense of control of their condition (Averill et al., 2007).

There are many cross-cultural differences in the mental health of ALS patients. American patients were reported as the least distressed overall among all the ALS patients (Albert et al., 2007). This could be because of the quality of hospice care and the availability of more improved technology compared to less-resourced countries. Israeli patients were reported as the country with the highest levels of distress, pessimism, and suffering (Albert et al., 2007). This could be because of the quality of the care and the quality of the technology as well. German patients were reported between the American and Israeli patients in terms of distress and other mental health indicators (Albert et al., 2007).

Qalsody + Other treatment options

Qalsody, also known as Tofersen, is an antisense oligonucleotide a treatment for ALS. Tofersen was recently approved about a year ago, but only for patients with a mutation in the *SOD1* gene. Tofersen can bind to the *SOD1* mRNA, degrading the *SOD1* mRNA and reducing the synthesis of the *SOD1* protein. The Tofersen was tested on patients with the *SOD1* mutation, reducing the total cerebrospinal fluid *SOD1* by 35% and 2% in placebo patients (Blair, 2023). Tofersen also reduced the plasma NfL by 55% and 12% increase in placebo patients (Blair, 2023). The cerebrospinal fluid’s (CSF) maximum concentration is reached after the third dose of Tofersen. Tofersen is transferred from the CSF into the systemic circulation, which helps the maximum plasma concentrations be reached after 2-6 hours. No statistical differences exist between age, sex, race, and body weight and the impact on tower exposure in the plasma (Blair, 2023). Metabolism of Tofersen is expected to happen because of exonuclease-mediated

hydrolysis (Blair, 2023). Qalsody (Toferson) is a very significant advancement in the treatment of ALS, especially for individuals who have the *SOD1* mutation.

Other pharmaceutical treatments include Riluzole and Edaravone. Riluzole, an FDA-approved medication that can slow down the progression of ALS, is often prescribed early in the disease course. Edaravone, e, is an FDA-approved drug that may slow the decline in daily functioning for some ALS patients. Additional treatments may include multidisciplinary care: ALS treatment typically involves a team of specialists, including neurologists, physical therapists, occupational therapists, speech therapists, nutritionists, and respiratory therapists. Finally, physical therapy is recommended to maintain mobility and prevent complications from inactivity.

There are also some “Upstream” therapies, such as target DNA (CRISPR/Cas9), where the gene itself “heals” or the mutation is deleted; target RN; antisense oligonucleotides (ASO); micro-RNA; target protein-immuno-depletion; and target transcriptional networks. “Personalized” biological therapies may be particularly beneficial in FALS caused by *SOD1* and *C9orf72* gene mutations.

Caregiver Stress: Mental Health Disorders in Caregivers and Genetics

Caretakers have many different responsibilities for patients with ALS, including assisting with daily activities (e.g., bathing; dressing; eating; medicine; secretions), operating medical equipment and learning how to use it, coordinating medical appointments, providing emotional support, and making decisions about care and treatments.

Caregiver burden, or caregiver stress, is the strain or load a caregiver feels helping ill, disabled, or elderly family members. Stress is a self-perceived, multifaceted strain (physical, emotional, social, and financial) and includes a temporal aspect (burden over time). Many caregivers need more financial resources experience multiple responsibility conflicts, and don’t have social support systems. As the disease progresses, provisions for caregivers decrease, quality of life declines, and physical and psychological health deteriorates (Cabral et al., 2014).

ALS caregivers are exposed to a variety of stressors, ranging from financial, physical, and emotional, among others. High costs of medical care and equipment, loss of income, expenses for home modifications, and costs of medications and treatments not covered by insurance all contribute to financial stress. Physical demands include assisting with mobility and physical transfers, helping with personal care tasks, managing feeding and nutrition needs, and lack of sleep due to nighttime care requirements. Emotional and psychological challenges encompass the experience of watching a loved one’s progressive decline, anticipatory grief, feelings of isolation and loneliness, stress from constant vigilance and decision-making, and potential depression and anxiety. There are also logistical stressors, such as time management; balancing caregiving with other responsibilities; coordinating medical appointments and therapies; and managing medication schedules. Communication challenges between a patient and caregiver develop throughout the disease; adapting to changes in the patient’s ability to communicate and learning to use assistive communication devices can cause substantial stress. There are also behavioral changes that come with ALS, which for the caregiver include dealing with mood swings or personality changes, managing frustration or depression in the patient, and handling potential cognitive changes in some ALS patients. Beyond physical tasks, there are specific medical and nursing tasks: learning to use and maintain medical equipment, administering medications, and monitoring for complications, as well as navigating the healthcare system (e.g., coordinating care between multiple specialists, advocating for the patient’s needs, and understanding and making decisions about treatment options). Social

impacts are inevitable, with a reduced social life and personal time and strain on relationships with other family members or friends. Finally, self-care challenges are common, including neglecting one's own health needs and having difficulty finding respite care to allow for time for self-care.

Several adverse mental health outcomes come with being a caregiver for ALS patients, including chronic stress, depression, anxiety, grief, burnout, isolation, guilt, and strains in relationships. In terms of chronic stress, the constant demands of caregiving lead to stress, which affects both physical and mental well-being (Schischlevskij et al., 2021). Regarding depression, caregivers witness a loved one's physical decline slowly and face different daily challenges, leading to sadness and depression (Penning & Wu, 2016). Research on caregiving anxiety shows that worrying about the future, managing medical care, and navigating financial concerns can lead to increased anxiety symptoms and anxiety disorders (Penning & Wu, 2016). Grief and guilt are also a significant concern; witnessing the gradual decline of a loved one could lead to grief (Liu et al., 2020), and caregivers may feel guilty about taking time for themselves. Taking care of ALS patients can lead to exhaustion, detachment, and a sense of hopelessness, which encapsulates caregiver burnout (De Wit et al., 2018). Caregivers also see ripple effects in their social network - taking care of an ALS patient could take time away from social support systems (De Wit et al., 2018); relationships also change, leading to emotionally challenging relationships (Penning & Wu, 2016).

Over 50% of caregivers reported chronic health issues, such as heart problems and hypertension. Sleep deprivation has also been reported: caretaking may ruin sleep patterns, leading to changing mental health and cognitive function (Burke et al., 2015). Overall, there is a decrease in caregivers' overall health.

Conclusion

This review sought to explore the mental health effects of caregiving for a person with ALS. As a neurodegenerative disease, it is known that ALS is a focal onset disease that progresses relatively fast. However, there still needs to be more research about the core biology of ALS, its genetics, and more research about ALS in different ethnic groups. Some data shows that ALS patients' and caregivers' mental health is affected as the disease progresses into further stages, with evidence supporting correlations between quality of life and psychiatric disorders, including depression and anxiety, as well as others. Although it is known that these effects are devastating and last beyond the disease for caregivers, research on caregiving stress and caregiving trauma is scarce. Given the deficit of research on caregivers, definitive conclusions cannot be made on the long-term effects of caregiving stress, which includes financial, physical, and emotional stress. More research is necessary to determine potential treatment options or ways to create healthier bonds between patients and their caregivers, as well as efforts to treat caregiver stress while ALS patients are receiving treatment. While federal funding supports ALS research, specific financing must also be allocated for caregiving research. In regards to treatment options for ALS, more widespread and efficacious treatment options need to be developed and widely advertised to ALS patients and caregivers. Both ALS patients and their caregivers deserve adequate and practical support during ALS treatment and beyond.

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