The Terminal Disease of Amyotrophic Lateral Sclerosis

Abstract

Amyotrophic lateral sclerosis is a neurodegenerative disease that is incurable and results in paralysis of the muscles. Different forms of amyotrophic lateral sclerosis are explained with case studies to demonstrate how they are diagnosed in real patients. Two forms of magnetic resonance imaging (MRI) are discussed showing how the disease affects the human brain. Electromyography is used to diagnosis amyotrophic lateral sclerosis. The discussion concludes with a few palliative care techniques currently used in treating patients with amyotrophic lateral sclerosis.

Introduction

Lou Gehrig was a legendary baseball player who played for the New York Yankees. He was inducted into the hall of fame in 1931 and was awarded the Triple Crown in 1934. In 1939 his season did not start off as he had planned which he attributed to his age. When he started struggling with tying his own shoelaces he checked himself into the Mayo Clinic and was diagnosed with Amyotrophic Lateral Sclerosis. Because of the nature of this disease he checked himself out of the lineup and passed away in June of 1941. Lou Gehrig’s diagnosis shed light on the disease of amyotrophic lateral sclerosis (ALS) and it became more commonly known as Lou Gehrig’s disease.

ALS is a neurodegenerative disease that paralyzes the muscles because of the loss of functioning motor neurons. Amyotrophy refers to the atrophy of the muscle fibers, which then produces spasms and muscle weakness. Lateral sclerosis refers to the hardening of the anterior and lateral horn of the corticospinal tract. There are many forms of ALS which include:

- Progressive bulbar palsy
- Progressive muscular atrophy
- Primary lateral sclerosis
- Flail arm syndrome
- Flail leg syndrome.
Each form of ALS has its own set of symptoms but all eventually lead to the same degenerative and fatal outcome. ALS is terminal and eventually leads to death caused by respiratory distress. The goal is to explain the different types of ALS, how imaging is currently being used to diagnose the disease and a few palliative care methods used to care for ALS patients.

**Progressive Bulbar Palsy**

Progressive bulbar palsy (PBP) is the first form of ALS to be discussed. It is restricted to only the loss of motor neurons of the lower brainstem that could possibly involve the cortico-bulbar tract. Symptoms include painful or difficulty swallowing and inability to articulate words clearly. This particular form of ALS does not exhibit any muscle fasciculations or muscle spasms when first diagnosed which allows those with the disease to be able to continue on with normal life longer than those that are having symptoms in the limbs. Within a few months of being diagnosed, however PBP patients usually negatively progress and are diagnosed with ALS. The patients begin to have symptoms in their arms and legs.

**Progressive Muscular Atrophy**

The second type of ALS is progressive muscular atrophy (PMA). PMA is characterized by degeneration of the lower motor neurons without any symptoms of upper motor neuron degeneration. These patients lose control of their limbs and trunk. PMA progresses slowly with bulbar and respiratory problems appearing later. Compared to typical ALS, PMA shows up earlier but also allows a longer survival time. Patients must have other diseases and disorders ruled out before there can be a confirmed diagnosis of PMA. Spinal muscular atrophy (SMA) is the disorder with the closest diagnosis. SMA patients have proximal and symmetrical fasciculations that involve the anterior horn of the spinal cord and corticospinal tract. PMA patients on the other hand usually have distal and asymmetrical onset of symptoms. If the PMA is truly a form of ALS the upper motor neuron symptoms will begin within a year of onset.

**Primary Lateral Sclerosis**

Primary lateral sclerosis (PLS) is described as the loss of upper motor neurons and sparing of lower motor neurons. Patients diagnosed with PLS have a longer life span than those strictly diagnosed with ALS. Floeter’s et al study showed that once a limb started showing
symptoms the function decreased rapidly. The body would then hit a plateau before it started decreasing again. PLS progresses in stages. For example, one limb will decrease in function and then the patient will be stable for a while before the next set of symptoms starts. There are two subtypes of PLS. The first one has an increase in symptoms that ascend up the body and the second type progresses randomly. The subtypes do not affect the rate at which the PLS affects the patient. PLS eventually leads to mainstream ALS which will slow the patient down and lead to respiratory problems.

**Flail Arm and Flail Leg Syndrome**

The final form of ALS is flail arm and flail leg syndrome. Flail arm syndrome’s biggest symptom is the patient only has weakness or fasciculations in their arms with no other issues being present. The difficulty in diagnosing flail arm syndrome is that there are many other possible explanations for the weakness in the arms. Cervical spondolysis is a common misdiagnosis but an MRI will rule that out. Good clinical follow up visits are the best way of making the correct diagnosis. Flail leg syndrome has the same affects as flail arm syndrome except for the fact that it starts in the lower limbs instead of the upper limbs. Flail arm and flail leg syndrome usually takes the longest of any of the subtypes of ALS to diagnose, but it has also been shown that it is also the slowest progressing form of ALS.

**Medical Imaging**

MRI is the only imaging modality that is currently used to diagnose ALS. The majority of the time MRI is used to rule out other ALS mimicking diseases. In the effort to gain knowledge about the ALS disease new MRI techniques have been developed to image the brain differently.

One version of structural MRI is the voxel-based morphometry (VBM) which measures volumetric changes within the brain. During this three dimensional MRI the patient’s structural changes are compared to control MRIs creating greater neuroanatomical differences. The VBM shows grey matter loss in the frontal, temporal, parietal, occipital and limbic regions (see Figure 1). Another type of structural MRI is diffusion tensor imaging (DTI) which demonstrates the movement of the protons in the white matter of the brain. The corticospinal tract is the area most studied with DTI and is correlated with the directedness of the proton movement. The correlation
concluded that the lower the movement of the protons the more progressed form of the disease. DTI is the preferred structural MRI technique when imaging ALS patients.

Functional MRI (fMRI) demonstrates different regions of the brain in action. The resting state of the brain in ALS patients is studied with fMRI. There are two types of networks in the brain that demonstrate the differences between ALS patients and healthy control subjects. The first is the default-mode network (DMN). It is a standalone network that includes most of the frontal area of the brain. The major difference between healthy controls and patients with ALS in the DMN of the brain is the impairment of higher level executive functions (see Figure 2). The second type of network is the sensori-motor network. The only difference shown between the healthy control group and the ALS group is in the premotor area (see Figure 3). Speculations have been made that the results could be skewed because it is harder for an ALS patient to complete motor tasks so there would be an increase in the premotor cortex activity. However, because the fMRI was conducted during a resting state there is no chance that the premotor cortex could be more stimulated in an ALS patient versus a healthy control. DTI and fMRI are the two imaging techniques used most often, and are the most revolutionary imaging techniques in the world of ALS.

Electromyography

A second way to diagnose ALS is electromyography (EMG). Often used to rule out other muscular disorders EMG measures the amount of muscle movement over a particular area and then it is shown in wave form. A fasciculation potential (FP) is when there is a spontaneous contraction of muscle bundles. When diagnosing ALS, FPs are the determining factor. If there are a lot of FPs then it is more than likely that the patient has ALS. EMGs can be measured on the surface or through a needle. Needle based EMGs are more common when diagnosing ALS. Because the needle is injected directly into the muscle, it provides a quicker response time.

The tricky part of an EMG is determining how long to leave the electrodes on the patient while waiting for a potential to be manifested. The newest form of EMG is the high definition surface EMG which arranges more electrodes closer together to give better spatial information. The surface EMGs allow the patient to be at complete rest. For example, in a high definition surface EMG study done by Ping et al the electrodes were placed on the hand, biceps brachii, and the elbow. Because of the increased spatial information given specific muscles were able to
be disregarded because they did not show any FP's in the time given. In this study the researchers found that if an electrode was left on the muscle for an average of 70 seconds it would manifest whether the muscle was having FP's. High definition surface EMG is now being used as an earlier detection test for ALS than the traditional needle EMG especially if the patient has already been showing symptoms of ALS.

**Drug Treatment**

Once diagnosed with ALS there is currently no cure. There is a lot about the disease that is unknown. There has only been one drug that has been approved by the FDA that increases the life span of an individual living with ALS. Riluzole was developed in the 1950s as a centrally acting muscle relaxant but was found to also be a neuroprotectant. It was approved in 1995 to be the only treatment for ALS. The drug minimizes the amount and size of the fasciculations. The clinical trials performed showed that riluzole had the greatest effect in the earlier and mid stages of the disease but did not really help during the later stages. The trials also revealed the drug to be most helpful in those diagnosed with the bulbar onset of ALS.

Bellingham reported, “A meta-analysis of controlled double blind clinical trials concluded that drug safety was not a major concern in treatment, with nausea, asthenia, and elevated serum alanine transaminase being the only side effects which were significantly increased in patients receiving riluzole.” At therapeutic doses riluzole blocks repetitive firing, but it requires a higher than therapeutic dose to block a single action potential generation. By lowering the individual motor neuron firing rate and causing a single muscular twitch to turn to tetany could contribute to the asthenia.

**Maintaining Weight: A Case Study**

Weight loss is a phenomenon in ALS patients. When ALS patients get to advanced stages of the disease they begin to lose weight because they are unable to eat. In this study, Korner et al discusses how weight loss affects the quality of life, mood and survival of ALS patients. They state that the “hypothesis to explain weight loss in ALS includes higher waste of energy because of muscle fasciculations, increasing respiratory efforts, hypermetabolism and decreased food intake due to depression.” A lower body-mass-index decreases the chance of survival. Inserting a tube directly into the stomach to allow easier feeding also known as a percutaneous
endoscopic gastrostomy (PEG) is usually not considered early enough in treatment but dietary and high calorie supplements are used by up to 80% of those diagnosed with the disease.\textsuperscript{10}

In this study, 68 of the 121 participants reported weight loss. The patients who had lost weight also had an increased level of depression and a decreased quality of life. Of the 68 who lost weight 23 patients started consuming high calorie supplements with their meals and 60% of the 23 had weight stabilization or weight gain.\textsuperscript{10} Those with ALS who take a dietary supplement are shown to have a higher quality of life and feel less affected socially. Korner et al\textsuperscript{10} describes that patients feel better socially when taking dietary supplements or conversely that patients take the dietary supplements because they have more visitors and social company. This allows the patients to feel more a part of society and less like someone living with a terminal disease.

Ten of the affected ALS patients after having PEG gained or stabilized weight which improved the quality of life.\textsuperscript{10} PEG has not been studied frequently in these situations. The criterion to put in a PEG is based off of the presence of dysphagia and the patient’s nutritional status. Neurologists tend to put off the discussion of PEG placement and therefore when patients finally have the procedure the complication rate is 50%.\textsuperscript{10} This is the first quantitative study demonstrating how PEG insertion increases quality of life. The data shows that weight was stabilized post PEG and those who lost weight after the PEG still had an increased quality of life due to less time used for feedings.\textsuperscript{10}

Weight is an important factor when it comes to maintaining a good quality of life for those living with ALS. Dietary supplements and PEG are a few of the foremost ways to help those suffering from ALS gain or stabilize weight. According to Korner et al\textsuperscript{10} “the effect of high calorie nutritional supplements and PEG is higher than expected.”\textsuperscript{(+p. 7)} Although the trial was retrospective it provides a sound basis which will help ALS patients manage their weight and their quality of life. If weight loss can be controlled sooner the prognosis may be better with a longer life expectancy.\textsuperscript{10}

**Progressive Bulbar Palsy: A Case Study**

A woman visited an oral medicine specialist after going to see a general dentist, ear-nose-throat specialist, neurologist and dermatologist without being given a diagnosis. The patient complained of having a hard time chewing, swallowing and talking for the past 18 months with
pain in her neck and shoulders. Her intraoral examination showed difficulty moving the tongue in any direction with multiple fasciculations evident by the amount of tongue irregularities (see Figure 4). She did not present with any other abnormalities such as weakness or trouble walking or moving her limbs.11

The patient’s biochemistry, hematology, CT and MRI all came back negative. The electromyographic tests of the orofacial muscles showed increased use of the masticatory muscles because the muscles of the tongue were used significantly less. The patient was then diagnosed with PBP. Her follow up examination showed increased pain in the neck, increased loss of facial movement and she was using her fingers to push her food down her pharynx. The patient was not able to move her tongue, had increased saliva production and showed no evidence of muscular fasciculations (see Figure 5). When the study concluded 44 months after the onset of symptoms the patient was still in good health.11

Flail Arm Syndrome: A Case Study

A 65 year old male presented with weakness and wasting away of arm muscles for six months. He had no significant involvement with other parts of his body. When the patient was examined his shoulders were slumped with his arms, forearms, and hands pronated. Fasciculations were demonstrated in his upper arms but there were no other apparent problems with his bulbar region or lower limbs. His EMG and MRI were both clear and his blood test was negative for any abnormalities.6 The patient was then diagnosed with flail arm syndrome because his symptoms were only in his upper limbs with no other symptoms present. At the 24 month follow up the patient had begun to have weakness in his legs and was having trouble speaking and swallowing.6 The patient was then later diagnosed with ALS.

Voxel-based Morphometry and Magnetization Transfer Imaging

Recent imaging research has been turning to the study of upper motor neurons at the cortical level. These imaging techniques have been answering questions about how ALS affects the mind and whether or not dementia is a side effect of ALS. “Voxel-based morphometry (VBM) is a quantitative automated method which performs a whole brain voxel-wise comparison of the local concentration of gray matter (GM) between two groups of subjects.”12(p.1) VBM studies show that cortical atrophy is not confined to the primary motor cortex but extends to
premotor and parietal areas. Atrophy of the prefrontal and temporal cortex is seen in ALS patients with and without dementia.\textsuperscript{12}

Magnetization Transfer Imaging (MTI) is a MR technique that is used to explore the microstructure of the cerebral cortex.\textsuperscript{12} The magnetization change between the spins of free water and the spins of water connected to macromolecules is the basis behind MTI. The Magnetization Transfer ratio is the easiest way to measure the efficiency of the exchange phenomena. The MTI studies show decreased tissue integrity in ALS patients in the same places as the VBM studies.\textsuperscript{12}

Cosottini et al\textsuperscript{12} conducted a study that tested 18 ALS patients against 18 control patients who were in similar age to compare their GM between VBM and MTI. The VBM results show several reduced cortical clusters of GM in ALS compared to the healthy controls. The VBM shows loss in superior, middle and inferior frontal gyri, supplementary motor area and the temporal lobe.\textsuperscript{12} The GM loss is in both hemispheres but consistently more on the right side. The MTI results show greater reduction in tissue integrity in ALS patients in comparison to that of their healthy counterparts. The areas that are affected include superior, middle and inferior frontal gyrus, gyrus cinguli, supplementary motor area, insula, and temporal lobe.\textsuperscript{12}

Because the atrophy was not just in the primary motor cortex but also in the extramotor area, it reveals that ALS is a multisystem disease. “ALS is emerging as a multi-system disease involving several frontal-temporal structures beside motor structures and functions.”\textsuperscript{12(p.3)} The information found through this case along with other neuroimaging, functional tests, and pathological data shows that ALS is consistent with frontal-temporal dementia. In 50% of ALS cases frontal-temporal dementia is present.

Both sets of testing show loss of GM in the majority of the same areas. VBM and MTI show atrophy of not just the cortex of the brain, but also frontal-temporal areas.\textsuperscript{12} VBM and MTI should be used simultaneously to learn more about the disease.

**Conclusion**

ALS is a horrible disease without a cure. Because of the vast amount of different presentations of the disease it is very difficult to diagnose. Advancing technology helps the physicians to see more of the brain and learn more about the disease. fMRIs are ground breaking along with the high definition surface EMG to measure the muscle fasciculations.
diagnosed dealing with the disease brings its own set of problems. As the fasciculations and loss of motor function increases it affects the patient's quality of life and can cause depression. By keeping the patient nourished and slowing down the progression of the disease helps to sustain life. Even though ALS has been around since the 1800s it was not a very well known disease until Lou Gehrig was diagnosed in the 1940s. There is a lot that is unknown about ALS and what causes it. Although there is no cure for ALS, knowledge has increased significantly in the past several years and is helping those who are newly diagnosed.
References


Figures and Captions

**Figure 1.** This image shows the decrease in brain activity in an ALS patient compared to the healthy controls which are highlighted in the red and yellow areas. Image courtesy of Kollewe K, Korner S, Dengler R, Petri S, Mohammadi B. Magnetic resonance imaging in amyotrophic lateral sclerosis. Neurol Res Int. 2012;2012:608501.
Figure 2. (a) shows the DMN in healthy patients and (b) shows the DMN in ALS patients. There is decrease in the ALS patients activity. Image courtesy of Kollewe K, Korner S, Dengler R, Petri S, Mohammadi B. Magnetic resonance imaging in amyotrophic lateral sclerosis. Neurol Res Int. 2012;2012:608501.
Figure 3. (a) shows the sensorimotor network in healthy patients and (b) shows the sensorimotor network in ALS patients. Image courtesy of Kellewe K, Korner S, Dengler R, Petri S, Mohammadi B. Magnetic resonance imaging in amyotrophic lateral sclerosis. Neurol Res Int. 2012;2012:608501.