2015

The role of chronic traumatic encephalopathy on amyotrophic lateral sclerosis

Steen, Andrea Lee

http://hdl.handle.net/2144/16051

Boston University
THE ROLE OF CHRONIC TRAUMATIC ENCEPHALOPATHY ON
AMYOTROPHIC LATERAL SCLEROSIS

by

ANDREA STEEN
B.A., University of Kansas, 2010

Submitted in partial fulfillment of the
requirements for the degree of
Master of Arts
2015
Approved by

First Reader
Maryann MacNeil, M.A.
Faculty Advisor, Medical Sciences
Instructor, Anatomy and Neurobiology

Second Reader
Theresa A. Davies, Ph.D.
Director, M.S. Oral Health Sciences Program
Assistant Professor of Medical Sciences & Education
DEDICATION

I would like to dedicate this work to my father-in-law, Mark, for his bravery while battling ALS.

In 1962, the neurologist Macdonald Critchley stated

“Nothing has been said about the possible role in etiology of the previous habit of athleticism. I have the uncomfortable feeling that a past history of unnecessary muscular movement carried out for no obvious reason may be followed in later life by the development of motor neuron disease in a statistically significant number of cases.”
THE ROLE OF CHRONIC TRAUMATIC ENCEPHALOPATHY ON AMYOTROPHIC LATERAL SCLEROSIS

ANDREA STEEN

ABSTRACT

It has been postulated that there could be a connection between traumatic brain injury (TBI) and motor neuron disease (MND), including amyotrophic lateral sclerosis (ALS). As chronic traumatic encephalopathy (CTE) is caused by repeated TBI and is a newly examined disease, there has been little evaluation of the potential relationship between CTE and ALS. It was proposed that CTE is a risk factor for not only MND, but also ALS. There is significant evidence that even a single TBI is a risk factor for Parkinson’s disease (PD), thought to be invoked by the inflammatory process that the brain undergoes following a TBI. General rigorous physical activity with trauma to the trunk or extremities does not appear to be a risk factor for ALS. However, physical activity with associated head traumas, especially repeated head traumas, does seem to increase the likelihood of developing ALS. The biological mechanism for this is suspected to be increase in free radicals during exercise in individuals who are predisposed to decreased antioxidant function. Additionally, individuals who have suffered repeated head trauma, even amongst the general population in a non-athletic setting, has been shown to drastically increase the individual’s chance of developing ALS.

CTE, which is most common in athletes, is speculated to be caused by TAR DNA-binding protein 43 (TDP-43), tau neurofibrillary tangle (NFT), and beta-amyloid (Aβ)
protein inclusions in brain tissue following a multitude of TBI during high level sport activity. There are individuals who suffer initially CTE, followed by ALS, indicating CTE is clearly a risk factor for ALS. Anatomically, the TDP-43, NTF, and Aβ inclusions are present in the brain tissue of both individuals with CTE alone as well as the individuals with CTE and ALS. The anatomic difference between these two pathologies is the inclusion of these three proteins in the spinal cord of ALS patients as well.

Unfortunately, there are indications that previous studies of professional athletes and their development of ALS have presented with significant issues including confounding factors of the subpopulation and sample sizing. Additionally, the anatomical cause of TBI leading to ALS is still unknown. Further evaluation on the relationship between head injury and ALS must be dedicated to investigating the mechanism involved in developed PD versus ALS following TBI. The biologic sequence following TBI that leads to ALS must be examined and compared to individuals whom develop ALS but did not suffer TBI. Moreover, an assessment must be made to determine what causes some individuals to develop protein inclusions solely in the brain tissue, leading to CTE, and some individuals to have an advancement of the protein inclusions into the spinal cord, leading additionally to CTE followed by ALS.
# TABLE OF CONTENTS

TITLE.................................................................................................................................................i  
COPYRIGHT PAGE...................................................................................................................................ii  
READER APPROVAL PAGE....................................................................................................................iii  
DEDICATION.............................................................................................................................................iv  
ABSTRACT.................................................................................................................................................v  
TABLE OF CONTENTS..............................................................................................................................vii  
LIST OF TABLES.......................................................................................................................................ix  
LIST OF FIGURES.....................................................................................................................................x  
LIST OF ABBREVIATIONS.........................................................................................................................xi  
INTRODUCTION.......................................................................................................................................1  
  Amyotrophic Lateral Sclerosis .............................................................................................................1  
  Traumatic Brain Injury .......................................................................................................................11  
  Chronic Traumatic Encephalopathy .................................................................................................18  
  Specific Aims/Objectives.......................................................................................................................24  
PUBLISHED STUDIES...............................................................................................................................25  
  TBI and PD ........................................................................................................................................25  
  Rigorous Physical Activity and ALS................................................................................................28  
  Rigorous Physical Activity and MND/ALS: A Review .................................................................32
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The ALSFRS-R</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>The GCS and score</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>The definition of mild, moderate, and severe head injury by GCS score</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>ALS incidence by age classes</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>ALS incidence by playing position</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>ALS incidence by number of years as a professional IF player</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>Summary of published studies investigating physical activity and ALS</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>ALS association with physical injury</td>
<td>40</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MRI of patient with primary lateral sclerosis (PLS)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>The genetic factors and molecular pathways involved in motor neuron death in ALS</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Coronal sections comparing normal brain and CTE brain</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>Comparing the presence of Tau protein in control versus CTE brains</td>
<td>21</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

ALS ...................................................................................... amyotrophic lateral sclerosis
AD ...................................................................................... Alzheimer’s disease
ALSFRS ............................................................................. ALS Functional Rating Scale
ALSFRS-R ........................................................................... Revised ALSFRS
Aβ ................................................................. Beta-amyloid
APP ................................................................................... amyloid precursor protein
CTE ........................................................................... chronic traumatic encephalopathy
CNTF ........................................................................... ciliary neurotrophic factor
FTD .................................................................................. frontotemporal dementia
GCS ........................................................................... Glasgow Coma Scale
IF ...................................................................................... Italian football
MND .................................................................................. motor neuron disease
NFT .............................................................................. neurofibrillary tangle
NICE .......................................................... National Institute for Health and Care Excellence
PEG .............................................................................. percutaneous endoscopic gastrostomy
PD .............................................................................. Parkinson’s disease
PLS .............................................................................. primary lateral sclerosis
SIGN .......................................................... Scottish Intercollegiate Guidelines Network
SIS ............................................................................... second impact syndrome
SOD1 ........................................................................... superoxide dismutase 1
TBI ........................................................................... traumatic brain injury
TDP-43 ................................................................. TAR DNA-binding protein 43

VEGD ................................................................. vascular endothelial growth factor
INTRODUCTION

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also commonly known as Lou Gehrig’s disease, “is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord” (ALS Association, 2010). Degeneration of the motor neurons leads to neuronal death, which in turn leads to atrophy of the muscles innervated by those motor neurons (Figure 1). Ultimately the brain loses its ability to communicate with those muscles as well as the ability of the body to make voluntary movements (ALS Association, 2010). At this time, there are no bioidentifiers of ALS, making it a disease of exclusion secondary to clinical presentation (Kiernan et al. 2011).

Figure 1. 3D MRI of patient with primary lateral sclerosis (PLS). The increased size of the sulci and decreased size of the gyri near the arrows are most commonly seen in PLS patients, however, they do appear in ALS patients as well. This is representative of the atrophy of the motor neurons in the brain (Kieman et al. 2011).
There are four phenotypes of ALS currently identified. Limb-onset ALS is characterized by changes of the limbs, lower and/or upper (Kiernan et al. 2011). Specifically, flail-arm variant affects the upper motor neurons and arms and typically causes weakness and uncontrolled tendon reflexes, whereas flail-leg variant affects the lower motor neurons and legs and presents with weakness and wasting (Wijesekera et al. 2009). There is also the progressive muscle atrophy presentation that is associated solely with the lower motor neurons, and the primary lateral sclerosis presentation that is characterized by spastic movements only in the upper motor neurons (Kiernan et al. 2011). The final presentation is bulbar palsy that uniquely affects the oropharyngeal muscles resulting in distorted speech, tongue wasting, and gag and jaw jerk (Duffy et al. 2007). Pure bulbar palsy ALS is associated with the worst prognosis, i.e. the fastest progression of the disease, and strangely, typically only affects women over the age of 65 (Talbot 2009).

A significant complication from ALS is dysphagia, difficulty swallowing associated with an increase in the amount of time it takes to move food from the mouth to the stomach (Kiernan et al. 2011). This complication is what often contributes to the secondary complication of malnutrition. Another issue experienced by ALS patients that contributes to malnutrition is hypermetabolism (Funalot et al. 2009). Hypermetabolism, defined as an abnormally elevated basal metabolism, is present in 50-60 % of ALS patients and associated with a decrease in life expectancy (Desport et al. 2005).

Leigh (2003) also describes how the weakening of the respiratory muscles, including the diaphragm, leads to significant associated respiratory conditions such as
hypoventilation. Dyspnea, or difficulty breathing, is also an associated symptom of ALS and initially is seen connected with exertion (Leigh 2003). Additionally “death becomes imminent once patients develop dyspnea at rest” without the intervention of a tracheostomy and ventilator (Kiernan et al. 2011). The weakening of respiratory muscles also frequently causes a secondary infection of pneumonia.

Hypersalivation is another symptom of ALS that also causes pneumonia, specifically aspiration pneumonia (Miller et al. 2009). This hypersalivation often times has psychological effects on ALS patients such as embarrassment. ALS patients often have a multitude of other psychological effects associated with their disease. Anxiety is the most common mental health issue with 30% of ALS patients experiencing anxiety, and often times linked insomnia (Kurt et al. 2007). Between 9-11% of ALS patients suffer from depression, which is also connected to insomnia. In addition to risk of depression, according to a population-based study in Sweden of 6,642 ALS patients between 1965 and 2004, there is a significant increased risk of suicide, especially in the first year after diagnosis of the disease (Fang et al. 2009). Another psychological change affecting 20-50% of ALS patients is pseudobulbar affect characterized by uncontrolled emotional expression including excessive laughing or crying (Miller et al. 2009).

Kiernan et al. (2011) claims that approximately 10% of ALS cases are caused by genetic familial inheritance with six known mutations leading to the disease:

- Superoxide dismutase 1 (SOD1) - encodes for copper/zinc ion-binding superoxide dismutase, with mutation causing a toxic gain of function
• TAR DNA-binding protein 43 (TDP-43) - encodes for TDP-43 that is involved in gene expression and regulation
• FUS (also called TLS) - encodes fusion in sarcoma that is involved in gene expression and regulation
• ANG - encodes angiogenin, ribonuclease, RNase A family, 5 and is a hypoxia-sensitive gene that regulates RNA transcription
• OPTN - encodes optineurin, where mutations inhibit the inhibition of activation of NFκB, and change the cytoplasmic distribution of optineurin
• C9ORF72 - a GGGGCC hexanucleotide repeat expansion in a non-coding region of the chromosome 9 open-reading frame 72 gene (Stewart et al. 2012)

There is also a unique ALS-PD combination that is caused by ingesting a species of bat (flying fox) that consumes cycad seeds (Cox et al. 2002). Cycad seeds contain a large concentration of neurotoxic amino acid, β-methyl-amino-L-alanine, that leads to a constellation of neurodegenerative disease processes similar to ALS and PD. This disease process was found in high frequency in a population of people living in Guam, as these bats are considered a delicacy by Guam natives.

There is an interesting additional disease process caused by mutations of TDP-43 or FUS, each a DNA/RNA binding protein (Kiernan et al. 2011). These proteins have a multifunctional role in transcription, RNA splicing and transport, and microRNA processing. Because they are involved in these significant processes of the cell, mutations of these proteins cause not only ALS, but also a second disease process called
frontotemporal dementia (FTD), but with less frequency than ALS. FTD and ALS, as well as other neurodegenerative diseases, commonly have atypical intracellular protein aggregation as a pathological element of their disease process (Mackenzie et al. 2010). It has recently been identified that almost all cases of sporadic ALS demonstrate TDP-43 ubiquinated cytoplasmic inclusions of neurons (Kiernan et al. 2011).

SOD1 appears to be the most common mutation present in familial ALS at 20% of total cases, and curiously mutations in SOD1 are present in 5% of sporadic ALS cases (Kiernan et al. 2011). The function of SOD1’s involvement in the early death of motor neurons is not fully understood, however, it is known that the gain of function mutation causes formation the generation of free radicals causing cell injury and death. SOD1 mutation is also responsible for misfolding of peptides leading to a second type of intracellular aggregate, which eventually the disruption of axon transportation and essential cellular activity (Figure 2). In general, though, the death of motor neurons in ALS is a very complicated and multifactorial.
Figure 2. The genetic factors and molecular pathways involved in motor neuron death in ALS. The square has a TDP-43/FUS aggregate enclosed. The circle has a SOD1 aggregate enclosed. These aggregates lead to disruption of neuron-to-neuron communication as well as fundamental intracellular processes and eventual death of the cell (figure amended from Vucic et al. 2014).

Sporadic ALS makes up the remaining 90% of cases. A study done in 2000 found that sporadic ALS might be caused by an enterovirus nucleic acid sequence present in the gray matter of spinal cord (Berger et al. 2000). The nucleic acid sequence was found in the gray matter in 88% of ALS cases versus 3.4% of controls. Sporadic ALS is also connected to several potential environmental risk factors. Among them includes exposure to formaldehyde as well as smoking (DynaMed, Feb 2014). Strangely, the number of younger siblings a person has is also connected to the development of ALS; the more younger siblings an individual has, there is an increased likelihood of
developing the disease (Fang et al. 2008). Within that finding, there is an even greater increase in the potential for an individual to develop ALS if their younger siblings are born six or more years after the patient. Additionally, maternal age at birth has been shown to increase the chances of developing sporadic ALS, including mothers who are either less than twenty years old or greater than forty-one years old at the time of the individual’s birth. A newly suggested risk factor for sporadic ALS is a lifetime of strenuous physical activities including professional sports, but the cause for this development remains unknown (Kiernan et al. 2011).

Factors that have been found to not be associated with increased risk for developing ALS includes individuals taking statins for treatment of high cholesterol (DynaMed, Feb 2014). According to data collected by the FDA, there is no increase incidence of ALS in people taking statins versus controls. Huss et al. also did a study examining the potential relationship between individuals living near power lines, specifically 220-380 kilovolts, and development of neurodegenerative disease and found no connection (Huss et al. 2008).

The life expectancy of ALS is dependent on clinical presentation, the rate of its progression, timing of diaphragm involvement, and nutrition of the patient (Kiernan et al. 2011). The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) is a number scale that was created for physicians to monitor the progression of ALS in several categories as well as assess the response to interventions and treatment (Cedarbaum et al. 1999). The original scale placed an inappropriately large emphasis on limb and bulbar changes and was revised to place the proper emphasis on respiratory
decline. The Revised ALSFRS (ALSRFS-R) was created to account for the assessment of dyspnea and need for ventilator intervention (Table 1). Scoring ranges from 40 points in a healthy individual to 0 points being the worse prognosis.

Table 1. The ALSFRS-R. The symptomatologies of ALS and points associated with current clinical presentation (table amended from Cedarbaum et al. 1999).

| 1. Speech                  | 4 | Normal speech processes |
|                           | 3 | Detectable speech disturbance |
|                           | 2 | Intelligible with repeating |
|                           | 1 | Speech combined with nonvocal communication |
|                           | 0 | Loss of useful speech |
| 2. Salivation             | 4 | Normal |
|                           | 3 | Slightly but definite excess of saliva in mouth; may have nighttime drooling |
|                           | 2 | Moderately excessive saliva; may have minimal drooling |
|                           | 1 | Marked excessive of saliva with some drooling |
|                           | 0 | Marked drooling; requires constant tissue or handkerchief |
| 3. Swallowing             | 4 | Normal eating habits |
|                           | 3 | Early eating problems – occasional choking |
|                           | 2 | Dietary consistency changes |
|                           | 1 | Need supplemental tube feeding |
|                           | 0 | NPO (exclusively parental or enteral feeding) |
| 4. Handwriting            | 4 | Normal |
|                           | 3 | Slow or sloppy; all words are legible |
|                           | 2 | Not all words are legible |
|                           | 1 | Able to grip pen but unable to write |
|                           | 0 | Unable to grip pen |
| 5. Cutting food and handling utensils | 4 | Normal |
|                               | 3 | Somewhat slow and clumsy, but no help needed |
|                               | 2 | Can cut most food, although clumsy and slow; some help needed |
|                               | 1 | Food must be cut by someone, but can still feed slowly |
|                               | 0 | Needs to be fed |
| 6. Dressing and hygiene    | 4 | Normal function |
|                           | 3 | Independent and complete self-care with effort or decreased efficiency |
|                           | 2 | Intermittent assistance or substitute methods |
|                           | 1 | Needs attendant for self-care |
|                           | 0 | Total dependence |
Table 1. (Continued) The ALSFRS-R.

<table>
<thead>
<tr>
<th>7. Turning in bed and adjusting bed clothes</th>
<th>4: Normal</th>
<th>3: Somewhat slow and clumsy, but no help needed</th>
<th>2: Can turn alone or adjust sheets, but with great difficulty</th>
<th>1: Can initiate, but not turn or adjust sheets alone</th>
<th>0: Helpless</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Walking</td>
<td>4: Normal</td>
<td>3: Early ambulation difficulties</td>
<td>2: Walks with assistance</td>
<td>1: Nonambulatory functional movement</td>
<td>0: No purposeful leg movements</td>
</tr>
<tr>
<td>9. Stair climbing</td>
<td>4: Normal</td>
<td>3: Slow</td>
<td>2: Mild unsteadiness or fatigue</td>
<td>1: Needs assistance</td>
<td>0: Cannot do</td>
</tr>
<tr>
<td>10. Dyspnea (new)</td>
<td>4: None</td>
<td>3: Occurs when walking</td>
<td>2: Occurs with one or more of the following: eating, bathing, or dressing</td>
<td>1: Occurs at rest, difficulty breathing when either sitting or lying</td>
<td>0: Significant difficulty, considering using mechanical respiratory support</td>
</tr>
<tr>
<td>11. Orthopnea (new)</td>
<td>4: None</td>
<td>3: Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows</td>
<td>2: Needs extra pillows in order to sleep (more than two)</td>
<td>1: Can only sleep sitting up</td>
<td>0: Unable to sleep</td>
</tr>
<tr>
<td>12. Respiratory insufficiency (new)</td>
<td>4: None</td>
<td>3: Intermittent use of BiPAP</td>
<td>2: Continuous use of BiPAP during the night</td>
<td>1: Continuous use of BiPAP during the day and night</td>
<td>0: Invasive mechanical ventilation by intubation or tracheostomy</td>
</tr>
</tbody>
</table>
Currently, there is no cure for ALS and there is no treatment that stops or reverses the progression of ALS (ALS Association, 2010). Miller et al. states that treatment for ALS is solely for the purpose of symptomatic control as well as maintenance and comfort for the patient (Miller et al. 2009). There are suggested treatments for specific symptoms and while many treatments increase a patient’s ALSFRS-R, it appears there is little evidence for prolonging life (DynaMed, Feb 2014). For example, once patients develop difficulty with swallowing it has been suggested that they be given percutaneous endoscopic gastrostomy (PEG) in order to help stabilize weight loss and nutrition; however there is a very low level of evidence demonstrating that a PEG prolongs the life of ALS patients. Another symptomatic care that is frequently used with ALS patients is endurance-type exercises for the trunk and limbs of patients that may help reduce spasticity of muscles, however it does not appear to improve quality of life, fatigue, or muscle strength for them (Dal Bello Haas et al. 2013). For respiratory compromise experienced by ALS patients, it appears that noninvasive ventilation does improve quality of life for them as well as length survival time and slow the progression of the decline of their forced vital capacity (Miller et al. 2009). Tracheostomy is also considered an appropriate surgery for improvement of quality of life for patients looking for long-term ventilation support.

Currently there are only two medications suggested as suitable treatment for ALS (DynaMed, Feb 2014). While there is only a borderline statistical significance for Riluzole based on Cochrane review, there is evidence to support prolonged survival for ALS patients up to 2-3 months (Miller et al. 2012). When taken twice a day, Riluzole 50
mg is shown to not only prolong life and delay the progression of ALS, but also provide a benefit for and limb function. Unfortunately, it does not appear that Riluzole improves muscle stamina or strength in any way. The second medication commonly prescribed to ALS patients is Lithium (DynaMed, Feb 2014). Unfortunately, there is insufficient data to show any improvement in patients’ symptoms or slow of the progression of the disease even when combined with Riluzole (Aggarwal et al. 2010). In fact, the original study done by Aggarwal et al. (2010) was terminated early due to the ineffectiveness of the medication in changing the outcome for patients.

**Traumatic Brain Injury**

Traumatic brain injury (TBI) is characterized by new onset of any or a multitude of the follow symptoms: observed neurologic dysfunction, intracranial lesion, and/or any period of confusion, disorientation, change in consciousness, or amnesia that may or may not be transient. Additionally, there are three TBI classifications of mild, moderate, and severe depending on the presence and/or length of the previously listed symptoms (DynaMed, Dec 2014). Concussions can be considered a subset of TBI that cannot have structural injury to the brain as part of their presentation and are classified as mild TBI (DynaMed, Oct 2014).

In addition to the symptoms listed above, The National Institute for Health and Care Excellence (NICE) created the Glasgow Coma Scale (GCS) to be utilized when evaluating intracranial processes, both traumatic and non-traumatic (NICE, 2014). The best possible score on the GCS scale is a 15 (being most normal baseline neurologic
function), with 4 points given for spontaneous eye opening, 6 points given for following verbal commands, and 5 points given for oriented conversation Scottish Intercollegiate Guidelines Network (SIGN, 2009). The GCS additionally provides a breakdown of the points given to a patient depending on their history and presentation as well as the evaluation and physical examination performed by the clinician or medical provider (Table 2). The total number given to a patient equals the patient’s “Coma Score” out of the best possible 15, determining the level of brain injury. Because GCS can be used clinically for both TBI as well as non-traumatic intracranial processes, there is an additional breakdown provided by the Scottish Intercollegiate Guidelines Network specifically utilized to classify TBI severity levels (Table 3).

Table 2. The GCS and score. This is the scale utilized by medical providers for clinical assessment with this breakdown of points associated with clinical behaviors (SIGN, 2009).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Scale Responses</th>
<th>Score Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye opening</td>
<td>Spontaneous</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>To speech</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Verbal response</td>
<td>Orientated</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Confused conversation</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Words (inappropriate)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sounds (incomprehensible)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Best motor response</td>
<td>Obey commands</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Localise pain</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Flexion - normal</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>- abnormal</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Extend</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL COMA ‘SCORE’</td>
<td></td>
<td>3/15 – 15/15</td>
</tr>
</tbody>
</table>
Table 3. Definition of mild, moderate, and severe head injury by GCS score. This score range is applied to patients with a history of a blow to the head or the presence of evidence of head trauma, including lacerations, abrasions, or contusions (SIGN, 2009).

<table>
<thead>
<tr>
<th>Degree of head injury</th>
<th>GCS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>13-15</td>
</tr>
<tr>
<td>Moderate</td>
<td>9-12</td>
</tr>
<tr>
<td>Severe</td>
<td>8 or less</td>
</tr>
</tbody>
</table>

Common symptoms associated with a concussion and/or TBI include physical symptoms such as dizziness, balance problems, sleep disturbances, and seizures, cognitive symptoms including attention trouble, memory problems, and altered judgment, and behavioral and emotional changes causing depression, irritability, and aggression (DynaMed, Dec 2014). More serious physical complications from severe TBI include paralysis, muscle weakness, and spasticity. Guskiewicz et al. (2003) found that with minor TBI or concussion, acute neurologic symptoms typically resolve in a patient gradually within seven days. A total of 91% of American college football players, who were diagnosed with a concussion during their study, were back to baseline with seven days, including total resolution of balance and mild cognitive deficits (Guskiewicz et al. 2003).

There can be chronic consequences of TBI, however (DynaMed, March 2014). A review done by Nampiaparampil found that chronic pain is present in 75.3% of patients who experienced a mild TBI and chronic headaches are present in 57.8% of patients (Nampiaparampil 2008). Chronic tinnitus secondary to TBI when compared to non-traumatic tinnitus has some significant differences; specifically patients who suffer a TBI
are typically younger at the onset of the tinnitus and experience a louder and more severe tinnitus (Folmer et al. 2013). The same survey done by Folmer et al. (2013) found that there are more associated symptoms including depression. Additionally, a systematic review and two observational studies also found that 30% of patients greater than sixteen years of age who experienced a TBI developed depression (Guillamondegui et al. 2011). Some psychiatric conditions found concurrently with depression included anxiety in 31%-61% of cases, PTSD in 37% of cases, and the less common panic disorder in 15% of cases.

Generalized personality changes including increased irritability, frustration, impulsiveness, apathy, and paranoia are present in 50% of patients within the first three months after a TBI and 66% of patients during the 6-12 months following a TBI (Franulic et al. 2000). Depending on the degree of head injury, there is a connection with development of PTSD in war veterans as well (Hoge et al. 2008). Nearly 50% of veterans who suffered a TBI with associated loss of consciousness met criteria for PTSD. For veterans who experienced an altered mental status following a TBI, but no loss of consciousness, 27% of them met the PTSD criteria. Interestingly, for children with families with a predisposition for schizophrenia, there is an increased risk for developing schizophrenia later if life after experiencing a TBI (Abdel Malik et al. 2003). An additional correlation was found that more severe head injury is related to an earlier onset of schizophrenia.

A single TBI can also lead to a diagnosis of Parkinson disease (PD) (Rugbjerg et al. 2008). According to their population-based case-control study on 13,695 patients with
a primary diagnosis of PD there is “an overall 50% increase in prevalence of hospital
contacts for head injury was seen before the first registration of Parkinson's disease in
this population.” Furthermore this association was found to be almost entirely due to TBI
that occurred within the three months preceding the PD diagnosis. This is an example of
TBI leading to a terminal motor neuron disease (MND). MND include PD, ALS, and
Huntington disease.

Interestingly, a seizure following a mild TBI or concussion is not associated with
the development of the long-term or chronic seizure disorder, epilepsy (McCrory et al.
1997). Based on a cohort study of 22 Australian rugby football players who experienced
a post-concussion or mild TBI seizure within two seconds of the injury, none had
developed epilepsy within the first 3.5 years after the trauma. However, there may be an
increased risk for developing epilepsy following a more severe TBI and post-trauma
seizure (Annagers et al. 1998). Another risk factor associated with development of
epilepsy following a TBI seizure is the patient being greater than 65 years of age.

While minor TBI rarely lead to anatomical or structural changes in the brain, there
is a significant increased risk in development of intracranial hemorrhage following even a
seemingly benign TBI if an individual is anticoagulated, taking Coumadin (Parmar et al.
2006). Patients who have undergone a cardiac procedure, such as valve replacement or
cardiac stent placement, or patients who are at risk of clot formation following an
orthopedic procedure are prescribed Coumadin to anticoagulate their blood to prevent
clotting and eventually causing thromboembolism (DynaMed, September 2014). Of an
evaluation of the outcome of thirteen patients taking Coumadin who received medical
care following a minor TBI, it was found that nine of the patients were found to have intracranial hemorrhage and five of the patients died (Parmar et al. 2006). It was concluded that Coumadin patients who have sustained even a very minor TBI or concussion require CT head imaging and close monitoring.

Generally, TBI occurrence is under represented and under diagnosed in the United States. This is assumed to be due to a variety of factors usually including a lack of seeking medical care if the patient does not lose consciousness (Silver et al. 2011). Another factor affecting the under representation of TBI, especially in sports, is the fact that the athletes do not realize they have had an injury or do not feel it is serious enough to report (Meehan et al. 2009). Meehan et al. (2009) found that only 19% of Canadian Football League players suffering from a TBI realized they had a concussion.

It is estimated that between 1.6 and 3.8 million cases of sports-related concussion occur annually in United States (Giza et al. 2013). According to a population cohort study performed in the United States between 1997 and 2007, sports-related concussion accounted for half of the emergency department visits for concussion between the ages of 8-13, with ice hockey and American football being the most common sports associated with concussions. The number of children in the 14-19 age category reporting to the emergency department for concussions caused by sports was double that of the 8-13 year olds (Bakhos et al. 2010). An additional retrospective cohort study evaluating the trends of utilizing the emergency department for sports-related TBI in the United States found that 15% of all TBI complaints in the emergency department are sports related among 0-
19 year olds. The most common sport causing TBI that required admission to the hospital was American football (Hanson et al. 2013).

In addition, especially in the sports community, there is an increased incidence of repeated TBIs (Silver et al., 2011). There was a specific study done by Guskiewicz et al. (2003) looking at the cumulative effects of repeat TBI on American college football players. The prospective cohort study found that after following American college football players for three years, 6.5% of the players had repeat concussions within the same season, and those players who had had three previous TBIs were three times more likely to experience a fourth concussion than those who had no personal TBI history (Guskiewicz et al. 2003). This could be due to a number of factors including the sport and style of play, the position of the player, increased playing time, and the fact that the brain could be at increased risk for injury after a first concussion (Meehan et al. 2009). Interestingly, there does not appear to be any evidence linking TBI with the action of heading a European football (American soccer ball) during play, according to a prospective cohort study done over the course of six years including 20 men’s and women’s FIFA tournaments (Fuller 2005).

A complication of TBI that is experienced by many athletes is second-impact syndrome (SIS). While technically not considered a repeat concussion, this can occur when an athlete experiences a second episode of trauma, such as a minor chest impact or direct head contact, while still symptomatic from a previous TBI. This second-impact syndrome can lead to a significant and swift neurologic decline (Meehan et al. 2009). The mechanism causing the quick neurologic decline has been theorized; it is postulated
that the autoregulated blood flow over the cerebrum is upset, leading to “vascular engorgement and increase in intracranial pressure” followed by herniation of the cerebellum (Cantu 1995).

**Chronic Traumatic Encephalopathy**

Boxers in the 1920s suffering from chronic traumatic encephalopathy (CTE) before it was formally named were describes with terms such as punch-drunken, goofy, or slug-nutty (Gavett et al. 2011). Then CTE was given the diagnosed name dementia pugilistica, meaning boxing dementia, because of its frequent presentation in retired boxers, however it was eventually realized that this pathology occurs in many other individuals, and was therefore named CTE. DynaMed (March 2014) defines CTE as a “form of neurodegeneration related to repeated head injuries [that] can be associated with boxing, American football, hockey, professional wrestling, soccer, physical abuse” (DynaMed, March 2014). Similarly to the risk of repeated TBI, the factors associated with likelihood of developing CTE in athletes include the specific “sport, position, duration of exposure, and age at the time of initial or subsequent head trauma, as well as with additional variables such as genetic predisposition” (Gavett et al. 2011). While statistically, boxing has an 8-25% incidence of CTE, it appears that CTE only occurs in isolated incidences in American football (Silver et al., 2011).

One specific difference between post-TBI symptoms and CTE is the fact that while post-TBI symptoms occur almost immediately following the injury, resolve within approximately thirty days, and “represent temporary states of neuronal and axonal
derangement,” CTE symptoms do not manifest until many years after full recovery from TBI (Gavett et al. 2011). Additionally, CTE typically presents in mid-life following retirement from professional sports and has a gradual progression similar to other neurodegenerative diseases. CTE, as described by the family members of individuals who suffered from it, effects behavior of the individuals in that they become more irritable, angry, and have shorter fuses. Cognitive difficulties can also appear early in the disease process with deficits in episodic memory and executive functioning. More progressive symptoms include abnormal movement, speech, and ocular movement, and the less common and most progressive symptom of dementia. Sadly, a very unfortunate outcome of CTE has been shown to be suicide and/or suicide attempts (parasuicide), making the accurate assessment of the development of dementia difficult to determine and potentially under-represented, as those patients who commit suicide die at earlier ages than the onset of the final symptom (Omalu et al. 2010). Another life-threatening symptom of CTE is the loss of inhibitory control in the brain, which can lead to death from accidents as well as put patients at an increased risk for problems with drug and alcohol abuse (Gavett et al. 2010).

In general CTE is difficult to diagnose pre-mortem because there is a lack of concise diagnosis criteria (Gavett et al. 2010). Additionally, the presentation of CTE can frequently appear similar to Alzheimer’s disease (AD), Parkinson’s disease (PD), and frontotemporal dementia (FTD), therefore eliminating those differential diagnoses is very challenging without the option for neuropathologic studies of the individual’s brain.
However, CTE is a distinct disorder from AD, PD, and FTD, as proven by post-mortem neuropathologic studies of the individual’s brains.

There are gross pathologic as well as microscopic consistencies between CTE brains (Gavett et al. 2010). Enlargement of the lateral and particularly the third ventricle is present in CTE (McKee et al. 2009). There is atrophy of the frontal and temporal lobes, shrinkage of the mamillary bodies, and lightening in the color of the substantia nigra (Figure 3). Atrophy is present in many other areas of the brain, causing a general reduction in total brain mass (McKee et al. 2009).
Figure 3. Coronal sections comparing normal brain and CTE brain. A. Normal brain with normal ventricular and size relationship. B. CTE brain with widening of lateral ventricle (1), widening of the third ventricle (2), atrophy of the temporal structures (4), and shrinkage of the mammillary bodies (5) (figure amended from Stern et al. 2011).

On a microscopic level, the three main proteins present in CTE are tau, beta-amyloid (Aβ), and TDP-43 (McKee et al. 2009). Tau makes up the neurofibrillary inclusions called neurofibrillary tangle (NFT), and while NFTs are also present in AD patients, they have a distinct distribution in CTE. In CTE, NFTs are distributed to more confined areas of the frontal, temporal, and insular cortices and remain fairly superficial, whereas in AD the NFTs are distributed diffusely through the cortices and also invade large projection neurons deeper in the cortices (Figure 4). Additionally, NFTs in CTE
are typically perivascular, indicating interference of the microvasculature and blood brain barrier (McKee et al 2009).

**Figure 4. Comparing the presence of Tau protein in control versus CTE brains.**
Left. Hemi-section of a control brain immunostained for tau protein and counterstained with cresyl violet showing no brown tau deposition. Right. Hemi-section of a CTE brain immunostained for tau protein and counterstained with cresyl violet showing extensive brown tau deposition in the frontal and temporal grey matter (BU CTE Center, 2015).

Amyloid precursor protein (APP) is a protein that is known to be upregulated in patients who suffered a TBI and Aβ inclusions are present in 30% of patients who die immediately following a TBI (Gentleman et al. 1993). Aβ protein deposits are present in 40-45% of cases of CTE, in contrast to its 100% presence in ALS patients, and when Aβ are present in CTE, they are less dense and more diffuse (McKee et al. 2009). It is unclear what the role of the excess APP and Aβ is in CTE, whether the protein’s presence in damaged axons leads to neurodegeneration or neuroprotection (Gentleman et al. 1993).
The final protein involved in CTE microscopic pathogenesis is TDP-43. Recently, it was found that there is a diffuse presence of pathogenic TDP-43 present in CTE brains (McKee et al. 2010). Interestingly, there is also evidence showing that in individuals with CTE who also developed neurodegenerative diseases prior to death, there were TDP-43 inclusions extending into the spinal cord, specifically proteinopathy in the anterior horns of the spinal cord. This disease process tends to clinically present very similar to ALS.

It is not clear if the diagnosis of CTE must precede an ultimate development of ALS, because there is also evidence that shows an increased early onset ALS in Italian football players (American soccer) that is not considered to be a sport with large diagnosis of CTE (Chiò et al. 2004). This supports additional evidence to suggest that rigorous athletic activity could be responsible for MND, an additional term used for ALS. There are possible genetic factors associated with MND that are upregulated or altered due to physical activity and could therefore help connect these two events (Hardwood et al., 2009). In addition, there seems to be an increase in neurotoxicity of TDP-43 following TBIs; TDP-43 is the protein normally involved in neurofilament-binding and mRNA-stability. Due to the similar immunoreactivity of TDP-43 in CTE and ALS as well as the increased association between TBIs and ALS, it appears that there may be similar mechanisms involved in the pathologic expression of TDP-43 (Costanza et al. 2011).
Specific Aims/Objectives

There is clear evidence of the relationship between extreme activity and an increased incidence of ALS. There is also evidence showing that athletes who experience TBI or CTE tend to develop MND. However, there has only been little done to determine how athletes, TBI, CTE, and ALS as well as other MNDs are all connected.

This paper is aimed at discovering the relationship between athletics or strenuous exercise, TBI, CTE, and ALS. Specifically this thesis will examine:

1. The extent of athletes that are diagnosed with CTE during their extended years of activity and the development of ALS
2. The incidence of athletes developing ALS versus other MND and any potential differences in their mechanisms
3. The neurologic mechanism of athletes who develop ALS relative to those who develop ALS without having participated in multiple years of athletic activity.

We hope this study will reveal a correlation between athletes diagnosed with CTE and the specific mechanism that is associated with CTE that leads to ALS. Additionally, there could be a connection between the mechanism variation leading to ALS versus a different MND. This could potentially help lead to further therapeutic implications for CTE and their success in prevention of the development of ALS as well as other MNDs.
PUBLISHED STUDIES

TBI and PD

Prior to the article published by Annals of Neurology investigating the risk of PD following TBI, the epidemiologically evidence linking the two was inconsistent (Goldman et al. 2006). There also appears to potential confounding factors, for example, head injury may be genetically related to high-risk behavior or careers such as farming. Goldman et al, undertook a study to attempt to eliminate these confounding factors and investigate the relationship of TBI and PD. To control for the confounding factor of genetic high-risk behavior, the study evaluated twins, one with PD and one without PD. These twins are either genetically identical monozygotes or genetically very similar dizygotes, eliminating the genetic confounding factor. Additionally, evaluating twins allowed for generally similar environmental exposures compared to typical cases and controls, eliminating environmental confounding factors. This study successfully eliminated confounding factors including genetic predisposition, genetically associated high-risk behavior, and nonspecific “male lifestyle factors” because twins tend to behave similarly. This study also evaluated twins who both have PD to determine if TBI causes acceleration in the development of PD.

Participants were not informed of the study hypothesis and the selected individuals were provided with a questionnaire where they indicated if they suffered a TBI resulting in loss of consciousness or memory loss, at what age the TBI occurred, and whether or not they were hospitalized for their TBI (Goldman et al. 2006). Twins who
were both suffering from PD were evaluated separately from twins where only one twin had PD.

The study successfully showed that there is a significant relationship between TBI and associated PD with twins where only one of them had diagnosed PD (Goldman et al. 2006). Individuals evaluated were shown to be three times more likely to develop PD after experiencing TBI. The risk of developing PD goes up significantly to four times if the individual has suffered two TBIs. Interestingly, the associated risk for PD following TBI was shown in both monozygotic and dizygotic twins, however, it was found that there is an increase in the association of TBI leading to PD in monozygotic twins.

The study also attempted to remove the possibility of the bias associated with a TBI being caused by the early motor changes in the not yet diagnosed but diseased Parkinson’s patients (Goldman et al. 2006). In attempt to do this, the researchers excluded any individuals who had suffered a TBI within the ten years prior to the diagnosis of PD. As the average time of onset of PD following a TBI is thirty years, it was felt that removal of TBIs within ten years of the onset of PD was appropriate. It appears that there is still a statistically significant direct causal relationship between TBI and subsequently developing PD. Also excluded from the study were twin sets whose control non-PD twin died before the PD diagnosis in the other twin, attempting to eliminate a survival bias.

When comparing twins who both were diagnosed with PD there was an association found that the twin who had suffered a TBI was likely to develop earlier onset of PD; potentially showing that TBI may lead to more rapid clinical expression of PD
(Goldman et al. 2006). This finding, however, was not statistically significant and the number of twin sets both diagnosed with PD was small, therefore it requires further investigation.

An additional concern about the study is the increased frequency of TBI in the population when compared to the occurrence of TBI in previous studies (Goldman et al. 2006). This is potentially though to be partially due to the fact that all of the individuals in the current study were male and men are twice as likely to undergo a TBI in their lifetime. Also the participants all participated in either World War II or the Korean conflict, some experiencing active combat that could lend itself to increased risk for TBI. Furthermore, more than 33% of participants grew up farming which is an occupation associated with increased risk for TBI.

According to the Goldman et al. (2006) study, the proposed biological causes of TBI leading to PD have several potential elements. There is an inflammatory response that begins to occur in the brain within minutes of a TBI and this response can last for months. Initially, the blood brain barrier breaks down followed by leukocyte infiltration and microglial (a central nervous system immune cell) activation. In PD patients, there is an ongoing inflammatory response occurring in the substantia nigra pars compacta and inflammation in this area of the brain following a TBI can last for decades. Additionally, mitochondria function becomes decreased leading to an increased production of free radicals, and mitochondrial dysfunction is present in many PD cases, but its role is in the disease progression remains unclear. Finally, TBI increases the production of tau protein and synuclein; these two proteins together contribute to proteinopathy and inclusions of
each other. Alpha-synuclein is a known component of Lewy bodies, which are accumulated in PD brains and essential for post-mortem diagnosis of PD.

Goldman et al. (2006) proposed a potential treatment following TBI that could help prevent PD. The average period of dormancy of 30 years before onset of PD is clinically significant. It appears that this prolonged period between TBI and PD is essential for the full degeneration of the brain, however, it also allows for the opportunity for extensive intervention in the years following the injury. As the inflammatory response of the brain appears to contribute to PD, it seems that the use of antiinflammatory medications could help reduce risk for developing PD. This specific treatment needs to be investigated further, but it does appear to be a plausible solution, as there have been two studies confirming the therapeutic use of antiinflammatories in preventing PD following TBI.

**Rigorous Physical Activity and ALS**

According to a study done by Chiò et al. (2004), prior to their study, the hypothesis that participation in sports had been proposed since the 1970s without consistent results. The Chiò et al. (2004) study was inspired by an investigation into the cause of death of in a cohort of 24,000 Italian football (IF) players (American soccer players), which turned up with a statistically unusually high number of deaths attributed to ALS. Based on standard population statistics, the expected number of incidences of ALS-related deaths in the 375 athletes who were deceased was 0.69, however there were 8 deaths attributed to ALS (Chiò et al. 2004). The goal of their study was to
retrospectively investigate the potential cause of developing ALS amongst this disproportionately large number of ALS-caused deaths in IF players.

For their study they used all male professional IF players who played in Italian First or Second Divisions between September 1, 1970 and June 30, 2002 (Chiò et al. 2004). The individuals had to have played at least one official game. The age at which the participants played Italian football, their position on the field, and the number of years they participated in the professional sport were all included and evaluated for statistical significance in developing ALS.

To assure the individuals were indeed suffering from ALS, conformation was obtained from multiple sources including death certificates, the archives of the Italian ALS Association, and self-report as well as family report (Chiò et al. 2004). Each ALS case was further investigated by obtaining detailed information from the individual, family members, healthcare providers about the patient’s past personal and medical history, work and trauma following retirement from Italian football, exposures to potentially toxic environmental factors, as well as thorough family history focused on neuromuscular disease.

It was found that out of the total 7325 professional IF players, there were fifteen Italian-born IF players who played IF between 1970 and 2001 who were diagnosed with ALS (Chiò et al. 2004). Interestingly, none of the five individuals had suffered an injury significant enough to require hospitalization nor had they been exposed to metals or solvents. To determine the expected number of incidence of ALS in the normal Italian population they utilized the northern Italy and southern Italy Registers for ALS.
Applying this expected incidence of ALS within the subgroup of 7325 professional athletes, it was determined the expected incidence of ALS including subgroups of number of years played, position played, and age of the player. It was found that in all three cases, the incidence of athletes who developed ALS was statistically significantly higher in the cohort IF players when compared to the general Italian population (Tables 4-6).

Table 4. ALS incidence by age classes. This is a comparison of the expected incidence of ALS within the 7325 cohort of IF players and the actual incidence of ALS found separated into age class onset (table amended from Chiò et al. 2004).

<table>
<thead>
<tr>
<th>Age Classes</th>
<th>Expected Cases</th>
<th>Observed Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-49</td>
<td>0.53</td>
<td>4</td>
</tr>
<tr>
<td>50-69</td>
<td>0.24</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5. ALS incidence by playing position. This is a comparison of the expected incidence of ALS within the 7325 cohort of IF players and the actual incidence of ALS found separated by position played (table amended from Chiò et al. 2004).

<table>
<thead>
<tr>
<th>Playing Position</th>
<th>Expected Cases</th>
<th>Observed Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward</td>
<td>0.09</td>
<td>-</td>
</tr>
<tr>
<td>Midfield</td>
<td>0.33</td>
<td>4</td>
</tr>
<tr>
<td>Back</td>
<td>0.24</td>
<td>1</td>
</tr>
<tr>
<td>Goalkeeper</td>
<td>0.11</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6. ALS incidence by number of years as a professional IF player. This is a comparison of the expected incidence of ALS within the 7325 cohort of IF players and the actual incidence of ALS found separated by number of years as a professional player (table amended from Chiò et al. 2004).

<table>
<thead>
<tr>
<th>Number of years</th>
<th>Expected Cases</th>
<th>Observed Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5 years</td>
<td>0.57</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>0.20</td>
<td>3</td>
</tr>
</tbody>
</table>
This was the first large prospective cohort study to show a high significant causation between playing professional Italian football and ALS (Chiò et al. 2004). Playing professional IF was found to be the strongest potential risk factor for developing ALS as of yet. It was also clearly demonstrated that the more number of years an individual played professionally lead to an increased risk of ALS as well as the average age onset of ALS amongst Italian football players being somewhere near 20 years earlier than the average age of onset in the general population. There was also an abnormally high percentage of clinically bulbar ALS by comparison to the ALS Registers.

The causative factoring leading to ALS is still unknown leading to the proposal of new hypotheses:

i. ALS could be cause solely by participating in strenuous physical activity and is not directly linked to IF.

ii. ALS is caused by traumas that could be IF specific such as heading the ball, leg traumas, or training trauma.

iii. ALS is related to the use of illegal substances used to attempt to improve performance.

iv. ALS is related to toxic herbicides or fertilizers used on IF fields.

It was concluded that ALS being caused by strenuous physical activity is unlikely as previous studies have been inconclusive (Chiò et al. 2004). IF specific trauma is still possible as trauma has been indicated to be a risk factor for ALS. The bulbar clinical
presentation of ALS could be linked with heading a ball, an IF specific head trauma. It remains possible that the early age onset of ALS within the cohort of IF players could be caused by the toxic substances in fertilizers and herbicides, however, toxins leading to ALS are still generally unidentified. Further studies evaluating environmental exposures as well as the pathology of ALS are required.

*Rigorous Physical Activity and MND/ALS: A Review*

An article published in the *Journal of Amyotrophic Lateral Sclerosis* in 2009 reviewed previously published studies on strenuous exercise and ALS, called NMD in the study. According to the review, the etiology of most cases of ALS is not clear but seems to be a combination of fixed genetic predisposition and environmental factors (Hardwood et al. 2009). There are nine genetic mutations that currently give rise to ALS via familial inheritance with a most recent discovery of the pathologic power of TDP-43. There is thought to be a genetic component to sporadic onset ALS, although the evidence is lacking. The genes thought to cause predisposition for ALS have been suggested to be angiogenin, survival motor neuron, and haemochromatosis but again, findings are inconsistent.

Environmental factors that have been demonstrated to contribute to ALS are currently male gender, family history, increasing age, and smoking; however, smoking as a risk factor is still debated (Hardwood et al. 2009). Most studies up to this point investigating activity as a factor in ALS have had issues with confounding factors, selection bias, small sample sizes, and additional environmental exposures. This article
by Hardwood et al. (2009) reviews the evidence surrounding general and sport-specific physical activity as a risk factor for ALS. Eleven previously published studies since 1995 were found using the terms ‘ALS’ or ‘MND’ and ‘physical activity’ or ‘sport’ or ‘exercise’ or ‘football’. The overall findings from each study were summarized (Table 7).
Table 7. Summary of published studies investigating physical activity and ALS. These studies were found to be the most relevant and provided conclusions conducive to a literature review of the evidence for rigorous activity as a risk factor for ALS (Table amended from Hardwood et al. 2009).

<table>
<thead>
<tr>
<th>Author, year and study design</th>
<th>Research question/aims</th>
<th>Reported findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strickland DJ et al. (1996). Case-control study.</td>
<td>Is MND associated with previous PA or trauma?</td>
<td>MND associated with sweating at work, sweating in leisure PA and receiving recognition in organized school or college sports.</td>
</tr>
<tr>
<td>Longstreth WT, et al. (1998). Case-control study.</td>
<td>Is MND associated with previous PA?</td>
<td>No overall association of MND with PA; MND cases more likely to have participated in school sports.</td>
</tr>
<tr>
<td>Valenti MJ, et al. (2005). Case-control study.</td>
<td>Are sport and sport-related trauma risk factors for MND?</td>
<td>No association between sport or sport-related trauma and MND.</td>
</tr>
<tr>
<td>Belli S, Vanacore M (2005). Retrospective mortality study.</td>
<td>To identify the causes of death in Italian professional footballers.</td>
<td>† MND incidence (SMPR 1158) and earlier age of onset than expected.</td>
</tr>
<tr>
<td>Tiihoni E (2007). Follow-up mortality study.</td>
<td>To identify the causes of death in Italian professional footballers.</td>
<td>† MND incidence (SMR 18.18) and earlier age of onset than expected.</td>
</tr>
<tr>
<td>Chio A, et al. (2005). Retrospective cohort study.</td>
<td>Is MND associated with playing professional football?</td>
<td>† MND incidence (SMR 6.5), earlier age of onset, † bulbar disease incidence. † risk if played &gt;5 years and in a midfield position.</td>
</tr>
<tr>
<td>Abel EL (2007). Retrospective cohort.</td>
<td>To describe the rate of MND in NFL American footballers.</td>
<td>Significant † prevalence of MND in American footballers.</td>
</tr>
</tbody>
</table>

The first five articles listed in Table 7 had the goal of investigating general physical activity and ALS (Hardwood et al. 2009). The following six articles were aimed
to evaluate soccer as a risk factor for ALS. Based upon these eleven studies, the evidence that physical and athletic activity increases an individual’s risk for ALS is inconsistent. No significant conclusions can be made from these studies, as there were noteworthy issues within the structure of the majority of the studies. Some key problems encountered include selection bias, poor study definitions, attempted investigation of multiple hypotheses in individual studies, and small participant numbers. An additional factor affecting these outcomes is the relatively small amount of cases of ALS in general, as the disease is quite rare. It is clear, though, that the outcome in several of these studies did show a positive relationship between rigorous physical activity and this needs to be investigated further.

The Harwood et al. (2009) review also presented the potential biological and genetic relationships of athletic activity and ALS (Hardwood et al. 2009). Non-ALS research has found that strenuous activities modify several mechanisms, including the oxidative stress process. There is already substantial evidence in post-mortem ALS patients that oxidative damage of the nervous system is a contributor to the disease. It is reasonable then that intense use of the muscles of the body leads increased metabolism in the body, and therefore excessive free radical production and an increase in reactive oxygen species. The normalizing process of the body to increase antioxidant enzyme activity during moderate exercise is thought to not occur or occur less successfully in extreme exercise including professional sports, therefore causing the buildup of reactive oxygen species and damaging effects to the cells of the body, including cell death.
Another proposed biological mechanism is glutamate excitotoxicity (Hardwood et al. 2009). While glutamate is a common and necessary neurotransmitter, in excess, it can be detrimental. During intense exercise, motor neurons are required to fire extremely quickly and frequently, leading to an increase in the release of glutamate. This large amount of neurotransmitter leads to large calcium influx into the neuronal cells, toxicity, and finally cell death. This proposition seems to be supported by the small benefit provided by the drug Riluzole, which inhibits glutamate release from presynaptic terminals of neurons.

There are several proposed genetic predispositions that are theorized to link physical activity and ALS (Hardwood et al. 2009). MND patients have been found to have mutations in their hypoxia-induced genes. As motor neurons have such a high oxygen demand, it is plausible that these neurons are at a higher risk of death than other cells if their response to hypoxia is faulty. Variations in the vascular endothelial growth factor (VEGF) gene have been previously tied with ALS. Decreases in the amount of serum VEGF and altered VEGF protein have been found in ALS patients. Intriguingly, in control individuals, VEGF is found to increase in serum and VEGF receptor transcription is upregulated. Angiogenin, an additional hypoxia-response gene that works in tandem with VEGF, is normally upregulated during heavy exercise, but is found to mutant in ALS patients. Individuals with these gene abnormalities could certainly lack the ability to amount the appropriate response to extreme exercise and be as risk for motor neuron death.
Neurotrophic factors, including ciliary neurotrophic factor (CNTF) as well as others, have been found to be protective to motor neurons in cultures and animals (Hardwood et al. 2009). Mutations in CNTF are associated with early onset ALS in individuals with other genetic predispositions. CNTF is also found to be in at unusually high levels in the serum of ALS patients, and it is also upregulated in the motor neurons of the spinal cord. Neurotrophic factors are increased during exercise; it was found that in mice placed on a 21-day exercise regimen, CNTF was upregulated two fold.

These genetic predispositions appear to be a potential link between strenuous exercise and ALS (Hardwood et al. 2009). It was recognized that further studies should integrate epidemiology and basic science to lead to consistent and clear evidence. While the previous epidemiologic studies have had flaws, including these biological and genetic factors will strengthen the outcome. Successfully identifying rigorous activity as a risk factor for ALS will give specific direction to potential therapeutic endeavors.

**TBI and ALS**

A study published in the *American Journal of Epidemiology* in 2007 was a direct response to the published study done in 2004 evaluating IF as a risk factor for ALS. While the study on IF players concluded that repeated traumas might be a risk factor for ALS, this study aimed to further investigate the relationship between head trauma as well as trauma to other parts of the body, and the later development of ALS (Chen et al. 2007).

Participants in this study were gathered from the Neuromuscular Research Unit at Tufts-New England Medical Center and the Neurophysiology Center at Brigham and
Women’s Hospital in Boston, Massachusetts (Chen et al. 2007). A total of 109 patients were selected for the study based on the criteria that they had to have been diagnosed with ALS by the World Federation of Neurology standard, diagnosed within the previous two years, live in New England more than 50% of the year, and exhibit mental competence. Population controls were selected based on the same criteria except they could not have been diagnosed with ALS, Parkinsonism, dementia, neuropathy, or any other neurodegenerative disease. A total of 255 controls were matched based on age, gender, and area code in a 3:1 or 2:1 ratio to ALS participants.

For gathering history about the cases as well as controls, the individuals were asked if they had ever experienced trauma that required medical attention (Chen et al. 2007). They were also asked their age when they sustained the trauma and on what body part the trauma occurred. Up to three injuries were included in the study. Additional social history, including smoking cigarettes as well as highest level of education, were also questioned as these appear to already be considered risk factors for ALS.

The study also included a meta-analysis of seven of the right previous publications about TBI and ALS; one study was left out due to inconsistencies and risk estimation was unable to be calculated (Chen et al. 2007). Cases and controls were separated into groups according to exposures of “ever vs. never,” with regard to general injury as well as location of injury and injury that had more than one body location. This was also adjusted for “never vs. ever” for smoking and “high school or less vs. more than high school” for level of education. Overall, it was found that having sustained an injury requiring hospitalization or medical attention did not increase an individual’s chances of
developing ALS. However, when comparing all of the body parts, it did appear that there was a strongest causal relationship between head injury as a risk factor for ALS except it was not statistically significant.

Individuals who endured repeated TBIs or suffered a head injury within the ten to three years prior to diagnosis were found to be three times more at risk for developing ALS (Table 8). Further investigation found that individuals who had experienced multiple TBIs with the most recent one occurring in the last ten years had an eleven-time increase in their risk for ALS (Chen et al. 2007). Cases with a history of multiple TBIs were additionally found to be more likely to develop bulbar clinical presentation; they were 33.3% of cases when compared to the rate of bulbar presentation of 22.4% within the cases. Lastly, the average age of onset of ALS was 54 years for individuals with multiple TBIs in their past compared to the average of all of the cases having the average age of onset of 59.5 years.
**Table 8. ALS associated with physical injury.** This compares case individuals versus controls in the type of injury sustained as well as the number of years since their injury (table amended from Chen et al. 2007).

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 109)</th>
<th>Controls (n = 255)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of head injuries</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (Never injured)</td>
<td>78</td>
<td>83.5</td>
</tr>
<tr>
<td>1</td>
<td>11.9</td>
<td>12.5</td>
</tr>
<tr>
<td>&gt;1</td>
<td>10.1</td>
<td>3.9</td>
</tr>
<tr>
<td><strong>Years since last injury</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (Never injured)</td>
<td>78</td>
<td>83.5</td>
</tr>
<tr>
<td>&gt;30</td>
<td>4.6</td>
<td>5.9</td>
</tr>
<tr>
<td>11-30</td>
<td>10.1</td>
<td>8.2</td>
</tr>
<tr>
<td>≤10</td>
<td>7.3</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>No. of head injuries and years since last injury</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (Never injured)</td>
<td>78</td>
<td>83.5</td>
</tr>
<tr>
<td>1 injury at any time</td>
<td>11.9</td>
<td>12.5</td>
</tr>
<tr>
<td>≥1 injury with the last one &gt;10 years prior</td>
<td>6.4</td>
<td>3.5</td>
</tr>
<tr>
<td>&gt;1 injury with the last one ≤10 years prior</td>
<td>3.7</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Age (years) at last injury</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>78</td>
<td>83.5</td>
</tr>
<tr>
<td>30-40</td>
<td>11.9</td>
<td>12.2</td>
</tr>
<tr>
<td>&gt;40</td>
<td>2.8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>7.3</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Involvement of other body sites in the same incident</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never injured</td>
<td>78</td>
<td>83.5</td>
</tr>
<tr>
<td>Head only</td>
<td>14.7</td>
<td>12.2</td>
</tr>
<tr>
<td>Head with other body sites</td>
<td>7.3</td>
<td>4.3</td>
</tr>
</tbody>
</table>
This study by Chen et al. (2007) as well as the meta-analysis of previous studies evaluating the relationship of TBI and ALS, are consistent with the recent findings of the study of IF players. While this study was unable to completely exclude the possibility of the preclinical symptoms of ALS causing injury, it seems that it can potentially rule it out as a cause, as merely sustaining an injury did not show to be a risk factor for ALS. This issue was also attempted to be addressed as cases who sustained a significant injury within the previous three years were not included in the study. Additionally, this study gave more specific parameters to the nature of the trauma sustained by the individuals participating; lack of specificity in regards to the type of trauma was an issue with previous studies and in the past gave inconclusive results. Unfortunately, the biology of TBI and ALS was not investigated and is still unknown. It is clear, however, that the mechanisms of inflammation, blood brain barrier disruption, and mitochondrial dysfunction involved in progression of PD following TBI should be considered as potential proponents of ALS as well.

**CTE and ALS**

McKee et al. (2010) had an article published by the *Journal of Neuropathology and Experimental Neurology* in 2010 directly investigating the differences in the post-mortem brains of individuals with diagnosed CTE alone compared to the post-mortem brains of those with CTE with ALS. This study was directly inspired by the published articles of Chiò et al. (2004) and Chen et al. (2007) as well as several others. TDP-43 inclusions were originally thought to be unique to ALS; however, it is now known that
TDP-43 protein pathologies are present in a multitude of neurodegenerative diseases, including CTE (McKee et al. 2010). This study directly compared the presentation of TDP-43 in twelve control brains and spinal cords, twelve sporadic onset ALS brains and spinal cords, and the brains and spinal cords of twelve former athletes with diagnosed CTE, three of which had clinical symptoms of ALS.

These subjects were all matched for age and gender (McKee et al. 2010). Prudent information of the deceased individuals was obtained through history of trauma, behavior history, motor symptoms, and status at the time of death both through the medical record and interviews when possible and/or necessary. Two of the three individuals with MND presentation played professional football and one was a professional boxer. The three individuals with CTE and ALS all had clinical presentations of severe muscle atrophy, weakness, and fasiculations, beginning in the upper extremities, neck, and shoulders with bulbar signs following shortly after. Sections of these brains were processed and stained for tau, TDP-43, ubiquitin, alpha-synuclein, and Aβ, as well as several others. The processing procedure was established by Boston University Alzheimer’s Disease Center, Mount Sinai Alzheimer’s Disease Center, and Massachusetts Alzheimer’s Disease Research Center Brain Bank.

In the sporadic ALS cases, TDP-43 was ever present as expected in variable manifestations within the tissue and rarely was there tau protein present (McKee et al. 2010). The cases of CTE without ALS manifestations appeared consistent with CTE with tau-positive NFTs in the frontal and temporal lobes as well as the basal ganglia and brain stem and TDP-43 as inclusions in the shapes of rings and filaments were
widespread through the frontal and temporal cortex, subcortical white matter, and brainstem. The three brains with both CTE and ALS appeared very similar to the CTE only brains with the exception of atrophy of the ventral roots of the spinal cord. The CTE and ALS brains also had extensive tau NFTs and TDP-43 ring and filament shaped inclusions, but interestingly these cases had a substantial increase in the amount of TDP-43 rings and filaments within the brain tissue and spinal cord when compared to CTE alone.

Two of the three CTE plus ALS cases had more severe MND and were found to have remarkable amounts of astrocytosis and loss of myelin and axons in the lateral corticospinal tracts (McKee et al. 2010). The ventral roots of the spinal cord were atrophies and there was a marked reduction in the number of anterior horn cells. Additionally, there were activated inflammatory cells, microglia and macrophages, diffusely distributed through the brains and spinal cords of these two cases. Tau NFTs were also found in the posterior, lateral, and ventral horns of the spinal cord.

As it is already clearly known that TDP-43 inclusions are presents in ALS patients, McKee at al. (2010) also have found these inclusions in 80% of CTE with the expected presence of tau NFTs (McKee et al. 2010). The individuals with CTE that developed ALS later in their disease process had both the TDP-43 and tau NFT proteins but additionally had these pathologies present in their spinal cords. The simultaneous presence of both tau and TDP-43 pathogenic forms implies that a similar mechanism is responsible for the accumulation of these proteins, and that CTE with MND is not a happenstance.
TBI causes the brain and spinal cord to experience shear stretching of the axons (McKee et al. 2010). During attempted repair of these damaged axons, there can be pathologic accumulation of neurofilament proteins. As TDP-43 is prone to aggregation, during its upregulation and involvement in the repair mechanism for axon damage, there is an opportunity presented for problematic aggregate formation. It is possible then that sports such as football and boxing lead the pathologic accumulation of TDP-43 in the brain and in some cases accumulation of TDP-43 in the spinal cord. It remains unclear what causes these anatomical changes to remain in the brain versus extend into the spinal cord.
DISCUSSION

As demonstrated by this review of the previously published articles, it is clear that trauma to the head can have long-term neurologic side effects including development of a multitude of diseases such as PD, AD, and ALS. Goldman et al. (2006) successfully eliminated potential confounding factors such as occupation, genetic predisposition to particular behavior, and environmental exposures in their investigation about the relationship between TBI and PD. It was found that even a single significant TBI could cause the terminal illness of PD. The proposed mechanism behind this development was the inflammatory response within the neural tissue that is present following a TBI and is also present in individuals diagnosed with PD (Goldman et al. 2006). However, this relationship needs to be further explored to determine the significance of CTE versus single TBI and PD, as well as the causes that allow TBI to lead to PD versus ALS, if there is a similar response occurring in the brain following a TBI in either case. This could certainly be related to genetic predisposition in individuals as well as a unique inflammatory response from person to person. Also, a better confirmation that inflammation is a potential causation to PD following TBI should be investigated in the future, as it is considered a risk factor for PD but has not been confirmed. Pathologic and anatomic studies would be best suited to validate inflammation as the main side effect of TBI that leads to PD.

The study by Chió et al. (2004) appeared to be conclusive in examining the relationship between professional athletes and ALS with strong statistical significance on
the increased prevalence of ALS within the professional athletic community. While there were several proposed explanations to this finding, it appears that the most valid possibility is repeated microtraumas to the brain during the contact sport (Chió et al. 2004). The review of studies inquiring the relationship between rigorous activity as well as soccer leading to ALS demonstrated that there were flaws within the soccer and ALS articles, such as small sample sizes and selection bias. The issues found in the Chió et al. (2004) study included testing multiple hypotheses as well as the lack of evaluation of environmental confounding factors such as smoking. Additionally, the study used comparative measures with the general population incidence of ALS, which could be unsuitable, given that IF players could represent a genetically unique group of individuals. The studies interested in the relationships between physical activity and ALS that were reviewed by Hardwood et al. (2009) had extremely inconsistent outcomes and more generally lacked proper definitions for cases and controls. Hardwood et al. (2009) did also propose some potential biologic explanations behind why exercise could lead to ALS. These ideas should be evaluated as it appears they are an area lacking information, but when studied thoroughly, could provide significant insight into this relationship.

The Chen et al. (2007) response research to the review of ALS and physical activity as well as soccer was successful at essentially eliminating a substantial relationship between general trauma in the general population and the development of ALS. While the study removed the physical activity element from the possibilities of causes, it opened up the cases to include persons in the general population, eliminating
the potential problem of genetic predisposition of the soccer players. This research was particularly important as it identified that the most significant risk factor found for developing ALS was multiple TBIs as well as more recent TBIs (Chen et al., 2007). This perpetuated further investigation into the biological mechanisms and changes to the brain following multiple TBIs.

As CTE is a rather newly defined disease that typically involved athletes, there have been new and profound investigative studies about the pathology of the disease and damage that multiple TBIs has on the brain to explain the long-term clinical presentation. CTE is most common among athletes, and there seems to be a relationship between athletes and ALS, as well as multiple TBIs and ALS. Since the association of repeated TBIs and ALS exists, it seemed reasonable to investigate a possible relationship between CTE and ALS, as multiple TBIs leads to CTE.

McKee et al. (2009) was able to successfully identify the unique neuropathology of CTE at an anatomic level. Based on the relationships of multiple TBI, athletes, and ALS that had been found, McKee et al. (2009) successfully distinguished the pathologic variances between sporadic ALS, CTE alone, and CTE with ALS. This study was the first to identify the biologic differences of CTE versus ALS. There were distinct similarities between the CTE and CTE with ALS brain tissues of these former football players and boxer as they both had TDP-43 and tau depositions. The most exciting finding was that CTE and ALS patients had these depositions within their spinal cords as well. This could imply that CTE is an additional risk factor for developing ALS, as the presence of the tau depositions is unique to CTE when compared to ALS alone.
With this anatomical information, it seems prudent that there should be further research to determine what would cause one individual to have pathogenic destruction limited to the brain tissue whereas another individual who suffered from CTE has damage that extends beyond the brain tissue to the spinal cord, causing MND. As not all individuals who undergo multiple TBIs develop CTE, it could be assumed that there is a genetic predisposition that with the appropriate environmental experiences triggers the later development of the disease. In the same light, there could certainly be a genetic factor that causes certain individuals to develop CTE initially, followed by ALS. Research should be focused on discerning what those genetic variables could potentially be, as experiencing CTE and ALS simultaneously is an even more devastating terminal situation.
CONCLUSION

There is certainly evidence to support the notion that participation in professional sports with associated head traumas can cause neurologic issues including the development of ALS, however general exercise without trauma as a risk factor for ALS still remains inconclusive. It is postulated that it could be a risk factor for individuals predisposed to problems such as poor response to increased metabolism, lack of neuroprotective elements, and inability to adequately remove oxidative elements from the body, but this has not been examined. There is also inconsistent evidence about the relationship between soccer and ALS as many of the studies on this subject had a multitude of confounding issues.

The concept of even a single TBI potentially leading to PD has fairly significant data to support it (Goldman et al. 2006). The proposed explanation for this is the inflammation of the brain as a response to TBI, though this has not yet been researched. There is also a clear causative relationship between individuals suffering multiple TBIs and later developing ALS, and as this association seems quite strong, the risk factor of soccer for ALS could potentially be explained by repeated TBIs suffered while playing the sport (Chen et al., 2007). The same study also effectively ruled out any noteworthy relationship between suffering trauma to other parts of the body besides the head, as there was rarely a statistical difference in the prevalence of ALS between cases and controls.

There is an anatomical difference between ALS, CTE, and CTE with ALS that is clearly demonstrated through post-mortem staining of brain and spinal tissue. This data supports the hypothesis that CTE can be a risk factor for ALS, as long as ALS has a
separate neuropathological presentation in tissue than does ALS following CTE. The reasons as to why one individual suffers CTE versus both CTE and ALS were not speculated, and this needs to be further investigated to determine why CTE is a risk factor for developing ALS.

As there is generally a large time window between initial TBIs and the much later development of PD, CTE, and/or ALS, it seems that discovering the biological and genetic factors involved in these diseases is essential. It is not fully known what changes in the brain and spinal cord are occurring during this extensive, relatively clinically dormant period of time. As there is such a significant delay in the onset of these terminal diseases, this would potentially allow for years of intervention and treatment, and possible prevention and/or delay of disease development overall. There is still extensive knowledge to be gained about these injuries, these diseases, and how they related to each other.
REFERENCES


CURRICULUM VITAE

ANDREA STEEN

Address: 40 Montcalm Ave. Unit #2
Brighton, MA 02135
913.530.4937

Email: asteen19@gmail.com

Year of Birth: 1985

Education:
University of Kansas
Bachelor of Arts in Human Biology, December 2010
Boston University School of Medicine, Boston, MA
Candidate for Master of Arts of Medical Science, May, 2015
Coursework: Biochemistry & Cell Biology, Medical Histology, Pathology & Pathophysiology, Advanced Human Physiology, Biostatistics

Presentations and Publications

12/12 Poster Presentation
• American Society for Cell Biology Annual Meeting
• San Francisco, CA

Research Experience: Employed

08/11-06/13 UMKC Neuroscience Brain Research Laboratory
• University of Missouri – Kansas City School of Medicine
• Kansas City, MO
• Managed all research and maintained the lab. Worked on schizophrenia research via brain tissue homogenization, spectroscopy, gel electrophoresis, western blots, and protein analysis. Identified unknown protein in schizophrenic thalamus via western blot.

Research Experience: Volunteer/School Credit
05/09-08-09, 08/10-12/10  Department of Pharmacology & Toxicology  
• University of Kansas School of Pharmacy  
• Lawrence, KS  
• Maintained the laboratory to help provide a successful research environment. Gained familiarization with techniques such as Q-PCR, PCR, reverse transcription, western blot, and northern blot. Observed liver perfusion.

Medical Volunteer Work

01/10-02/13  Social Services Volunteer at Jaydoc Free Clinic  
• University of Kansas Medical Center  
• Kansas City, KS  
• Interacted with other volunteers, including translators, student physicians, and physicians to provide adequate healthcare for those who lacked insurance. Referred patients to other clinics based on care type needed and location in the Kansas City area.

01/11-02/11  Observer of Physician David B. Lyons, MD, FACS  
• Sabetes Eye Center  
• Leawood, KS  
• Observed three ophthalmic reconstructive surgeries.  
• Observer of Physician Barry Nickell, MD, Internist  
• St. Luke’s Hospital  
• Kansas City, MO  
• Observed general care of twenty patients.

10/08-05/10  Member of Student Health Advisory Board  
• University of Kansas  
• Lawrence, KS  
• Worked with fellow members to participate in Health Services by reviewing and recommending changes to Student Health Services budget and participating in health promotion activities, with a focus of smoking prevention on campus.

11/08-12/09  Medical Corps Volunteer  
• Douglas County Medical Reserve Corps  
• Lawrence, KS  
• On-call volunteer for emergency situations. Trained in crisis emergency skills and response. Completed blood-
borne pathogens, CPR, storm spotter, animals in disasters, and psychological first aid training sessions. Helped raise awareness of public health issues by participating in hand-washing seminars and community health fair presentations

Non-Medical Volunteer Work

10/09-05/10   Morale Committee Member for KU Dance Marathon
  • University of Kansas
  • Lawrence, KS
  • Teamed with other volunteers to work year-round to organize a 24-hour fundraiser. Dance Marathon is a charity event that supports the Children’s Miracle Network. The year was spent organizing family events, building community awareness, and choreographing a dance for the final fundraiser. At the final fundraiser, was responsible for teaching participants the dance.

01/09-06/09   Refreshment Committee Member for Music for Jeremy’s Cherubs Foundation
  • Music for Jeremy’s Cherubs Foundation
  • Overland Park, KS
  • Solicited vendors, determined available inventory, assisted in food distribution, and decided on staff break areas.

Employment

02/06-12/08, 10/10-06/13   Server
  • The Kansas City Country Club
  • Mission Hills, KS
  • Communicated with and met the needs of all members at the Country Club as well as trained new employees.

Awards/Honors

12/09   National SMART Grant
08/08-05/09   University of Kansas Freshman Honors Scholarship
08/08-05/09   University of Kansas Fine Arts Dance Scholarship
01/01-2003   Selected Dance Performer – European Tour
07/02   American Ballet Theatre Summer Intensive