Comparing General Health Status and the Risk of Comorbid Autoimmune Diseases Between Sleep Apnea and Narcolepsy Patients

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Comparing General Health Status and the Risk of Comorbid Autoimmune Diseases

Between Sleep Apnea and Narcolepsy Patients

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Abstract

Background — Sleep disorders such as narcolepsy and sleep apnea are known to cause significant health problems if left untreated. The disorders are quite similar in terms of symptoms, but greatly differ in their etiology and also in how they are treated. Autoimmunity and comorbidity play roles in sleep disorders, especially narcolepsy, but a better understanding is needed.

Methods and Results — To compare and contrast narcolepsy and sleep apnea in terms of general health status and autoimmune comorbidity, a retrospective cohort study was done by reviewing patient charts. Data collected was organized and a machine learning algorithm was used to predict which variables best differentiated the two disorders. Further statistical analyses, such as chi-square testing, were performed with these variables. The results indicate that both sleep disorders decrease a patient’s general health status, but narcolepsy has a greater likelihood of comorbid autoimmune diseases and psychiatric disorders.

Conclusions — There are strong associations between narcolepsy and comorbid autoimmune diseases as well as a lesser association between sleep apnea and autoimmune diseases. In terms of general health status, both sleep disorders are detrimental to a patient’s health, but sleep apnea patients tend to develop negative health factors more than narcolepsy patients.
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Chapter 1
Introduction

Sleep is a basic biological process, but its exact role or function has yet to be determined. Understanding sleep requires an understanding of the cognitive and psychological functions of the brain as well as metabolic health. Through decades of research and observations, we know that poor sleep is harmful for one’s health especially for children and adolescents. Healthy development and growth in the young requires more hours and good quality of sleep. Yet the young tend to take sleep for granted by depriving themselves of sleep. This may exacerbate or even cause many negative effects on their health such as hyperactivity, moodiness, and lack of concentration and memory. Furthermore, it can lead to bigger health concerns including obesity, heart disease, diabetes, hypertension and sleep disorders.

With the current electronic lifestyle, the young are more vulnerable to acquiring these diseases. A common symptom of poor sleep quality is daytime sleepiness, which leads to poor performances at school or work and thus is perceived as a factor that affects the quality of life (Meyer et al., 2017). Excessive daytime sleepiness can also be harmful for patients and sometimes even others. For example, a patient with excessive daytime sleepiness falls asleep while driving and causes an accident with another car. It is essential that patients with excessive daytime sleepiness are checked and diagnosed if shown to have a sleeping disorder. The field of sleep is broadening and, with more research, we are now able to characterize certain sleep disorders. However, there is much
still to learn about sleep disorders. This paper is intended to help this progression by helping us understand more about narcolepsy and sleep apnea, sleep disorders with increasing trends in cases globally.
Definition of Terms

Apnea: Temporary but complete cessation of breathing, which usually occurs during sleep. There are three main types of apneas: obstructive, central and mixed.

Autoimmune diseases: Diseases caused by the body attacking its own tissues by antibody production usually leading to damage and eventually deterioration of these tissues. Examples of autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, type I diabetes mellitus, and Hashimoto’s thyroiditis.

Body mass index (BMI): An index that relates weight to height and sometimes age. A BMI of 18 or less is considered underweight. A healthy BMI ranges from 18 to 25. BMI over 25 is considered overweight and if above 30 then considered as obesity.

Cataplexy: Muscle weakness or paralysis that occurs suddenly and is uncontrollable while the person is awake. This usually happens when certain intense emotions are triggered and can be found in some narcoleptic patients.

Central Sleep Apnea (CSA): A sleep disorder usually caused by medical problems, such as Parkinson’s disease and stroke, where the brainstem is affected. It causes the brain to temporarily fail to signal muscles responsible for controlling breathing and thus causing a
complete blockage of breathing. Unlike another sleep apneas, this type of apnea is caused by a communication error between the brain and the muscles involved in breathing.

Comorbidity: Occurs when a person has two or more pathologic conditions or diseases at the same time.

Diabetes Mellitus: A disease that causes an impaired response by the hormone insulin to blood glucose changes. This results in elevated blood glucose due to abnormal metabolism of carbohydrates. There are two main types: I and II. Type I, considered autoimmune, leads to the body not producing enough insulin. Type II leads to the body not responding properly to insulin. Inflammatory responses and metabolic abnormalities may link Type II diabetes to obstructive sleep apnea.

Epworth sleepiness score (ESS): A scale that measures daytime sleepiness by a self-report questionnaire and helps to diagnose sleep disorders. The following are the ranges for ESS scores:

0-10 Normal range in healthy adults
11-14 Mild sleepiness
15-17 Moderate sleepiness
18-24 Severe sleepiness
Hypertension: Diagnosis given when a person’s blood pressure is repeatedly exceeding a systolic pressure of 140, a diastolic pressure of 90 or both.

Hypopnea: Abnormally slow or shallow breathing due to the partial blockage of air that usually occurs while sleeping. It is characterized as a decrease in airflow for at least 10 seconds during respirations, a 30% reduction in ventilation, and a decrease in oxygen saturation.

Narcolepsy (NCL): An autoimmune and neurological disorder that is characterized by a sudden, uncontrollable need to sleep when relaxed. It is usually associated with loss of orexinergic neurons, cataplexy, sleep paralysis, and hypnagogic hallucinations.

Non-rapid eye movement (NREM) sleep consists of three stages (N1, N2, and N3) that make up the majority of the time spent sleeping. Compared with wakefulness and REM sleep, NREM sleep is characterized by lower frequency and higher amplitude brain waves, lower blood pressure, and a slower heart rate.

Orexin (also known as hypocretin): A neuropeptide that is produced in two forms (A or B) by the mammalian hypothalamus and regulates appetite and sleep. When there is a loss of this neuropeptide, narcolepsy with cataplexy is frequently seen.

Rapid-eye movement (REM) sleep: During REM sleep, eye movements can be seen and dreaming is more often reported. Most individuals have between 3-5 REM periods per
night depending upon the number of 90-120 minute sleep cycles. REM periods tend to occupy a greater proportion of each sleep cycle across successive cycles. This type of sleep is characterized by high frequency low amplitude brain waves similar to wakefulness, irregular heart rate and breathing, and sometimes, involuntary muscle movements.

Obstructive Sleep Apnea (OSA): A sleep disorder characterized by the stopping of breathing that occurs in short periods of time. This condition usually leads to excessive daytime sleepiness due to the poor quality of sleep. Severity is determined by the number of apnea or hypopnea events that occur per hour of sleep. 5 or more events per hour are categorized as sleep apnea. The following is the Apnea-Hypopnea Index (AHI) —a scale OSA severity:

- <5 Normal
- 5-15 Mild
- 15-30 Moderate
- >30 Severe
Brief Glossary of Abbreviated Definitions

AHI (Apnea-Hypopnea Index): an index used to indicate the severity of sleep apnea.

BMI (Body Mass Index): attempt to quantify the amount of tissue mass in an individual.

CSA vs. OSA (Central Sleep Apnea vs. Obstructive Sleep Apnea): Central sleep apnea is a sleep disorder in which you briefly stop breathing during sleep while obstructive sleep apnea is the interruption of breathing due to blocked airways.

ESS (Epworth Sleepiness Scale): diagnostic tool used to assess daytime sleepiness through a questionnaire.

MSLT (Multiple Sleep Latency Test): a sleep disorder diagnostic tool used to measure the time elapsed from the start of 5 daytime nap periods to the first signs of sleep.

NREM vs. REM Sleep (Non-rapid eye movement vs. Rapid eye movement sleep): During non-rapid eye movement sleep, electroencephalograph recordings are higher in amplitude and lower in frequency with slow and regular breathing and heart rate. During rapid-eye movement sleep, faster pulse and breathing is noticed and generally more dreaming and bodily movements occur.
Physiological basis of sleep

Sleep is a reversible state of losing awareness of the external environment, relatively inhibited sensory activity, and inhibition of nearly all voluntary muscles. Homeostasis is the tendency of physiological mechanisms to maintain a stable equilibrium. Sleep homeostasis is the regulation between sleep and waking, which is known as the sleep wake cycle. Homeostatic mechanisms regulate sleep intensity, while, the circadian clock, which is a biochemical, 24-hour internal clock, regulates the timing of sleep (Borbély, 1980). During NREM sleep, most voluntary muscle movements and skeletal muscle tone diminish and, during REM the body is actually in a paralyzed state. However, this does not mean that there is no activity within the brain and the body. We associate sleep with the brain, but it is also associated with physiological activity all across the body. Sleep is also not a uniform process but consists of distinctive stages that alternate in a cyclical manner across the night. There are two main states of sleep: NREM and REM. For an adult, there are usually between four and six cycles within one night of sleep, each lasting approximately 90 minutes. Of the 90 minutes, most of the time is spent in NREM sleep, which consists of three stages: N1, N2, and N3 (Silber et al., 2007).

Sleep stages are distinguished by the dominant frequencies and amplitudes of brain waves. The transition from beta to alpha wave frequencies is associated with eye closure while awake and increasing dominance by theta frequencies is characteristic of stage N1, which is known as the transition period from being awake to falling asleep. During this time the following occur: drifting off to sleep, being sometimes aware of the
external environment, and being easily aroused back to a state of wakefulness. One can hear conversations and sounds, but will be unwilling to respond due to drowsiness. Muscles are still active during this stage and slow rolling eye movement can be noted. As the stage progresses, the breathing rate and heart rate gradually become slower. Sudden twitches or muscle jerks ("hypnic jerks") are quite common. Hypnagogic "dreams", which can be very visual and dream-like, although brief, may occur. They are typical of the N1 stage, but it is unknown if they differ from NREM and REM dreams. The N1 stage does not last long. On average, a person spends approximately 10 minutes per night during this light sleep phase. If a person wakes up during this stage, they will often believe that they were awake the whole time (Krahn et al., 2010).

Most of time spent in NREM is spent in N2 stage sleep, which is dominated by theta frequencies. K-complexes and sleep spindles. K-complexes are negative high voltage peaks that are immediately followed by a slower but positive complex and then it ends with a final negative peak. These complexes last approximately 1-2 seconds. Each sleep spindle, which is a short burst of brain activity consisting of 12-14 Hz waves, lasts about half a second. These two phenomena help the sleeper remain sleeping. They suppress the body’s response to external stimuli so that sleep can be protected and progress onto the N3 stage and eventually REM sleep. It has also been noted that K-complexes and sleep spindles aid in memory consolidation and information processing that occurs during sleep (Krahn et al., 2010).
The next stage, N3, may be a regenerative stage because during this period, brain metabolism is lowest, parasympathetic output dominates and growth hormone is secreted. When in this stage, a person is even less responsive to external stimuli and is completely unaware of their surroundings. Some sleep spindles can also be seen, but not to the extent found in the N2 stage. Breathing and heart rates slow down to their lowest levels in N3, which is also known as delta sleep or slow wave sleep based upon the delta and lower frequencies dominating the EEG. This stage is the longest during the first half of sleep. As one ages, this stage decreases and sometimes cannot be seen at all. However, this does not indicate ill health and is quite normal in elderly people. Dreaming can occur in this stage, but is less common than in lighter NREM and REM sleep (Krahn et al., 2010) (Cavallero et al., 1992).

REM sleep occurs after NREM at about 90-110 minutes of sleep. The periods of REM sleep are usually longer later in the night. During REM, the body is temporarily paralyzed, dreaming is frequently reported following awakenings, the heart rate and breathing rate increase and becomes irregular, the brain becomes extremely active, and the eyes, which are closed, begin to move rapidly horizontally, in a manner similar to waking saccades, as isolated movements or in bursts (phasic REM) separated by periods without eye movements (tonic REM). It is believed that processing of emotional memory takes place during this stage. Aging causes a reduction in REM sleep but not to the extent of N3 and this is normal in elderly people. However, the need to sleep or the need for quality sleep should not change as we age. No matter what age, the lack of both the
quantity and quality of sleep may indicate a health problem such as a sleep disorder (Krahn, 2010).

Sleep Disorders

For centuries, physicians and healers knew that sleep was an essential component of good health, however, the field of sleep medicine is relatively new. Disorders pertaining to sleep can cause significant health problems and often remain undiagnosed among those who suffer from them. The current lifestyle of the average American has led to an increase in sleep disorders. Sleep disorders are becoming common in the United States due to excessive electronic use, too much stress, the obesity epidemic, and also other health problems. Current research estimates that over 75% of the population in the United States within the age bracket of 20 and 59 have complained about having fairly regular difficulties in falling or staying asleep. Once these issues become regular and start to interfere with daily life, they may point to the development of a sleep disorder. Over time, not having adequate quality sleep can cause people to feel extremely tired during the day and can also have a negative impact on overall health, work life, school life, and even home life (American Academy of Sleep Medicine, 2014).

Not all sleep disorders are due to changes in lifestyle or the quality of sleep. In some circumstances, other medical conditions can have sleep disorders as a symptom or as a comorbid illness. In these cases, treating the initial medical condition may also treat
the sleep disorder. If not, then generally sleep disorders are treated with a combination of medicines, equipment, and changes in one’s lifestyle. It is beneficial for anyone suffering from a sleep disorder to get diagnosed and treated as soon as possible so that they can avoid any further health consequences. Furthermore, physicians should consistently evaluate the patient’s condition to see whether or not the sleep disorder is still present. This is relatively difficult as the field of sleep is still quite new and much more research is needed in diagnosing and treating sleep disorders.

Clinicians first attempted to classify sleep disorders in the 1970s and, since then, they have been organized into six broad categories: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias and sleep-related movement disorders (American Academy of Sleep Medicine, 2013). Sleep apnea is categorized as a sleep-related breathing disorder and consists of two main types, obstructive and central. Obstructive sleep apnea, the most common, occurs when there is a partial or full blockage of the upper airway when asleep. Central sleep apnea occurs when the respiratory drive diminishes thus causing a lack of respiratory movements. Both conditions are usually diagnosed by the presence of apneas or hypopneas (Thorpy, 2012). A temporary but complete stop in breathing for a period of ten or more seconds is called an apnea, whereas, hypopneas are due to partial closing of the airways and cause abnormally slow and shallow breathing. Other respiratory related events such as respiratory effort related arousal (RERA) may occur that are not apneas or hypopneas but cause an arousal or a decrease in oxygen saturation (Hosselet et al., 2001).
Narcolepsy is categorized as one of the central disorders of hypersomnolence, which are a group of disorders that all have the same primary complaint of excessive daytime sleepiness not caused by disturbed sleep at night or altered circadian rhythms. Identifying these disorders has been difficult due to not having enough information on the disorders and not having sufficient methods to distinguish these disorders from one another. During the last 30-40 years, many techniques to test or diagnose sleep disorders have begun to emerge, but many improvements can be made to provide better patient diagnosis and treatment (Thorpy, 2012).

Testing for Sleep Disorders

The best diagnostic tool to study sleep and sleep disorders is sleep history. Acquiring a patient’s sleep history is the easiest and most cost-efficient method to diagnose sleep disorders. A sleep history includes a description of a person’s daily sleep and wake cycles. This includes the times within a day when the patient felt alert or tired, times when they are working versus their leisure time, and when and how long they sleep including any naps. The quality of sleep is also noted as well as whether any changes in mood or willingness to do daily activities due to tiredness is present. It is important for the physician to know the environmental, social and medical aspects so they can properly diagnose the type of sleep disorder present and help the patient understand which type of test they will need to confirm the diagnosis (Haponik et al., 1996).
Sleep physiology is studied using the polysomnogram (PSG), a diagnostic overnight sleep study. A minimum of 12 channels and 22 wires attached to the patient are required for the study. These channels record three types of biosignals, electroencephalography (EEG), electrooculography (EOG), and surface electromyography (EMG), all of which are needed to assess sleep stages. EEG monitors brain functions and helps determine whether the patient is sleeping and what sleep stage the patient is currently in. EOG measures eye movements and EMG measures skeletal muscle tone. During PSG, a person’s sleep architecture is monitored and recorded during the night by a sleep technician and is later used by physicians to evaluate a person’s sleep and diagnose any sleep disorders present. Sleep architecture refers to the patient’s sleep stages and cycles. Looking at sleep architecture can help physicians determine whether or not disturbances in sleep are present and, if so whether they can be attributed to a particular sleep disorder. Polysomnography is used to diagnose many sleep disorders including sleep-related breathing disorders such as obstructive sleep apnea and also central disorders of hypsomolence such as narcolepsy. Though this test is performed during the night, it may also be done during the day if a patient displays problems with their circadian rhythm or excessive daytime sleepiness. For example, patients suspected of having narcolepsy may take this test during the day to measure the level of daytime sleepiness and their REM latency during naps (Kushida et al., 2005).

Physicians use the Multiple Sleep Latency Test (MSLT) to assess patients for daytime sleepiness and based on the results they may also provide the patient with a diagnosis. The test measures how quickly one falls asleep while in a quiet environment at
during the day. MSLT is usually used to diagnose narcolepsy, but while the study is occurring, sleep specialists may be able to pick up sleep apnea symptoms. The test takes up a full day and consists of five scheduled naps that are separated by two-hour breaks. During each trial, the patient lies in bed with sensors attached and tries to go to sleep once the lights are turned off. The time it takes for the patient to fall asleep after the lights are off is averaged across naps as the mean sleep latency. The quicker the patient falls asleep, the sleepier the patient is during the day. After 15 minutes, all patients are awoken and the trial will end. If the patient has yet to fall asleep then the trial will end at 20 minutes. The specialist then interprets the results of the test and combines the results with the Epworth Sleepiness Scale and other information they have received from the patient to form a proper diagnosis (Carskadon et al., 1986; Johns, 1991).

The Epworth sleepiness scale is a questionnaire that queries the patient’s likelihood of falling asleep during eight normal situations. The patients rate the likelihood on a scale of 0-3 with 0 being no likelihood and 3 being high likelihood. The general interpretation is that higher scores correlate with more severe symptoms of a sleep disorder (Johns, 1993). Compared to the MSLT, this test is much quicker, can help assess daytime sleepiness, and may even be more accurate. It is now used to validate symptoms of sleep apnea and narcolepsy (Chervin et al., 1997).
Narcolepsy

Narcolepsy (NCL), an autoimmune disorder with abnormal REM sleep, is closely associated with excessive daytime sleepiness. Due to better diagnostic techniques, more is known about this sleeping disorder, which was first described in the late 1800s. Frequently seen symptoms of narcolepsy include uncontrollable sleep attacks, cataplexy, sleep paralysis and hypnagogic hallucinations. The latter two symptoms are not specific for this disorder and thus are only used to support a diagnosed based on the other symptoms (Silber et al., 2002).

Most, if not all, patients are initially identified through reports of inappropriate, severe daytime sleepiness interfering with their day-to-day lives. This symptom is quite disabling in the sense that it can cause social problems, difficulties at work or school, and can even lead to accidents. It is common for patients with narcolepsy to fall asleep at inappropriate times when they are relaxed, bored or inactive. It has been noted that narcoleptic patients may also experience sleep attacks. During these episodes, the patient, without any preceding drowsiness, has multiple periods of sleep. Afterwards, most patients report feeling better and more alert after the nap. However, there are times when the patient feels drowsy before the episode, but begins to lose awareness of the surrounding and also of their actions. They may not be able to recall certain automatic behaviors such as driving. Though excessive daytime sleepiness is one of the main symptoms physicians look for, they also look for another symptom that is the most specific to narcolepsy: cataplexy (Silber et al., 2002).
Cataplexy, paralysis of the muscles while awake due to rapid transition from wake into REM with atonia, is seen in only some patients and these patients are diagnosed with narcolepsy type I. Those who do not show cataplexy are diagnosed with narcolepsy type 2. However, patients are not bound within these types as patients without cataplexy can be diagnosed with it in the future. More than half the population of narcoleptic patients has cataplexy. Scientists are still researching the reason for developing cataplexy, but they do have some theories. Some studies have shown a correlation between cataplexy and the loss of neurons that contain orexin that are believed to have been destroyed by an autoimmune mechanism (Slowik & Yow, 2017).

Cataplectic episodes occur suddenly and are usually triggered by emotion, specifically laughter. Other strong emotions that can induce episodes include excitement, surprise, pride, anger and fear. These episodes cause a transient loss of muscle tone that occurs bilaterally and internal muscle weakness that can last from a few seconds to several minutes. Loss of consciousness does not occur and injuries are minimal as the patient will be able to feel the buildup of the muscle sensations leading to an episode and may take precautionary measures, such as sitting down, before the full episode occurs. Cataplexy usually develops within four years after the onset of excessive daytime sleepiness. Patients may have either a partial or complete cataplectic attack. In complete cataplectic attacks, muscle tone in all except the respiratory and extra-ocular muscles are lost. Complete attacks are rare in most patients. Partial attacks, on the other hand, are more common and cause the loss of deep tendon reflexes. Examples of this include the
buckling of the knees, facial sagging, and weakness of the neck and jaw. Patients do not lose sensory input, consciousness or memory during these attacks. Most of these episodes last from seconds to minutes. During long cataplectic attacks, patients may experience dreamlike hallucinations and may also enter REM sleep. These experiences are commonly referred to as hypnagogic hallucinations, which occur at the transition between wakefulness and sleep, or hypnopompic, which occur immediately before waking up. It is hard for some patients to differentiate these hallucinations from dreams during the beginning of sleep and end of sleep (Krahn et al., 2005).

Patients may also develop REM sleep behavior disorder (RBD) due to having fragmented nocturnal sleep. Normally, paralysis occurs during REM sleep, but in patients with RBD, this characteristic is lost and causes the person to act out his or her dreams, which could be vivid, intense and violent. Nightingale et al. [DATE] found a strong correlation between narcolepsy and RBD, even more so than other common symptoms of narcolepsy such as cataplexy. Interestingly, it was also seen that narcolepsy patients are at a higher risk of developing these symptoms and that RBD may lead to arousal parasomnias, such as sleepwalking and sleep terrors, and also restless leg syndrome. It is speculated that RBD in narcolepsy may be a late symptom of an early onset motor disorder. This was supported by the study of Mayer and Meier-Ewert [DATE], which consistently observed that when compared to narcoleptic controls, narcoleptic patients with RBD had significantly higher levels of electromyographic or skeletal muscle tone and patient histories showed a higher frequency of parasomnias (Nightingale et al., 2005). Another issue that greatly affects the health of patients with narcolepsy is a change
in their body mass. Many studies have shown that the body mass index of patients with narcolepsy tends to be higher than control patients. Some narcoleptic patients have noted that they had an increase in food cravings and began binge eating around the onset of the disorder. The reason behind this change is unknown but there are a few possibilities. There are hypotheses that mention weight gain in narcolepsy patients may be due to orexin deficiency, which leads to a decreased appetite, and even more so, decreased energy expenditure (Chabas et al., 2007). Another possibility may be the lack of or reduced amount of physical activity due to sleepiness (Silber et al., 2002). Patients often mention the fatigue they experience due to unstable sleep cycles, especially during the night where they experience frequent awakenings. Orexin has been found to cause sleep state instability, meaning that the periods of wakefulness and REM sleep were brief and transitions between wake and sleep states occurred quite frequently (Gauci et al., 2017).
Role of Orexin

Orexin, also known as hypocretin (Hcrt), is a neuropeptide that is produced in the lateral hypothalamic and perifornical areas in mammals and functions as a homeostatic, metabolic and arousal system regulator (Peyron et al., 1998). There are two types: orexin-A (hypocretin-1) and orexin-B (hypocretin-2). The main differences between the two types are the chain length. Orexin-A is larger than orexin-B by 5 amino acids, and has a more compact N-terminal with two disulfide bridges, which allows variability in activity. Their activity is regulated by specific receptors that have distinctive affinities for each type of orexin. It is known that the orexin system plays an integral role in maintaining a wakeful state (Sakurai 2005). When orexinergic neurons are lost, symptoms such as excessive daytime sleepiness, cataplexy, sleep attacks, and hypnagogic hallucinations can be seen (Sakurai 2013). Experiments done with animal models have also shown that orexin deficiency may cause obesity even with proper diet and exercise (Chieffi et al., 2017). The loss of orexin has been noted in narcoleptics, but currently there have been no associations reported between changes in orexin and sleep apnea.

In 1999, the connection between narcolepsy and orexin was found through the Hcrt or orexin neurotransmitter system. Two individual teams coincidentally discovered that when the orexin receptor-2 gene was deleted, narcolepsy arose in their dog and mouse animal models (Lin et al., 1999; Chemelli et al., 1999). In the study done with a mouse model, the mutant mice developed episodes of either abnormal REM sleep during the day while awake or episodes of cataplexy. Since both animal models showed
symptoms of narcolepsy, researchers began to search for a connection between orexin and narcolepsy in humans (Kornum et al., 2011).

Sure enough, researchers were able to measure orexin levels in the cerebrospinal fluid and found extremely low to absent levels of orexin in patients with narcolepsy (Mignot et al., 2002). Further studies including autopsy studies of the brain have found absent concentrations of orexin in the brains of narcoleptics in the hypothalamus, cortex and pons. Peyron et al. (2000) also examined melanin-concentrating hormone neurons, which are usually intermixed with orexin, and found that they were still present in the hypothalamus in normal concentrations. Thus, it was orexin that was causing the narcoleptic-like symptoms (Peyron et al., 2000). This is reasonable as it was previously known that orexin neurons project to the brainstem and facilitate arousal mechanisms and thus its absence would cause hypersomnolence.
Autoimmune Diseases and Sleep

Autoimmunity pertains to the responses sent by the immune system to one’s own cells and tissues for destruction. The immune system’s function is to protect us from disease and infection. However, sometimes this mechanism misfires and can cause autoimmune diseases, which can affect many areas of the body. Currently, we have yet to find a definite cause for this occurrence, but it is well known that autoimmune disorders tend to run in families and particularly affect women more than men. There are many types of autoimmune diseases and many have very similar symptoms thus making it difficult for health care providers to diagnose a patient with an autoimmune disease. The main symptom that patients with autoimmune diseases complain about is inflammation (Franks & Slansky, 2012). Sleep is essential for these patients. During sleep, our body maintains and repairs itself and can benefit these patients by reducing inflammation, which has also been associated with obstructive sleep apnea (Kang & Lin, 2012). Researchers have hypothesized that narcolepsy may have an autoimmune origin. They theorized while studying autopsies that an immune attack may target the orexin-synthesizing neurons in the hypothalamus (Mahlios et al., 2013). However, it has proven to be difficult to prove as the experiment of finding the autoimmune origin is challenging to perform. Martinez-Orozco et al., in 2014, then turned to T-cell receptors and HLA proteins that attach circulating antigens and then bind to the receptors, which then recognize the specific peptide antigens. HLA typing test became a useful tool to help find connections between autoimmune diseases and narcolepsy (Martinez-Orozco et al., 2014). It is understood that the mechanisms responsible for the loss of hypocretin
producing neurons strongly suggests an autoimmune pathogenesis, but no firm evidence is currently available (Martinez-Orozco et al., 2016).

Sleep Apnea

Obstructive sleep apnea (OSA), a more common disease than narcolepsy, is a sleep and breathing disorder that affects the opening of the airways of patients when asleep. Due to apneas and hypopneas, proper sleep cycles cannot be maintained and poor sleep quality follows. This leads to excessive daytime sleepiness as well as other health issues. Continuous positive airway pressure (CPAP) is a common treatment used for OSA. Other variants include BiPAP and APAP. CPAP has been found to be of limited benefit to patients who are also suffering from psychiatric disorders due to poor compliance (Diamanti et al., 2013). If the first line of treatment does not work, dental appliances can be tried before surgery, which is the last line of treatment. There seems to be a strong correlation between sleep apnea and mental health, especially the connection between obstructive sleep apnea and depression. Mental health problems, such as anxiety and depression, arise in many patients with sleeping disorders, specifically obstructive sleep apnea due to apneic events causing low oxygen saturation levels within the brain, severe sleep fragmentation, and excessive daytime sleepiness (Haddad & Chen, 2017).

Furthermore, research has yet to find a connection between sleep apnea and orexin, but past studies have shown that there may be a correlation between sleep apnea
and obesity. In these studies, patients were asked to exercise and diet in an effort to lose weight, of at least 10kg, while the severity of their sleep apnea was monitored. Three randomized controlled studies showed consistent results of weight loss decreasing the severity of sleep apnea (Calik, 2016). Besides obesity, Lin et al. 2017 found that obstructive sleep apnea independently increased the incidence of heart failure. This study also showed that, compared to patients without OSA, patients with OSA have triple the risk of heart failure. It was also reported that there was a gender difference in the study and found that there was a higher prevalence of acute heart failure and more severe comorbidities in females than males (Lin et al., 2017). The study did not state possible reasons why this occurs. However, another study found that OSA patients have impaired coronary flow reserves, which is an indicator of coronary microvascular function. They noted that OSA patients might be prone to developing atherosclerosis, the narrowing of arteries due to plaque buildup (Bozbas et al., 2017). OSA has also been linked to obesity and inflammation. Studies have reported that the number of apneic events is correlated with insulin resistance, which causes patients to have higher fasting blood glucose levels and higher plasma insulin levels, independent of obesity. Obesity is a common symptom seen in patients with OSA. It appears that obesity may link inflammation to OSA because obesity has appeared to be a proinflammatory condition, but the exact mechanisms that link OSA to the inflammatory cascade are unknown (Calvin et al., 2009). It has also been noted that inflammation along with circulating leptin, which is a hormone that regulates energy expenditure, and intermittent hypoxemia may be the link that connects OSA to depression (Chirinos et al., 2017).
Background of Problem and Hypothesis

Autoimmune diseases such as rheumatoid arthritis and type I diabetes are chronic disorders that occur when one’s immune system attacks its own body’s tissues. It has been noted in previous literature that the presence of one autoimmune disease increases the chances of developing other autoimmune diseases simultaneously (Somers et al., 2006). Recent studies have reported that narcolepsy belongs in the family of autoimmune diseases (Yong, 2013). Sleep apnea, on the other hand, has not been categorized as an autoimmune disease. Narcolepsy and sleep apnea are similar in that they both have the same main symptom, excessive daytime sleepiness. Patients have been noted to have both conditions either simultaneously or separately, but any significant association has yet to be proven. Generally, both conditions affect a patient’s lifestyle and their health status due to other coexisting symptoms such as fatigue, headaches, mood swings, and weight gain (Sansa et al., 2010).

This thesis aims to compare these two similar conditions, narcolepsy and sleep apnea, and analyze the similarities and differences they have in terms of general health status and comorbid autoimmune diseases. Of these, my specific aim is to characterize the similarities and differences in the comorbid health conditions and family histories of persons suffering from obstructive sleep apnea and narcolepsy. I hypothesis that:

1) Sleep apnea will be more detrimental to general health than narcolepsy.

2) Narcolepsy will have higher probabilities of comorbid autoimmune diseases since it is itself an autoimmune disease.
I will also address the following questions:

1) Does having either of these conditions increase the probability that a patient will have an autoimmune disease?

2) Does a history of autoimmune diseases increase the probability of one of these conditions being seen in a patient?

3) What main similarities and differences can be seen in chart reviews of narcolepsy and sleep apnea patients?

4) Is one of these conditions associated with poorer general health status than the other?

5) If so, what possible factors are causing this condition to be more damaging?

6) Do psychiatric and general family histories increase the probability of developing these conditions?

The research strategy will start methods used in the field of machine learning, which uses algorithms and statistical techniques to find patterns within data without specific programming. Specifically, the decision tree algorithm will be used to find the associated features most capable of distinguishing narcolepsy from sleep apnea and then use conventional statistics to see if the identified features individually differ between narcolepsy and sleep apnea. Findings from this study could then lead to more in-depth research with more complete longitudinal or retrospective data that would be able to better examine the associations noted in this paper. A better understanding of both conditions and associated comorbidities and health status may help the scientific community on their journey to providing better health care and medicine for patients.
Chapter 2

Methods

Study Type

A retrospective cohort study was done by reviewing charts of patients with narcolepsy and comparing them to patients with sleep apnea. Past patient charts were reviewed from a population within the New Orleans area, specifically at the Advanced Neuro Clinic under the supervision of Dr. Morteza Shamsnia, who is affiliated with Tulane University. Patients had undergone polysomnography for subsequent detection of apnea-hypopnea events and calculation of AHI and to evaluate whether or not they suffered from a sleep disorder and the severity of their condition. The clinic was used patient’s Epworth score to assess daytime sleepiness. In addition, gender, age, family history, psychiatric history, other health conditions, BMI, cataplexy incidences in narcoleptics, blood pressure and pulse rate were queried and noted. HLA typing test results were only found for a few patients and thus could not be used to evaluate the data. Since a prospective study in these patients was not conducted, only pre-existing data were used, data were not obtained in a research-directed manner and patient follow-up was not possible.
Multiple Sleep Latency Test Analysis

The Multiple Sleep Latency Test (MSLT) is a common procedure used by sleep clinics to assess excessive daytime sleepiness in sleep apnea and narcolepsy patients. Patient files were reviewed and MSLT results were recorded with the exception of nine patients who did not take the test due to various reasons. For the past few decades, the MSLT has been considered the gold standard for objective assessment of excessive daytime sleepiness. The test consists of four or five daytime naps and measures the mean sleep latency or the time required to fall asleep during these naps. Scores are evaluated based on both the number of naps taken and the mean sleep latency during those naps. Lower mean sleep latency values, usually less than 8 minutes, indicate more severe daytime sleepiness. This test aids physicians to diagnose multiple sleep disorders such as sleep apnea and narcolepsy. However, there are a few drawbacks of the procedure such as time spent at clinic, equipment needed, and costs for the test.

Epworth Sleepiness Scale Analysis

The ESS is a questionnaire that asks about eight scenarios during which self-reports of excessive daytime sleepiness (EDS) are queried. All patients in the clinic were required to take this test during their initial visit. For each scenario, patients must respond on a scale of four points (0 meaning never and 3 meaning high chance of occurrence) to indicate the likelihood that they will fall asleep or dose off during this situation. At the end of the questionnaire, the responses were totaled. The scores range from 0 to 24, with
lower scores indicating normal behavior and higher scores indicating excessive daytime sleepiness during common daily activities. Although there is a conventional cut-off score of 10 and above for EDS, most clinics do not currently diagnose certain sleep disorders based only on ESS scores due to it being a subjective assessment. A few limitations of this technique include the ability of patient to read and respond to the questionnaire correctly and the lack of a strong correlation between ESS scores and scores of other known tests such as the MSLT.

Machine Learning

Machine learning is a field within computer science and artificial intelligence that uses statistical techniques in the form of algorithms that to give computer systems the ability to learn from the data provided without relying on specific rules of programming. It is similar to statistical modeling in the sense that it is a branch of predictive modeling, but there are a few differences. Compared to statistical modeling, machine learning algorithms can capture all patterns of data beyond certain boundaries that are placed in statistics such as the boundary of linearity. Furthermore, machine learning does not require the modeler to understand the relations between variables before using the algorithm and thus, in general, is a much quicker method for finding hidden patterns in the data (Langley and Herbert, 1995).

Python was the programming language used to help make sense of the vast and various data collected at the Advanced Neuro clinic. First, the data collected were
separated into categorical and numerical data (Farran et al., 2013). Of the categorical data that were useable, numerical values were allotted to each possible response. For example, gender of a patient was recorded as 0 for female and 1 for male. The final set of useable data was then normalized and used k-means as the input algorithm. This clustering algorithm separated data into k clusters with each observation belonging to the cluster with the closest mean. It then placed a prediction of the data in a figure, which is the output of the algorithm. In the end, data will divide into two clusters, which represent the two groups of patient types, narcolepsy and sleep apnea, that are displayed in a figure that shows the prediction of the algorithm.

Using this method, we were able to plot prediction values and real values and see how accurately Python would be able to organize and analyze the data collected (Farran et al., 2013). This can be seen clearly in the figure below where one can see mostly yellow dots, representing sleep apnea that was given a numerical value of 1, in the positive range and mostly purple dots, representing narcolepsy that was given a numerical value of -1, in the negative range.
Figure 1. Cluster plot depicting the accuracy and precision of the clustering algorithm. The yellow dots represent sleep apnea, which was allotted the value of 1, and the purple dots represent narcolepsy, which was allotted the value of -1. Since the positive range consists mostly of yellow and the negative range mostly of purple, it can be said that the program can accurately and precisely analyze and organize the data collected so that a good differentiation can be made.

Then, to further analyze the data, the questions that were stated above in the “background of problem and hypothesis” section, were addressed using a decision tree model to create a decision path. Decision tree algorithms help find significance within the data by describing, classifying and generalizing the data (Murthy, 1998). We then printed the various metrics and found that our predictions were 67% accurate and 63% precise, both of which were above 50%, which were favorable values indicating that our predictions were more likely to be right than wrong. Then we used the program to find the feature importance, which gave us the categories of data with the most important data ranked in order of most significant to least. These categories were further analyzed and
the significant aspects within each category were found through statistical analyses such as chi-square testing and t-testing and respective graphs and tables were made.

Statistical Analyses

To seek patterns in these data a variety of techniques were used including machine-learning procedures to identify the best set of predictors for OSA vs. NCL within the diverse continuous and categorical data types available for these patients. For specific data type, chi-square tests were used to test for significant differences between the two groups of patients for categorical data. Unpaired t-tests were used to test for statistically significant results groups for continuous data. Distributions of continuous data were tested for normality and transformed through the logarithm function when needed.
Predictor and Outcome Variables

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Outcome Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Classification of patients having OSA or NCL or both</td>
</tr>
<tr>
<td>Gender</td>
<td>Likelihood of developing OSA and NCL based on past histories</td>
</tr>
<tr>
<td>Medical History</td>
<td>Likelihood of developing a comorbid autoimmune disease once diagnosed with either OSA or NCL or both</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
</tr>
<tr>
<td>Psychiatric History</td>
<td></td>
</tr>
<tr>
<td>Epworth Score</td>
<td></td>
</tr>
<tr>
<td>MSLT Results</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>Pulse Rate</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Variables, both predictor and outcome, within the scope of this study. The predictor variables were chosen based on availability of information from most, if not all patients. Through the methods used within the study, we noted the significance of the predictor variable on the various possible outcome variables, which are listed in the right column.
Research Limitations

Due to the types of data that were available, the current study was a retrospective examination of existing data. Thus, this study will be a stepping-stone for future studies in which data can be collected with specific questions and hypotheses in mind. Since the data were recorded in the past, there will frequently be information on potential confounding factors absent from the data set as a whole or missing for individual patients. Although this will limit interpretation of results, machine learning and other statistical tools will help analyze the available data in a thorough way.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Narcolepsy</th>
<th>Sleep Apnea</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>23 (76.7%)</td>
<td>13 (43.3%)</td>
<td>36 (60%)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (23.3%)</td>
<td>17 (56.7%)</td>
<td>24 (40%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>36.73 ± 16.82 (20-54)</td>
<td>50.8 ± 15.26 (36-66)</td>
<td>43.77 ± 17.43 (26-61)</td>
</tr>
<tr>
<td>Age diagnosed, years</td>
<td>34.2 ± 16.3 (18-51)</td>
<td>48.7 ± 15.14 (34-64)</td>
<td>41.47 ± 17.23 (24-59)</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
<td>80.97 ± 15.52 (65-96)</td>
<td>75.8 ± 10.43 (65-86)</td>
<td>78.38 ± 13.37 (65-92)</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>121.52/76.97 ± (103-140/67-87)</td>
<td>139.53/81.69 ± (117-162/69-94)</td>
<td>130.68/79.4 ± (108-153/68-91)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.34 ± 8.47 (21-38)</td>
<td>32.44 ± 6.15 (26-39)</td>
<td>30.91 ± 7.49 (23-38)</td>
</tr>
<tr>
<td>ESS score, n</td>
<td>14.63 ± 5.23 (9-20)</td>
<td>11.23 ± 6.45 (5-18)</td>
<td>12.93 ± 6.07 (7-19)</td>
</tr>
</tbody>
</table>

Table 2. Sample table depicting the variables used within the study for narcolepsy, sleep apnea and total study sample. A total of 60 patient charts were reviewed in this study, and of this, 30 were narcolepsy patients and 30 were sleep apnea patients. Of the variables listed, all variables except pulse rate and blood pressure were normally distributed. Pulse rate and blood pressure were significantly negatively skewed. For the female and male variables, the number and percentage of participants were noted for each sleeping disorder and in total for the study. For the variables that follow, the mean and standard deviations are printed on the top line and the values within the parenthesis on the bottom lines represent the approximate range of the mean and standard deviation.
Main Similarities and Differences Between Narcolepsy and Sleep Apnea

Using machine learning, specifically the decision tree algorithm, the data from 60 patients were organized from the most to least different. The results below, which are the outputs of the algorithm, show the descending order of importance/difference to be blood pressure, severity of the disease tested through MSLT, BMI, age and Epworth score.

```
In [90]: decTree.feature_importances_
   #age, severity criteria, epworth, systolic, height, weight
   # in order of importance: systolic, severity, height, weight, age, epworth
```

Figure 2. Results from decision tree algorithm. The order of importance based on random data collected was determined through a machine learning algorithm. It shows that these aspects of the study were worth looking further into.

The following figures detail the level of difference between narcolepsy, shown in purple, and sleep apnea patients, shown in yellow. The importance of each of the following variables as a predictor was determined by the machine learning algorithm, which helped differentiate the groups. Unpaired t-tests were then done to test the statistical significance of this difference.
Figure 3. Comparing blood pressure values, specifically systolic values, between narcolepsy (purple) and sleep apnea (yellow) patients. An important difference was noted by the decision tree algorithm. Using t-test values \( t = 3.3565, \text{df} = 58, \) standard error of difference = 5.224, p-value = 0.0014, result highly significant at \( p < .05 \), there was a significant difference showing that majority of patients with high blood pressure were sleep apnea patients.

Figure 4. Height and weight differences between narcolepsy (purple) and sleep apnea (yellow) patients. An important difference was noted by the decision tree algorithm. With heights evenly distributed within each group (no significant difference), there was some significance based on t-test values \( t = 2.2504, \text{df} = 57, \) standard error of difference =
Figure 5. Box plot depicting BMI differences between genders in narcolepsy patients. The box for each gender represents 50% of the data values, which are shown as circles. The error bars, which are considered whiskers here, indicate the level of variation within the data values from the smallest value (bottom error bar) to the largest value (top error bar) outside of the upper and lower quartiles within the box. Thus, longer error bars are interpreted as more variation within the data values. The median values of the data set, shown as the line within the box, are comparable between males and females, 29 and 27 respectively. The mean values of the data, depicted as X, are 28 for males and 29 for females. The size of upper and lower halves of the boxes depict whether or not there is any skewed data. Results indicate that there is no significant difference in BMI between genders in narcolepsy patients. There is more variation within the female BMI values and it is more skewed towards the risk of having a higher BMI than male BMI values. The non-significance of difference was determined by t-test (t = 0.4363, df = 28, standard error of difference = 3.516, p-value = 0.6659, result not significant at p < .05).
The median value of the data set, shown as the line within the box, for both males and females was 31. The error bars, which are considered whiskers here, indicate the level of variation within the data values from the smallest value (bottom error bar) to the largest value (top error bar) outside of the upper and lower quartiles within the box. Thus, longer error bars are interpreted as more variation within the data values. The mean value of the data, depicted as X, for both males and females was 32. The size of upper and lower halves of the boxes depict whether or not there is any skewed data. Results indicate that there is no significant difference in BMI between genders in sleep apnea patients. Male BMI values showed more variation and was more skewed towards the risk of having a higher BMI than female BMI values. The non-significance of these data values was determined by t-test ($t = 0.3679$, df = 28, standard error of difference = 2.301, p-value = 0.7157, result not significant at $p < .05$).
Figure 7. Comparing age of onset between narcolepsy (purple) and sleep apnea (yellow) patients. A difference, output of the decision tree algorithm, can be seen between patient types. The significance of these data values was determined by t-test ($t = 3.3922$, df $= 58$, standard error of difference $= 4.147$, p-value $= 0.0013$, result highly significant at $p < .05$). Onset for narcolepsy was diagnosed earlier than sleep apnea. The average age to be diagnosed for narcolepsy was 34.2 years and 48.7 years for sleep apnea. Results indicate a significant difference in the ages between narcolepsy and sleep apnea patients.
Figure 8. Comparing Epworth scores between narcolepsy (purple) and sleep apnea (yellow) patients. On average, narcolepsy patients had an Epworth score of 14.6 and sleep apnea patients had an Epworth score of 11.2. The decision tree algorithm output indicated a difference in the ESS score between narcolepsy and sleep apnea patients. Narcolepsy patients had noticeably higher score values, which corresponds with excessive daytime sleepiness. The significance of these data values was determined by t-test ($t = 2.2434$, $df = 58$, standard error of difference = 1.516, $p$-value = 0.0287, result significant at $p < .05$).
Statistical Analyzes

Statistical analysis using chi-squared independence testing, which is used to determine if there is a significant difference in proportional representation of a dependent variable between two categorical independent variables, showed that the following associations exist between the patient types:

1) Dominant gender between narcolepsy and sleep apnea patients (chi-square statistic is 6.94; p-value is .008; result significant at p < .05). Prevalent gender for narcolepsy was noted to be female while the prevalent gender for sleep apnea was noted to be male.

2) Normal versus high blood pressure between patient types (chi-square statistic is 15.15; p-value is .00001; result significant at p < .05). Sleep apnea patients had a significantly higher instance of high blood pressure than narcolepsy patients.

3) Mild versus moderate to severe severity of disease type (chi-square statistic is 0.3175; p-value is .573; result not significant at p < .05). This indicates not significant result between narcolepsy and sleep apnea regarding severity of disease as measured by the MSLT analyses. The majority of patients in both types had moderate to severe cases of their illness.
Probability of Correlation Between Autoimmune Diseases, Psychiatric Disorders and Sleep Disorders

<table>
<thead>
<tr>
<th>Autoimmune Diseases</th>
<th>Narcolepsy</th>
<th>Sleep Apnea</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Neuropathy</td>
<td>2 (6.67%)</td>
<td>0 (0.00%)</td>
<td>2 (6.67%)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>2 (6.67%)</td>
<td>1 (3.33%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Restless Leg Syndrome</td>
<td>2 (6.67%)</td>
<td>1 (3.33%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>2 (6.67%)</td>
<td>1 (3.33%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Sjögren's syndrome</td>
<td>1 (3.33%)</td>
<td>0 (0.00%)</td>
<td>1 (3.33%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>9 (30.0%)</td>
<td>3 (10.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Chi-square: 5  
p-value: 0.025; results significant at p<.05

<table>
<thead>
<tr>
<th>Psychiatric Disorders</th>
<th>Narcolepsy</th>
<th>Sleep Apnea</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>10 (33.3%)</td>
<td>9 (30.0%)</td>
<td>19 (63.3%)</td>
</tr>
<tr>
<td>ADD</td>
<td>2 (6.67%)</td>
<td>0 (0.00%)</td>
<td>2 (6.67%)</td>
</tr>
<tr>
<td>ADHD</td>
<td>0 (0.00%)</td>
<td>1 (3.33%)</td>
<td>1 (3.33%)</td>
</tr>
<tr>
<td>Depression</td>
<td>9 (30.0%)</td>
<td>7 (23.3%)</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>21 (70.0%)</td>
<td>17 (56.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Chi-Square: 4.143  
p-value: 0.042; results significant at p<.05

<table>
<thead>
<tr>
<th>Major Medical Illnesses</th>
<th>Narcolepsy</th>
<th>Sleep Apnea</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>4 (13.3%)</td>
<td>3 (10.0%)</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>4 (13.3%)</td>
<td>7 (23.3%)</td>
<td>11 (36.7%)</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>0 (0.00%)</td>
<td>1 (3.33%)</td>
<td>1 (3.33%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (10.0%)</td>
<td>15 (50.0%)</td>
<td>18 (60.0%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2 (6.67%)</td>
<td>1 (3.33%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Hypercholesteremia</td>
<td>1 (3.33%)</td>
<td>1 (3.33%)</td>
<td>2 (6.67%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>2 (6.67%)</td>
<td>1 (3.33%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>16 (53.3%)</td>
<td>29 (96.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Chi-square: 4.85  
p-value: 0.028; results significant at p<.05

Table 3. Numbers and percentages of patients with comorbid autoimmune diseases, psychiatric disorders and major medical disorders. More autoimmune comorbidities are seen in narcolepsy versus sleep apnea patients. Narcolepsy is slightly more likely to have a comorbid psychiatric disorder than autoimmune disease. Depression and anxiety are noted to be the most common comorbidity for both disorders. Chi-square testing, results shown in table, showed that there was no significant difference between groups in the prevalence of individual disorders of these three types, however, when totals of each type of disorder are compared between groups, significant differences between narcolepsy and OSA are seen.
Table 4. Overview of the numbers and percentages of family medical history illness of narcolepsy and sleep apnea patients. Narcolepsy patients, in general, have more comorbidities in their family history than sleep apnea patients. In the family histories for both sleep disorders, higher incidences of diabetes, heart disease, hypertension, arthritis and cancer can be seen compared to the remaining comorbidities. Chi-square tests showed that there was significant difference between groups in the prevalence of individual disorders in their family histories.
Chapter 4
Discussion

Significance of Results

The purpose of this study was to compare narcolepsy and sleep apnea patients and analyze the similarities and differences they have in terms of general health status and comorbid autoimmune diseases. From the information gathered through this retrospective study, the machine learning algorithm gathered categories of information and, in combination with statistical analyses, differentiated narcolepsy versus obstructive sleep apnea through outputting the variables it deemed important for further analyses. It showed that blood pressure, severity of the disease, BMI, age diagnosed, and Epworth scores were of importance when comparing narcolepsy and sleep apnea patients. As noted earlier, further analyses were done to confirm that these factors significantly differed between the two sleep disorders.

Blood pressure showed a significant difference between groups with sleep apnea patients having a higher risk of developing high blood pressure. Using a chi-square test, it was further confirmed that sleep apnea patients had a higher instance of high blood pressure. Surprisingly, there was only a slight significance in BMI between both types of patients. Patients with both disorders are at a high risk of obesity, which in turn may cause a gradual decrease in a patient’s general health status and also may have contributed to developing other diseases such as type-2 diabetes. Further analysis of the
BMI data showed that there was a gender disparity between narcolepsy and sleep apnea. Female narcolepsy patients and male sleep apnea patients were more likely to become obese than their counterparts. Patient health histories showed a higher prevalence of major medical illnesses in sleep apnea patients than narcolepsy patients. Based on chi-square and t-test results of all the above factors, it can be concluded that sleep apnea patients suffered more health problems thereby decreasing their general health status compared to narcolepsy patients. These results directly support the first hypothesis of sleep apnea being more detrimental to the general health of patients than narcolepsy. Of the factors studied, blood pressure and BMI scores are the biggest health issues in both patient types, but especially in sleep apnea.

Severity of the disorder, which is based on the clinic evaluations of MSLT testing done by the patients, showed no significant differences in both narcolepsy and sleep apnea patient. Epworth score showed that narcolepsy patients suffered more severe excessive daytime sleepiness than sleep apnea patients. Furthermore, age of diagnosis showed that narcolepsy patients tended to be diagnosed much earlier than sleep apnea patients. This may be due to the excessive daytime sleepiness that is common in narcolepsy. It could also mean that other disorders may not cause narcolepsy, but rather the opposite. Patient charts showed that patients of both disorders had a considerable amount of other diseases. Of these diseases, majority were psychiatric disorders followed by autoimmune diseases. Depression and anxiety were the main psychiatric concerns for both sleep disorders, but significantly so for narcolepsy patients. Narcolepsy, compared to sleep apnea, showed a greater association with comorbid autoimmune diseases,
especially those that target joint and nerve damage. Chi-square testing failed to support the second hypothesis in which we expected narcolepsy to have a stronger correlation with individual autoimmune diseases. When comparing of specific comorbidities, the small sample size made chi-square tests of limited usefulness because many of the expected frequencies fell below 1 and also more than 20% of the frequencies were less than 5. However, chi-square testing did find significant differences between narcolepsy and sleep apnea patients when comparing the sums of all autoimmune diseases. This showed that there were no specific autoimmune diseases that narcolepsy may be associated with, but in general, autoimmune diseases seem to be more prevalent in narcolepsy patients. In conclusion, support for both hypotheses were found during this study.

Genetics play an important role in many diseases. Family histories were noted to see if there were any significant correlations that show that genetics may play a part in developing narcolepsy and/or sleep apnea. Heart diseases such as diabetes, heart failure and hypertension were noted to be significant factors that may show a correlation between heart diseases and developing sleep disorders. Arthritis and cancer also showed a high correlation with narcolepsy and sleep apnea. Interestingly, there were some cases in which sleep disorders such as narcolepsy and sleep apnea were noted in the patient’s family history. Chi-square tests showed that there was a significant difference within family histories between narcolepsy and sleep apnea. There were more associations made between family health histories and narcolepsy. Diabetes and hypertension seem to be common occurrences in family histories of both patient types.
Future Research Directions

Based upon the data and results from this study, future research can be done to lead researchers to more in-depth research with a more controlled experiment that will be able to test the associations suggested in this study. Longitudinal studies and larger sample sizes from multiple sites throughout cities around the United States are two possibilities for future studies. A better understanding of both conditions and associated risk factors may help the scientific community on their journey to providing better health care and medicine for patients.
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