Retrospective Analysis of Metabolic and Medicinal Effects in Pediatric Narcolepsy Data

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Abstract:

Introduction: Narcolepsy is considered a crippling sleep disorder with a global prevalence of 0.05%. Recently, narcolepsy research has uncovered that it is possible for children to develop narcolepsy during early childhood. The objective of this study is to evaluate the potential risk of growth defects in children through retrospective analysis of growth charts.

Methods: Data were collected through growth charts and patient distributed surveys gauging the ante and post severity of narcolepsy through the patient's experience. We evaluated data against existing growth curves to determine any growth impairments correlated and/or caused by narcolepsy.

Results: During pubescent years, 75% of (all female participants) showed comprehensible signs of premature stabilization of growth and an erratic and/or sudden increase in weight near the age of narcolepsy onset. The data showed a strong correlation between narcolepsy and signs of impaired growth shown in pediatric growth charts in females.

Conclusion: Although the sample size was very small, there is still a strong correlation between narcolepsy and impaired growth. The findings of this study do not insinuate causation between the two variables. Since there is little to no published data regarding the analysis between pediatric narcolepsy and growth, further investigation, especially one with a much larger sample size, is most definitely needed.

Introduction:

Narcolepsy is a crippling sleep disorder that has a prevalence between .02 and .05% or about 1 in 2000 people (Mignot et al., 2007; Nishino, 2005; Peterson et al., 2008) of the world's population. It is a mysterious disorder that is starting to be intensely researched due to its complex nature. Some typical characterizing symptoms of Narcolepsy can include sudden sleep attacks, a lack of Orexin in the brain and usually episodes of cataplexy, which are, essentially, a sudden loss of coordination usually stimulated by sudden emotional change. Its severe nature is caused by that it can affect anyone due to its unknown genetic ties. Most research has been done on the effects of narcolepsy on adult patients. Until recent years, researchers solely focused on adult narcolepsy research and complete neglected to research the possibility that narcolepsy manifests itself in children as well. These advances in research have yielded a recent, greater awareness of Narcolepsy. During the 20th century, not much research had been done on what is thought to be rare and almost forgotten disorder. Only up until the 1970's, useful data that sparked worldwide concern had been found. Researchers in California had found the prevalence of Narcolepsy regionally and that influenced the need for worldwide investigation. Later tests had been done in Hong Kong, Finland, Australia, etc. (Mignot et al., 2007). This is why the need for pediatric research is appropriate. Since, Narcolepsy is known to usually manifest in children under the age of 12 years old - 75% of the time - (Wu et al., 2013), it is essential to start immediate research on the pediatric aspects of narcolepsy. Typical treatments involve drugs such as Xyrem (Gamma-Hydroxybutyric Acid) and Nuvigil (Armodafinil). Xyrem helps reduce arousals during the night, while Nuvigil helps to prevent sleep attacks. As of now, no known cures for narcolepsy have been discovered.

Review of Literature:

Narcolepsy is most famously, or rather infamously, known for its unique symptoms. Some of these symptoms are significant only to Narcolepsy. Symptoms of Narcolepsy can include daytime sleepiness, improperly sequenced sleep cycles (Mignot et al., 2007), occasionally nightmares (Pisko et al, 2014) and sleep paralysis. More often than not, cataplexy is also characterized as a fairly definitive diagnostic marker for narcolepsy patients by symptomatically appearing in 83.3% of all narcolepsy patients (Wu et al., 2013). Additionally, the aforementioned sudden sleep attacks are almost always a telltale sign of Narcolepsy. These sleep attacks, as well as cataplexy, are usually stimulated by quick emotional changes or reactions such as anger, happiness, and/or even being surprised (Huang et al., 2013). These correlations have all been shown in previous research, however, these pieces of research concerned adults rather than children.

A topic that usually goes ignored when concerning possible ailments for children affected by narcolepsy is how they grow. This is reflected in the amount of research done on the correlation. It had already been found that the longer a narcolepsy patient waits to be diagnosed, the more severe their symptoms will be (Thorpy, 2014). This, alone, is a very compelling reason to start to consider further research in this field. Many scientists have appeared to neglect this area of study regarding research done with it. Only recently has the apparent need for new research or even treatments for Narcolepsy come to the surface (Strambi, 2013). As researchers learned that the 75% of pediatric onset of happens before the age of 12 (Wu, 2013), narcolepsy research migrated to fill the new hole of potential knowledge. According to this research, children are being affected by narcolepsy as severely as adults are, all of them showing symptoms of excessive daytime

sleepiness (Huang et al., 2013) and 83.3% showing symptoms of cataplexy (Wu, 2013). Additionally, many pediatric patients experience frequent nocturnal arousals and awakenings. Just as adults are, children diagnosed with Narcolepsy – Cataplexy (N- C) could be suffering from growth deficits when compared to their peers.

The brain's lack of control of the lateral hypothalamus (LHA) (Nishino et al., 2005) and the LHA's close relationship with the endocrine system (Okun et al., 2004) produces narcolepsy. The LHA controls the secretion and amounts of Orexin/Hypocretin distributed throughout the body. Orexin/Hypocretin control a variety of functions in the body. Three main actions that Orexin controls in the body are the desire to eat or one's appetite – 77.8% of patients showed weight gain (Wu et al., 2013) – wakefulness, and arousal. These three metabolic functions are quite pertinent to the study of Narcolepsy because they can heavily affect ones weight and growth (Sinton, 2011). When Orexin is activated by the LHA and secreted to the body, the body is alerted to stay awake. This is typically during the day. When a patient has Narcolepsy, this cycle is not as regular. Throughout the day, their Orexin hormone levels vary and cause a patient to experience fluctuations in the aforementioned symptoms.

Obstructive Sleep Apnea and Posttraumatic Stress Disorder (PTSD) are both known to produce poor quality of sleep and frequent disturbances during the night for those afflicted. Two studies done in 2011 and 2015 investigated the effect that these disorders had on adult and infantile growth, respectively. In the first study, Saskia van Liempt studied the patterns of growth hormone secreted nocturnally in PTSD patients (veterans with diagnosable PTSD), trauma controls (veterans with no signs of PTSD) and healthy controls (non-veterans with no PTSD). PTSD patients showed a significantly

lowered Intravenous Growth Factor-1 measurement: almost 7 times lower (Liempt, et al. 2011). The number of nocturnal arousals identified the presence of PTSD. Growth Hormone deficit is already thought to be associated with frequent nocturnal arousals and this study confirmed it. Since the number of the arousals during the night as well as the quality of life and sleep is similar in both cases of PTSD and narcolepsy, this gives reason to believe that narcolepsy will have this effect as well. The second study that supports this hypothesis is a study done by Xiao Man Zhang in 2015 regarding sleep apnea in infants. In all respects, the value for height, weight, and IGF-1 was lower for OSAS patients than it was for the controlled group. Additionally, the values prior to the patient's tonsillectomy and adenoidectomy procedures were less for all patients as well. These two procedures are known to be extremely effective at reducing apneas and the tendency for nocturnal arousals and awakenings, which includes quality of sleep and life (Zhang et al., 2015). These symptoms are significant in diagnosing PTSD as well as narcolepsy.

Research Questions:

RQ_1: Do adolescent patients with narcolepsy grow at a normal progression?

RQ_2: Do treatments designed to regulate sleep and/or mitigate the effects of narcolepsy, such as Xyrem and/or Nuvigil, contribute to a higher quality of life?

RQ_3: Do pediatric patients with Narcolepsy show signs of being overweight?

Hypotheses:

H_1: If Narcolepsy in children is related to growth, then children affected by Narcolepsy will show clear signs of stunted growth when compared to other children in their age group.

H_2: Pediatric Narcolepsy patients will show signs of rapidly gaining weight after onset occurs.

H_3: Children will show signs of restored growth when under the treatment of Xyrem and/or Nuvigil.

H_0: If children are diagnosed with Narcolepsy, then no physiological nor growth effect will be observed.

Methods:

Participants

Adolescent patients under the care of Dr. Kass at the Westchester Pulmonology and Sleep Center were filtered for diagnosis and age to collect my population. After certain limitations were put in place, the age filter was relaxed slightly in order to allow more patients to fit this age restriction. Ultimately, the range fit the notation: $9 \leq \text{Age} \leq 20$. Patients that fit the criteria were sent letters and consent forms describing the study, an Epworth Sleepiness Scale as well as a request for any available growth charts: n=16. Of the patients who fit the criteria, four patients attached growth charts with their response showing a 25% effective response rate. Of the four who responded and included legible growth charts, 25% were male (n=1) and the remaining 75% were female (n=3). There

was a mean age, of the four who included growth charts, of 15.5 years. Those who did not respond and/nor include legible growth charts also had files in the Westchester Pediatric and Sleep Medicine Center (WPSMC) that were analyzed and evaluated for possible sources of pertinent data. The mean age of this total group was 17.31 years with 25% being male (n=4) and 75% being female (n=12).

Confidentiality

A confidentiality agreement was signed stating that under no circumstances will any of the information inside patient files be disclosed at any time. All participants will be required to fill out a consent letter and a disclosure agreement allowing all researchers confidential access to the growth charts attached in their response. The process of confidentiality was stricter for the patients who responded with growth charts since that was extra data not contained in the WPSMC database.

Patient Consent and Forms

This research relies heavily on patient medical data including growth charts prior to diagnosis and treatment. The Westchester Pediatric Pulmonology and Sleep center in Mount Kisco, NY and the Norwalk Sleep Disorder Center in Norwalk, CT do not have access to these files and must be obtained separately though the participants. To access these records, consent letters must be issued to the patient's parents/guardians to confirm confidentiality and a reserved legal right to use their medical data for research purposes only. Patient mailing information will be used from the patient database and letters will be distributed to such location. Enclosed in the envelope will be an informational passage

similar to an abstract, outlining the basis of this research and why participation is needed, a document disclosure agreement and two copies of the Epworth sleepiness test, for before and after diagnosis evaluation. These will be delivered in a business envelope with a folded self-addressed envelope for return shipping.

After agreeing to consent, patients were asked to fill out the Epworth Sleepiness Scale as well as attach their growth charts detailing height and weight since birth. No incentives, financial or otherwise, were used to influence patient response. The participants were only advised that their participation could potentially benefit their child. The consent form made sure that all participants were aware that they would not receive compensation for their cooperation.

Epworth Sleepiness Scale

The Epworth Sleepiness scale is a primitive yet universal and effective measure of one's circadian sleep health. The premise of this scale is to assign numbers to rate the severity and/or validity of a statement regarding to the chance of falling asleep in given circumstance. An example of a statement regarding sleep might be "I fall asleep while doing homework." If this statement is particularly true the subject could choose the number three out of the maximum three to represent that he/she agrees strongly with the aforementioned statement. These values are aggregated and a final point value is found. This point value represents the severity of the subject's circadian sleep health. Two copies of this scale were administered along with the patient consent forms in each of the letters sent out to all 16 possible participants to represent values from before and after the

diagnosis and treatment of narcolepsy. This was used to establish correlation between the effectiveness of treatment and the relative benefits in terms of patient sleepiness.

Analysis (Qualitative and Quantitative)

The majority of the findings for this experiment will be contained within growth charts accessed through pediatric growth charts. These findings will be mostly qualitative due to the lack of the usual statistical nature of the graphs. Most quantitative figures will be contained within patient files and accessed through extensive searching. These figures will be generally analyzed for general trends and common patterns. Statistical analysis includes t-tests and residual tests. The data found on the growth charts will be compared to standard growth curves supplied by the Center for Disease Control (CDC).

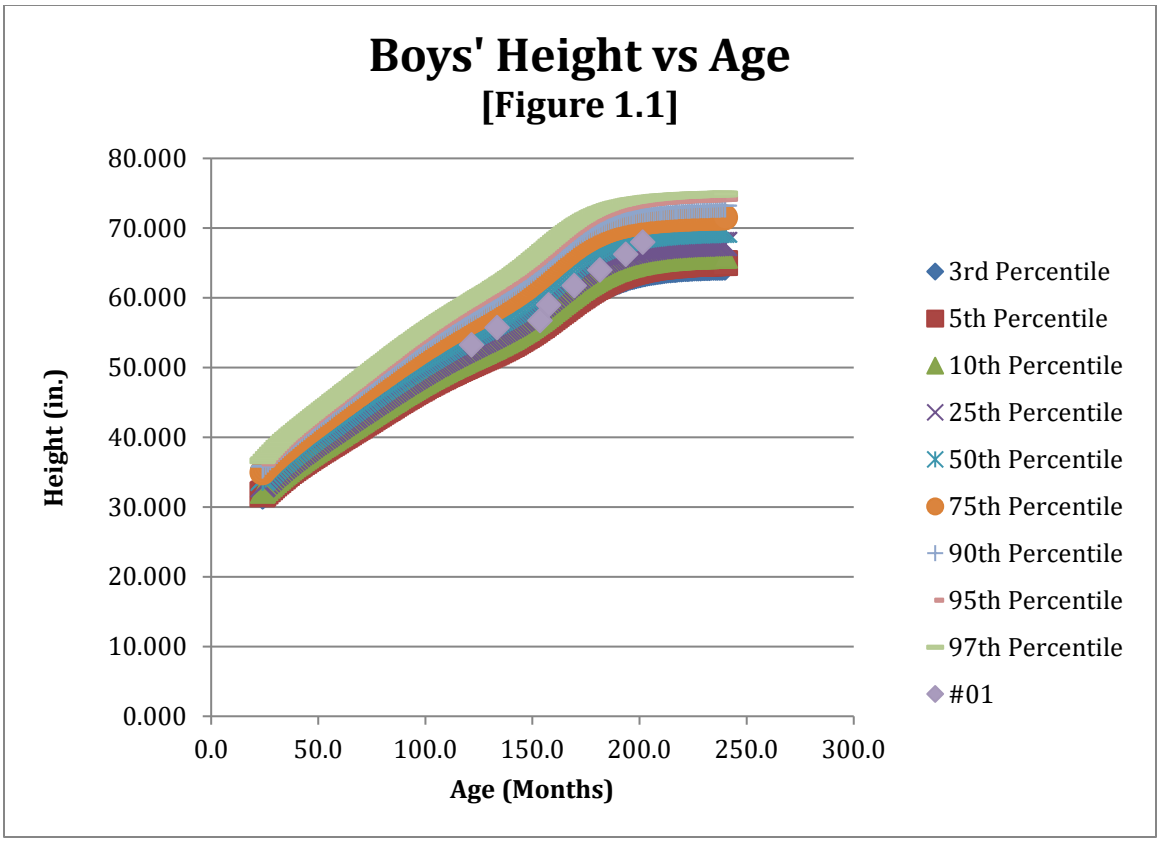
Results:

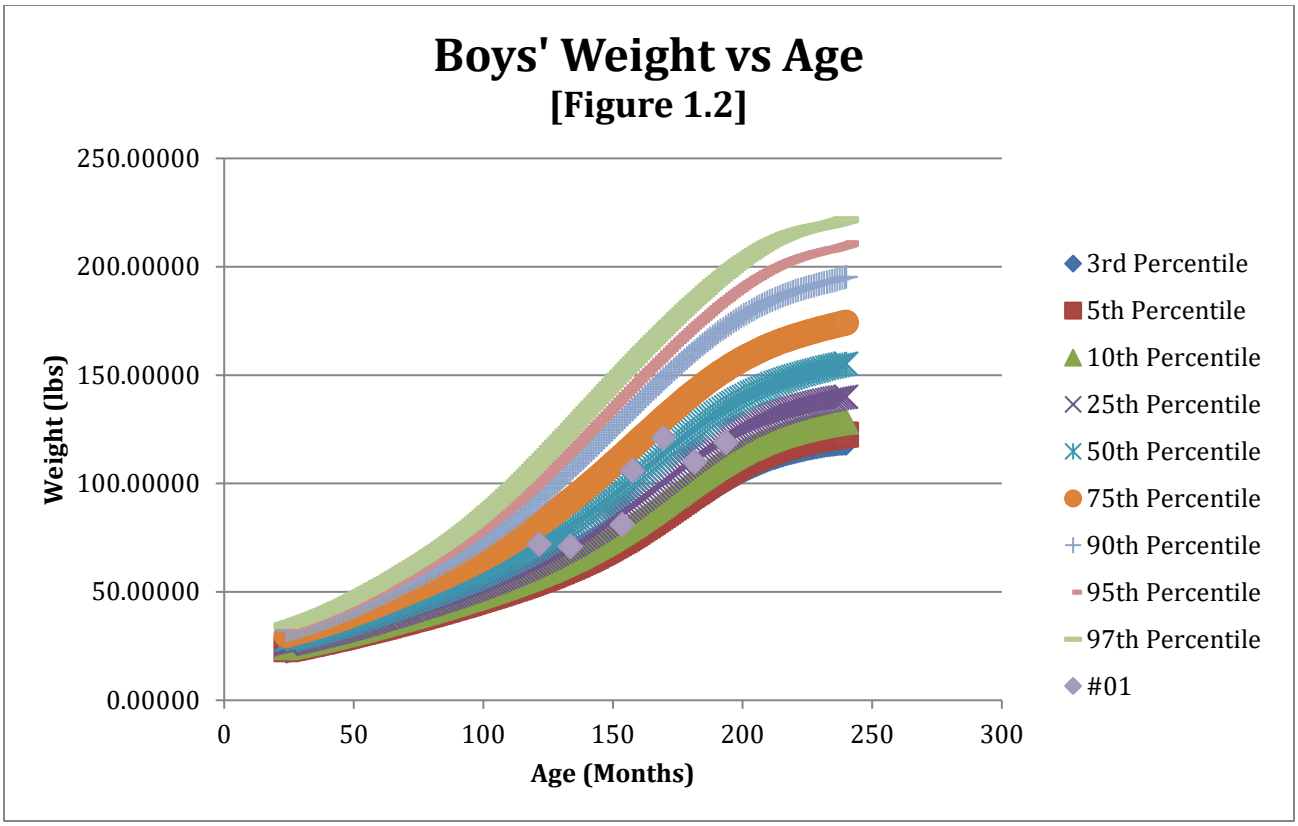
The data was collected and analyzed throughout the summer and autumn of 2015 (July 2015 – October 2015). Participants were sent out a request to attach growth charts for analysis. These charts were reviewed and inspected for noticeable trends and patterns that seem to be particularly strange. An example of a trend or pattern would be the premature stabilization of height relatively near the age of onset of narcolepsy.

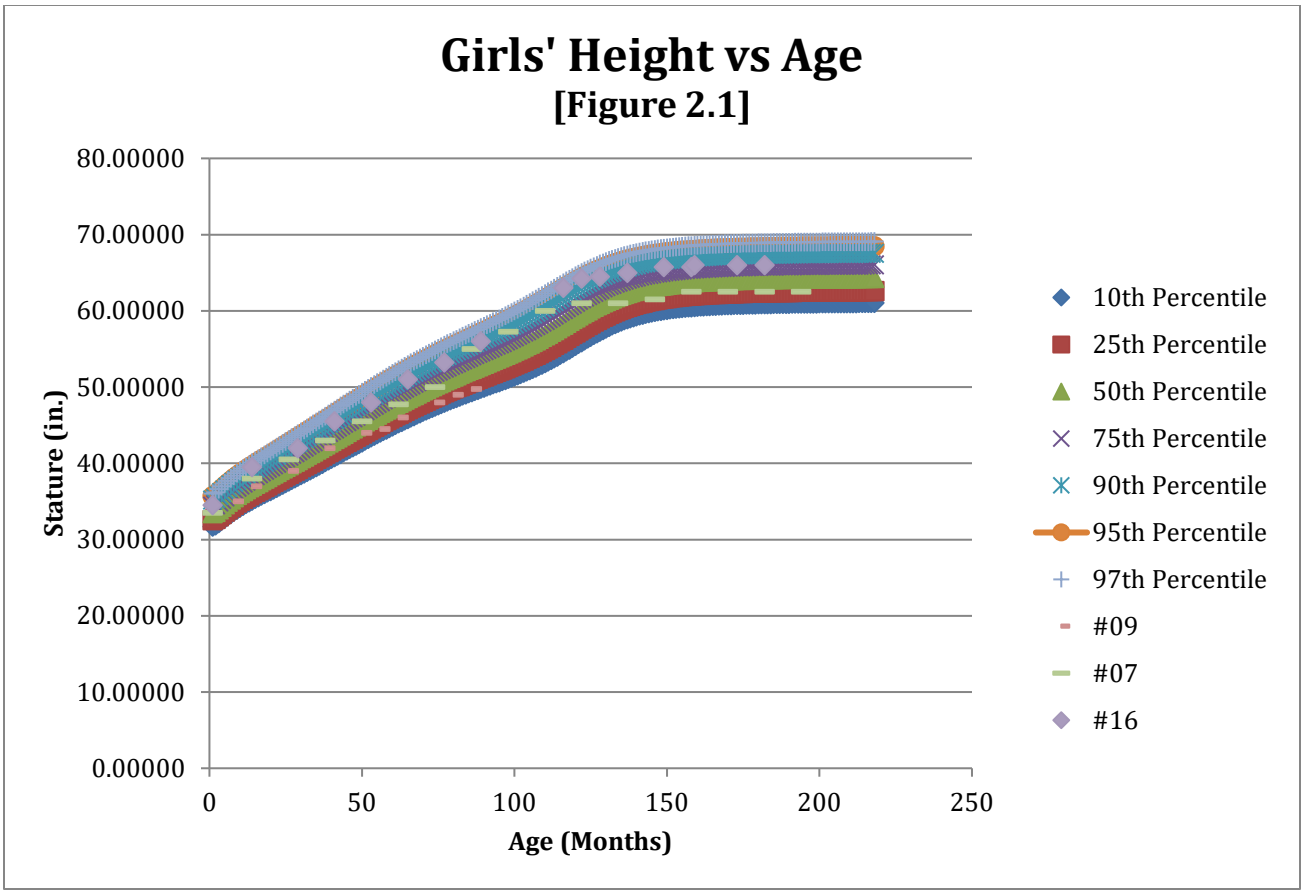
As shown in many of the following graphs, height seems to level off prematurely. During adolescence, a teenager is expected to experience a plethora of growth. Especially in girls, the height seems to flatten prematurely. In all three of the patients, specifically

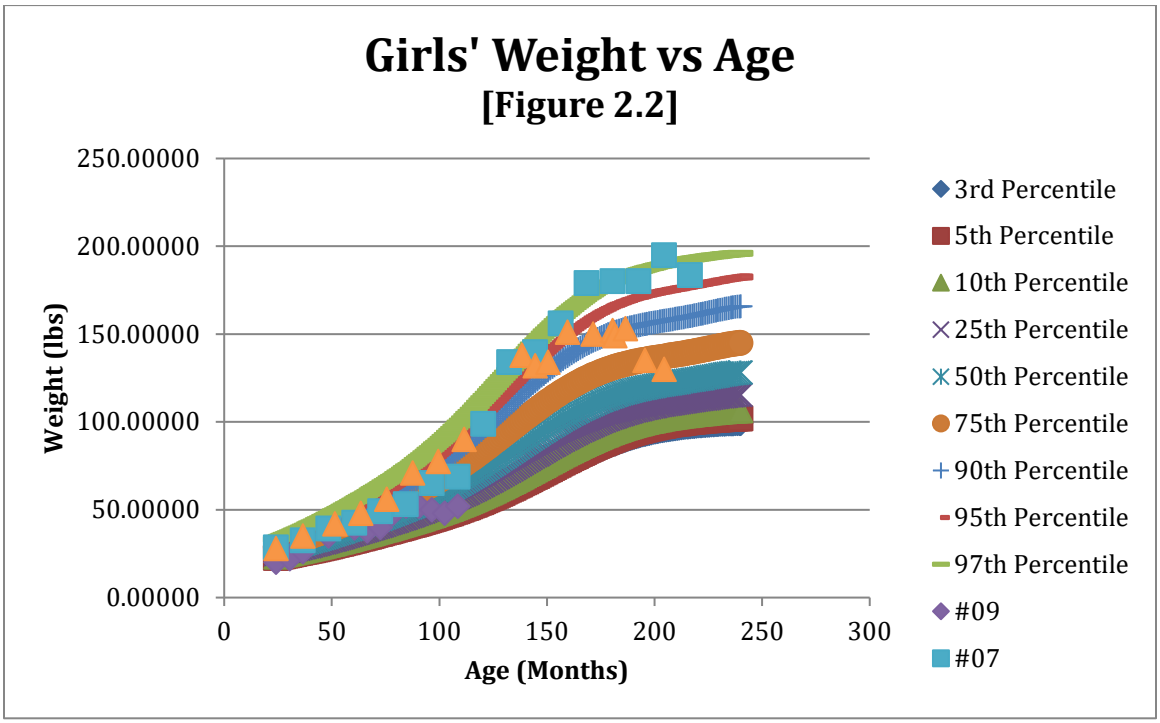
patients #07 and #16, who are in their late teens, their heights negatively cross over percentile lines. Patients #07 and #16 both experience a growth rate decrease many months, if not a few years, before they are expected to. Patient #09, who is just entering her pubescent stage, also shows signs of premature growth leveling. Patient #01, the only male who responded, did not show the obvious deviation that the girls' exhibited in height or weight.

Additionally, weight is fairly skewed in the female graphs as well. The weights seem to be quite sporadic. Even after a visual inspection of the growth charts, there was a particular chaos to the weights of narcoleptic females. There was not one individual female that displayed a constant or normal weight curve. All four displayed very chaotic and disorganized weight values throughout childhood and well into adolescence. This sort of chaos also appeared in the boys' weight curve. Both sexes were observed to rapidly gain and lose weight with no seemingly obvious correlation to their height.


Boys' Height vs Age
[Figure 1.1]
80.000
70.000
60.000
50.000
40.000
30.000
20.000
10.000
0.000
Height (in.)
0.0
50.0
100.0
150.0
200.0
250.0
300.0
Age (Months)
3rd Percentile
5th Percentile
10th Percentile
25th Percentile
50th Percentile
75th Percentile
90th Percentile
95th Percentile
97th Percentile
#01

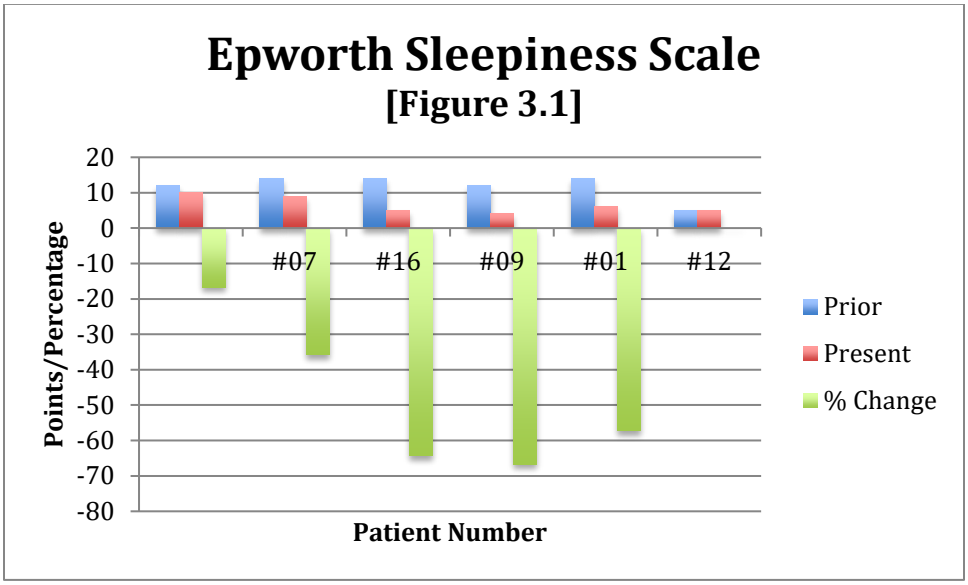

Boys' Weight vs Age
[Figure 1.2]
250.00000
200.00000
150.00000
100.00000
50.00000
0.00000
Weight (lbs)
0
50
100
150
200
250
300
Age (Months)
3rd Percentile
5th Percentile
10th Percentile
25th Percentile
50th Percentile
75th Percentile
90th Percentile
95th Percentile
97th Percentile
#01


Girls' Height vs Age
[Figure 2.1]
80.00000
70.00000
60.00000
50.00000
40.00000
30.00000
20.00000
10.00000
0.00000
Stature (in.)
0
50
100
150
200
250
Age (Months)
10th Percentile
25th Percentile
50th Percentile
75th Percentile
90th Percentile
95th Percentile
97th Percentile
#09
#07
#16


Girls' Weight vs Age
[Figure 2.2]
250.00000
200.00000
150.00000
100.00000
50.00000
0.00000
Weight (lbs)
0
50
100
150
200
250
300
Age (Months)
3rd Percentile
5th Percentile
10th Percentile
25th Percentile
50th Percentile
75th Percentile
90th Percentile
95th Percentile
97th Percentile
#09
#07

The preceding charts depict lines on growth percentiles shown in order or increasing percentiles: 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th.

The following chart depicts the scores of six patients, five of which were included in the overall study and four of those who additionally supplied growth charts. Each potential participant was asked to fill out two identical surveys. The Epworth Sleepiness Scale varied in one aspect; the participant was asked to reflect on their condition prior to diagnosis and treatment (D&T). This aspect of the study is completely anecdotal, but still holds gravitas as it provides insight into the quality of life the patients endure. After diagnosis and treatment (using Xyrem and/or Nuvigil) the patients averaged a 40.1% reduction in points from prior to D&T with a five number summary of 0,16.67,46.425,64.29 and 66.67. The data is clearly skewed left, showing that most participants experienced a larger percent reduction in their score than the mean. This data illustrates the effectiveness of the treatment on the quality of life as well as establishes a correlation between Xyrem/Nuvigil treatments with the quality of life of the patient.



Discussion and Conclusion:

After analysis of the data, two correlations have been drawn. The first, that narcolepsy in adolescents, especially in females, is strongly correlated with impaired growth and skewed weight during key developing years (as shown in figures 1.1 and 2.1). As I predicted in H_1, narcoleptic adolescents show clear signs of impaired growth. However, since the sample size was very small, the severity of narcolepsy has yet to be quantified and the growth skewing may be caused by other factors not explicitly detailed in this study, no causation can be created and the validity of this experiment must be confirmed through future research. Additionally, the claim that adolescent narcolepsy patients rapidly gain weight is not entirely true. According to figures 1.2 and 2.2, no definite claim can be made about weight in relation to narcolepsy. There is evidence to support the fact that narcolepsy may influence weight in some way, yet it cannot be deduced whether that association is positive or negative, for it is most likely a combination of the two. This uncertainty renders H_2 partially incorrect because whether or not narcolepsy directly causes rapid weight gain is not entirely supported yet some evidence exists.

The second, that using Xyrem and/or Nuvigil as treatment for narcolepsy is extremely effective in increasing the quality of life for adolescent narcoleptics. Although this may be true, there is no evidence to support the statement that these forms of treatment can reverse any impaired growth caused by narcolepsy. This renders H_3 incorrect because no

signs of restored growth are present especially not ones that are a direct result of Xyrem/Nuvigil treatment.

Of all patients, patient #07 supported H_1, H_2, and H_3, the most definitively. However, there was some proof of comorbidity found within the patient's file. This may have been a source of skewing. Likewise, narcolepsy is very frequently found to be comorbid with a variety of diseases. Whether or not this may have had an effect is, again, at the whims of future investigation.

The main source of error for this study would be the sample size, which is admittedly quite small. Another possibility for error is found within the growth charts themselves. Patient #01 submitted growth information that was written down on a piece of paper with a lack of consistency. Additionally, other charts had handwritten data on the chart. Although the validity of their doctor is not being questioned, it is important to note that this may have been the reason why the boys' height and weight did not deviate as radically as the girls' height and weight. Lastly, the final possibility for error is found within human error, which may only be ruled out through repetition.

In this study, I measured the growth effects on adolescent narcolepsy patients and found correlation between female height and adolescent narcolepsy as well as Xyrem/Nuvigil treatment and the quality of life of narcoleptic recipients. It is important to note that this study severely lacked in sample size and future research is not only suggested but also

highly encouraged to ensure validity, especially in a field where little to no prior published data exists.

Acknowledgments:

I would like to thank my parents for guiding through this process as well as persuading and encouraging me to pursue research as a high school student. Additionally, I'd like to thank both of my adult sponsors, Mr. Michael Inglis and Mrs. Annemarie O'Brien for providing support and guidance where otherwise I would be completely lost. Lastly, I would like to send my dearest and upmost gratitude to Dr. Lewis Kass for allowing me to intern with him and eventually work with him on this study.

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