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Psychosocial factors and their significance towards pain: a case study comparing monozygotic twins with AIS after spinal surgery

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PSYCHOSOCIAL FACTORS AND THEIR SIGNIFICANCE TOWARDS PAIN: A CASE STUDY COMPARING MONOZYGOTIC TWINS WITH AIS AFTER SPINAL SURGERY

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ABSTRACT

Introduction: Adolescent Idiopathic Scoliosis (AIS) is one of the most common spinal abnormalities in children, affecting 2% to 3% of adolescents in the United States. Its cause remains unclear. Many previous studies conclude that AIS may be caused by a combination of genetic and environmental factors, with very few consistencies. Severe scoliosis is usually treated with corrective surgery, and the etiology of post-surgical pain is even more unclear and has the opportunity to affect the patient well into adulthood.

Study Aims: By following a monozygotic twin pair with identical DNA, our retrospective case study can control for genetic disposition, and can look toward other possible causes for the pain the patients experienced. This study attempts to shed light on the complexities of AIS and pain with a focus on environmental and psychosocial factors.

Case Presentation: We present a single pair of monozygotic twins treated for AIS with comparable spinal fusion surgeries performed at a large northeast urban children's hospital. Twin A and Twin B were initially treated with a brace for their scoliosis. Despite bracing, their curves progressed and warranted spinal fusion, with Twin A having a Cobb angle of 53°, and Twin B with 50°. The surgery was conducted simultaneously at the age of 13 by two different orthopedic surgeons. At age 7.5, Twin B was treated for Ebstein's anomaly of the tricuspid valve and significant dysrhythmias.

Methods: After the patients were discharged, a comprehensive retrospective chart review of the patients' pre-op, inpatient, and post-op pain and drug regiment was conducted. The patients were also asked to note their pain as they recovered after discharge. The patients and their mother completed self-report measures of multiple psychosocial variables both before and after surgery through REDCap. A Quantitative Sensory Test (QST) was also performed by the patients to assess their sensory sensitivity and pain thresholds. Mechanical, pressure, and thermal scores were obtained with the use of von Frey hairs, a pressure Algometer, and a Thermode. The QST was administered on the patients' palm/ thenar eminence (distant non-surgical site), and on their lower back (surgical site). The QST results were compared to a previous study's median cohort data, to discern if the patients presented hyper- or hyposensitivity for that particular test.

Results: Due to the limitations of case studies, the results presented here should be considered strictly preliminary. Twin B experienced more significant pain during both the acute and chronic recovery phases after surgery, and showed lower sensitivities during most pre-op QST trials. Twin B also scored markedly higher on a number of sub-variables in the psychosocial surveys. A notable correlation was the parent protective measure, indicating that the mother may have been more protective of Twin B.

Conclusions: What is unique to this study is that age, gender, Cobb angle, fusion length, and genetic disposition are all controlled for, allowing us to analyze the patients based on other risk factors. Twin B shows consistently higher pain scores while in the hospital as well as while recovering at home. The parent self-report measures support these findings, showing a slight bias in favor of Twin B in regards to protectiveness, which also

coincides with large-scale studies. Although preliminary, it is important not to underestimate the role environmental and psychosocial factors play in post-surgical pain.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ARCS ..... Adult Responses to Children's Symptoms

AIS ..... Adolescent Idiopathic Scoliosis

BCH ..... Boston Children's Hospital

cDI ..... Children's Depression Inventory

cFDI ..... Child Functional Disability Inventory

cFoPQ ..... Child Fear of Pain Questionnaire

cPCS ..... Child Pain Catastrophizing Scale

FOPQ ..... Fear of Pain Questionnaire

IRB ..... Institutional Review Board

MASC ..... Multidimensional Anxiety Scale for Children

NRS ..... Numeric Rating Scale

pFoPQ ..... Parent Fear of Pain Questionnaire

pPCS ..... Parent Pain Catastrophizing Scale

PO ..... *per os* (by mouth, orally)

PRN ..... *pro re nata* (as needed)

PT ..... Physical Therapy

QST ..... Quantitative Sensory Testing

REDCap ..... Research Electronic Data Capture

SPSS ..... Statistical Package for the Social Sciences

TV ..... Tricuspid Valve

INTRODUCTION

Twin pairs can be categorized as being either identical or fraternal, and the implications of both differ greatly. Fraternal, or dizygotic, twins, share the same date of birth and little else. Fraternal twins are two separate fertilized eggs that gestate together in their mother's womb to term, and are as genetically similar as any other biological siblings. Identical, or monozygotic twins, originated from a single fertilized egg and share the exact same DNA sequence (Flais, 2009). Identical twins have matching genetic sequences, and with that, duplicate genetic dispositions to hereditable diseases. Exploiting this characteristic, monozygotic twins have been used to discern genetic influences on the penetrance of complex diseases.

The term "identical twins" was coined because it was historically believed that identical twins were in fact genetically identical, but new information has since changed how "identical" monozygotic twins actually are. The environment plays a significant part in a person's development, and its role in causing dissimilarities between monozygotic twins should not be underestimated (Zwijnenburg et al., 2010). Although identical twins start off with identical DNA sequences at birth, post-zygotic changes to gene expression could cause phenotypic changes between monozygotic twins. A PubMed search yields many studies publishing their findings of identical twins with discordant pathologies (Burri et al., 2015, Dempster et al., 2014). With genetic make-up being initially identical, post-zygotic changes are the scientific community's paramount argument for the variance of disease found in monozygotic twins (Grauers et al., 2012).

This case study highlights two complex conditions: Adolescent Idiopathic Scoliosis (AIS), and pain after invasive surgery. This study aims to shed light upon AIS and post-surgical pain following spinal fusion surgery, one of the treatment options available to AIS patients. The heritability of AIS has been shown to be incredibly intricate, and pain is such an objective aspect of physiology that it too eludes concrete etiology. Taking advantage of the genetic similarities of identical twins, this case study hopes to provide a preliminary look at how genetic, environmental, and psychosocial aspects contribute to the etiology of AIS and pain following corrective surgery. In presenting an identical twin pair, this study controls for demographic (age, sex, socioeconomic class) and key surgical variables (Cobb angle, fusion length, surgery length). We hypothesized that higher sensory functioning and psychosocial measures would contribute to a poorer improvement of pain during recovery after surgery.

Adolescent Idiopathic Scoliosis

Scoliosis is not a new disease; it is believed to have been first described by Hippocrates (*scolios* – crooked or curved) as an abnormal spinal curvature (Vasiliadis et al., 2009). The diagnosis Idiopathic Scoliosis was not introduced until the 20th century by Kleinberg, indicative of patients whose spinal deformity cannot be explained. Currently, the scientific community believes Adolescent Idiopathic Scoliosis can be attributable to a multitude of environmental and genetic risk factors, with very few consistencies (Negrini et al., 2012). Adolescent Idiopathic Scoliosis (AIS) is the most common spinal abnormality in children, with the literature reporting statistics ranging from 1% to 12%

(and usually 2%-3%) worldwide (Negrini et al., 2012). Although early scoliosis diagnoses occur similarly in boys and girls, progression of AIS occurs more frequently in females (5:1), with severe AIS being 7 times more prevalent in girls than boys (Konieczny et al., 2012).

A definitive etiology of AIS has alluded physicians, and many large-scale studies attribute the disease to a multifactorial culmination of environmental and genetic factors. Studies consistently associate family history and monozygosity with higher AIS prevalence vs the general population (Andersen et al., 2007), and new findings continue to define potential gene mutations responsible for AIS (Aulisa et al., 2007). Dr. Grauers utilized the world's largest twin database to assess concordance of AIS among mono- and dizygotic twins, and could only attribute 40% of the liability to develop AIS to genetic disposition (Grauers et al., 2012).

Diagnoses of scoliosis are determined based on spinal curve, and many physicians utilize the Cobb angle – the largest degree of tilt between two vertebrae – because it is the most consistent statistic for spinal deformity (Keynan et al., 2006). The most common cut-off diagnosis for AIS is a Cobb angle above 10° (Weinstein et al., 2008), with about 10% of diagnosed cases of AIS requiring nonsurgical bracing treatment (*see Table 1*). Only about 0.1%-0.3% of AIS patients will undergo corrective spinal surgery (Negrini et al., 2012). If a patient's Cobb angle continues to deteriorate despite bracing or other interventions, a physician may recommend corrective surgery based on their skeletal maturity. The surgery involves correcting the patient's spinal deformity through the use of screws and a titanium rod to prevent further progression of the scoliosis (Logue, 1994).

The scientific evidence defending the use of bracing is inconsistent, as successful bracing treatment can be contingent upon a number of aspects, including dosage (hours/ day), patient compliance, and brace type (Landauer et al., 2003). If used, the main goal of bracing is to slow the progression of scoliosis until skeletal maturity is achieved, with emphasis on keeping a patient's Cobb angle stable or to improve it over time. A severe scoliotic curve has the potential to affect critical life processes such as breathing and heart function later in adult life (Weinstein et al., 2008, Chan et al., 2013), and many physicians will recommend corrective surgery to severe patients.

Posterior Spinal Fusion Surgery for AIS

Spinal fusion surgery is an invasive surgery with inherent risks, including persistent post-surgical pain; virtually all physicians will attempt to brace a patient before resorting to spinal fusion (Sieberg et al., 2013, Andersen et al., 2006, Aurori et al., 1985). In many cases the high pain experienced by adolescents after surgery is transient and will decline expectedly to normal levels after discharge. Other times, however, the pain can persist for months or even years after surgery, causing problems in everyday functioning (Sieberg et al., 2013, Andersen et al., 2006). Identifying risk factors that influence recovery after spinal fusion surgery therefore has important clinical implications.

Post-surgical pain, especially in adolescent patients, is a grossly neglected topic in the medical field, and can bring about long term effects in patients into adulthood (Kissin et al., 2012, Page et al., 2012). With approximately 6 million children and adolescents undergoing surgery each year in the United States, research into the role of pediatric post-

surgical pain is an important topic that is given little attention (Ahn et al., 2012). If a child experiences acute post-surgical pain and it is not properly addressed, the patient is at a higher risk of emotional burdens and chronic pain later in life (Sieberg et al., 2013). By following a pair of identical twins concordant for AIS along their recovery from surgery, this case study hopes to dissect characteristics that may put a patient at increased risk to develop long-term post-surgical pain.

Post-surgical pain for AIS patients is a crucially underserved topic. Only in the past several years has pain even been routinely incorporated into pediatric spinal fusion surgery notes (Landman et al., 2011). With so many underlying factors contributing to pain, looking into psychosocial factors and quantitative sensory testing were attractive aspects when designing this case study. These tests will help quantify the cognitive and physiological influences upon pain, and will provide a means of analysis for the pain reported by the presented case. Research into the genetic, environmental, and psychosocial implications of chronic post-surgical pain could lead the way towards a means of predicting patients who are high risk, and persuade physicians to seek alternate treatment.

Table 1. Classifications of AIS via Age/ Cobb angle. Table adapted from Negrini et al.

Chronological		Angular		
Age at diagnosis (years.months)		Cobb degrees		
Infantile	0-2.11	Low	Low	5-15
Juvenile	3-9.11		Low to moderate	16-24
Adolescent	10-17.11	Moderate	Moderate	25-34
Adult	18-		Moderate to severe	35-44
		Severe		45-59
		Very severe		60 or more

METHODS

All QST trials, REDCap surveys, and access to patient medical records were approved by the IRB, certifying that the study, "protects the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Institution (Boston Children's Hospital, Boston, MA)" (IRB Mission, Chapter 2). The following subsections have been adapted from Dr. Christine Sieberg, Ph.D.'s protocol for the study on, "*Biopsychosocial predictors of the development of persistent postsurgical pain in adolescents with idiopathic scoliosis undergoing spinal fusion surgery"* (IRB-00000428-17). Recruitment for this retrospective case study was through this IRB protocol. Patient assent and written informed parental consent was provided during recruitment.

Recruitment

The patients in this case study were selectively chosen from a large recruitment initiative under Dr. Christine Sieberg's study protocol IRB-00000428 at Boston Children's Hospital (BCH) in 2014. Adolescents aged 10-17 diagnosed with AIS planning to undergo spinal fusion surgery or currently receiving nonsurgical bracing treatment met our inclusion criteria for recruitment. Those who present with co-morbid diseases that result in pain (e.g., rheumatoid arthritis, Sickle Cell), do not have proficiency in English, have severe cognitive impairment, or have medical co-morbidities that may confound pain were excluded from the study. Potential participants were

identified before their pre-operative appointment using BCH's online medical record and scheduling software, PowerChart (Cerner, UK). By screening an orthopedic surgeon's clinic notes, a database of patients who met our inclusion criteria was compiled. Patients who passed preliminary eligibility were mailed flyers illustrating the study and its aims and significance. Upon receipt of the flyer, the patient and their families may opt-out of the study by mailing back the included opt-out card. About a week after the postmark date of the flyer, these eligible patients were contacted by telephone to see if they had any follow-up questions after reading the flyer, and to inquire whether or not they would be interested in participating. Those who expressed interest in the study would give their verbal consent, and would be approached during their next hospital appointment or pre-op date to obtain formal written consent. Patients enrolled in the surgical arm of the study (including Twin A and Twin B of this case study) would be asked to come in for a QST before their scheduled spinal fusion, which usually was their pre-op date, and for a 6-month follow-up QST. Patients who are currently being treated with a brace can come in at any time before their bracing treatment was discontinued. At the conclusion of their QST, study participants are compensated with a 25$ Gift Card from American Express. At the time of this write-up, Twin A and Twin B had completed their pre-op QST, and were soon due for their six month post-op QST. Both visits would be compensated with a $25 gift card as spelled out in the study protocol.

Case Study Recruitment

While screening possible study participants in PowerChart, Twin B's orthopedic note revealed a twin sister also indicating progressive AIS. When approached over the phone, both patients and their parents expressed interest to join the study. Twin A and Twin B both had Cobb angles at or above 50°, and were planning to undergo spinal fusion surgery at the recommendation of their orthopedic surgeon.

REDCap Surveys

After Twin A and Twin B were recruited and gave verbal consent, the patients and their parents were asked to complete the following validated psychological, pain, and disability self-report questionnaires: the Multidimensional Anxiety Scale for Children (MASC) (March et al., 1997, Baldwin et al., 2007); the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995, Osman et al., 1997); the Child Fear of Pain Questionnaire (cFoPQ) (Simons et al., 2011); the child Functional Disability Inventory (cFDI) (Walker et al., 1991, Claar et al., 2006); the child Depression Inventory (cDI) (Kovacs, 1985, Allgaier et al., 2012); and the Adult Responses to Children's Symptoms (ARCS) questionnaire (Walker et al., 2006, Claar et al., 2010, Noel et al., 2015). For surgical patients (including Twin A and Twin B of this case study), questionnaires are to be completed by the study participants and their parents before surgery, 1-month post-surgery, 6-month post-surgery, and at 1-year follow-up. At the time of this write-up, the pre-op and 1-month post-surgery measures were completed. For the purposes of this case study, the parent measures were filled out exclusively by the mother for consistency.

The tool used to administer the self-report measures, REDCap (Research Electronic Data Capture) (Harris et al., 2009), is a secure, web-based application designed to support data capture for research studies. The application provides: an intuitive interface for validated data entry; extensive audit trails for data manipulation; automated, seamless export of data into common statistical analysis software; and procedures for external data import. Study data for this case study were collected, managed, and exported using REDCap electronic data capture tools hosted at Boston Children's Hospital. As with the larger study with Dr. Sieberg, Twin A and Twin B were compensated with a $10 Gift Card from American Express at the completion of each survey.

The MASC (March et al., 1997) is a 39-item questionnaire that assesses four sources of anxiety in children. Children are asked to rate the extent to which each of the statements are true about them on a scale from 0 (never true) to 3 (often true), with high scores indicating higher levels of anxiety. The test assesses physical symptoms (either somatic or tension/ restlessness), harm avoidance (either anxiety or perfectionism), social anxiety (either humiliation or performance anxiety), and panic/ separation anxiety. In addition to the subscales, T-score totals are computed from the MASC total and subscale raw data, with clinical significance falling outside 1 SD from the normal range. For females aged 12-15 years old, this range is 44.23 +/- 14.44 (March et al., 1997). Strong validity and reliability data has been produced by multiple studies (March et al., 1997, Rynn et al., 2006). While a parent iteration of the measure exists, only the child self-assessment was administered in our study.

The PCS (Sullivan et al., 1995) is a 13-question survey that evaluates three dimensions of catastrophic thinking. In this context, catastrophic thinking is defined as an exaggerated negative mental state brought about during an actual or anticipated painful experience. The three subscales assess rumination, magnification, and helplessness. Dr. Sullivan describes each subscale with a quote from the perspective of the patient. The magnification dimension of pain catastrophizing relates to how a patient may "worry that something bad may happen." The helplessness aspect of the PCS refers to pain that is "awful and I feel that it overwhelms me." The rumination subscale may in fact be the most directly relatable to current pain, and represents the dialog, "I cannot stop thinking about how much it hurts". The PCS asks participants to reflect upon painful experiences, and to indicate to what degree each prompt applies to their pain. Each item is answered with a 5-point scale from 0-4, with 0 indicating not at all and 4 indicating all the time. The PCS yields both a total score and the three subscales, with higher scores indicating higher levels of catastrophic mindsets (ranging from 0-54). Research indicates that a total cPCS score of 15+ represents a clinically significant level of pain catastrophizing. For the parent measure, clinically significant levels of catastrophic thinking were associated with pPCS scores above 23 (Pielech et al., 2014).

The FOPQ (Simons et al., 2011) assesses pain-related fear in children with chronic pain. Initial pilot studies were extensive, and showed strong internal consistencies between the pFoPQ and cFoPQ across both subscale and total scores. While many of the items were taken from previously-validated questionnaires, some questions and subscales were eventually dropped. The final measure used in our study consisted of

24 prompts with two subscales: fear of pain, and avoidance of activities. Clinical significant "cut-offs" can also be evaluated from the total cFoPQ score, with a range of 35-50 indicating moderate fear of pain, and scores ranging 51-96 denoting high fear of pain (Simons et al., 2011). Only the child-form was administered for this case study.

The cFDI (Walker et al., 1991) is a 15-item functional assessment of physical and psychosocial limitations in children and adolescents due to disease or illness. The measure has been used in multiple studies to analyze acute and chronic pain in a number of pediatric conditions, including recurrent abdominal pain, headache, and fibromyalgia. In 2005, the cFDI was validated as a measure for psychometric properties of disability in children with chronic abdominal pain (Claar et al., 2006). This recent justification using a large sample size strengthens the analysis this case study wishes to discuss. The questionnaire itself refers only to activities over the past 2 weeks. The participant is tasked to rate their ability to perform each activity (i.e., "walking to the bathroom", "being at school all day", and "watching TV") ranging from "impossible" to "no trouble". The parallel parent measure rates the extent of their child's disability during the last 2 weeks, but was not administered for our case study. A total cFDI score is computed, with higher scores being associated with higher disability. Child-form scores above 12 indicate a clinically significant level of disability, and total child FDI scores over 30 indicate severe disability (Flowers et al., 2011).

The cDI (Kovacs, 1985) is a 27 item self-report measure assessing cognitive and behavioral aspects of depressive symptoms in children over the previous two weeks. Each of the prompts represent different depressive symptoms, and the participant is asked

to rate each item on a 3-point scale. Higher scores indicate higher levels of depression, and clinical cut-offs are commonly used to screen adolescents for possible depressive moods. For a normative demographic representative of Twin A and Twin B, the appropriate clinical cut-off score is above 12 (Allgaier et al., 2012). Although the cDI can also assess various subscales related to sources of depression, only total cDI scores were calculated for this case study.

The ARCS (Walker et al., 2006) is a parent self-report measure of 29 items originally developed to assess parent's responses to their children's chronic abdominal pain, and has since been validated for other pediatric conditions (Claar et al., 2010). The questionnaire includes three subscales: parental protectiveness, minimization of pain, and encouraging responses. The question-stem for every prompt is, "When your child has pain, how often do you …?" Responses are rated on a 5-point scale ranging from never (0), to always (4). Subscale scores are a computed mean for items associated with each subscale. The Protect subscale refers to protective parent behavior such as giving their child special attention or limiting their normal activities. The Minimize subscale rates the parent discounting or criticizing their child's pain as excessive. The Encourage subscale essentially foils the protect dimension, and assesses the parent encouraging their child to still engage in activities. For the purposes of this case study, we only looked at the Minimize and Protect subscales.

The REDCap data was initially compiled into an Excel spreadsheet (Microsoft, 2013), and was exported into SPSS (IBM, 2013) for subscale computation and

descriptive analysis. Syntax scripts were designed to compute subscale analysis from the REDCap survey data to ensure accurate arithmetic between both patients.

QST – Quantitative Sensory Testing

With lower back pain being a hallmark consequence of spinal fusion surgery, our case study needed a way to objectively gauge pain perception in our patients. Quantitative Sensory Testing (QST) has been used in the past as a non-invasive way to assess underlying mechanisms responsible for changes in pain sensitivity. For our case study, we used a computer-assisted QST apparatus to test mechanical, pressure, and thermal detection and pain thresholds. Because the patients will need to interact verbally with the QST operator during the test, it is not completely objective. However, by adhering to a validated script for each aspect of the sensory test, we attempted to remove possible context biases of how and when the patients respond.

Light Touch (LTDT) and Pain Detection Thresholds (PDT)

To test our patients' detection and pain thresholds to mechanical stimuli, we used von Frey monofilaments (von Frey Semmes-Weinstein monofilaments, Stoelting, IL). When applied to the skin perpendicularly, these blunt-ended probes will bend against the skin, exerting a calibrated and reproducible force to the sensory area. The kit used during our QST trials included 20 nylon von Frey hairs of increasing diameter. The kit's 20 filaments are calibrated along a logarithmic scale from 0.008 to 300g (0.08 to 2943 mN) of force, within a 5% range of error. The von Frey hairs themselves are numbered 1.65 to

6.65, representing the log-10 of the mg force. During the QST, the von Frey hairs were placed at a non-surgical control site (palm below the thumb, the thenar eminence), and on the surgical site (lower back over the spine).

In the case of the LTDT test, monofilaments were applied in increasing order until the patient was able to detect it. Starting from the finest von Frey hair, the QST operator would apply the monofilament three times on the sensory area, with a ten second pause between successive levels to avoid temporal summation (increased sensitivity). The monofilament was applied to the skin perpendicularly with uniform force until the nylon bent, and held against the skin for approximately one second. The patient is asked to report when they are able to detect any sensation on the target sensory area. In order to obtain a positive LTDT for the patient, the participant must have been able to detect the stimulus in at least two of the three trials with the same von Frey hair. To remove bias from the patient, they were asked to keep their eyes closed for the entirety of the test, and are unaware when the hair will be applied to the skin. At the start of each trial, the patient is reminded to give a clear verbal signal when a stimulus was detected.

After touch detection level is calculated, the QST operator will continue on with successive von Frey hairs, this time instructing the patient to report when the sensation from the monofilament is no longer perceived as a touch and is more like a prick. Once a pain threshold is reached, the mechanical portion of the QST is completed (Keizer et al., 2007).

Pressure Pain Threshold (PPT)

For reporting pressure thresholds, we used an electronic pressure algometer (Somedic, Sweden). Pressure algometry is a commonly used method to test static mechanical pressure sensations in the skin and in deep tissues. The pressure algometer used in our study delivers a quantifiable pressure through a flat, rubberized plate pressed against the skin. The hand-held instrument is rectangular shaped with a detector rod at the top. The tip is a pressure-sensitive strain gauge connected to a pressure transducer built into the algometer's handle, covered by a 0.5 cm^2 circular probe. The probe tip is rubberized and covered with a soft polypropylene disk to prevent injury to the skin. As the QST operator applies the algometer to the patient's skin perpendicularly, the pressure is transduced, amplified, and converted to a digital reading that is reported on the LCD screen. The QST operator applies slowly increasing force against the skin, at a rate of roughly 1N/ sec. The patient will have their eyes closed during the test, and are asked to immediately express when the pressure becomes uncomfortable/ painful. When the QST operator is so alerted, they will remove the algometer from the skin, removing with it the pressure exerted on the patient. The operator will note the algometer's LCD, which will display the highest pressure reached (in Newtons) before the trial was ended (Brennum et al., 1989). This process is repeated three times, with 20 seconds of rest between successive trials to prevent increased sensitivity and irritation to the skin. For the purposes of this case study, the mean measurement of the three trials is reported for both the surgical and non-surgical control sites.

Thermal Detection and Pain Thresholds

The last component of the QST is the thermal testing. Using a Medoc TSA-2001 device (Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel) connected via USB to a mobile computer, we are able to determine the patient's thermal detection and pain threshold levels. At the start of the thermal trials, the patient is shown the thermode. Appearing like a black block with a Velcro fabric strap, the Peltier thermode is controlled by the Medoc processor and utilizes a water reservoir and fluid current to uniformly change temperature. Using the Velcro strap, the active surface of the thermode is securely fastened to the skin testing site, either the control region or the surgical site. The QST operator will then load the Medoc TSA-II NeuroSensory Analyzer software – the component controlling the thermode – and instruct the subject with how to proceed with the thermal sensory test. The subject will have their eyes closed to remove bias alike the previous trials, but the participant will instead be communicating with the computer system. The patient is given a corded computer mouse and is instructed to press any key on the mouse when they detect a change in temperature (in the case of the detection trials), or when the temperature change reaches a point that it is so uncomfortable that they want it removed (in the case of the pain threshold tests). Halting the stimulus with the mouse button will cause the thermode to rapidly return to baseline (at a rate of 10°C/sec), and the computer system to record the temperature reached.

At the start of every trial, the thermode is zeroed to baseline: 32°C (room temperature). The max/ min temperature range set for the thermode for all tests is 0°-50°C. The ranges were set with safety in mind, to prevent tissue injury from participation

in the QST. The thermode is programmed to change temperature from baseline at a rate of 1°C/ sec for the thermal detection tests, and 1.5°C/ sec for the thermal pain threshold tests.

The format of the thermal detection test is a continuous train of four trials with an inter-stimulus interval of 6 seconds for the cool and warm detection tests, and as a train of three stimuli 10-sec apart for the cold and hot pain detection tests. The means of the multiple trials for each test were calculated and reported as the thermal thresholds for Twin A and Twin B (Meier et al., 2007). Detection scores were obtained for both the surgical site (lower back on the spine), and at a non-surgical control site (palm at the base of the thumb, the thenar eminence).

Retrospective Chart Review

Following their discharge from the hospital, a thorough retrospective chart review of Twin A and Twin B was performed, taking specific note of analgesic use and prior surgeries. Among the variables highlighted during Twin A and Twin B's postoperative hospital stay were: self-identified pain levels each day during physical therapy (PT); detailed surgical notes from the spinal fusion; daily PRN and Rx medications for pain management (with emphasis on reported doses); and general demographic information. Pre-operative pain was measured during the QST performed on the patients' pre-op date (the day preceding surgery). Post-operative inpatient pain ratings were assessed during the patients' physical therapy sessions. Acute phase pain reporting after discharge was reported by the patients themselves as a monthly pain diary. These data points were

gathered to provide additional insights into Twin A and Twin B's REDCap and QST scores.

Pain Reporting

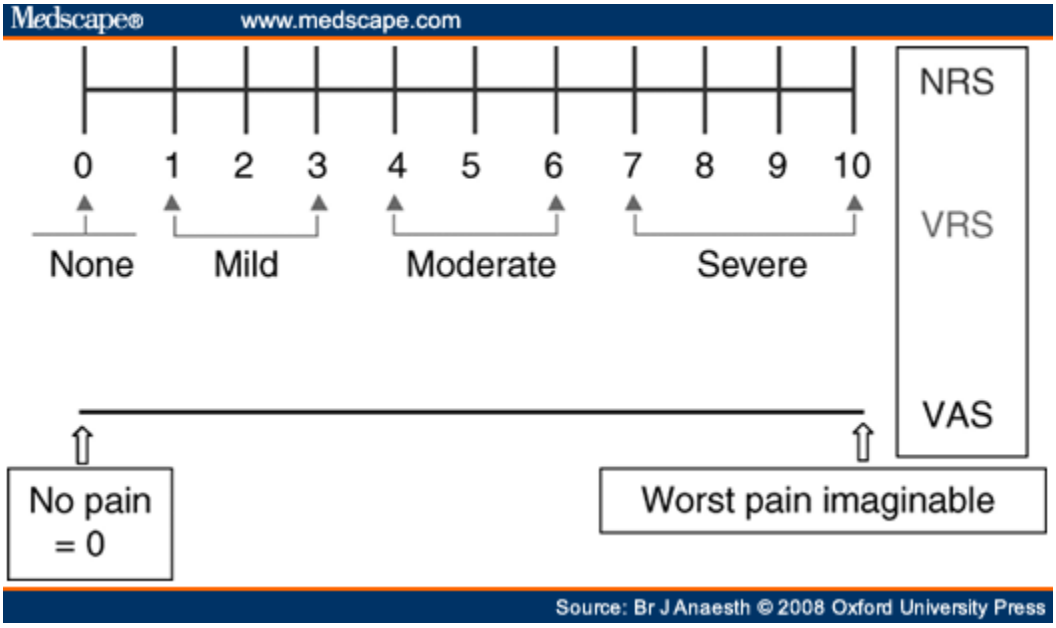

Figure 1. NRS-11 (Numeric Rating Scale). Figure taken from Oxford University Press, 2008.

Pain was an ideal statistic to keep in mind for our case study because it is an important but poorly understood topic, and is a significant indication for patients suffering from AIS. While the physiology of pain through sensory nerve firing has been discovered, accurate data collection could prove troublesome. When reporting pain from patients of any age, social, cultural, cognitive and contextual factors may confound results (von Baeyer et al., 2009). Reporting pain accurately and objectively is a difficult endeavor in the medical community, and this undoubtedly holds true for adolescents. The

most well-known way to report pain is on a scale from zero to ten, and in the medical community it is termed the NRS-11 *(see Figure 1).*

For our case study, data on pain-reporting relied on inpatient hospital staff during recovery. After the spinal surgery, Twin A and Twin B were interviewed by hospital staff from multiple departments to rate their pain along the NRS-11. A medical standard long used with adult patients, the NRS is an 11-point numeric scale ranging from no pain (0), to the worst pain imaginable (10) (von Baeyer et al., 2009). Current literature supports the validity of the NRS-11 given verbally to report pain in adolescent patients older than eight. In the interest of consistency and reliability, only the pain ratings taken during the physical therapy sessions were used for inpatient pain analysis.

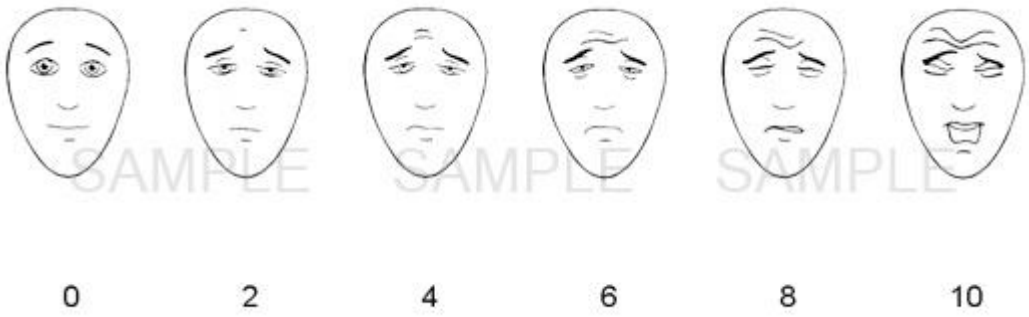

Figure 2. Faces Pain Scale – Revised (FPS-R). For the FPS-R, each expression represents two integers along the NRS-11. Figure taken with permission from ©2001, International Association for the Study of Pain.

During the QST, data on typical, highest, and pre-operative pain was reported using the FPS-R (*Figure 2*), a more accepted self-report of pain for children. The original Faces Pain Scale (FPS) (*Figure 3*) uses sketched faces of increasing expressions of pain intensity (starting from a neutral, non-smiling face), and was developed specifically for children. In comparison to other pain scales, the FPS alleviates the opportunity for bias

from context and question stem/ anchors affecting accurate pain reporting in adolescent patients. The revised iteration of the FPS scale uses 6 faces instead of 7, and better correlates with the widely accepted NRS-11 metric. Several studies have shown validity and reproducibility in adolescent pain reporting between the NRS-11 and the FPS-R (Tomlinson et al., 2010, von Baeyer et al., 2009, Miro et al., 2009). *Figure 3* illustrates how responses from the FPS cannot easily be translated to the NRS-11, because unbalanced weights are given to some expressions over others when superimposed. The figure also includes the visual descriptor scale (VDS) that categorizes the NRS-11 into groups, but was not used in this study.

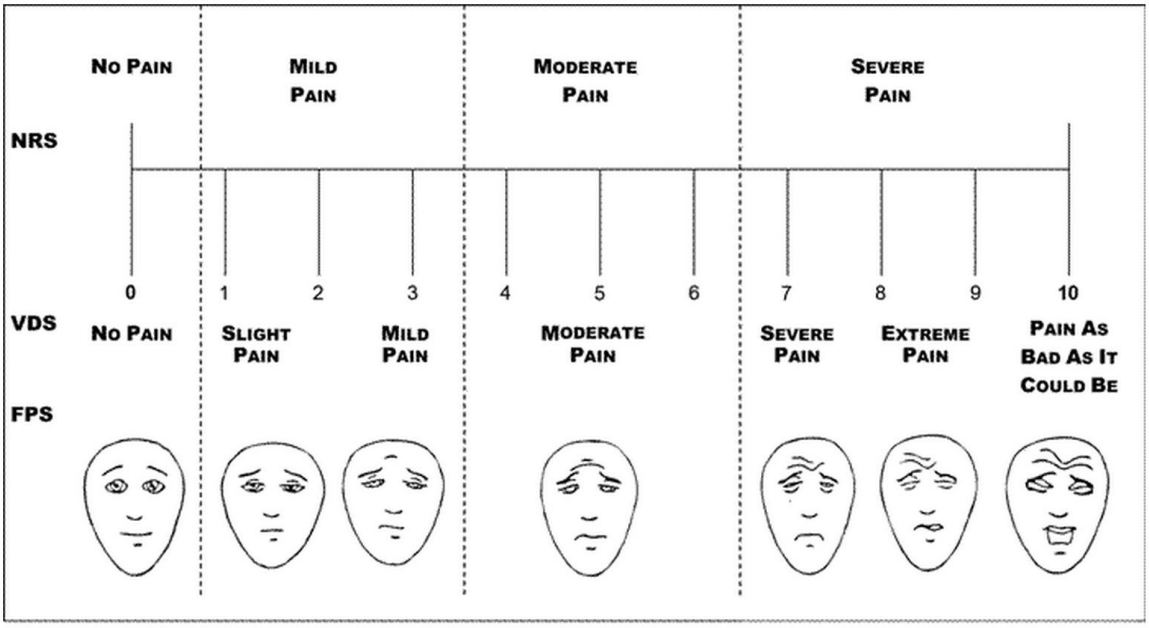

Figure 3. FPS superimposed on NRS-11. Figure taken from Jones et al., 2007.

RESULTS

Case Presentation

We present a case of monozygotic twins, female, who were diagnosed with severe Adolescent Idiopathic Scoliosis. Their monozygosity was initially defined by the twins' physical similarities (identical brown hair color, eyes, skin type) and concordance for AIS. Later, the mother confirmed that they were in fact identical. The twins were initially treated with a bracing regimen to prevent further progression of their scoliosis. Despite compliant bracing for several months the Cobb angles for both twins progressed to severe thoracic AIS (*see Table 1*), and were advised by their orthopedic surgeons to consider spinal fusion surgery. "Progression" of scoliosis is indicated by a difference of greater than 5° between two X-ray of the spine, and is used to document if a scoliotic curve has improved or deteriorated (Soucacos et al., 1998).

Twin A is a 13.5 year old Caucasian American female that is 162.5 cm tall. She was born prematurely after 34 weeks via caesarian section, weighing 4lb 7oz at birth. Due to a prolapsed cord, Twin A was intubated for 7 days in the NICU (Neonatal Intensive Care Unit) before being released. Twin A had no significant childhood medical illnesses or surgeries. At age 13, Twin A was diagnosed with severe AIS with a Cobb angle of 53°, and opted for spinal fusion of seven vertebrae (T3-T10). *Figure 4* has been included to get a sense of where the surgeries will take place. The procedure was completed in just under 5 hours with no complications by orthopedic surgeon Dr. Hedequist. The T3 to T10 spinal fusion was performed using a CD HORIZON Danek 5.5

mm Solera cobalt chrome and titanium spinal system (Medtronic, Memphis, TN). This instrument system allows the surgeon to place special pedicle break-off setscrews directly into the spinal column that will bind the titanium rod to correct the scoliotic curve. Dr. Hedequist inserted the pedicle screws from T10 to T3 using the Lenke freehand technique. Intra-operative protocol for spinal surgeries includes MEP (Motor-evoked potential) and SSEP (Somatosensory-evoked potential) monitoring. With the spine being an important component of the central nervous system (CNS), its neural functioning must be confirmed at every step of the surgery. Once the screws are in place, the screw positions were confirmed via fluoroscopy. With the screws confirmed and evoked potentials remaining normal, an appropriate titanium alloy rod was then placed into the scoliosis, and captured with the screws. With the rod in place, the surgeon then placed the allograft and autograft (to reform the spinal bone tissue), and the surgical site was closed.

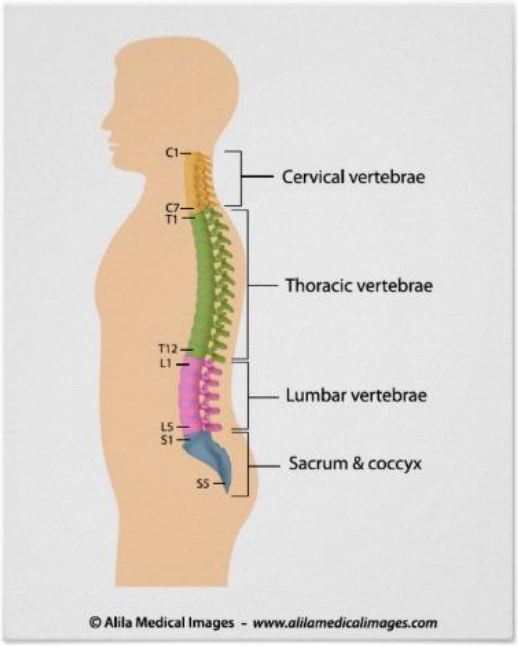

Figure 4. Spine Regions and Vertebrae Numbers. Figure taken from Alila Medical Images

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Twin B is also a 13.5 year old Caucasian American female, and is 161 cm tall. She was born premature after 34 weeks via caesarian section, weighing 4lb 11oz. At age 7.5, Twin B was diagnosed with Ebstein's Anomaly of the Tricuspid Valve with dysrhythmia, and was treated with a cone procedure. Normally, the tricuspid valve (TV) separates the right ventricle from the right atrium in the heart. With Ebstein's Anomaly, the tricuspid valve is abnormal and dislocated, causing blood to leak back into the right atrium. If the backflow of blood into the right atrium is exceedingly high during development, the atrial pressure at birth will prevent the foramen ovale from closing. A patent foramen ovale (PFO) is a pathological persistence of an opening between the left and right atria of the heart, which physiologically shunts blood away from the inactive lungs during gestation (Negoi et al., 2013). The cone procedure performed on Twin B is an optimization of the Carpentier technique developed in 1989, and allows for markedly less TV regurgitation by maintaining the tricuspid valve's geometry vs techniques that leave the TV a mono-cuspid. In addition, because sutures were made superficially to the AV node, there is less risk of AV block complications with the cone procedure (da Silva et al., 2007). Twin B endured two separate episodes of ventricular tachycardia since her cone procedure, and was treated with catheter ablation. An ablation procedure uses a catheter threaded through a vein in the groin to correct structural problems in the heart that cause arrhythmias. By scarring or damaging the conductive tissue responsible for

abnormal heart signaling, cardiac ablation is used to prevent future abnormal heart rhythms, including ventricular tachycardia (Iturralde et al., 2006).

Given that Twin B has a history of cardiac disease with progressive AIS, her orthopedic surgeon strongly recommended surgical stabilization of her curve. At age 13, Twin B was diagnosed with severe AIS with a Cobb angle of 50°, and opted for recommended thoracic spinal fusion surgery of seven vertebrae (T5-T12). The procedure was completed in just under 5 hours with no complications by orthopedic surgeon Dr. Glotzbecker. The T5 to T12 spinal fusion was performed using a Danek 6 mm Solera cobalt chrome and titanium instrument (Medtronic, Memphis, TN) similar to Twin A, but with a larger screw diameter. Once the screws were confirmed via fluoroscopy and spinal monitoring showed no changes from baseline, an appropriate titanium alloy rod was placed into the scoliosis. Despite an upper thoracic curve still present above T5, the orthopedic attending decided not to pursue the correction at increased surgical risk. With the rod in place and captured by the screws, the surgeon then placed the allograft and autograft (to reform the spinal bone tissue), and the surgical site was closed. After the spinal fusion surgery, Twin B was admitted into the MSICU (Medical Surgical Intensive Care Unit) for close post-operative monitoring for respiratory insufficiency, hemodynamic instability and neurologic instability. After 24 hours of close monitoring, Twin B was released to inpatient care, and instructed to resume her home aspirin treatment.

Chart Review Data Reporting

A thorough chart review of Twin A and B shows that their spinal fusion surgeries were not only performed on the same day, but were almost identical. Both spinal fusions were across 7 vertebrae, and were conducted with a standard posterior approach from the back of the spine. Although a small difference in Cobb angle is seen at the time of surgery, both were considered to be in the severe range as defined by the 2011 SOSORT Consensus Paper (*Table 1* - Negrini et al., 2012). Twin A reported a lower average pain rating (using the NRS-11) than Twin B over both short- (in-hospital PT report) and longer- (self-reported pain diary) term pain scores (*see Table 2).*

Table 2. Collected Retrospective Chart Review Data

	Age at Surgery (yrs)	Fusion length (vertebra; total)	Surgery length (hr:min)	Cobb Angle	Hospital stay (days)	Pre-Op Pain (NRS-11)	Avg post-op pain (thru Feb 2015)
Twin A	13	(T3-T10); 7	4:30	53	6	2.5	2.075
Twin B	13	(T5-T12); 7	4:45	50	6	2.5	2.45

During the inpatient recovery phase, Twin B was using more opiate and non-opiate drugs for pain than Twin A. Also, while both twins were given an increase in their Oxycodone (PO) dosage for their pain, Twin B's increase occurred a day earlier than her sister's. After the increase, both patients' PT-reported pain levels decreased significantly for the duration of their inpatient recovery (*see Figures 5A, 5B*). It is also worth noting that although Twin B had the earlier increase in opiate dosage due to high pain, Twin A had the higher inpatient pain score.

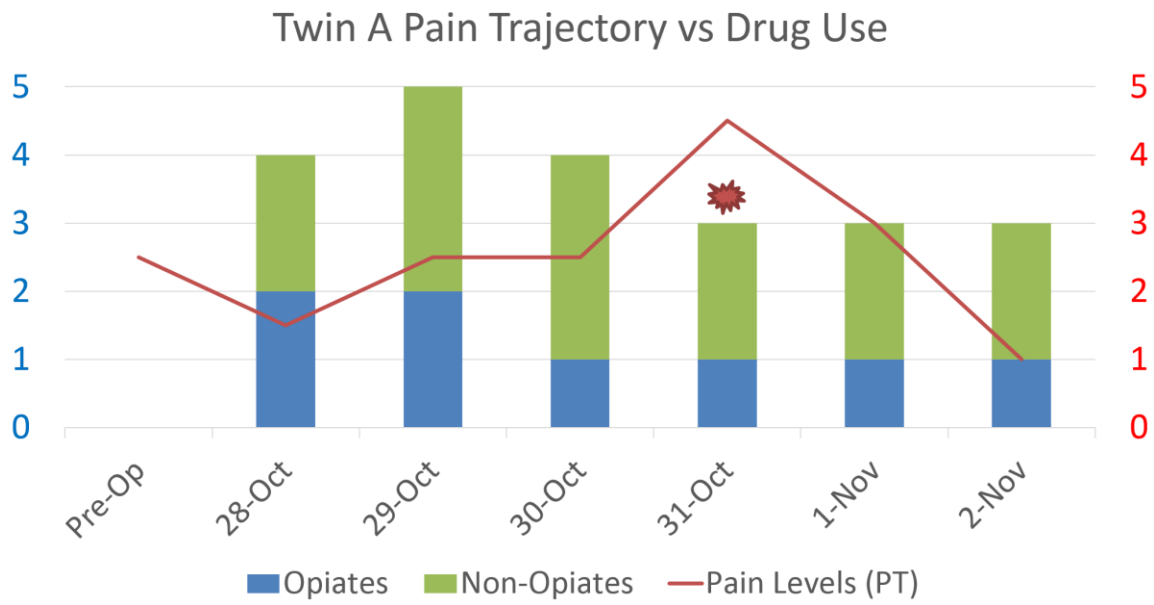

Figure 5A. Twin A's PT-reported pain via NRS-11. The red star denotes the opiate dosage increase. Bar graphs denote confirmed analgesic doses.

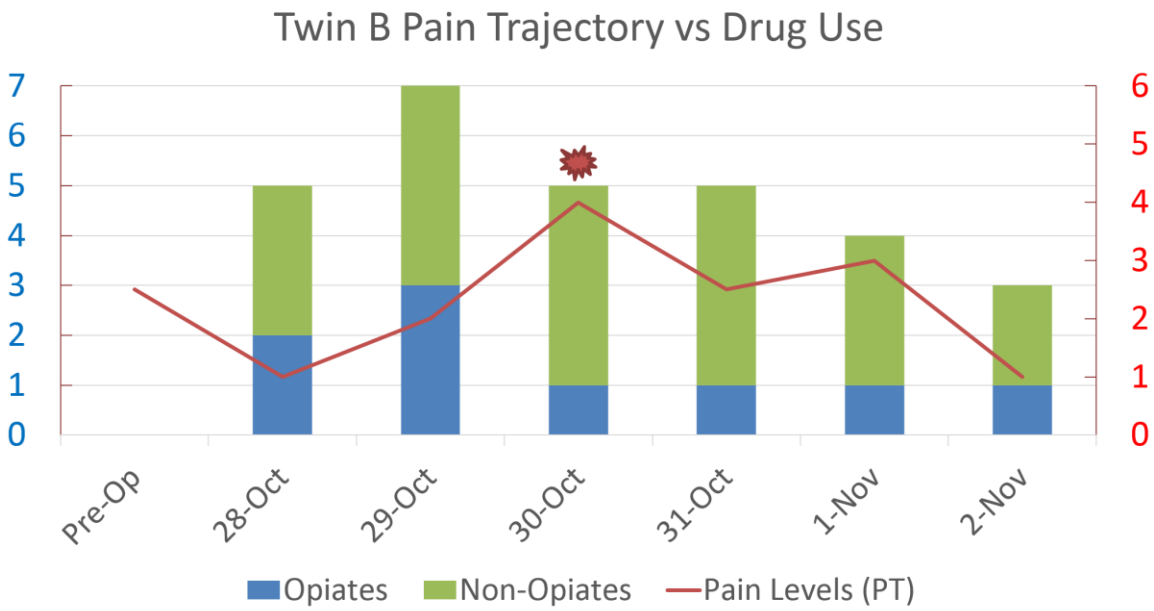

Figure 5B. Twin B's PT-reported pain via NRS-11. The red star denotes the opiate dosage increase. Bar graphs denote confirmed analgesic doses.

Consistent with the findings reported in *Figures 5A and 5B,* Twin B had a lower pain rating than her sister for most of the in-hospital recovery phase due to her earlier opiate increase. Following discharge, however, Twin B's pain rose significantly, and had a slower rate of pain resolution than Twin A. This is illustrated in *Figure 6.*

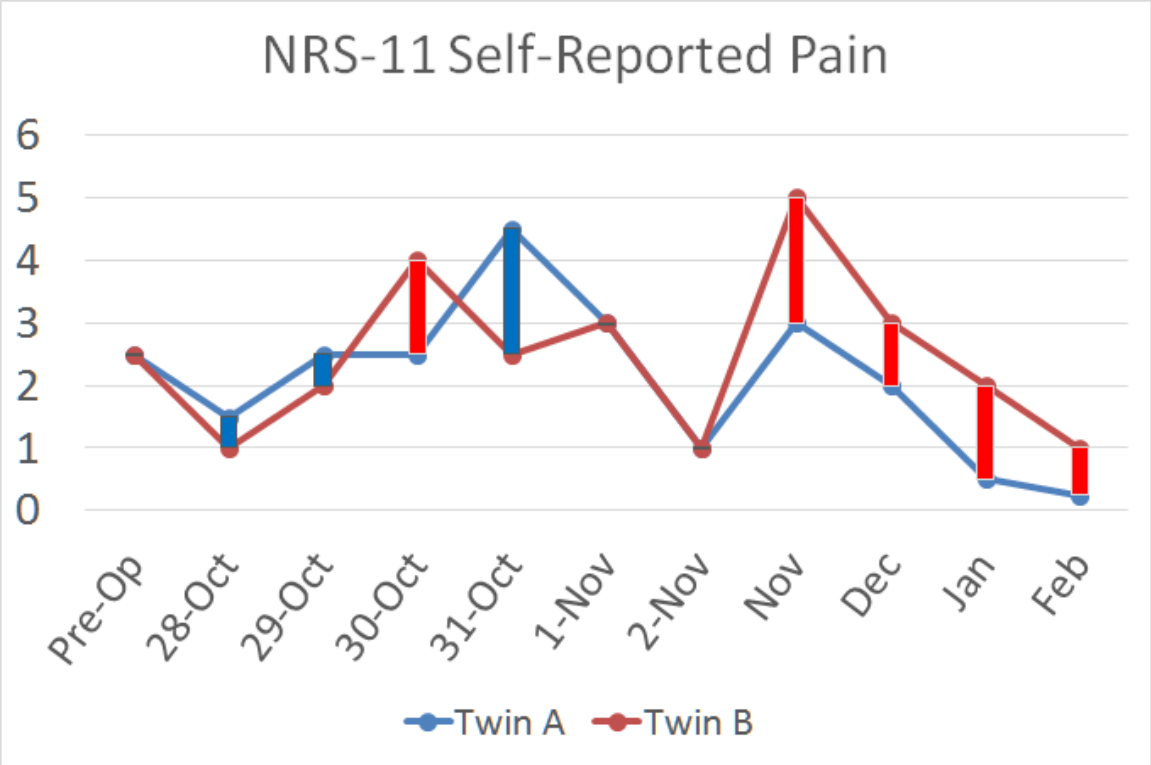

Figure 6. NRS-11 pain scores during recovery. The (day-month) scores reflect the pain reports from physical therapy (PT) during inpatient recovery, and subsequent data points were from monthly pain diary reports. *Blue bars represent data points when Twin A had a higher pain rating, and red bars indicate higher pain scores for Twin B.

QST Results

The QST data suggests that Twin A has an increased sensitivity as compared to her sister. *Table 3* shows the collected QST data from Twin A and Twin B, as well as a normal adolescent population. Items bolded on the graph show which twin had increased sensitivity for that particular test. For the mechanical trials with the von Frey

monofilaments, Twin A had increased sensitivity at the surgical site, and Twin B had increased sensitivity at the non-surgical site. With respect to the pressure testing, Twin A's results illustrate an increased pressure sensitivity on the back, but a lower pressure sensitivity at the non-surgical control site. For the thermal tests, Twin A had higher sensitivity for the cool/ warm detection tests at both the surgical and non-surgical sites, as well as increased pain sensitivity for the cold pain thresholds on the hand and the hot threshold on the back. The only thermal test Twin B showed increased sensitivity for was the cold pain threshold along the spine. There was no discernable difference between the twins in the heat pain threshold for the palm.

Using a large QST study on a normal adolescent population conducted by Dr. Meier and colleagues, we were able to adapt threshold points to determine if Twin A or Twin B show signs of hypo- or hypersensitivity for the control site thermal tests. Our data suggests that the twins are hyposensitive for most thermal tests when compared to the sample population, and have normal sensitivity for only the cool temperature detection test.

Table 3. QST of Twin A and Twin B vs normal population.

Measure	Twin A ($\bar{x}$, s)	Twin B ($\bar{x}$, s)	Normal population*
Hand			
Von Frey Hairs			
LTDT	2.44/ 0.04g	**2.36/ 0.02g**	
PDT	3.61/ 0.4g	**2.44/ 0.04g**	
Thermal			
Warm Detection	**34.73°, 0.772**	36.967°, 1.193	33.7°
Heat Threshold	45.83°, 0.84	45.6°, 1.015	41.7°
Cool Detection	31°, 0.3	30.475°, 0.55	30.5°
Cold Threshold	**13.9°, 2.63**	10.03°, 0.874	14.9°
Algometer - PPT	35.6 N, 3.504	**28.2 N, 0.53**	
Back			
Von Frey Hairs			
LTDT	**2.36/ 0.02g**	3.04/ 0.6g	
PDT	**4.31/ 2g**	4.56/ 4g	
Thermal			
Warm Detection	**34.375°, 0.222**	36.55°, 0.451	
Heat Threshold	**41.73°, 1.858**	44.93°, 2.155	
Cool Detection	**30.7°, 0.48**	25.85°, 1.893	
Cold Threshold	1.2°, 2.08	**2.867°, 4.965**	
Algometer - PPT	**25.67 N, 4.456**	32.73 N, 1.405	

All temperatures values expressed in Celsius
Bolded = increased sensitivity for measure
*Expressed as median value adapted from Meier et al., 2007.

Results from REDCap Psychosocial Measures

We present the results of the psychosocial measures completed by Twin A, Twin B, and their mother in *Table 4*. In order to classify clinical significance, we also report cut-off data from earlier studies when available/ appropriate. Results indicating clinical

significance were bolded. Depressive attitudes were clinically significant at both time-points for Twin A and Twin B. Functional disability was insignificant, however, Twin B showed a marked increase in her score after surgery compared to her sister. Fear of pain and catastrophizing scores were clinically minimal for both twins. With respect to normative means, Twin B had an increased MASC total score before surgery, and all other MASC totals were elevated but not clinically significant.

The parent REDCap measures showed elevated catastrophic thinking toward Twin B, but not Twin A. The ARCS subscale scores defend the results from the pPCS measure, with the Minimize subscale being higher for Twin A, and the Protect subscale being elevated in Twin B. The Encourage subscale was very similar for both twins, and is not reported.

Table 4. REDCap Reporting of Psychosocial Measures. Clinical cutoffs included when appropriate.

Measure	Twin A - pre, post-op	Twin B - pre, post-op	Parent - Twin A (post-op)	Parent - Twin B (post-op)	Clinical Cut-Offs
ARC - minimize	N/A	N/A	1.6	1	-
ARC - protective	N/A	N/A	2.3125	2.625	-
cDI *	**15, 13**	**18, 13**	N/A	N/A	x > 12; optimal clinical cut-off
cFDI **	0, 2	0, 8	N/A	N/A	Minimal: 0-12, Moderate: 13-29, Severe: 30-60
cFOPQ ***	5, 7	3, 11	N/A	N/A	Minimal: 0-34, Moderate: 35-50, Severe: 51-96
cPCS ^*	11, 10	12, 9	N/A	N/A	Minimal: 0-14, Moderate: 15-25, Severe: 26-52
MASC-C T-score ^**	44, 41	**56**, 30	N/A	N/A	44.23; SD = 14.44
MASC - Harm Avoidance	20, 19	22, 17	N/A	N/A	-
MASC - Physical	6, 6	10, 10	N/A	N/A	-
MASC - Separation	6, 9	10, 6	N/A	N/A	-
MASC - Social Anx	12, 6	14, 5	N/A	N/A	-
pPCS ^*	N/A	N/A	17	**27**	Non elevated: 0-22, Elevated: 23-52

Data compiled from REDCap, compiled in Excel, and computed in SPSS.
Bolded = clinically significant.

* CDI cut-off: Allgaier et al., 2012
** FDI cut-offs: Flowers et al., 2011
*** CFOPQ cut-offs: Simons et al., 2011
^* PCS cut-offs: Pielech et al., 2014
^** MASC cut-off: March et al., 1997

DISCUSSION

The cause(s) of AIS remain largely unknown to the medical community. With environment and genetics playing significant roles in the etiology of AIS, it has eluded scientists' efforts to screen for consistent risk factors for developing the disease. While many studies show concordance between identical twins, a large twin study by Grauers and colleagues concluded that it is not the whole story (Grauers et al., 2012).

Discussion of Results

Looking at the REDCap reports of the psychosocial measures, we can infer that Twin B had stronger indications that may have contributed to a more painful post-surgical recovery. With respect to the child Depressive Inventory, both twins were indicated for depression before the surgery, and at the 1-month follow-up, their scores decreased to just above the clinical cutoff. With a major surgery on the horizon, an elevated depressive mood could be expected from any patient, and after the surgery, both twins' scores dropped significantly. Looking at the MASC totals, we see that Twin B had a significant indication of anxiety preoperatively, while her sister was not near the threshold. What is interesting, however, is at the one-month follow-up, Twin B's MASC total fell below both the cutoff as well as her sister's score. We predict that because Twin B has had surgery in the past, she is more accustomed to post-surgical recovery and is less anxious about it. Another interesting finding was in the PCS results. Twin A and Twin B both expressed low levels of pain catastrophizing based on their cPCS total scores, however, the pPCS measure is elevated for Twin B and not Twin A. We infer

from these results that although Twin B does not have elevated catastrophic thoughts about pain, her mother believes she does. These findings are supported by the ARCS measure. In the Protect subscale of the ARCS, the mother scored higher for Twin B, showing that she may show more protective attitudes toward Twin B than Twin A. In addition, for the ARCS's Minimize subscale, the mother scored higher for Twin A than Twin B, indicating a potential bias in the mother's reaction favoring Twin B. The final ARCS subscale, Encourage, was almost the same for both twins, and was not included in our psychosocial analysis.

Looking at the QST data, we found it unusual that Twin A showed increased sensory sensitivity in many of the trials compared to her twin sister, but reported lower pain scores throughout her recovery. The only thermal sensory test Twin B showed increased sensitivity for was the cold pain test at the surgical site. Previous findings in adults also found that cold pain hypersensitivity was a significant independent predictor of chronic low back pain (Hübscher et al., 2014). Based on the results of a retroactive chart review of Twin A and Twin B along with their QST data, we might tentatively conclude that cold pain sensitivity is a possible risk factor for post-surgical pain that warrants further research.

Although hyperalgesia to cold pain at the surgical site is associated with post-surgical pain in this and one other study, our hypothesis predicted to find a difference specifically in the heat pain test. A systematic review of 15 separate QST studies found heat pain thresholds to have the strongest correlation to post-operative pain (Abrishami et al., 2011). Although we did not find a correlation between heat pain and post-surgical

pain, our QST findings are nevertheless interesting and require future study to deduce their relevance. As one possible explanation to the correlations we see in Twin A and Twin B's QST data, the twins were only showing normal sensitivity levels for the cool detection tests when compared to the normal sample population. Although speculation, this could be indicative of the twins having impairments in their warmth detection/ heat pain sensory pathways, preventing hyperalgesia to the warm/hot tests.

This case study brings to light a question about the meaning of concordance: though the twins have the same disease, their recovery trajectories are significantly different, and have potential to affect them into adulthood if left unchecked. How much time should pass from the surgical date until the medical community should diagnose a patient with persistent post-surgical pain? The twins presented here are concordant for AIS, but show a marked difference in their pain recovery after corrective surgery. Are the twins discordant for post-surgical pain? The etiology for pain is unknown, but future studies with larger cohorts of twin pairs should attempt to find statistically significant differences, and determine baseline characteristics that may be attributable. Preliminary evidence from this case study suggests that signs of cold hyperalgesia compounded by high scores on psychosocial measures have potential to be a predictive screen for poorer pain trajectories, and should be tested with a larger trial to assess the validity of our findings.

Limitations

The presented case study must be viewed in light of its many limitations. As this is a case study following a single twin pair, data cannot be generalized to the population; however, we can use results from this investigation to inform future research. Furthermore, race and ethnicity limits the inferences that can be made by this data, though it is beneficial Twin A and Twin B fall in a high AIS incidence demographic. Future studies should look into these factors for males and underrepresented ethnicities. As previously mentioned, the pain diary, REDCap, and QST measures are currently on-going for Twin A and Twin B. At the time of this write-up, it has been 5 months since their surgery date, and new data at the 6 month post-op date may bring new insights to the current data. With respect to the REDCap measures, it is impossible to determine statistical significance with a sample size so small. With no cutoff statistic for the ARCS subscales, we are cautious to make any conclusions from the results we see other than the correlations previously stated.

In regards to study design, the REDCap measures were completed incorrectly at the pre-op time point for the caregiver, and were not included in the write-up for this case study. Secondly, with respect to unbiased reporting, blinding the study during data collection was not possible. Lastly, the monozygosity of the twins presented should eventually be confirmed via highly polymorphic single nucleotide polymorphisms (SNPs).

Future Directions

Alongside the larger clinical trial this case study stemmed off of, Dr. Sieberg is also part of a collaborative effort to test these predictors in a mouse model. In addition, saliva or blood samples were taken from all patients who participated in the QST for genotyping analysis. By collecting genetic samples, we hope to eventually test surgical participants against a normal population of patients to deduce any differences in gene expression. Twin A and Twin B are among the pool of genetic samples we will one day test.

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CURRICULUM VITAE

Domenic Joseph Filingeri

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Birth Year: 1989

Education

M.S. in Medical Sciences, Pre-Medical -- GPA 3.65

- Boston University Medical Center, graduation May 2015
- Coursework: Biochemistry, Cellular Organization of Tissues (Embryology + Histology), Physiology, Pharmacology.
- Thesis project: Investigating factors for post-surgical pain in surgical patients, Boston Children's Hospital, Boston MA. (PI: Dr. Christine Sieberg)

B.A. in Biochemistry & Molecular Biology, Pre-Medical Track – GPA 3.35

- Boston University, graduated May 2011
- Coursework: Physical Biochemistry, Molecular Biology, Biochemistry, Organic Chemistry, Systems Physiology, Genetics, Cell Biology, Carcinogenesis, Statistics

Academic Awards & Honors

- Awarded Undergraduate Research Fellowship (UROP) by Boston University, Summer 2010
- College of Arts and Sciences Dean's List Recipient (Spring 2008, Spring 2009, Fall 2010, and Spring 2011)

Academic Presentations

- **Filingeri D**, Matos M, Ho A. "Dissecting the Interaction between Leucine-Rich Repeat Transmembrane proteins and APP," *13th Annual Undergraduate Research Symposium*, Boston University, Boston MA – October 22, 2010.
- **Filingeri D**, Chan J. "Lymphatic signals in development and disease & Lymphangiogenesis in the Zebrafish requires VEGFR3 and MAPK/ERK signaling," *30th Annual Vascular Biology Program Retreat*, Children's Hospital Boston, Boston MA – November 2, 2012.

- **Filingeri D**, Chan J. "Lymphangiogenesis requires VEGFR3 and ERK Signaling," *Local Joint Zebrafish Meeting*, Boston Children's Hospital, Boston MA – January 11, 2013.

Academic Publications

- *Blood*. 2013 Jan 24;121(4):707-15. doi: 10.1182/blood-2012-05-433045. Epub 2012 Dec 3. "Transcriptional repression of VEGF by ZNF24: mechanistic studies and vascular consequences in vivo," Jia D, Hasso SM, Chan J, **Filingeri D**, D'Amore PA, Rice L, Pampo C, Siemann DW, Zurakowski D, Rodig SJ, Moses MA.

Research Work Experience

2014-2015 **Graduate Researcher, Anesthesia/ Pain Treatment Service, Boston Children's Hospital, Harvard Medical School, Boston MA.**
Advisor: Dr. Christine Sieberg (email: Christine.sieberg@childrens.harvard.edu)

- Graduate research for master's degree thesis project
- Conduct individual project for thesis, and helped with the core studies of the lab

2011-2013 **Research Assistant, Vascular Biology Department, Boston Children's Hospital, Harvard Medical School, Boston MA.**
Advisor: Dr. Joanne Chan (email: angiofish@gmail.com)

- Conduct simultaneous experiments for grant proposals, collaboration projects, and my own research
- Optimize multiple laboratory techniques and instruct others in the new methodology
- Monitor use of lab supplies and generate orders as needed

2009-2011 **Undergraduate Researcher, Department of Biology, Boston University, Boston MA.**
Advisor: Dr. Angela Ho (email: aho1@bu.edu)

- Awarded UROP grant funding
- Conducted independent projects and experiments with the guidance of the Principal Investigator, research fellows, and graduate students

Relevant Volunteer/ Non-research Work Experience

2014-Current **Volunteer, Neural Wing, Boston Children's Hospital, Boston MA.**

- Volunteer 4 hours per week to entertain and hold activities with the patients
- Provide support for the parents, nursing staff, and physicians on the floor

2013-Current **Bartender, Multiple Locations, Boston MA.**

- TIPS certification earned from Harvard Bartending School.
- Undertook many roles in the restaurant/ hotel bar
- Fast-paced position at a high-volume, fully serviced bar

Spring 2015 **Teaching Fellow, Boston University Medical School, Boston MA.**

- Teaching fellow for Critical Reading and Analyses of the Medical Literature, an elective course offered to 4th year medical students
- Prepare course materials, maintain course website, run discussions with Professor

Fall 2014 **Teaching Fellow, Boston University Medical School, Boston MA.**

- Teaching fellow for Cellular Organization of Tissues (Embryology/ Histology course)
- Run histology labs, proctor exams, and tutor students that need help with the material

Summer 2014 **Team Advisor, National Student Leadership Conference, Harvard Medical School, Boston MA.**

- Leader and teacher position; acted as role model for high school students
- Summer program that provides an excellent opportunity for students interested in medicine to get early exposure to the field, and to instill leadership qualities

2013-2014 **Volunteer, bWell Center, Boston Medical Center Pediatrics**

- Volunteer 3-6 hours per week providing patients, parents, and guardians free health education with fun, dynamic and educational activities

2012-2013 **Vascular Anomalies Center, Boston Children's Hospital, Boston MA.**

- Attended clinic hours to observe firsthand the syndromes I am researching
- Shadowed Dr. Fishman and his colleagues during rounds with Dr. Chan

Summer 2011 **Physician Shadowing, The Valley Hospital, Ridgewood, NJ.**

- Observed Dr. Russo's surgeries; accompanied him on rounds

2009-2011 **Tutor, Education Resource Center, Boston University, Boston MA.**

- Tutored Boston University undergraduates; led group and individual sessions
- Instructed tutees in Organic Chemistry I/II, Statistics, and Genetics

2009-present **Private Tutor, UniversityTutor.com/ Boston University Job Board**

- Tutored high school students via one-on-one sessions
- Guided students through high school Chemistry and Biology, Statistics, Algebra, Trigonometry, SAT and ACT review, Pre-Calculus, and Calculus

2008-2011 **Student Panel Member, Boston University College of General Studies**

- Provided input to a committee consisting of the Dean and a Board of Overseers regarding the college's curriculum (one of two students selected for the opportunity)

2008-2011 **Fenway Park Green Team, Boston University, Boston MA.**

- A great way to give back to the community and reduce our impact on the environment
- Granted admission into Fenway Park during various Red Sox home games to collect recyclables in-between innings

2008-2009 **Dean's Host, Boston University College of General Studies**

- Represented and promoted BU, encouraging prospective students to apply
- Led tours and answered questions about the University