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Exploring pediatric chronic regional pain syndrome (CRPS) diagnostic criteria and determining the efficacy of multidisciplinary treatment in managing pediatric CRPS

Son, SungJun

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Boston University
EXPLORING PEDIATRIC CHRONIC REGIONAL PAIN SYNDROME (CRPS) 
DIAGNOSTIC CRITERIA AND DETERMINING THE EFFICACY OF 
mULTIDISCIPLINARY TREATMENT IN MANAGING PEDIATRIC CRPS 

by 

SUNGJUN SON 

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ABSTRACT

Currently, there is a dearth of knowledge regarding pediatric Complex Regional pain syndrome (CRPS), whether it is in regards to its pathophysiological mechanisms, pediatric-specific diagnostic criteria, validated diagnostic tests, conclusive treatment regimens, or validation of invasive and noninvasive treatment protocols in the pediatric CRPS population. It is imperative to first explore and establish a pediatric CRPS diagnostic criteria in order to optimize diagnostic accuracy for clinical and research purposes.

This study first examined the efficacy of the Budapest criteria, a validated diagnostic instrument for adult CRPS, in the pediatric population. The test was administered to 221 pediatric patients at the Pediatric Pain Rehabilitation Center (PPRC), an intensive day treatment program at Boston Children’s Hospital for youth with chronic pain, and included both CRPS and non-CRPS chronic pain patients. Utilizing the Budapest criteria, secondary analyses were performed to determine whether the pediatric CRPS patients had an alleviation of their diagnosis from admission to discharge from the program.
The Budapest clinical decision rule (to satisfy at least 2 signs categories and 3 symptoms categories) was utilized in examining the data. The sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of the Budapest criteria in the pediatric sample were 0.56, 0.95, 10.39, and 0.47, respectively. The low sensitivity and high specificity was in contrast to the adult findings, and suggests that the Budapest criteria would be appropriate when the primary purpose is to identify stringent research samples as opposed to maximizing clinical diagnoses of CRPS. The likelihood ratios indicated that while satisfying the Budapest clinical decision rule may conclusively increase the probability of the pediatric patient actually having CRPS, a negative test does not significantly decrease the probability of the patient having CRPS. Therefore, modifications that appropriately increase the sensitivity while maintaining the high specificity of the Budapest Criteria are recommended.

Repeated measures ANOVA resulted in a significant decrease of the Budapest signs and symptoms score in the 94 pediatric CRPS patients in the sample, both in the Clinician + Budapest (satisfied the Budapest clinical decision rule) and Clinician Diagnosed (did not satisfy the Budapest clinical decision rule) CRPS cohorts (p < 0.001). This further authenticated the use of a multidisciplinary treatment approach in managing pediatric CRPS, as the program was successful in alleviating the patients’ signs and symptoms.

Further research must be conducted to explore the improvements that can be made to the Budapest Criteria for its use in pediatric CRPS so as to maximize its diagnostic accuracy. Overall, this study corroborated the use of interdisciplinary treatment regimens
for pediatric CRPS, but further rigorous investigation is necessary to elucidate the
mechanisms behind pediatric CRPS and the rehabilitation programs’ success in managing
CRPS.
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LIST OF ABBREVIATIONS

ANOVA ................................................................. Analysis of Variance
CI ................................................................. Confidence Interval
CRPS ......................................................... Complex Regional Pain Syndrome
IASP ......................................................... International Association for the Study of Pain
IBM ........................................................ International Business Machines
NLR ........................................................ Negative Likelihood Ratio
PLR ........................................................ Positive Likelihood Ratio
PPRC ....................................................... Pediatric Pain Rehabilitation Center
SPSS ......................................................... Statistical Package for the Social Sciences
INTRODUCTION

Complex Regional Pain Syndrome (CRPS), also commonly referred to as Reflex Sympathetic Dystrophy and causalgia, is a debilitating chronic pain condition that often affects one of the extremities, the upper extremity in particular (Harden et al., 2007; Borchers & Gershwin, 2014; Wolter et al., 2016; Imani et al., 2016). Generally, CRPS manifests following trauma such as nerve injury, surgery, immobilization, or a musculoskeletal injury, in which the severity is disproportionate to the degree of pain; however, the condition may even occur spontaneously (Goebel, 2011). Designated as a rare disease, it has been reported that the estimated overall incidence of CRPS in the Netherlands was 26.2 cases/100,000 person years, whereas that in the United States was 5.5 cases per 100,000 person years (Sebastin, 2011). Moreover, the incidence of CRPS is higher in patients between ages 40-49 and in women with a prevalence of 23% and 76%, respectively (Veldman et al., 1993).

There have been several studies investigating the influence of psychosocial factors and their degree of influence in precipitating CRPS. In fact, several studies have demonstrated that psychosocial factors are not predispositional to the onset of CRPS. De Mos et al. (2008) examined whether preexisting psychological factors such as depression, anxiety, and stress were associated with CRPS onset, but did not find any significant relationships. Furthermore, a prospective study was conducted to observe whether psychological factors predict the precipitation of CRPS following total knee arthroplasty, as this surgery is associated with development of CRPS (Harden et al., 2003). Results
showed that although CRPS patients reported more anxiety and depression after the surgery, anxiety and depression before the surgery did not predict the onset of CRPS, suggesting that the two factors are not predictive but rather an outcome of CRPS (Harden et al., 2003). An additional area of interest in CRPS patients is their quality of life; a study showed that discharged CRPS patients reported decreased social and emotional function, impaired physical function, and heightened physical pain compared to healthy controls (Savas et al., 2008). A small-sample study also observed that CRPS patients reported significant impairments in daily activities such as work, sleep, and social activities (Galer et al., 2000). These studies demonstrate that while the predicting role of psychosocial factors in the development of CRPS is not fully corroborated, the findings clearly show how psychological impairments such as depression and anxiety commonly follow the onset of CRPS (Lohnberg & Altmaier, 2013). Treatment of CRPS further poses a financial burden to the patients just like other chronic pain conditions, and since patients with continuing pain from CRPS are discouraged to work, the overall healthcare costs are higher and quality of life poorer (Goebel, 2011). This emphasizes the importance of addressing the psychosocial and socioeconomic factors along with the physical factors in understanding and treating CRPS patients.

Pediatric CRPS is a relatively recent diagnostic entity. Similar to the adult population, pediatric CRPS is more common in females, yet it is mainly confined to the lower extremities (Low et al., 2007). Recently, there has been considerable progress in research regarding the effectiveness of noninvasive, interdisciplinary treatment approach for pediatric CRPS, with a high success rate in improving the conditions (Lee et al., 2002;
Logan et al., 2012; Logan et al., 2015; Low et al., 2007; Katholi et al., 2014). Examples of such improvement in children with CRPS include occupational performance, emotional functioning, physical ability, and sleep habits (Logan et al., 2015; Logan et al., 2012). Until recently, pain in children has been inadequately managed at institutions (Dowden et al., 2008). But novel advancements have been proposed and executed to establish pediatric pain treatment programs that incorporate the interdisciplinary approach (Kost-Byerly & Chalkiadis, 2012; Evans et al., 2012; Hechler et al., 2014).

Currently, pediatric CRPS lacks standardized diagnostic tests, thus it is imperative to first validate a pediatric diagnostic test in order to accurately diagnose pediatric CRPS patients with high specificity and sensitivity.

**Pathophysiology of CRPS**

In addition to the significant pain, the signs and symptoms of CRPS include but are not limited to: swelling, allodynia (experiencing pain from non-painful stimulus), hyperalgesia (disproportionately increased sensitivity to pain), dystonia, edema, decreased range of motion, abnormalities in skin color, temperature, and changes in hair and nail growth (Bean et al., 2014). Despite an increase in CRPS research during the past decade to elucidate its etiology, the exact pathophysiologic mechanisms behind this neuropathic pain disorder remains largely unknown. The widely accepted theory is that it is multifactorial in nature; the condition may be due to a dysfunctional interaction between the peripheral and central nervous system, inappropriate inflammation, maladaptive sympathetic and catecholaminergic function, psychosocio-physiologic
interactions, and genetic risk factors (Rockett, 2014; Sebastin, 2011; Blaes et al., 2004; Marinus et al., 2011; Bruehl, 2010). The degree to which these mechanisms contribute to the symptoms of CRPS may vary on an individual basis and may even change within a patient over time (Bruehl, 2010). Determining the pathophysiological mechanism of CRPS and establishing explanatory models for the specific symptoms will not only aid in developing sensitive and specific diagnostic measures, but will also facilitate in the design of optimal treatment protocols and identify potential risk factors of CRPS after trauma, which may drastically decrease the incidence of CRPS following an initial noxious injury.

**Pediatric CRPS**

CRPS has been underreported in pediatric populations until recently, with a study in 1999 being one of the first publications regarding treatment outcomes for pediatric CRPS (Sherry et al., 1999). The majority of the research regarding pediatric CRPS has been conducted in the past decade (Stanton-Hicks, 2010; Goldscheider, 2012; Kachko et al., 2008; Logan et al., 2013; Rodrigues et al., 2015). Consequently, there is sparse clinical data and information regarding pediatric CRPS, which subsequently reiterates the urgency in advancing research for progress towards optimal treatment and prevention (Goldscheider, 2012). In fact, the data regarding pediatric CRPS is mainly derived from adult studies and findings (Goldscheider, 2012). This may be troublesome, as there may be various factors that are unique to pediatrics due to their developmental changes and growth. There is also a lack of information concerning the efficacy of the treatment
methods available for pediatric CRPS patients (Rodrigues et al., 2015). It has been shown that psychological factors have played a larger role in precipitating the disorder in children, and how multidisciplinary treatment is particularly successful in the pediatric population (Wilder, 2006).

One study regarding pediatric CRPS suggest that it occurred predominantly in females (90%), with a mean age of 11.8 years at diagnosis and mainly occurred in the lower extremities (85%), following a minor traumatic event (80%) (Low et al., 2007). This has been consistent with other studies regarding pediatric CRPS (Stanton-Hicks, 2010; Wilder, 2006). Furthermore, it was found that there were significant diagnostic delays with an average of 13.6 weeks that resulted in postponing appropriate treatment (Low et al., 2007). This may have a negative affect to the treatment outcome, and may prolong treatment durations and complex pain amongst the patients.

Currently, there is a lack of pediatric-focused diagnostic criteria, validated diagnostic tests that are highly sensitive and specific, age-based medication recommendations, and definitive and validated treatments in pediatric populations (Katholi et al., 2014). There have been several studies discussing the efficacy of an intensive, interdisciplinary rehabilitation approach in treating pediatric CRPS (Logan et al., 2012; Rodriguez-Lopez et al., 2015; Katholi et al., 2014; Wilder, 2006). One study discussed that physical therapy, in combination with appropriate invasive procedures and medications may be the most effective therapy in the treatment of CRPS (Wilder, 2006). Katholi et al. (2014) further concluded that children respond better to noninvasive approaches than adults in managing pain, and that family-centered therapies tailored
around the individual personality of the patient was the optimal model for treating pediatric CRPS. Another study utilized physiotherapy, psychological therapy, and pharmacological agents for the management of CRPS and performed invasive techniques like neuraxial bupivacaine infusion and spinal cord stimulation when noninvasive options did not alleviate the symptoms (Rodriguez-Lopez et al., 2015). Rodriguez-Lopez et al. (2015) also stated that early diagnosis is indicative of a better prognosis of the disorder, which is consistent with other studies’ findings (Low et al., 2007; Lee et al., 2002; Finniss et al., 2006; Berde and Lebel, 2005; Murray et al., 2000). In order to quickly and accurately diagnose pediatric CRPS and correspondingly offer multidisciplinary treatment, it is critical to validate diagnostically specific pediatric CRPS criteria.

**Current Treatments for CRPS**

Due to the lack of information regarding the etiology and pathophysiology of CRPS, a standardized treatment plan or a consistent objective diagnostic test is not yet available. However, a multimodal program that integrates various therapies such as intensive physical therapy, occupational therapy, and cognitive behavioral therapy have consistently demonstrated improvement in decreasing pain levels and increasing function in adults and children afflicted with CRPS (Logan et al., 2012; Parkitny et al., 2015; Sahil et al., 2013). Yet the scarcity of evidence-based treatment regimens highlights how there are limited pharmacological agents and methods available for treating CRPS (Forouzanfar et al., 2002). Some of the agents used for pharmacological therapy of CRPS are: corticosteroids, calcitonin, nonsteroidal anti-inflammatory drugs (NSAIDs), gamma-
aminobutyric acid (GABA) agonists, beta-blockers, and oral-sympatholytic agents (Tran et al., 2010). Additionally, there are several interventional procedures such as selective sympathetic ganglion nerve blocks, ketamine infusion, spinal cord and peripheral nerve stimulation, and surgical sympathetctomy, though it is not commonly used since such procedures are still controversial with unstable outcomes (Hsu, 2009).

**Interdisciplinary Approach to CRPS**

Recently, a more comprehensive approach to CRPS has gained attention in decreasing pain and increasing function of CRPS patients. Interdisciplinary programs that incorporate psychotherapy, pharmacotherapy, drug therapy, and interventional treatment have reported success in the practical management of CRPS (Singh et al., 2004). Physical therapy and occupational therapy have also shown efficacy in alleviating the symptoms of CRPS (Hugle et al., 2011; Van de Meent et al., 2011; Tran et al., 2010). Furthermore, noninvasive, multidisciplinary treatments for CRPS that are family-oriented have reported high recovery rates, especially in the pediatric population (Katholi et al., 2014). These studies reflect the complicated and multifactorial nature of CRPS and hint at how a holistic approach tailored to individual patients may be the future of treating CRPS.

**Diagnostic Criteria for CRPS**

An incomplete understanding of the etiopathology of CRPS resulted in a lack of a common, validated diagnostic criteria for CRPS. Thus in 1994, the International Association for the Study of Pain (IASP) developed the first diagnostic criteria for CRPS
in hopes to provide a standardized methodology for determining whether the unidentified pain represented CRPS or not (Table 1) (Sebastian, 2011; Merskey & Bogduk, 1994). This diagnostic measure did not imply any pathophysiology, but rather was descriptive and general, intended to enhance clinical communication and identifying research samples (Harden et al., 2007). Because the criteria were determined solely by consensus, its potential has been limited and has not been utilized frequently in literature. Moreover, although the sensitivity of the IASP diagnostic criteria was high (0.98), specificity was poor with 0.36, which led to an over-diagnosis of CRPS (Bruehl et al., 1999). This lack of specificity may be due to several factors, such as how the criteria may be met based only on self-reported symptoms, failure to include trophic and motor features, and how edema and disproportionate pain was sufficient for diagnosis (Harden et al., 1999). Over-diagnosis of CRPS may potentially lead to inaccurate or unnecessary treatments, and there was a dire need for an improvement to the original IASP CRPS criteria.

**Table 1: 1994 IASP Diagnostic Criteria for CRPS.** Criteria 2, 3, and 4 must be satisfied for diagnosis. If seen without “major nerve damage” diagnose as CRPS I; if seen in the presence of “major nerve damage” diagnose as CRPS II.

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<tbody>
<tr>
<td>1.</td>
<td>The Presence of an initiating noxious event, or a cause of immobilization.</td>
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<tr>
<td>2.</td>
<td>Continuing pain, allodynia, or hyperalgesia with in which the pain is disproportionate to any inciting event.</td>
</tr>
<tr>
<td>3.</td>
<td>Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.</td>
</tr>
<tr>
<td>4.</td>
<td>This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.</td>
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In 2003, an international consensus workshop was held in Budapest to discuss the issues pertaining to the limitation of CRPS diagnosis and to ultimately recommend modifications to the IASP criteria (Sebastin, 2011). In comparison to the IASP CRPS criteria, this modified diagnostic criteria, also known as the Budapest Criteria, was based mainly on published, empirically derived criteria (Harden et al., 2010). There are four main criteria: degree of pain, symptoms, signs, and diagnosis (Table 2) (Harden et al., 2007; Harden et al., 2010). If the patient presents or communicates any of the subcategories within each criteria—for example, hyperalgesia under sensory or dystonia under motor—it counts as satisfying that category. The first question regards to whether the patient is experiencing pain that is disproportionate to the initial noxious event, and is expected that those who actually have CRPS would generally satisfy this criteria. The last question regards to whether a different diagnosis better explains the patient’s signs and symptoms, further minimizing misdiagnosis of CRPS. In order to make a clinical diagnosis, a patient must have at least two or more signs and three or more symptoms; this led to a sensitivity of 0.85 and a specificity of 0.69 (Harden et al., 2007). This result demonstrated an acceptable decision rule that correctly identified many patients clinically while significantly decreasing false-positive diagnosis that was evident with the previous IASP criteria. For research purposes, the decision rule was to satisfy at least two or more signs and all four symptoms categories, which resulted in a sensitivity of 0.70 and a specificity of 0.94 (Harden et al., 2007). This difference in the decision rule was due to the fact that it is critical to minimize false positives in the selection of research samples. This revision of the IASP diagnostic criteria established by the Budapest group
formulated two similar yet distinct sets of criteria that are optimized for specific purposes.

**Table 2: CRPS Budapest Diagnostic Criteria.** For a clinical diagnosis, patients must present 2 or more signs and 3 or more symptoms. The decision rule for research purposes is to present at least 2 CRPS characteristics of the sign categories and in all 4 symptoms categories.

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<tr>
<td><strong>1. Pain</strong></td>
<td>Continuous which is disproportionate to inciting event</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td><strong>2. Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sensory</td>
<td>Hyperalgesia &amp;/or allodynia, &amp;/or deep somatic pressure pain, &amp;/or joint movement pain</td>
<td></td>
</tr>
<tr>
<td>• Vasomotor</td>
<td>Temperature &amp;/or skin color asymmetry</td>
<td></td>
</tr>
<tr>
<td>• Sudomotor</td>
<td>Sweating, dryness, &amp;/or edema asymmetry</td>
<td></td>
</tr>
<tr>
<td>• Motor</td>
<td>Decrease ROM, weakness, tremor, dystonia, &amp;/or changes in hair, nail or skin</td>
<td></td>
</tr>
<tr>
<td><strong>3. Signs on examination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sensory</td>
<td>Hyperalgesia &amp;/or allodynia, &amp;/or deep somatic pressure pain, &amp;/or joint movement pain</td>
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</tr>
<tr>
<td>• Vasomotor</td>
<td>Temperature &amp;/or skin color asymmetry</td>
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<td>• Sudomotor</td>
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<tr>
<td>• Motor</td>
<td>Decrease ROM, weakness, tremor, dystonia, &amp;/or changes in hair, nail or skin</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL Score:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4. Diagnosis</strong></td>
<td>Is there another diagnosis that better explains patient’s symptoms and signs?</td>
<td></td>
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<tr>
<td><strong>Additional Comments</strong></td>
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Validation of the Budapest Criteria

In order to directly compare the IASP criteria and the Budapest Criteria and analyze their respective diagnostic efficiency, a validation study was imperative. In 2010, a validation study of the Budapest Criteria against the IASP criteria was conducted that involved 113 CRPS patients and 47 non-CRPS neuropathic pain patients at multiple data collection sites internationally (Harden et al., 2010). Countries where the study sites were located were Israel (31%), Germany (29.2%), Netherlands (25.6%), and the United States (14.1%) (Harden et al., 2010). Some of the diagnoses among the non-CRPS patients, supported by clear neuropathic etiology and appropriate testing, include isolated peripheral neuropathy, radiculopathy, carpal tunnel syndrome, and diabetic peripheral neuropathy (Harden et al., 2010).

A CRPS database checklist was employed across the sites in order to standardize the assessment of signs and symptoms. This checklist was a comprehensive list of the signs and symptoms utilized to diagnose CRPS, and a informative video was provided to the respective physicians on how to perform the data collection procedures so that there will be maximal uniformity across study sites (Harden et al., 2010).

The results showed that the Budapest clinical criteria demonstrated excellent sensitivity (0.99) that was comparable to that of the IASP criteria (1.00), and a higher specificity (0.68) contrast to the latter criteria (0.41) (Harden et al., 2010). The Budapest research criteria had the highest specificity (0.79) but the lowest sensitivity (0.78), which was expected as its purpose is to minimize false positives at the expense of sensitivity (Harden et al., 2010). It also showed through examining the positive and negative
predictive power that the Budapest clinical criteria demonstrated a better overall
diagnostic accuracy compared to the IASP criteria, even under conditions where CRPS
diagnoses was common: with 70% prevalence of CRPS among the patient population, the
Budapest clinical criteria had 0.88 positive predictive power and 0.97 negative predictive
power compared to IASP’s 0.80 and 1.00, respectively (Harden et al., 2010).

The study examined the contributions of each to the overall diagnostic accuracy
of the Budapest Criteria, and found that although each individual component (sensory,
vasomotor, sudomotor, and motor) had a relatively high sensitivity, specificity was low
(Table 3) (Harden et al., 2010). Moreover, when the four components are used in
combination, the sensitivity was the highest with 0.95, and the specificity was highest as
well with 0.81 (Table 3). Thus it can be deduced that all the four diagnostic components
must be included in diagnosing CRPS using the Budapest Criteria for optimal accuracy.
In conclusion, this study validated the Budapest diagnostic criteria and highlighted its
credibility over the IASP criteria, suggesting the former to be the standardized measure
for clinical CRPS diagnosis (Harden et al., 2010).

Table 3: Comparison of the Diagnostic Efficiency of Individual Budapest Criteria
Diagnostic Components. The 4 individual components demonstrate relatively high
sensitivity, but not as specific. Combination of all the components demonstrates the

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<tr>
<th>Criterion</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>All signs/symptoms factor scores</td>
<td>0.95</td>
<td>0.81</td>
</tr>
<tr>
<td>Sensory factor only</td>
<td>0.83</td>
<td>0.57</td>
</tr>
<tr>
<td>Vasomotor factor only</td>
<td>0.94</td>
<td>0.68</td>
</tr>
<tr>
<td>Sudomotor/edema factor only</td>
<td>0.85</td>
<td>0.71</td>
</tr>
<tr>
<td>Motor/trophic factor only</td>
<td>0.86</td>
<td>0.67</td>
</tr>
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Objectives

Despite recent scientific progress and increased research in CRPS, there have been minimal advancements in pediatric CRPS. In order to develop pediatric-focused treatment protocols and appropriate medication recommendations, it is imperative to determine accurate diagnostic CRPS criteria for pediatric populations that have both high sensitivity and specificity. We utilized the Budapest Criteria, a validated diagnostic test that has demonstrated high sensitivity and specificity in an adult sample, and seek to analyze its diagnostic accuracy amongst the pediatric patient population.

The specific aims of the study are:

1. To evaluate the sensitivity and specificity of the Budapest Criteria in a pediatric sample, and compare with the adult criteria as well measure the likelihood ratios for the Budapest Criteria.

2. To assess whether a cohort of pediatric CRPS patients who satisfied (Clinician + Budapest CRPS cohort) and did not satisfy the Budapest Criteria (Clinician Diagnosed CRPS cohort) both report a decrease in Budapest signs and symptoms score from the course of admission to PPRC until their discharge using a repeated measures ANOVA.

We hypothesize that these studies will show:

1. A high sensitivity and specificity of the Budapest Criteria when administered to pediatric patients, comparable to the adult findings.
2. A significant decrease in Budapest signs and symptoms, scores over time when comparing the scores at admission to the PPRC to those at discharge in both Clinician Diagnosed and Clinician + Budapest CRPS patients.
METHODS

Pediatric Pain Rehabilitation Center

The Mayo Family Pediatric Pain Rehabilitation Center at Boston Children’s Hospital at Waltham, commonly known as the PPRC, is a facility that provides an intensive day hospital interdisciplinary treatment approach to children with chronic pain. It is a day treatment rehabilitative program that accepts youth between ages 7 and 18, who suffer from chronic pain even after outpatient treatment (Simons et al., 2013; Logan et al., 2012). Some of the conditions the program admits are: CRPS, neuropathic pain, and musculoskeletal pain. The program is dedicated in tailoring their care to each individual, combining occupational therapy, physical therapy, psychological therapy, medical and nursing management, and therapeutic recreation in their treatment protocol (Boston Children’s Hospital). The daily regimen consists of intensive physical, occupational, and psychological therapies eight hours a day, five days a week, for approximately three to four weeks (Simon et al., 2013). These are aimed to minimize pain and restore normal levels of functioning, and are coupled with a family-centered therapy that allows family members to provide care outside of the hospital setting. The psychological therapy is based on a cognitive-behavioral model, and patients engage in both individual and group-based psychological therapy to encourage them to develop healthy attitude and habits in managing pain.

Every patient who is admitted to the PPRC is administered the Budapest Criteria for data collection. Our primary aim is to analyze this data and compare it against the
actual diagnosis to determine the efficacy of the Budapest Criteria in pediatric patients, mainly by measuring its sensitivity and specificity in the given pediatric population. We hypothesize that the Budapest Criteria will demonstrate comparative specificity and sensitivity in the pediatric patients as those of the adults, corroborating its utilization in the pediatric population. Furthermore, our secondary aim is to determine whether the multidisciplinary approach employed in the PRRC actually alleviates the signs and symptoms of CRPS over time. We hypothesize that there will be a significant decrease in the Budapest signs, symptoms, and total score reported by the patients when comparing their data at admission against those at discharge.

**Data Collection**

The Budapest Criteria was administered to a total of 221 patients at admission. A single physician conducted the Budapest Criteria to each pediatric patient. The test was given at admission prior to any treatment and at discharge after successful completion of the program.

**Patient Demographics**

Of the 221 subjects, 182 of them were female, and 39 were male (Table 4). The subjects were predominantly Caucasian (87.3%) followed by Hispanics (3.2%) and Africans (3.2%), Asian subjects (1.4%), and 5 reporting as ‘other’ (2.3%) (Table 5). The mean age was 14.29 years old with a standard deviation of 2.77 years, and the mean duration of pain among them was 21.24 months (Table 6).
The sample included 106 patients diagnosed with CRPS prior to admission and 112 patients with other chronic pain diagnoses including 75 patients with musculoskeletal pain, 30 with headache or abdominal pain, and 7 with neuropathic non-CRPS pain. Furthermore, 94 of the 106 CRPS patients had Budapest scores from admission and discharge; thus their data was utilized to investigate our secondary aim. Within the 94 CRPS patients, 40 patients did not satisfy the Budapest clinical decision rule (Clinician Diagnosed CRPS group), and 54 patients did satisfy the Budapest clinical decision rule (Clinician + Budapest CRPS group).

**Table 4: Gender Distribution of Admitted Patients.** The pediatric patient population admitted to the PPRC predominantly consisted of females.

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>39</td>
<td>17.6</td>
</tr>
<tr>
<td>Female</td>
<td>182</td>
<td>82.4</td>
</tr>
<tr>
<td>Total</td>
<td>221</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 5: Demographic Distribution Among the Patients.** The racial demographics of 6 patients were missing in the collected data.

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Percent</th>
<th>Valid Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>193</td>
<td>87.3</td>
<td>89.8</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>African American</td>
<td>7</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Total</td>
<td>215</td>
<td>97.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Missing</td>
<td>6</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Cumulative Total</td>
<td>221</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>
Table 6: Age and Pain Duration Characteristics of the Pediatric Sample (n = 221) at Admission.

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.22</td>
<td>22.25</td>
<td>14.29</td>
<td>2.77</td>
</tr>
<tr>
<td>Pain Duration</td>
<td>-37</td>
<td>186</td>
<td>21.24</td>
<td>27.53</td>
</tr>
</tbody>
</table>

Statistical Analyses

Sensitivity and specificity of the Budapest were analyzed using SPSS Version 21. The clinical diagnostic decision rule for CRPS was utilized: for a clinical diagnosis, a patient must have at least 2 or more signs and 3 or more symptoms. Sensitivity is defined as a statistical measure that determines the proportion of positives cases that are accurately identified as positives: true positives / (true positive + false negative). Thus in this study, it reflects the accuracy of the Budapest Criteria in diagnosing CRPS in patients who actually have CRPS. Specificity is defined as a statistical measure that determines the proportion of negative cases that are accurately identified as negatives: true negatives / (true negative + false positives). In this study, it reflects the accuracy of the Budapest Criteria in verifying those patients who do not have CRPS.

Positive and negative likelihood ratios were also calculated using SPSS in order to evaluate the value of performing the Budapest diagnostic criteria in pediatric CRPS patients. Likelihood ratios incorporate both sensitivity and specificity of the given test and provide a calculated estimate of how much the test result will affect the odds of having or not having a disease/ disorder. Thus, a positive likelihood ratio (PLR) provides how much the odds of having the disease will increase when the test is positive. For example, if the PLR of a given diagnostic test for a disease is 10, and the pre-test odds—
such as prevalence—of having the disease is 1%, the post-test odds = pre-test odds *
PLR, so the probability of having the disease after the positive test result would be
approximately 10%. PLR is calculated as: PLR = sensitivity / (1 - specificity). Similarly,
a negative likelihood ratio (NLR) provides how much the odds of having the disease will
decrease when the given test is negative. If the NLR of a given diagnostic test for a
disease is 0.5, and the pre-test odds of having the disease is 10%, the post-test odds after
multiplying those values would be 5. So with the negative test result, the probability of
having the disease decreases to 5%. NLR is calculated as: (1 – sensitivity) / specificity.

Analyses were conducted to determine whether those diagnosed with CRPS
experienced a decrease in the Budapest signs and symptoms score from admission to
their discharge. The Budapest scores of 94 pediatric CRPS patients were used to run this
analysis. There were four groups that were analyzed: signs scores of Clinician + Budapest
CRPS patients, signs scores of Clinician Diagnosed CRPS patients, symptoms scores of
Clinician + Budapest CRPS patients, and Clinician Diagnosed CRPS patients. Two
repeated measures ANOVA were performed; one that analyzed the Budapest signs and
symptoms scores of the Clinician Diagnosed CRPS cohort, and another that analyzed the
Budapest signs and symptoms score of the Clinician + Budapest CRPS cohort. IBM’s
SPSS predictive analytic software was utilized, and a repeated measure ANOVA was
performed to analyze the data.
RESULTS

Among the 221 patients who were admitted to the PPRC, 106 patients were diagnosed with CRPS prior to admission. The patients’ Budapest Criteria data was analyzed to determine who met the clinical decision rule (report at least 2 or more signs and 3 or more symptoms) in order to calculate the sensitivity. Fifty-nine out of the 106 patients met the clinical diagnostic criteria, whereas the other 47 patients did not (Table 7). This resulted in a sensitivity of 0.56 (Table 8).

Table 7: Contingency Table Examining the Association Between the Actual Diagnoses of the Patients and Their Reports on the Budapest Criteria.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CRPS</th>
<th>Non-CRPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>59 (True Positive)</td>
<td>6 (False Positive)</td>
</tr>
<tr>
<td>Negative</td>
<td>47 (False Negative)</td>
<td>106 (True Negative)</td>
</tr>
</tbody>
</table>

Table 8: Statistical Values for the Budapest Criteria in Pediatric Patients as Calculated from the SPSS Data

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.56</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.95</td>
</tr>
<tr>
<td>Positive Likelihood Ratio</td>
<td>10.39</td>
</tr>
<tr>
<td>Negative Likelihood Ratio</td>
<td>0.47</td>
</tr>
</tbody>
</table>
The 112 patients that were admitted to the PPRC with non-CRPS pain disorders (musculoskeletal, headache or abdominal pain, and neuropathic non-CRPS pain) provided data to calculate specificity. Only 6 of the 112 patients met the clinical decision rule for CRPS, and the other 106 patients did not (Table 7). This resulted in a specificity of 0.95 (Table 8).

The values for sensitivity and specificity were used to calculate the likelihood ratios. The positive likelihood ratio was calculated to be 10.39, and the negative likelihood ratio was 0.47 (Table 8). The positive likelihood ratio of 10.39 corresponded to a value that is considered to significantly increasing the post-test probability of having the disorder when tested positive. The negative likelihood ratio corresponded to a value that fell in the range of only having a modest effect on decreasing the post-test probability of having the disorder when tested negative.

In order to determine whether the Clinician Diagnosed CRPS group (pediatric CRPS patients who satisfied the Budapest clinical criteria) and the Clinician + Budapest CRPS group (pediatric CRPS patients who did not satisfy the Budapest clinical criteria) experienced a significant decrease in pain, the CRPS patients’ Budapest scores at admission and discharge were analyzed. Out of the 106 CRPS patients, 94 patients’ Budapest scores were available. Within those 94 patients, there were 40 Clinician Diagnosed CRPS patients and 54 Clinician + Budapest CRPS patients.

We conducted a repeated measures ANOVA to explore changes in CRPS signs and symptoms from admission to discharge for both the Clinician + Budapest CRPS group (diagnosed by a physician prior to admission & verified by Budapest) and the
Clinician Diagnosed CRPS group (diagnosed by physician prior to admission but not meeting criteria on the Budapest). When looking at the signs and symptoms of patients who presented to the PPRC with a diagnosis of CRPS but which was not verified by the Budapest criteria at admission (see Figure 1), there was a main effect for time from admission to discharge, $F(1, 78)=36.35$, $p < 0.001$, indicating that both signs and symptoms significantly decreased over the course of treatment for this group as well. However, there was no significant interaction effect. When looking at the signs and symptoms of patients who presented to the PPRC with a diagnosis of CRPS and which was verified by the Budapest criteria at admission (see Figure 2), there was a main effect for time from admission to discharge, $F(1, 106)=360.20$, $p < 0.001$, indicating that both signs and symptoms significantly decreased over the course of treatment. There was no significant interaction effect, indicating that both signs and symptoms significantly improved over the course of treatment and but that the change in neither signs nor symptoms was more pronounced (i.e., a steeper slope) from admission to discharge. At admission, the mean Budapest signs scores were 1.40 and 3.31 for the Clinician Diagnosed and Clinician + Budapest CRPS group, with a standard deviation of 0.928 and 0.639, respectively (Table 9). At discharge, the mean Budapest signs scores were 0.70 and 1.33 for the Clinician Diagnosed and Clinician + Budapest CRPS group, with a standard deviation of 0.608 and 0.739, respectively (Table 10). The mean symptoms scores at admission were 1.45 for the Clinician Diagnosed CRPS group and 3.54 for the Clinician + Budapest CRPS group, with a standard deviation of 0.904 and 0.503, respectively (Table 9). The mean symptoms scores at discharge were 0.67 for the
Clinician Diagnosed CRPS group and 1.46 for the Clinician + Budapest CRPS group, with a standard deviation of 0.730 and 0.926, respectively (Table 10).

Figure 1. Repeated measures ANOVA analyses for Budapest signs and symptoms score of Clinician Diagnosed pediatric CRPS cohort.
Figure 2: Repeated measures ANOVA analyses for Budapest signs and symptoms score of Clinician + Budapest pediatric CRPS cohort.
Table 9: Descriptive Statistics of Budapest Criteria at Admission (Clinician Diagnosed n = 40, Clinician + Budapest n = 54).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>95% CI for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Signs of Clinician Diagnosed CRPS Group</td>
<td>1.40</td>
<td>0.928</td>
<td>0.145</td>
<td>1.112</td>
</tr>
<tr>
<td>Signs of Clinician + Budapest CRPS Group</td>
<td>3.31</td>
<td>0.639</td>
<td>0.078</td>
<td>3.160</td>
</tr>
<tr>
<td>Symptoms of Clinician Diagnosed CRPS Group</td>
<td>1.45</td>
<td>0.904</td>
<td>0.145</td>
<td>1.162</td>
</tr>
<tr>
<td>Symptoms of Clinician + Budapest CRPS Group</td>
<td>3.54</td>
<td>0.503</td>
<td>0.078</td>
<td>3.382</td>
</tr>
</tbody>
</table>

Table 10: Descriptive Statistics of Budapest Criteria at Discharge (Clinician Diagnosed n = 40, Clinician + Budapest n = 54).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>95% CI for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Signs of Clinician Diagnosed CRPS Group</td>
<td>0.70</td>
<td>0.608</td>
<td>0.106</td>
<td>0.489</td>
</tr>
<tr>
<td>Signs of Clinician + Budapest CRPS Group</td>
<td>1.33</td>
<td>0.739</td>
<td>0.126</td>
<td>1.083</td>
</tr>
<tr>
<td>Symptoms of Clinician Diagnosed CRPS Group</td>
<td>0.67</td>
<td>0.730</td>
<td>0.106</td>
<td>0.464</td>
</tr>
<tr>
<td>Symptoms of Clinician + Budapest CRPS Group</td>
<td>1.46</td>
<td>0.926</td>
<td>0.126</td>
<td>1.212</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Assume 70% CRPS prevalence</th>
<th>Assume 50% CRPS prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IASP</td>
<td>1.00</td>
<td>0.41</td>
<td>0.80</td>
<td>1.00</td>
</tr>
<tr>
<td>Budapest clinical</td>
<td>0.99</td>
<td>0.68</td>
<td>0.88</td>
<td>0.97</td>
</tr>
<tr>
<td>Budapest research</td>
<td>0.78</td>
<td>0.79</td>
<td>0.90</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Note: positive predictive power (PPP) and negative predictive power (NPP) are dependent on the assumed prevalence of CRPS in the population being considered. For illustrative purposes, two scenarios are presented in which either 70% or 50% of patients referred to rule CRPS in or out actually have the disorder. IASP = diagnosis based on presence of CRPS signs or symptoms using the International Association for the Study of Pain criteria.


<table>
<thead>
<tr>
<th>Positive LR</th>
<th>Negative LR</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10</td>
<td>&lt; 0.1</td>
<td>Generate large and often conclusive shifts in probability</td>
</tr>
<tr>
<td>5 – 10</td>
<td>0.1 – 0.2</td>
<td>Generate moderate shifts in probability</td>
</tr>
<tr>
<td>2 – 5</td>
<td>0.2 – 0.5</td>
<td>Generate small but sometimes important shifts in probability</td>
</tr>
<tr>
<td>1 – 2</td>
<td>0.5 – 1</td>
<td>Alter probability to a small and rarely important degree</td>
</tr>
</tbody>
</table>
DISCUSSION

This study presents an investigation in the use of the Budapest Criteria in the pediatric population, along with an evaluation of PPRC’s multimodal treatment program in mitigating the signs and symptom of CRPS. The Budapest Criteria was evaluated by analyzing its sensitivity, specificity, and the likelihood ratios in the pediatric sample of this study. The efficacy of the PPRC’s multidisciplinary treatment approach in managing pediatric CRPS was measured according to the changes, if any, in the Budapest scores of pediatric CRPS patients at admission compared to those at discharge.

The primary hypothesis, that the Budapest Criteria will demonstrate both high sensitivity and specificity, has not been supported from this study. Compared to the sensitivity of the Budapest Criteria in the adult population observed in the validation study (0.99), the sensitivity of it in the pediatric sample was lower with 0.56 (Table 8; Table 11). This indicated that the proportion of pediatric CRPS patients that actually tested positive (satisfied the clinical decision rule) was 0.56 in the study, suggesting that a little less than half of the pediatric CRPS patients actually did not meet the Budapest Criteria. However, the specificity in the pediatric sample, which was 0.95, was considerably higher compared to that of the adult population, which was 0.68 (Table 8; Table 11). This result indicated that the proportion of non-CRPS patients that did not meet the Budapest Criteria decision rule was 0.95, highlighting that the vast majority of those without CRPS were correctly tested as so. Hence the hypothesis was partially supported in that regards. Such differences between the adult and pediatric populations
may be attributable to the fundamental differences between adult and pediatric CRPS. An example of one such difference is how CRPS mainly affects the upper extremities in adults whereas it involves mainly the lower extremities in children (Low et al., 2007; Wolter et al., 2016).

The secondary hypothesis that the Budapest signs and symptoms score will decrease from admission to discharge from the PPRC has been supported. Both the Clinician Diagnosed CRPS group and the Clinician + Budapest CRPS group displayed a significant decrease in the Budapest signs and symptoms score from admission to discharge, according to the repeated measures ANOVA conducted (Figure 1; Figure 2). The mean signs and symptoms scores for the Clinician Diagnosed CRPS group at admission were 1.40 and 1.45, respectively, but decreased to 0.70 and 0.67 when measured again at discharge (Table 9; Table 10). The mean signs and symptoms scores for the Clinician + Budapest CRPS group were 3.31 and 3.54, and those at discharge were 1.33 and 1.46, respectively (Table 9; Table 10). It is evident that although the signs and symptoms scores of the Clinician + Budapest CRPS group were higher at admission, the scores decreased at a greater rate than that of the Clinician Diagnosed CRPS group (Figure 1; Figure 2). These results further supported the hypothesis that the pediatric CRPS patients will report a significant decrease in their respective Budapest scores from admission to discharge.

Sensitivity of the Budapest Criteria in Pediatric Sample
The sensitivity, which directly measure the proportion of those with CRPS is accurately diagnosed as having CRPS, being relatively low with a value of 0.56 connoted that a considerable amount of pediatric CRPS patients did not satisfy the clinical diagnostic criteria of having at least 2 or more signs and 3 or more symptoms on the Budapest Criteria. This may be due to the Budapest Criteria itself; the Budapest Criteria was created mainly using data from adult CRPS studies, and was validated using an adult population (Harden et al., 2007; Harden et al., 2010). Therefore, the subcategories that have been incorporated in the signs and symptoms, along with the diagnostic decision rules, are solely based on the CRPS presentations and prevalence in the adult population.

Most of the data regarding CRPS are derived from adult studies (Goldschneider, 2012). First, the role of neurogenic inflammation has been mainly investigated in adults. Protein extravasation, elevations in proinflammatory cytokines, and related inflammatory mediators have been observed in adult CRPS (Weber et al., 2001; Huygen et al., 2002; Munnikes et al., 2005; Schinkel et al., 2006). Furthermore, there have been a few studies examining whether there are alterations in peripheral innervation in adults with CRPS, but no data are reported in children (Albrecht et al., 2006; Oaklander et al., 2006). Thus the question remains unanswered as to whether children demonstrate similar changes in peripheral innervation and if so, how such changes contribute to the severity and presentation of the symptoms. The role of autonomic nervous system dysfunction has also been investigated in adults. For example, adult CRPS patients have reported with both cold and warm variants, while pediatric CRPS patients predominantly reports a cyanotic, cool extremity (Veldman et al., 1993; Tan et al., 2008). Hence these differences
in clinical presentations and studies, or lack thereof, may underlie the low sensitivity that resulted from this study, as the Budapest Criteria was created mostly with data on adult findings. The pathophysiology of CRPS in adult and children may not completely overlap, thus pediatric CRPS patients may not experience the exact signs and symptoms that adults do. This would result in not satisfying some of the criteria in the Budapest Criteria, which may partially explain why the sensitivity was low in this case.

Furthermore, this is consistent with the statement that pediatric CRPS is not well recognized by clinicians, resulting in diagnostic delays (Low et al., 2007). Perhaps the low sensitivity of the Budapest Criteria is contributing to the diagnostic delays, as it may improperly diagnose CRPS patients as not having CRPS. In the clinical setting, this misdiagnosis could lead to inaccurate treatment protocols, exacerbation of symptoms, unnecessary referrals, and delay of administering proper treatment regimen. Moreover, this could partially explain why pediatric CRPS has been underreported; if true pediatric CRPS patients are often misdiagnosed as having other pain disorders or neuropathic pain, the sheer number of true CRPS patients that qualifies for research purposes will be lower.

**Specificity of the Budapest Criteria in Pediatric Sample**

The specificity was extremely high with a value of 0.95, which is higher than any of the diagnostic criteria investigated in the validation study (Table 8; Table 11). In fact, it was even higher than that of the Budapest research diagnostic decision rule (0.79). This is significant as the Budapest research decision rule (satisfy all 4 symptom categories and have at least 2 or more sign categories) was established to minimize false negatives at the
extent of sensitivity for research purposes. This indicates that the Budapest Criteria was extremely successful in accurately diagnosing pediatric patients who are not afflicted with CRPS as not having CRPS; out of 112 non-CRPS patients, only 6 patients resulted in satisfying the Budapest clinical decision rules whereas the other 106 patients were distinguished as not having CRPS (Table 8). This indicates the potential usefulness of the Budapest Criteria when utilized in the pediatric population. It would be preferential to utilize the Budapest Criteria in a setting where the chief purpose is to minimize false negatives, such as when recruiting for stringent research samples, as opposed to identifying as many CRPS patients as possible in a clinical setting (Harden et al., 2007).

This high specificity, coupled with the low sensitivity, indicates that a majority of pediatric non-CRPS patients, along with a considerable fraction of CRPS patients, did not satisfy the Budapest clinical diagnostic criteria. When looking simply at the specificity, it appears that the Budapest Criteria is effective in screening out those who do not have CRPS; but when observing the considerably low sensitivity (hence even true CRPS patients do not meet the criteria), it may be implied that in general, the pediatric CRPS and non-CRPS population do not satisfy the Budapest clinical criteria.

Such observation points to whether the clinical presentations of CRPS in the pediatric populations are not entirely similar to those of the adults. It could be that the signs and symptoms are more pronounced in adults compared to children. This could contribute as to why 47 out of 106 pediatric CRPS patients did not meet the Budapest clinical diagnostic decision rule. This underlies the fact that the etiology and
pathophysiologic mechanisms of CRPS is still currently unknown, especially so in pediatric terms.

The PPRC is a tertiary referral center, admitting children and adolescents that experience exacerbating chronic pain despite outpatient treatment at other facilities. Since the PPRC mostly admits the extreme cases of chronic pain, the signs and symptoms of non-CRPS chronic pain has been well examined and diagnosed at other facilities prior to admission. Thus there was a clear and established neuropathic etiology to the conditions non-CRPS patients had, whether it was headache, abdominal pain, musculoskeletal pain, or non-CRPS neuropathic pain. This further explains how most of the pediatric non-CRPS patients successfully did not meet the Budapest Criteria, as the patients presented with obvious, non-overlapping chronic pain conditions differing from CRPS.

**Likelihood Ratios**

Likelihood ratios were calculated in order to determine the efficacy of the Budapest Criteria in its ability to change the probability that CRPS is present or not present in the respective patients. Positive and negative predictive values were not calculated because the sample sizes in the CRPS and non-CRPS groups did not reflect the actual prevalence of the disorder in reality.

The PLR, which reflected the change in probability that CRPS is present when the Budapest diagnostic clinical decision rule is met, was 10.39 (Table 8). This value may be interpreted as: the Budapest Criteria, when met, significantly increases the probability of the pediatric patient having CRPS (Table 12). In other words, the confidence in the
diagnosis of CRPS increased about 10-fold after the patient satisfied the Budapest Criteria. This result actually supports the Budapest Criteria in diagnosing CRPS, as the test conclusively shifts the probability of disease if tested positive.

The NLR, which reflected the change in probability that CRPS is present when the Budapest diagnostic clinical decision rule is not met, was 0.47 (Table 8). Thus it may be implied from the study that if a pediatric patient did not satisfy the Budapest Criteria, the probability that the patient actually has CRPS would decrease by approximately 47%. Generally speaking, if a diagnostic test has a NLR of 0.47, it is considered to have a moderate effect on decreasing the probability of having the disorder (Table 12).

It can be concluded from the PLR and the NLR that while the Budapest Criteria significantly increases the probability of a pediatric patient having CRPS when the clinical decision rule is met, the diagnostic test only modestly decreases the probability of having CRPS when the clinical decision rule is not met. This parallels the notion that the larger the PLR value the better the diagnostic test, and the smaller the NLR value the better the diagnostic test. However, the utility of the test decreases when either of the likelihood ratios approaches 1. It is important to note that likelihood ratios may influence clinical decision-making in three possible ways (Straus et al., 2005). First, the likelihood post-test probability is very high, indicating that the condition is present and further testing is unnecessary. This would be in the case when utilizing a diagnostic test with a very high PLR. Second, the likelihood of having the condition is so low that the clinician can rule out the diagnosis. Third, if the shift in probability of having the disease is inconclusive, it encourages clinicians to consider other alternate diagnostic tests. Hence
likelihood ratios are a powerful tool that integrates the results of a diagnostic test into clinical decision-making, in order to optimize the respective diagnoses (Hayden & Brown, 1999; Grimes & Schulz, 2005). The PLR and NLR values from this study indicate that while Budapest Criteria is excellent in substantiating confidence that CRPS is present when testing positive, the test should be used with caution when the patient does not meet the criteria and supplemental testing may be necessary.

The Efficacy of Intensive Rehabilitation Treatment on CRPS Outcomes: Repeated Measures ANOVA

Repeated measures ANOVA comparing the Budapest signs and symptoms scores at admission with those at discharge for the Clinician + Budapest and Clinician Diagnosed CRPS cohorts indicated a significant main effect for time, meaning that patients with CRPS had a significant resolution of signs and symptoms from admission to discharge (Figure 1; Figure 2). There were no significant interaction effects observed in both the Clinician Diagnosed and Clinician + Budapest CRPS cohorts. The mean Budapest signs and symptoms score at admission for the 40 Clinician + Budapest CRPS patients were 3.31 and 3.54, whereas those at discharge were 1.33 and 1.46, respectively (Table 9; Table 10). The Clinician Diagnosed CRPS cohorts also demonstrated a decrease in the mean Budapest signs and symptoms score, from 1.40 and 1.45 to 0.70 and 0.67, respectively (Table 9; Table 10). This significant decrease in the Budapest score indicates that the PPRC’s holistic approach, which integrates occupational therapy, physical therapy, psychological therapy, recreational activities, among others, has been
successful in not only managing CRPS, but also in alleviating the signs and symptoms associated with it.

This finding is consistent with other findings that suggest that interdisciplinary, noninvasive treatment regimen is effective in reducing disability and improving psychological and physical performance (Logan et al., 2012; Low et al., 2007; Wilder, 2006; Katholi et al., 2014). It is particularly encouraging since PPRC is a tertiary referral center, meaning that the facility receives patients that have already been unsuccessful with outpatient treatment. Therefore, this corroborates the utilization of multidisciplinary care in treating pediatric CRPS, even if the patient is resistant to traditional medications and pharmacological therapy.

**Overall Evaluation of the Budapest Criteria**

The diagnosis of pediatric CRPS using the Budapest Criteria is recommended with reservation. After evaluating its sensitivity and specificity (relatively low and high compared to the adult findings, respectively), it may be deduced that the Budapest Criteria is effective in terms of minimizing false negatives, but not necessarily in maximizing clinical identification of CRPS patients. Thus the Budapest Criteria may be beneficial when used to identify stringent research samples but not necessarily in clinical decision-making.

The likelihood ratios also provided insight regarding the utility of the Budapest Criteria by exploring the diagnostic results and its potential effects on clinical judgment. The high PLR (10.39) and the moderate NLR (0.47) suggested that while a positive test
significantly increases the odds of the patient actually having CRPS, a negative test only moderately decreases the odds of the patient actually having CRPS (Table 8). Thus if a patient is tested negative on the Budapest Criteria but the clinician still harbors a considerable suspicion, additional testing may be required.

These results suggest that a modified pediatric CPRS criteria must be explored that will demonstrate a high sensitivity while maintaining the high specificity that was demonstrated in this study. Pediatric CRPS may have similar pathophysiologic mechanisms to adult CRPS, but clinical manifestations may differ. Some possible differences might include but are not limited to: pain threshold, degree of signs and symptoms, and the nature of signs and symptoms. The Budapest Criteria was established upon adult CRPS studies and findings; therefore, it is imperative to fully examine the signs and symptoms prevalent for pediatric CRPS and create the appropriate subcategories in the Budapest Criteria to optimize diagnostic accuracy.

**Interdisciplinary Treatment of Pediatric CRPS**

Through repeated measures ANOVA analyses of the Budapest scores of pediatric CRPS patients, it has been exemplified that the PPRC has been successful in decreasing the patients’ pain levels through their enrollment to the day treatment rehabilitative program. This outcome is consistent with other studies examining the efficacy of multidisciplinary pediatric pain rehabilitation centers (Odell & Logan, 2013; Wilder, 2006; Stanos, 2012; Turk, 2002). However, compared to the abundance of studies regarding adult pain centers, there is a scarcity of research done on pediatric pain.
rehabilitation centers (Odell & Logan, 2013). Furthermore, the larger issue is that there are only a handful of studies actually examining the mechanisms behind the multidisciplinary approach (Odell & Logan, 2013). There is a dire need to elucidate the processes and mechanisms that enable programs like PPRC to be successful in significantly reducing pain and improving function. Thus observing and analyzing the multidisciplinary pediatric pain programs’ treatment regimens will first provide insight into optimal treatment structure. Further analyzing the CRPS patients’ profile and clinical manifestations through retrospective chart review may possibly clarify the pathophysiology of CRPS. Through these studies, it may be possible in the near future to develop a standardized protocol that will effectively manage and treat the signs and symptoms of not only CRPS, but also for other chronic pain conditions as well. Inter-program collaboration will indeed provide the data necessary to conduct further research into the field of pediatric chronic pain.

**Evaluation of Study Design**

One of the strengths of this study was that a single physician administered the Budapest Criteria to the pediatric patients at the PPRC. This allowed for consistency in evaluating the patients’ signs and symptoms, with minimal discrepancy in the evaluation method. Another factor that contributed to the validity of the study was the large sample size. Having 218 pediatric pain patients to evaluate the sensitivity, specificity, and likelihood ratios of the Budapest Criteria substantiated the results of the study. The large sample size not only is more representative of the pediatric pain population, but also
minimizes the effects of outliers and maximizes the accuracy of the extrapolated data regarding the Budapest Criteria. Being able to utilize 94 patients’ Budapest scores at admission and discharge (in order to assess whether PPRC was successful in alleviating the signs and symptoms of CRPS) also benefited from the advantages of having a large sample size.

The limitations of this study consist of the lack of Budapest data at certain time points for several patients. Out of the 221 admitted pediatric patients, 3 of the patients’ data were not available. Furthermore, we were not able to use 12 of the 106 pediatric CRPS patients’ Budapest Criteria to examine the difference at admission vs. discharge, as the data was missing at either one point or at both points. The decrease in sample size due to such factors may have slightly decreased the representative value of the results in this study.

**Future Directions**

In continuation of this study, we are determined to first relocate the Budapest Criteria reports of all 106 pediatric CRPS patients. This is made possible by consulting the electronic medical records with the physician that administered the Budapest Criteria to the patients and completing the Budapest Criteria for each patient accordingly. Because the physician administered these Budapest Criteria at various times—admission, discharge, first follow up (1 month), second follow up (6 months), and third follow up (1 year)—we will be able to perform a repeated measures ANOVA on the pediatric CRPS patients at five time points. The increase in sample size and in the number of time points...
will provide greater insight in regards to the efficacy of multidisciplinary treatment for pediatric CRPS.
REFERENCES


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CURRICULUM VITAE

SungJun Son
Juns@bu.edu
(404)-680-0280
Birth Year: 1991

Current Address: 1661 Washington Street #305
Boston, MA 02118

Permanent Address: 3-12-1-F901 Minami Karasuyama Setagaya-ku
Tokyo, Japan 157-0062

EDUCATION

Boston University School of Medicine, Graduate Medical Sciences
Master of Science in Medical Sciences
Sept 2014 – Present
Boston, MA

Emory University, College of Arts & Sciences, Atlanta, GA
Bachelor of Science in Neuroscience and Behavioral Biology
May 2014
Atlanta, GA

Dean’s List Fall 2010, Spring 2011, Fall 2011, Spring 2012, Fall 2013, Spring 2014

RESEARCH EXPERIENCE

Boston Children’s Hospital – Biobehavioral Pediatric Pain Lab, Research Intern
Aug 2015 – Present
Boston, MA

• Investigated how chronic mild stress specifically affect subsequent acute and chronic hypersensitivity responses in mice model.
• Analyzed the outcomes of youth and young adults with idiopathic scoliosis undergoing spinal fusion surgery.
• Explored the Budapest CRPS criteria in pediatric population and investigated the efficacy of multidisciplinary treatment in alleviating pediatric CRPS.

Dr. Mitsi Blount Renal Medicine Lab, Research Volunteer
Sept 2012 – Dec 2012
Atlanta, GA

• Investigated the role of water transport in calcification in diabetic Vas Deferens using a mice model.

Summer Undergraduate Research Program at Emory (SURE Program)
May 2012 – Aug 2012
Atlanta, GA

• Investigated microwave-assisted synthesis of 4 and 4’ substituted 3, 5-diphenylisoxazoles with Dr. Nichole Powell.
• Received Honorable Mention for research poster presentation at the SURE Program Poster Symposium.
• Poster presented at the 2013 Southeastern Regional Meeting.
Dr. Reza Saadein Chemistry Lab, Research Assistant
Sept 2011 – May 2012 Atlanta, GA
• Investigated synthesis and anti-cancer properties of 2, 9-disubstituted phenanthroline Gold (III) complexes.

LEADERSHIP EXPERIENCE

Boston University Graduate Medical Sciences Student Organization, Master’s Chair
Feb 2015 – May 2016 Boston, MA
• Exercised professional leadership via maintaining general correspondence between appropriate parties, addressing students’ concerns, and executing ways to improve the students’ experience in the community.
• Activities organized include Movember and Red Cross Blood Drive.

Masters in Science in Medical Science, Subcommittee Member
Feb 2015 – May 2016 Boston, MA
• Served as a liaison between current students, prospective students, and the faculty as a representative of Boston University’s M.S. in Medical Sciences program.
• Responsibilities included conducting campus tours, positioning myself as an available resource for prospective students, and organizing meetings with the faculty to discuss approaches to enhance the program and its students.

Emory Japanese Undergraduate Student Tutoring (EJUST), Founder
May 2013 – May 2014 Atlanta, GA
• EJUST is a student-led academic assistance program specifically designed to facilitate students in Japanese classes.
• The selected tutors regularly post their available times and location on the Facebook group page so that students may easily seek assistance from the tutors regarding Japanese.
• As the executive director, I organized the tutoring schedules, managed the program’s online platform, and worked closely with the Japanese department in order to maximize students’ success in learning Japanese.

TEACHING EXPERIENCE

Boston University Graduate Medical Sciences, Biochemistry and Physiology Tutor
Sept 2015 – May 2016 Boston, MA
• For the fall 2015 semester, I was a biochemistry tutor for 3 graduate students (Masters in Medical Sciences program (MAMS)), a physiology tutor for 8 graduate students (MAMS), and a physiology tutor for 3 dental students in Boston University School of Dental Medicine.
• For the spring 2016 semester, I was a physiology tutor for 4 graduate students (MAMS).
SERVICE EXPERIENCE

Boston Medical Center, Volunteer Ambassador
Feb 2015 - Present Boston, MA
• The duties include guiding patients to their destinations, manning the information desk, and being a reliable resource for patients at Boston Medical Center (BMC).

Winship Cancer Institute, Infusion Center Volunteer
June 2013 – July 2014 Atlanta, GA
• As a volunteer at the Infusion Center, I served as a liaison between patients and nurses, assisted the staff in transporting lab work and pharmaceutical drugs, and organized resources.

Project Students Helping in Naturalization and English (SHINE)
Jan 2013 – May 2014 Atlanta, GA
• Project SHINE (Students Helping in Naturalization and English) is a service learning initiative that connects Emory students with the Atlanta community’s new American-immigrants and refugees.
• I taught English to immigrants and refugees at Georgia Piedmont Technical College as a teacher’s assistant on a weekly basis.

HONORS AND AWARDS

Emory University
Aug 2010 – May 2014 Atlanta, GA
• Phi Eta Sigma National Honor Society
• Alpha Epsilon Upsilon
  ▪ Phi Sigma Biological Sciences Honor Society
  ▪ Phi Sigma Iota Foreign Language Honor Society
  ▪ Omicron Delta Kappa Leadership Honor Society
  ▪ 100 Senior Honorary