Characteristics and Outcomes of Children with Enthesitis in Juvenile Idiopathic Arthritis

By

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ABSTRACT

Objectives - To describe the prevalence, associated characteristics, and course of enthesitis in a inception cohort of children with juvenile idiopathic arthritis (JIA) and to estimate the impact of enthesitis on patient reported outcomes (PROs) in these children, irrespective of their JIA category.

Methods - Canadian children newly diagnosed with JIA between 2005 and 2010 followed for up to 5 years in the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) cohort were studied. The presence of entheseal tenderness by physician examination at 33 sites shown on a homunculus, Juvenile Arthritis Quality of life Questionnaire (JAQQ), Quality of My Life questionnaire (QoML), Childhood Health Assessment Questionnaire (CHAQ), and a pain severity visual analogue scale (VAS) were completed at enrolment, every six months for 2 years, and then yearly up to 5 years. Analyses consisted of descriptive statistics, linear mixed models for longitudinal data, and ANCOVA.

Results - Of 1406 patients, 219 (16%) had enthesitis and, of those with enthesitis, 141 (64%) were classified as having enthesitis-related arthritis (ERA). Children with enthesitis were more often older (10.7 versus 7.5 years), male (57% versus 31%), and with polyarthritis (57% versus 41%) and sacroiliac involvement (30% versus 4%). Entheseal tenderness was most frequent at the calcaneal plantar fascial insertion (39%), Achilles tendon insertion (31%), and tibial tuberosity (30%). The mean number of tender entheseal sites decreased in parallel with active joint counts. There was no difference in active joint counts over time in children with or without enthesitis ($p = 0.73$). A total of 1371 patients reported at least one PRO. These patients were

followed for a median of 35.3 months. After adjusting for JIA category and covariates, children with enthesitis reported higher JAQQ (mean raw score 2.71 vs 2.16; adjusted difference 0.41 points; 95% CI 0.22, 0.59), higher CHAQ (0.47 vs 0.31; 0.14 points; 0.07, 0.22), higher pain (3.01 vs 1.68; 0.94 points; 0.64, 1.25) and lower QoML (7.02 vs 8.23; -0.80 points; 95% CI -1.09, -0.51) scores than children without enthesitis. These differences persisted up to five years after diagnosis.

Conclusion - Enthesitis was observed in 16% of patients with JIA, but only two thirds were categorized as having ERA. Contrary to expectations, most children with enthesitis had polyarticular involvement. The course of enthesitis paralleled the course of active joint counts. Children with enthesitis, regardless of JIA category, report worse PROs than those without enthesitis. Physicians should assess for enthesitis in all children with JIA and, if present, make it a treatment target. Enthesitis should be considered as criterion for classification and assessment of treatment response in JIA.

PREFACE

This thesis is an original work by Dax Gerard Rumsey. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, "Characterizing Enthesitis in a Cohort of Canadian Children with Juvenile Arthritis: Clinical Course, Impacts on Quality of Life, and Response to Treatment," Pro00058892, January 2016 (renewed to November 2018).

The data for this thesis is from a National Cohort study called the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) cohort. This cohort was designed and implemented by the Canadian Alliance of Pediatric Rheumatology Investigators (CAPRI), of which Dr. Jaime Guzman and Dax G. Rumsey are members.

Chapter 2 of this thesis has been published as Rumsey DG, Guzman J, Rosenberg AM, Huber AM, Scuccimarri R, Shiff NJ, Bruns A, Feldman BM, Eurich DT; Research in Arthritis in Canadian Children Emphasizing Outcomes Investigators. Characteristics and Course of Enthesitis in a Juvenile Idiopathic Arthritis Inception Cohort. Arthritis Care Res (Hoboken). 2018 Feb;70(2):303-308. doi: 10.1002/acr.23256. I was responsible for the data organization, extraction, and analysis as well as the manuscript composition. I also helped develop the research questions. D. Eurich was my main research supervisor. He was responsible for deciding on the statistical analyses required. He guided me along the way and edited the manuscript extensively throughout. J. Guzman came up with the research questions for the project. He is also the main custodian for the data and did a lot of the data cleaning. He also helped guide me along the way and also edited the manuscript extensively throughout. A. Kozyrskyj provided additional support, guidance, and editing suggestions along the way.

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The author would like to acknowledge the additional support and guidance from his other supervisor, Dr. Anita Kozyrskyj. Dr. Kozyrskyj is a Professor in the Department of Pediatrics, Division of Pediatric Respirology, Pulmonary, and Asthma. She is the Principal Investigator of SyMBIOTA (Synergy in Microbiota), one of 7 CIHR funded Canadian human microbiome team grants and is an Adjunct Professor in the School of Public Health, University of Alberta.

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LIST OF ABBREVIATIONS

CHAQ – Childhood Health Assessment Questionnaire

ERA – Enthesitis-Related Arthritis

ESR – Erythrocyte Sedimentation Rate

HLA-B27 – Human Leukocyte Antigen-B27

HRQoML – Health-Related Quality of My Life

IBD – Inflammatory Bowel Disease

ILAR – International League of Associations for Rheumatology

JAQQ – Juvenile Arthritis Quality of Life Questionnaire

JIA – Juvenile Idiopathic Arthritis

MRI – Magnetic Resonance Imaging

Pain VAS – Pain Visual Analogue Scale

PRO(s) – Patient Reported Outcome(s)

QoML – Quality of My Life

ReACCh-Out – Research in Arthritis in Canadian Children Emphasizing Outcomes

RF – Rheumatoid Factor

CHAPTER 1: INTRODUCTION

1.1 Statement of the Problem

Juvenile Idiopathic Arthritis (JIA):

Juvenile idiopathic arthritis (JIA) is a chronic disease of childhood, affecting about 1 in 1000 Canadian children (1). By definition, the symptoms must start before the age of 16 years (juvenile), other causes of arthritis must be ruled out, such as infection, trauma, and other diseases like Inflammatory Bowel Disease (IBD) (idiopathic), and there must be inflammation in one or more joints (arthritis). It must also be chronic (lasting at least 6 weeks) (1).

There are 7 different categories of JIA recognized by the International League of Associations for Rheumatology (ILAR) (1, 2), which likely represent different disease entities with different underlying biology. These 7 categories include: oligoarticular JIA (arthritis involving 4 or less joints in the first 6 months of disease), polyarticular rheumatoid factor (RF) positive JIA (arthritis involving 5 or more joints in the first six months of disease, along with repeated positive RF blood tests), polyarticular RF negative JIA (similar to polyarticular RF positive except that RF is negative), systemic JIA (arthritis associated with systemic features, including fevers and characteristic rash), psoriatic JIA (arthritis and psoriasis or arthritis and at least 2/3 other characteristic features), enthesitis-related arthritis (ERA, arthritis and enthesitis (defined below) or arthritis or enthesitis plus at least 2/5 other features), or undifferentiated JIA (arthritis that does not meet criteria for any other category or meets criteria for more than one category). The ILAR classification system and its subsequent revisions were developed by consensus by an international taskforce of leading pediatric rheumatologists with the aim of achieving homogeneity within disease categories to facilitate clinical and basic research, and to eliminate

inconsistencies resulting from the use of previous classification systems (1, 2). It is by no means a perfect system, but it has been the generally accepted international classification system for JIA since its initial development in 1995. Research is currently underway to better characterize the biologic basis of each of these categories. As it stands, the etiology of JIA is unknown, but is felt to be multi-factorial. An environmental trigger(s) likely sets the disease in motion in a child who is genetically pre-disposed to developing JIA (1).

Most categories of JIA are felt to be autoimmune diseases, meaning that the adaptive immune system of these patients 'attacks' their joints and sometimes other organs, most notably the anterior part of the eyes (i.e. anterior uveitis). The exception is systemic JIA, which is felt to be an autoinflammatory disease, meaning that there is a defect(s) in these children's innate immune system (a more primitive system, relative to the adaptive immune system), resulting in fevers, rashes, and other 'systemic' symptoms, in addition to the arthritis (1, 3).

Overall, JIA is more common in females than males, but the ERA category is more common in boys. Reported male-to-female ratios in patients with ERA range from 1.4:1 (USA) to 8:1 (Spain) (4, 5). In two Canadian cohorts, the male-to-female ratios were 3.4:1 and 4.1:1 (6, 7). Juvenile ankylosing spondylitis (JAS), a term used by some for patients with axial involvement (typically, a subset of patients with ERA) has an even higher male predilection. Of 247 children with JAS across multiple studies, 216 were boys, for a male-to-female ratio of 7:1 (8-12). However, this predominance of boys may represent differences in disease presentation rather than the actual distribution of disease between the sexes. The strong correlation of JAS and ERA with the human histocompatibility antigen HLA-B27 and the equal distribution of this antigen in

males and females suggest that the true prevalence of JAS and ERA could be more equal between sexes than it appears. Furthermore, in radiographic surveys of HLA-B27-positive adult blood donors, arthritis of the sacroiliac joint(s) was as common in women as in men (13). In women, manifestations of the disease may occur later and be less severe, and they may have more peripheral and less axial disease. These differences in presentation may contribute to the relative infrequency of the diagnosis in women (14-17).

The cause of ERA is unknown. However, there are a lot of similarities (clinical, genetic, and epidemiologic) between ERA and diseases such as reactive arthritis. Reactive arthritis is known to be triggered by enteric and genitourinary tract infections. This suggests a potential infectious etiology of ERA, although this has yet to be proven. No organisms have been isolated from the joints of patients with AS (or JAS), but antibody and cellular immunity studies provide evidence of a local inflammatory response to an antigen. This is an area of active research at present (17-19).

Juvenile arthritis has a highly variable burden of disease, in terms of pain, disability, and impact on quality of life, depending on such factors as the category of JIA, extent of joint involvement, response to treatment, and side effects of treatment (20, 21). Oen et al. (20) found that most children with JIA followed a trajectory with minimally or mildly impaired health-related quality of life, but that a minority followed unfavourable trajectories, with persistent major impairment over time. A recent qualitative study of the parents of patients with JIA showed that these families often experience complex emotional rollercoaster-like journeys as the arthritis, pain, and treatments wax and wane over time (22).

Enthesitis:

Enthesitis, or inflammation at the sites of attachment of tendon, ligament, joint capsule, or fascia into bone, is a feature characteristically associated with ERA. However, according to the ILAR classification, it is possible to have ERA without having enthesitis. Further, enthesitis has been reported in several other categories of JIA, particularly psoriatic arthritis and undifferentiated arthritis (23). No prior study has systematically examined the characteristics and course of enthesitis in patients with all categories of JIA.

While joints enable the mobility of the skeletal system, entheses are essential structures for the transduction of mechanical forces from muscle to bone and, hence, are the basis for locomotion (24). Entheses contain a specific immune microenvironment that may be activated by a combination of mechanical stress, genetic susceptibility, and microbial-triggered immune activation (24). Enthesitis is associated with prostaglandin E2-mediated vasodilatation and activation of the IL-23-IL-17 axis, which leads to the influx of innate immune cells and homing of inflammation into the entheses. This is later followed by mesenchymal tissue responses and new bone formation (24).

Enthesitis is typically ascertained by clinical examination by assessing for tenderness at the entheseal site (17, 24). However, the question of whether entheseal tenderness reliably represents inflammation versus hyperalgesia is difficult to answer (8). Thus, in recent years, there has been a push to develop better methods for the detection and monitoring of enthesitis. Magnetic resonance imaging (MRI) and ultrasound have been used mostly in research to date

(24-28). These imaging modalities do not always show inflammatory changes at sites that are clinically tender and sometimes show 'subclinical' enthesitis. Whether the imaging is sensitive enough to detect 'early enthesitis' at certain sites and the relative importance of 'enthesitis' that shows up on imaging but is clinically quiescent are still matters of debate (24, 29).

In recent years, there has been a move to categorize JIA based more on underlying biologic similarity rather than on clinical features alone (30). It has been suggested that ERA is not a category of JIA with unique characteristics since it shares several features with some patients with psoriatic JIA, including older age at diagnosis, axial involvement, and enthesitis, among others (23). This suggests a shared underlying biology between these two categories. Other authors have proposed the term juvenile spondyloarthritis (JSpA) to encompass ERA, JAS, psoriatic arthritis, and inflammatory bowel disease (IBD)-associated arthritis (31).

Our cohort (i.e. The Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) Cohort, described below) was similar to previous cohorts of patients with ERA in that the children with enthesitis were predominantly adolescent boys in whom sacroiliitis (arthritis of the sacroiliac joint(s) in the lower back) and HLA-B27 positivity (a genetic marker associated with this 'family' of arthritis, including adult ankylosing spondylitis) were both more common than in the children without enthesitis (32-34). A key difference between our study and previous literature in this area is that we focused on all children who developed the clinical manifestation of enthesitis (irrespective of JIA category) and compared them to children without enthesitis, whereas previous studies compared children with ERA (regardless of whether they had enthesitis or not) and compared them to children with other categories of JIA.

Studies of enthesitis in children with JIA to date have been limited due to small sample size (i.e. less 100 subjects) (4, 32) and a focus on comparing patients with ERA to those with other categories of JIA instead of comparing children with versus without enthesitis (4, 32). Enthesitis is known to negatively affect quality of life and to contribute to disease activity in adult patients with ankylosing spondylitis (35). Among children with JIA, there have been no studies looking specifically at the frequency of enthesitis over time, its relationship to joint counts over time, or its impact on quality of life, pain, and function.

Since enthesitis is known to negatively affect quality of life and contribute to disease activity in adults, identifying and tracking it well over time in children would clearly be beneficial. It could and should be a target of treatment. Doing a better job of monitoring and treating enthesitis could change the clinical course of this population of children with JIA.

Most research on the treatment of JIA to date has focused on the impacts of treatment on reducing composite outcome measures that include such factors as joint counts, abnormal laboratory tests (e.g. ESR, an inflammatory marker), and physician global assessment scales. Little attention has been paid to patient-reported outcomes (PROs), until recently. Recent research has shown that there is poor correlation between physician assessments and PROs, suggesting that increased attention to PROs is warranted (36, 37).

Patient-Reported Outcomes:

Patient-reported outcomes (PROs) are becoming increasingly important in this age of well-informed patients and families, patient-centred care, and shared decision making (38). Pediatric rheumatology is no exception to this trend. PROs provide valuable insight into how the patients/families perceive that they are doing. As more PROs are studied, it has become clear that physician-based assessments often 'miss the mark,' at least from the patient's perspective. This provides physicians with humbling, but crucial, information (36, 37).

Common PROs used in the assessment of children with JIA include health-related quality of life measures (such as the Juvenile Arthritis Quality of Life Questionnaire or JAQQ and the Health-Related Quality of My Life (HRQoML) scale of the Quality of My Life (QoML) questionnaire), self-reported functional measures (such as the Childhood Health Assessment Questionnaire, CHAQ), and measures of pain (such as the pain visual analogue scale, pain VAS) (39-43; APPENDIX 1).

The JAQQ is a validated JIA-specific non-preference-based questionnaire which includes 74 items in four domains: gross motor, fine motor, psychosocial, and systemic symptoms. The items are scored from 1 (indicating no difficulty with a given activity) to 7 (indicating difficulty 100% of the time in the preceding 2 weeks). The mean of the 5 highest-scoring items within a domain comprise each domain score and the mean of the 4 domain scores comprises the total score (39, 42). The QoML questionnaire, on the other hand, is not specific to JIA. It is a preference-based questionnaire with two visual analogue scales (VAS) with two scales from 0 (worst) to 10 (best). The first scale is for overall quality of life and the second scale (HRQoML)

is for HRQoL (40).

The CHAQ is a JIA-specific instrument that measures functional deficits in daily living in children with this disease (41). Scores can range from 0 = no difficulty with any task to 3 = unable to do many tasks. The Pain VAS is a 10 cm horizontal line used to assess average pain attributed to arthritis in the last week from 0 indicating no pain to 10 indicating very severe pain (39).

Previous studies of PROs in JIA have been limited by sample size (i.e. < 400 subjects) and relatively short follow-up time for longitudinal cohorts (i.e., <3 years), or the use of cross-sectional data and a low prevalence of enthesitis (<5%) (4, 21). Moreover, not all the patients with ERA in the previous cohorts had enthesitis and some of the patients with other categories of JIA had enthesitis. No study to date has sought to estimate the impact of enthesitis, irrespective of JIA category, on PROs in children with JIA.

Several studies have shown that children with ERA report more frequent pain, higher pain intensity, and greater impairment of function and quality of life compared to children in the other categories of JIA. Weiss et al (4) noted that children with ERA in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry reported more frequent pain, higher pain intensity, and greater impairment of function compared to children with other categories of JIA. The presence of enthesitis was a risk factor for continued disease activity at 8 years of follow up in a Nordic cohort of children with JIA (44). Enthesitis is known to negatively affect quality of life (Ankylosing Spondylitis Quality of Life questionnaire) and to contribute to disease activity

(Bath Ankylosing Spondylitis Disease Activity Index) in adults with ankylosing spondylitis (35). Taxter et al. (21) looked at PROs over time in children with various categories of JIA. Among the 398 patients in that study, 92 (23%) were classified as having ERA, 27 (7%) had psoriatic JIA, and 31(8%) had undifferentiated JIA. Although they did not specifically report the number of patients in each of these categories who had enthesitis, these are the categories classically associated with the presence of enthesitis. Children with ERA and undifferentiated JIA reported a significantly higher prevalence of pain than other children with JIA. Children with ERA, psoriatic JIA, and undifferentiated JIA reported moderate and severe pain more frequently than children with other categories of JIA ($p<0.01$). In a multivariate analysis of the 92 children with ERA in that cohort, female sex and tender enthesis count were significant predictors of decreased quality of life, higher pain, and worse function (21). Oen et al. (20) have examined PRO trajectories in children with JIA. They found that the odds of following a JAQQ trajectory with persistent major impairment of quality of life versus one with minimal impairment were significantly increased for children with ERA relative to those with oligoarthritis (OR 3.20, 95% CI 1.30, 7.89). The same held true in terms of the odds of following an unfavourable quality of life trajectory when measured with the HRQoML scale (OR 11.72, 95% CI 3.76, 36.53) (20).

The Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) Cohort:

To help close the information and evidence gap in JIA, the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) cohort was established. This cohort is one of the largest prospective cohorts of children with JIA in the world to date. It includes approximately 1500 children with JIA from 16 pediatric rheumatology centres in Canada (14

academic and two community). Recruitment to the cohort occurred between January 2005 and December 2010 and these children were followed up to 5 years and contributed information on a total of almost 15,000 patient visits (45-47).

Detailed demographic, clinical (history, physical, physician assessments, medications, laboratory results), and PROs were collected. There were 8 main study visits (at enrolment, 6 months, 12 months, 18 months, 24 months, 3 years, 4 years, and 5 years), at which the most detailed information was collected. Then, if the patients came for additional visits in between these study visits, basic information was further collected. This cohort provided the data for my thesis work.

1.2 Summary

JIA is a common chronic disease of childhood, affecting 1 in 1000 Canadian children. There are 7 different categories of the disease. Several of these categories involve the clinical manifestation of enthesitis (inflammation at sites of attachment of tendon, ligament, joint capsule, or fascia into bone) in addition to arthritis. Enthesitis has yet to be properly characterized in children with JIA. There are suggestions that it negatively affects quality of life in those who experience it; however, studies have been limited. The ReACCh-Out cohort, a prospectively collected database of 1500 Canadian children with JIA followed for up to 5 years includes detailed information about enthesitis, various other clinical measures, demographic data, and PROs. Thus, it provided an ideal opportunity to describe enthesitis in children with JIA, its relation to other variables, and its effect on various PROs.

1.3 Objectives

My work has two major objectives, which are addressed in chapters 2 and 3 of this thesis.

The first objective is to describe the prevalence, associated characteristics, and course of enthesitis over time across children with JIA of all categories, and its relationship to active joint counts (arthritis) in these children.

The second objective is to estimate the impact of enthesitis, irrespective of JIA category, on various patient reported outcomes (PROs), i.e. measures of health-related quality of life, function, and pain, in children with JIA.

1.4 Program of Research

The focus of my thesis work is on children with JIA. In particular, I am interested in the manifestation of enthesitis (inflammation at sites of attachment of tendon, ligament, joint capsule, or fascia into bone). I described the characteristics and course of enthesitis in children with JIA and examined PROs in children with versus without enthesitis.

As described above, the ReACCh-Out cohort is a rich database of Canadian children with JIA. It is one of the largest inception cohorts of children with JIA to data and had all the necessary variables for my project.

Two manuscripts were written to fulfill the objectives of the thesis. Both studies used data from the ReACCh-Out cohort. The first study (Chapter 2) was largely a descriptive analysis of the

characteristics of children with enthesitis versus those without, the timing of enthesitis detection, the distribution of involvement of various anatomic sites of enthesitis, the frequency of enthesitis over time, and the relationship between active enthesitis and active arthritis (joint counts). This is the largest cohort of children with JIA in which the characteristics of enthesitis have been described and published (47).

The second study (Chapter 3) examined the impact of enthesitis on PROs in children with enthesitis, irrespective of JIA subtype, over time. The specific PROs analyzed were measures of health-related quality of life (including the JAQQ and HRQoML scale of the QoML questionnaire), a measure of function (the CHAQ), and a measure of pain (pain VAS).

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CHAPTER 2: CHARACTERISTICS AND COURSE OF ENTHESITIS IN A JIA INCEPTION COHORT[1]

2.1 Abstract

Objective - To describe the prevalence, associated characteristics, and course of enthesitis in a juvenile idiopathic arthritis (JIA) inception cohort.

Methods - Canadian children newly diagnosed with JIA between 2005 and 2010 were categorized using International League of Associations for Rheumatology criteria at the 6-month visit and followed in the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) cohort for up to 5 years. The presence of entheseal tenderness on examination at 33 sites shown on a homunculus was recorded at 0, 6, 12, 18, 24, 36, 48, and 60 months after enrolment. Enthesitis was defined as entheseal tenderness at more than 1 site or on more than 1 occasion. Analyses consisted of descriptive statistics and linear mixed models for longitudinal data.

Results - Of 1406 patients, 219 (16%) had enthesitis and, of those with enthesitis, 141 (64%) were classified as having enthesitis-related arthritis (ERA). Children with enthesitis were more often older (10.7 versus 7.5 years), male (57% versus 31%), and with polyarthritis (57% versus 41%) and sacroiliac involvement (30% versus 4%). Entheseal tenderness was most frequent at the calcaneal plantar fascial insertion (39%), Achilles tendon insertion (31%), and tibial tuberosity (30%). The mean number of tender entheseal sites decreased in parallel with active joint counts. There was no difference in active joint counts over time in children with or without enthesitis ($p = 0.73$).

[1]Rumsey DG, Guzman J, Rosenberg AM, Huber AM, Scuccimarri R, Shiff NJ, et al., on behalf of the ReACCh-Out Investigators. Characteristics and Course of Enthesitis in a Juvenile Idiopathic Arthritis Inception Cohort. Arthritis Care Res (Hoboken) 2018; Feb;70(2):303-308. doi: 10.1002/acr.23256.

Conclusion - Enthesitis was observed in 16% of patients with JIA, but only two thirds were categorized as having ERA. Contrary to expectations, most children with enthesitis had polyarticular involvement. The course of enthesitis paralleled the course of active joint counts.

2.2 Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood, with a prevalence of approximately 1 per 1,000 children in industrialized nations (1). Its etiology is unknown and its presentation heterogeneous. There are 7 categories of JIA, which likely represent different disease entities with different underlying biology. Enthesitis, inflammation of the attachment sites of tendon, ligament, joint capsule, or fascia into bone, is a feature that characterizes the JIA category of enthesitis-related arthritis (ERA). ERA is more common in males than females (17). This is in contrast to the other categories of JIA, most of which are more common in girls (except systemic JIA, which is equally prevalent in boys and girls). According to current International League of Associations for Rheumatology (ILAR) criteria (1), however, it is possible to have ERA without having enthesitis. Further, enthesitis has also been reported in other categories of JIA, including psoriatic arthritis and undifferentiated arthritis (23). No study has systematically examined in a prospective way the prevalence and course of enthesitis across all JIA categories.

It has been suggested that ERA is not a JIA category with unique characteristics, since some children with psoriatic JIA share characteristics, such as older age at diagnosis, axial involvement, and enthesitis. This suggests a similar underlying biology between these two categories (23). Other authors have proposed the term juvenile spondyloarthritides to encompass ERA, juvenile ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease–associated arthritis in an analogous way to the classification of spondyloarthritides in adults (31). This has therapeutic implications, since adults with spondyloarthritides and rheumatoid arthritis respond best to different treatment strategies. Spondyloarthritides are thought to result from

activation of the IL-23-IL-17 axis, so newer biologic therapies targeting this pathway in particular are now being used (mostly in the adult population at present). One such medication, Ustekinumab, is a human monoclonal antibody that binds to and interferes with the pro-inflammatory cytokines IL-12 and IL-23 (48). On the other hand, this drug is not typically used for patients with rheumatoid arthritis and, in fact, has been shown to be ineffective in these patients (49).

Enthesitis results from prostaglandin E2-mediated vasodilatation and activation of this same IL-23-IL-17 axis. This leads to the influx of innate immune cells and homing of inflammation into the entheses. This is later followed by mesenchymal tissue responses and new bone formation (24). It is a characteristic lesion of spondyloarthritis, both in children and adults.

Enthesitis is typically ascertained on clinical examination by assessing for tenderness at 'typical' entheseal sites (24). Rheumatologists (pediatric and adult) do this routinely during their examinations of patients with suspected or known spondyloarthritis. In our study, all the participating rheumatologists were instructed to check for enthesitis in all children, regardless of their category of JIA.

Key limitations in studies of enthesitis to date have been small sample size (32) and a focus either on comparing ERA to other JIA categories rather than describing enthesitis per se (4, 32) or on specific features of children with ERA (4). Weiss et al (32) described the characteristics of 32 children with ERA and found that enthesitis was most likely to occur in the lower extremities of adolescent males, and was likely to persist 6 months later. They found that the most

commonly observed tender entheses were the patellar ligament insertion on the inferior pole of the patella, the plantar fascial insertion on the calcaneus, and the plantar fascial insertion on the metatarsal heads (32). This was similar (but, not exactly the same) to what we observed in the present study [Figure 2-1(a)]. In that study, the odds of having active enthesitis at the 6-month follow-up visit were significantly higher with increased number of tender entheses present at the initial visit (32).

In a study of children in the Childhood Arthritis and Rheumatology Research Alliance registry, Weiss et al (4) noted that children with ERA reported more frequent pain, higher pain intensity, and greater impairment of function compared to children with other categories of JIA. This suggested that the current treatments (at the time, which are similar to today's treatments) may not be equally effective for disease manifestations that are particular to patients with ERA (namely, enthesitis and sacroiliac tenderness) (4).

The presence of enthesitis was a risk factor for continued disease activity at 8 years of follow up in a Nordic cohort of children with JIA (44). A major strength of that study was the near population-based cohort structure and long-term follow-up (88% of the patients were followed for at least 8 years) (44). Enthesitis is known to negatively affect quality of life (Ankylosing Spondylitis Quality of Life questionnaire) and to contribute to disease activity (Bath Ankylosing Spondylitis Disease Activity Index) in adult patients with ankylosing spondylitis (35). To date, there have been no published data on the frequency of enthesitis over time or its relationship to joint counts in children with JIA.

The Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) cohort is

one of the largest prospective JIA inception studies published to date (46). ReACCh-Out included prospective periodic determination of the presence of enthesitis at 33 defined body sites for up to 5 years after JIA diagnosis. We used this rich resource to describe the prevalence, associated characteristics, and course of enthesitis over time across all JIA categories, and its relationship to active joint counts.

2.3 Patients and Methods

The general methods of the ReACCh-Out study have been described previously (46). Briefly, children (<16 years) newly diagnosed with JIA, as defined by ILAR criteria (1), at 16 Canadian centers from 2005 to 2010 were followed for up to 5 years (46). JIA category was assigned by the attending rheumatologist based on information available at the 6-month visit and verified against ILAR criteria by the ReACCh-Out investigators. All children with >1 visit were included in this analysis.

Methods:

Research ethics board approval from the University of Alberta was obtained for this project. Ethics approval had been previously obtained from each of the 16 participating Canadian centers for data collection. The presence of entheseal tenderness on examination at 33 sites shown on a homunculus was recorded by practicing pediatric rheumatologists from each of the 16 participating centers in all enrolled children at 0, 6, 12, 18, 24, 36, 48, and 60 months after enrolment. For this study, a child was said to have enthesitis if entheseal tenderness was recorded on more than occasion or at more than one body site; in other words, a one-time report of entheseal tenderness at a single location was not sufficient. The rationale for this definition is that if a patient was tender at a single site on a single occasion only, then this could be from any number of causes of tenderness. However, if more than one site was involved or if tenderness persisted over time, then this was more likely to represent true enthesitis. This was felt to be a conservative and best available definition without the use of ultrasound, which would be impractical to use to routinely assess 33 sites at each visit.

Statistical Analysis:

The analysis was largely descriptive. All statistical analyses were performed using STATA, version 13 (50). Among children with enthesitis, the timing of enthesitis detection, the most frequent anatomic sites of involvement, and the frequency of enthesitis over time were described. The characteristics of children with enthesitis were compared to the characteristics of children without enthesitis using t-tests and chi-square analyses. The characteristics of children with enthesitis and ERA were compared to those of children with enthesitis and non-ERA JIA in a similar fashion. The mean number of tender entheseal sites over time was compared to the mean number of active joints using linear mixed models for longitudinal data to account for the repeated measures and variable timing of visits for each child.

2.4 Results

ReaCCh-Out recruited a total of 1497 children with JIA between 2005 and 2010. Of these, 5 were excluded due to unconfirmed JIA category and 86 because they only attended the enrolment visit. The characteristics of the remaining 1406 children are shown in Table 1. These 1406 subjects attended a total of 15,666 visits over the course of the study.

Enthesitis was detected in 219 children (16% of the cohort); 53% of them met the definition of enthesitis at enrolment and 93% within 2 years of enrolment. Children with enthesitis were older at JIA onset and were more often male (Table 1). The JIA category was ERA for 141 children (64%) and undifferentiated for 39 (18%). All JIA categories were represented, except for systemic arthritis. Of note, as per ILAR criteria, it is possible to have ERA without ever having enthesitis, and this was the case for 61 of our patients (5.1% of the no enthesitis group). Thus, there were 202 patients with ERA in our cohort.

The majority of children with enthesitis eventually had polyarticular involvement: 57% of children with enthesitis versus 41% of those without enthesitis ($P < 0.01$) (Table 1). Clinical sacroiliac involvement was reported in 30% of children with enthesitis and in 4% of children without enthesitis ($P < 0.01$). Only 2% of children with enthesitis and 7% of children without enthesitis were classified as having psoriatic JIA at onset, but more were reported as having psoriasis during followup (8% and 6%, respectively). HLA–B27 was reported as present in 32% of children with enthesitis versus in 6.3% of those without enthesitis. If we include only subjects in which an HLA–B27 result was available, then 44% of those with enthesitis had HLA–B27.

The most frequent sites of entheseal tenderness and frequency of affected locations over time are shown in Figure 1. The top 3 locations were the calcaneal plantar fascial insertion (39%), Achilles tendon insertion (31%), and tibial tuberosity (30%). The sternoclavicular and the symphysis pubis entheseal sites were never reported as involved throughout the study. The mean number of tender entheseal sites decreased over time, roughly in parallel with the number of active joints (P = 0.16) (Figure 2A). At the time of meeting the definition for enthesitis, the mean +/- SD number of tender entheseal sites was 4.6 +/- 4.0, but it decreased to 0.8 +/- 2.0 by 60 months (P = 0.02). The Spearman rank correlation between enthesitis counts and joint counts over time was 0.34 (P < 0.0001). The mean active joint count decreased over the study period to a similar degree in those with and without enthesitis. A mixed linear model analysis showed no significant difference in active joints over time between these 2 groups (P = 0.73) (Figure 2B).

Children with enthesitis and ERA were compared to those with enthesitis and non-ERA (Table 1). Children with enthesitis and ERA were more often male (64% versus 45%; P < 0.009) and had a higher frequency of sacroiliitis (35% versus 21%; P = 0.02). On the other hand, they had a lower frequency of psoriasis (2% versus 19%; P < 0.0001), polyarticular involvement (52% versus 67%; P = 0.03), and upper-extremity involvement (48% versus 67%; P = 0.009). In the 1204 patients without ERA, the prevalence of enthesitis was 17% in those with psoriasis and 6% in those without psoriasis (P < 0.0001).

2.5 Discussion

Enthesitis was frequent in this inception cohort of children with JIA, and was seen in all JIA categories except systemic arthritis. Two thirds of the patients who developed enthesitis during follow up were classified as having ERA by their 6-month visit. Contrary to classic descriptions (33), more than half the children with enthesitis had polyarticular involvement (57%). This held true even when we considered only children with enthesitis and ERA (52%). Another novel finding was that the mean number of tender entheseal sites decreased over time, in parallel with the active joint count. Furthermore, the decrease in mean active joint count over time was similar in those with and without enthesitis.

The characteristics of the children with enthesitis in our cohort were similar to those reported in patients with ERA (32-34); they were predominantly adolescent-aged males, in whom sacroiliac involvement and HLA–B27 were more likely to be present than in other children with JIA. These characteristics were even more pronounced when we restricted the analysis to those with enthesitis and ERA. The high frequency of polyarticular involvement in our cohort is contrary to traditional descriptions of ERA as an asymmetric oligoarticular arthritis of the lower extremities (32-34). The relationships between joint and enthesitis counts over time and between joint counts over time in those with and without enthesitis have not been previously reported. HLA-B27 was present only in approximately one third of our patients, even when analysis was restricted only to those with enthesitis and ERA. This is significantly less than previously reported in ERA (32). However, we included patients with unknown HLA–B27 status in the denominator, which differs from other studies. If we include only subjects for whom an HLA-B27 report was available, 44% were HLA–B27 positive, which is still lower than that reported in previous studies (32).

A key difference between our study and previous studies is that we considered all patients who developed enthesitis during follow-up over 5 years, whereas previous studies focused on children who fulfilled criteria for ERA. Criteria for ERA require arthritis or enthesitis and two of 5 other specific criteria to be present within 6 months of disease onset (17). In this study, we report the JIA category assigned at the 6-month visit, and did not change that classification. However, it is known that a substantial number of children develop findings after the first 6 months that may justify a change in JIA category (51). The complication in doing this is that the classification then becomes a moving target. Uneven length of follow up among children in the cohort would give these children different chances of being reclassified.

Our data support the suggestion by Colbert (31) that the spondyloarthritides represent a continuum across the age spectrum. The data provide evidence that this continuum includes at least some patients with psoriatic arthritis. Furthermore, among patients with non-ERA JIA, the prevalence of enthesitis was higher in those with psoriasis (17%) than in those without psoriasis (6%). It is felt that psoriasis is in the same 'family' of diseases as ERA, known as the spondyloarthritides. These conditions have similar underlying biology, involving the IL-23-IL-17 immune axis (52).

Eighteen percent of our patients with enthesitis were categorized as having undifferentiated JIA. The reasons for being undifferentiated in the ReACCh-Out cohort were recently examined by Chan et al (53). Having a first-degree relative with psoriasis was the most common reason (67% of undifferentiated cases), as this currently excludes patients from classification in any non-

psoriatic JIA category, including ERA. Without the family history exclusion criterion, many of those patients would have been classified as having ERA. This highlights one of the limitations of the ILAR classification system, as it currently stands.

Strengths:

This study has several strengths. The ReACCh-Out cohort is the largest cohort of children with JIA in which the characteristics associated with enthesitis have been described. The cohort included patients from all the major pediatric rheumatology centers in Canada, followed prospectively over a period of 5 years.

Enthesitis in this cohort was evaluated systematically by highly trained pediatric rheumatologists so it was likely as accurate as clinically possible. This study provides new information about the frequency, pattern of involvement, course, and association with other clinical characteristics of enthesitis in children with JIA. This has not been done previously.

Limitations:

This study has some limitations. The clinical assessment of entheseal tenderness is subjective, and Kehl et al have reported that enthesitis was underdiagnosed by physical examination relative to ultrasound (29). Yet, the clinical meaning of changes on imaging of entirely asymptomatic sites is unclear. This study involved the prospective determination of entheseal tenderness at 33 defined sites by practicing pediatric rheumatologists across Canada and is likely as accurate as it can be without the aid of diagnostic imaging as all are highly trained specialists. Conducting ultrasound and/or magnetic resonance imaging (MRI) assessments of entheses at 33 locations at

each visit in all children with JIA would be impractical. Despite instructions to perform an assessment of entheseal sites in all children, it is possible that children diagnosed with ERA were more thoroughly assessed for enthesitis than those in other JIA categories. This may have resulted in underestimation of the prevalence of enthesitis in non-ERA categories. We could not control for how closely these instructions were followed.

Another limitation of our study was that sacroiliitis was defined clinically. A patient was said to have sacroiliitis if the pediatric rheumatologist determined this to be so, based on history and physical examination. A recent study reported low predictive values of clinical examination to predict MRI findings (54). Prospective MRI ascertainment of sacroiliitis would have been ideal, but impractical in our study. A limitation that is not specific to this study *per se* is the use of the ILAR classification system for JIA. Some of our patients with ERA developed psoriatic rashes over the course of their disease (which is an exclusionary criterion for ERA), and many children with enthesitis were categorized as undifferentiated because of a family history of psoriasis. We hope our data inform current discussions to modify the ILAR criteria.

Clinical Implications:

This study provides new information about the burden and course of enthesitis in children with JIA. This is clinically useful for physicians and allied health professionals who see patients with JIA, as it will help them to better recognize this entity and better understand its clinical course and associations. This will result in improved counselling of these children and their families and will help us to better answer the families' questions and concerns.

Future Research:

Future research in this area should focus on several areas. One area is what the role of imaging (if any) is in the clinical assessment of this entity. Should we be using ultrasound and/or MRI to assess enthesitis? If so, in which patients and when? Another area is the treatment of enthesitis. Which treatments are effective for enthesitis and how aggressive should we be in our treatment of this entity? A third area, which is addressed in Chapter 3 of this thesis is what is the effect of enthesitis on patient-reported outcomes (PROs), including quality of life, pain, and function?

In conclusion, when practicing pediatric rheumatologists were asked to systematically assess for the presence of entheseal tenderness at 33 defined sites, up to 16% of children with JIA had enthesitis at some point during the 5 years after diagnosis, but only two thirds of them fulfilled the criteria for ERA at the 6-month visit. These children with enthesitis shared similar characteristics as those reported in ERA, except for a higher frequency of polyarticular involvement and a lower frequency of HLA–B27. The mean number of enthesitis sites over time paralleled the course of active joint counts, and the mean active joint counts of patients with and without enthesitis followed a similar course. This descriptive information will help better define the role of enthesitis in the diagnosis and classification of children with JIA.

2.6 Tables and Figures

Table 2-1: Characteristics of Children with JIA, With and Without Enthesitis

Characteristic	Without Enthesitis	With Enthesitis	p-value	With Enthesitis and ERA	With Enthesitis and non-ERA	p-value
Number of Patients	1187 (84%)	219 (16%)		141 (10%)	78 (6%)	
Mean age of onset of JIA in years (SD)	7.5 (4.6)[1]	10.7 (3.2)[1]	p<0.0001	11.1 (3.1)	10.2 (3.6)	p=0.05
Male Sex	365 (31%)[1]	124 (57%)[1]	p<0.0001	89 (64%)[2]	35 (45%)[2]	p=0.009
ANA Positive*	563 (47%)[1]	51 (23%)[1]	p<0.0001	24 (17%)[2]	27 (35%)[2]	p=0.01
HLA-B27 Present**	75 (6%)[1]	70 (32%)[1]	p<0.0001	51 (36%)	19 (24%)	p=0.07
JIA Subtype (At 6 month visit)	-	-	-	-	-	-
-ERA	61 (5%)[1]	141 (64%)[1]	p<0.0001	141 (100%)	-	-
-Oligoarticular	546 (46%)[1]	13 (6%)[1]	p<0.0001	-	13 (17%)	-
-Polyarticular RF –ve	256 (22%)[1]	17 (8%)[1]	p<0.0001	-	17 (22%)	-
-Polyarticular RF +ve	53 (5%)	4 (2%)	p = 0.07	-	4 (5%)	-
-Systemic	86 (7%)[1]	0[1]	p<0.0001	-	0	-
-Psoriatic	83 (7%)[1]	5 (2%)[1]	p=0.008	-	5 (6%)	-
-Undifferentiated	102 (9%)[1]	39 (18%)[1]	p<0.0001	-	39 (50%)	-
Uveitis (ever)	198 (17%)[1]	21 (10%)[1]	p=0.008	16 (11%)	5 (6%)	p=0.2
Sacroiliitis (ever)	43 (4%)[1]	66 (30%)[1]	p<0.0001	50 (35%)[2]	16 (21%)[2]	p=0.02
Psoriasis (ever)	71 (6%)	18 (8%)	p=0.2	3 (2%)[2]	15 (19%)[2]	P<0.0001
Polyarticular involvement (ever)	487 (41%)[1]	125 (57%)[1]	p<0.0001	73 (52%)[2]	52 (67%)[2]	p=0.03
Lower Limb Involvement (ever)	952 (80%)	175 (80%)	p=0.9	110 (78%)	65 (83%)	p=0.4
Upper Limb Involvement (ever)	605 (51%)	120 (55%)	p=0.3	68 (48%)[2]	52 (67%)[2]	p=0.009

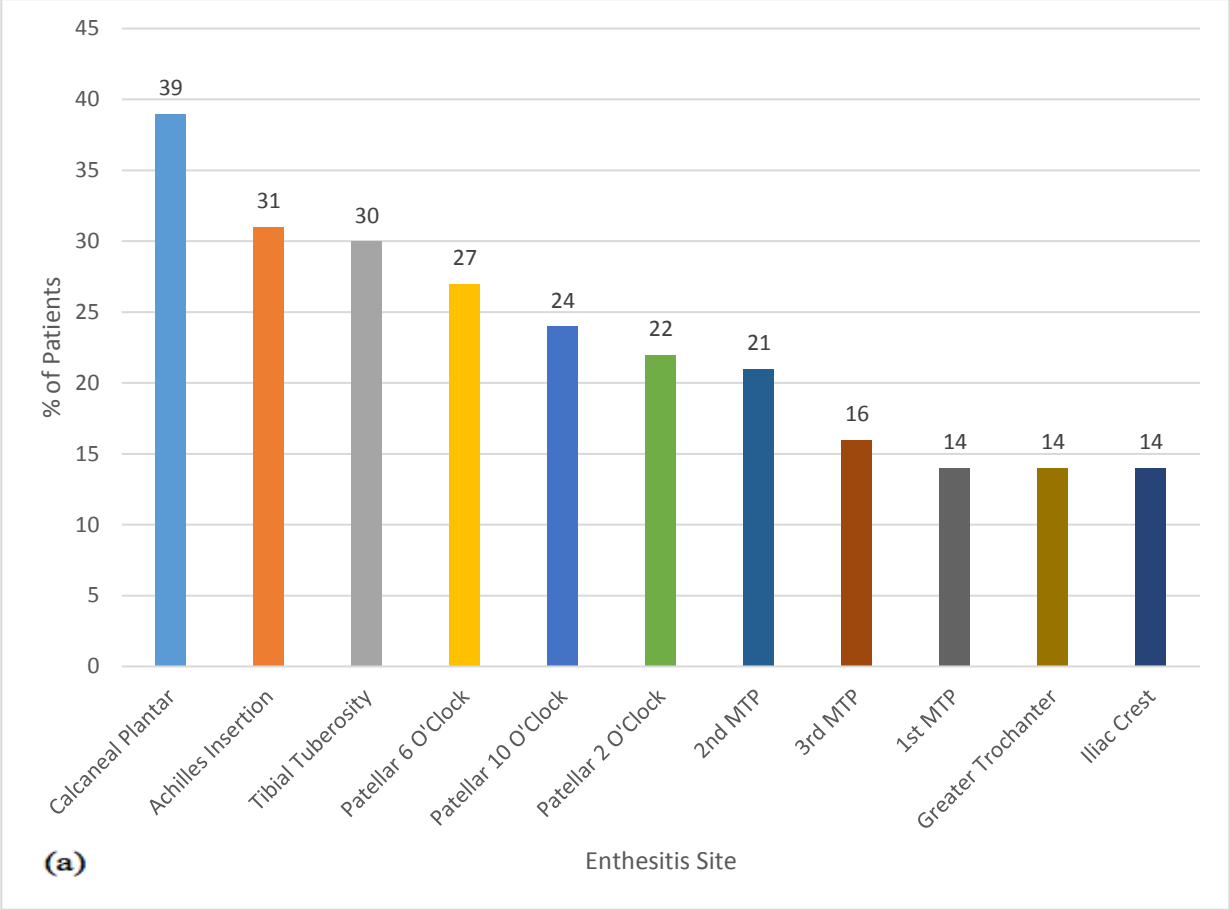
*ANA status unknown in 11.9% of the enthesitis group and 8.4% of the no enthesitis group

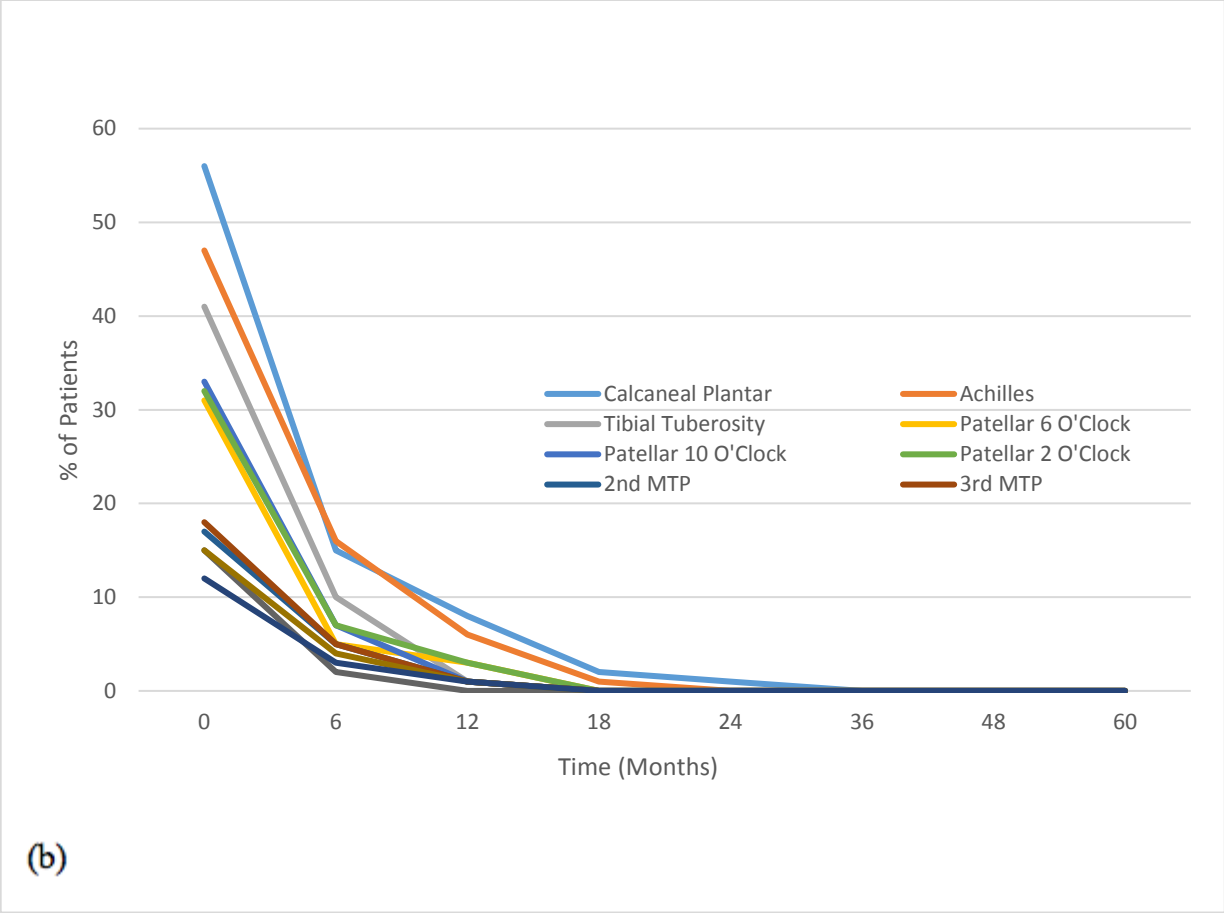
**HLA-B27 status unknown in 26.5% of the enthesitis group and 56.0% of the no enthesitis group

[1]These comparisons were significantly different (p<0.01 for all; between those with no enthesitis versus those with enthesitis).

[2]These comparisons were significantly different (p<0.05 for all; between the enthesitis + ERA versus enthesitis + Non-ERA groups).

Figure 2-1: (a) The Most Frequent Locations of Enthesitis and (b) Course of Enthesitis Sites Over Time by Site of Involvement[1,2,3]





[1]Based on those who had involvement at baseline and who had at least one follow-up visit
[2]The top 11 sites of involvement are presented for illustration purposes
[3]Out of 219 children with enthesitis in our cohort, 4 children (1.8%) appeared to have had isolated tibial tuberosity enthesitis, raising the differential diagnosis of Osgood-Schlatter; 3 of these 4 children had documented arthritis and the other child met criteria for ERA.

Figure 2-2: Mean Enthesitis and Active Joint Counts Follow the Same Trajectory in Children with Enthesitis (A) and Mean Active Joint Counts Follow the Same Trajectory in Children with Versus without Enthesitis (B)

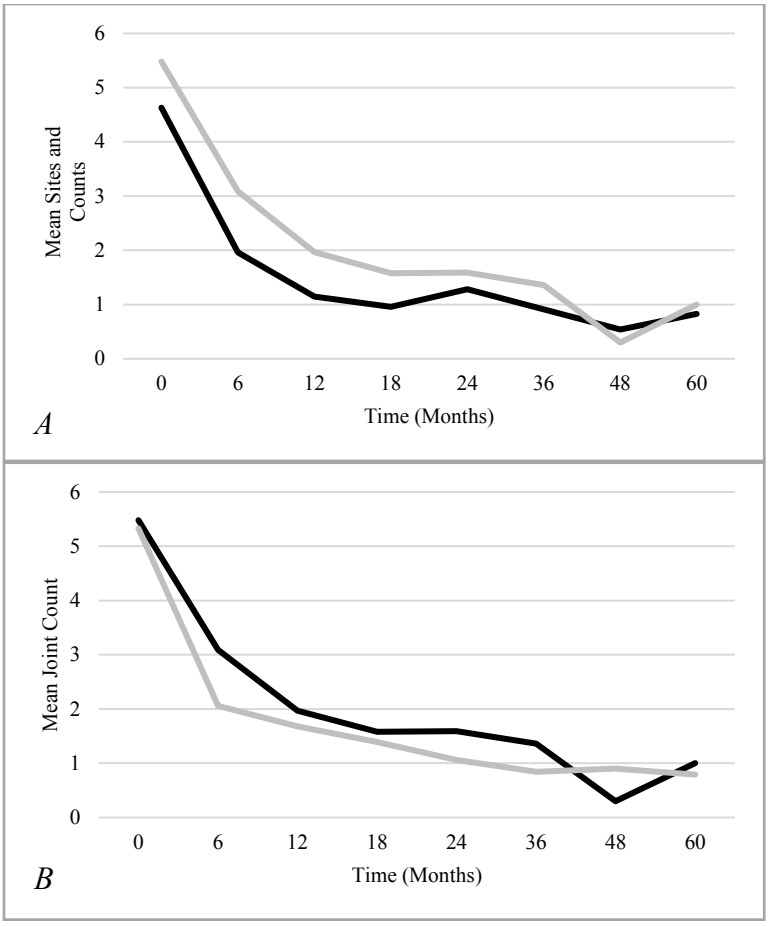


Figure Legend

Figure 2:

A: ▬ = Mean Enthesitis Sites, ▬ = Mean Joint Counts;

B: ▬ = Median Active Joints in Enthesitis Group, ▬ = Median Active Joints in No Enthesitis Group

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CHAPTER 3: CHILDREN WITH ENTHESITIS HAVE WORSE QUALITY OF LIFE, FUNCTION, AND PAIN, IRRESPECTIVE OF THEIR JUVENILE ARTHRITIS CATEGORY

3.1 Abstract

Objective - To estimate the impact of enthesitis on patient reported outcomes (PROs) in children with juvenile idiopathic arthritis (JIA), irrespective of their JIA category.

Methods - Children in the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) cohort were studied. Entheseal tenderness by physician examination in 33 defined locations, Juvenile Arthritis Quality of life Questionnaire (JAQQ), Quality of My Life questionnaire (QoML), Childhood Health Assessment Questionnaire (CHAQ), and a pain severity visual analogue scale (VAS) were completed at enrolment, every six months for 2 years, and then yearly up to 5 years. Analyses consisted of descriptive statistics, linear mixed models for longitudinal data, and ANCOVA.

Results - Among 1371 patients followed a median of 35.3 months, 214 (16%) had enthesitis, of whom 137 (64%) were classified as having enthesitis-related arthritis (ERA). After adjusting for JIA category and covariates, children with enthesitis reported higher JAQQ (mean raw score 2.71 vs 2.16; adjusted difference 0.41 points; 95% CI 0.22, 0.59), higher CHAQ (0.47 vs 0.31; 0.14 points; 0.07, 0.22), higher pain (3.01 vs 1.68; 0.94 points; 0.64, 1.25) and lower QoML (7.02 vs 8.23; -0.80 points; 95% CI -1.09, -0.51) scores than children without enthesitis. These differences persisted up to five years after diagnosis.

Conclusion - Children with enthesitis, regardless of JIA category, report worse PROs than those without enthesitis. Physicians should assess for enthesitis in all children with JIA and, if present, make it a treatment target. Enthesitis should be considered as criterion for classification and assessment of treatment response in JIA.

3.2 Introduction

It has been increasingly recognized that patient-reported outcomes (PROs) are fundamental in the care of children with rheumatic disease. PROs provide insight into how the patient [and/or his/her parent(s)] thinks he/she is doing. PROs are often surprisingly discordant with physician measured outcomes and can provide humbling, but crucial, feedback to the physician (36, 37, 55, 56). Common PROs used in studies of children with juvenile idiopathic arthritis (JIA) include health-related quality of life measures, self-report functional measures, and measures of pain (57, 58). Physicians' assessments typically focus on 'harder' (more objective) measures of disease activity, including active joint counts, inflammatory markers, and physician global assessments of disease (PGA). PROs, on the other hand, focus on other measures that, although no no less important (perhaps even more important), are different in kind. These 'softer' measures of how a patient is doing focus more on subjective measures, including how much pain their disease is causing him/her (e.g. pain visual analogue scale, VAS), how the disease is affecting their quality of life (e.g. Juvenile Arthritis Quality of Life Questionnaire, JAQQ), and how the arthritis is affecting their day to day functioning (e.g. Childhood Health Assessment Questionnaire, CHAQ).

As more is discovered about the biological basis for juvenile idiopathic arthritis (JIA), clinicians and researchers are realizing that the current ILAR classification system, although pragmatic, may no longer be adequate (30). This is perhaps best illustrated when considering what some authors have termed the juvenile spondyloarthritides (31). It has been suggested that enthesitis-related arthritis (ERA) is not a JIA category with unique characteristics since some children with psoriatic JIA share characteristics, such as older age at diagnosis, axial involvement, and

enthesitis. This suggests a similar underlying biology between these two categories (23). The term juvenile spondyloarthritides encompasses ERA, juvenile ankylosing spondylitis, psoriatic arthritis, and IBD-associated arthritis in an analogous way to the classification of spondyloarthritides in adults (31, 59).

Enthesitis, inflammation of the attachment sites of tendon, ligament, joint capsule, or fascia into bone, is a feature that characterizes the JIA category of enthesitis-related arthritis (ERA) (17). Entheses are usually located outside the joints, either inserting into the periarticular bone (e.g. the plantar fascial insertions into the heads of the metatarsal bones in the feet) or distant from any synovial joint (as in the Achilles tendon insertion into the calcaneus). There are, of course, exceptions to this rule, such as the entheseal region inside the knee joint, where the intra-articular cruciate ligaments of the knee insert. (These latter entheses are, however, difficult to examine and are not included in the routine clinical assessment of enthesitis.) (24). Children with enthesitis-related arthritis (ERA) report more frequent pain, higher pain intensity, and greater impairment of function compared to children with any of the other JIA categories (4, 21). Further, Taxter et al. (21) found that, in models limited to ERA, female sex and tender enthesis count were significant predictors of decreased function.

Key limitations of previous studies of PROs in JIA include limited sample size and follow-up time for longitudinal cohorts, such at that at the Children's Hospital of Philadelphia (CHOP), reported by Taxter et al. (21), or the use of cross-sectional data and a low prevalence of enthesitis in the study of children in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) reported by Weiss et al. (4). Further, according to current ILAR criteria (1, 2), it is

possible to have ERA without having enthesitis. So, the existing studies have examined the differences among patients with different categories of JIA, but have not examined patients with versus without enthesitis, per se. In adults, enthesitis is known to negatively affect quality of life (AS-specific quality of life index, ASQOL) and to contribute to disease activity (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI) in ankylosing spondylitis (35).

Our study aim was to estimate the impact of the presence of enthesitis, irrespective of JIA category, on health-related quality of life, function, and pain in a Canadian multi-centre prospective study of about 1500 children with JIA.

3.3 Patients and Methods

The general methods of the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) study have been described previously (46). Briefly, children (<16 years) newly diagnosed with JIA defined by ILAR criteria (1, 2) at 16 Canadian centers from 2005 to 2010 were followed for up to 5 years (7, 45, 46, 60). JIA category was assigned by the attending rheumatologist based on information available at the 6-month visit and verified against ILAR criteria by the ReACCh-Out investigators. All children with >1 study visit were included in this analysis.

Research ethics board (REB) approval from the University of Alberta was obtained for this project. Ethics approval had been previously obtained from each of the 16 participating Canadian centers for data collection.

The presence of entheseal tenderness on examination at 33 sites shown on a homunculus was recorded by practicing pediatric rheumatologists from each of the 16 participating centers in all enrolled children at 0, 6, 12, 18, 24, 36, 48 and 60 months after enrolment. For this study, a child was said to have enthesitis if entheseal tenderness was recorded on >1 occasion or at >1 body site; in other words, a one-time report of entheseal tenderness at one location was not sufficient. The rationale for this definition is that if a patient was tender at a single site on a single occasion only, then this could be from any number of causes of tenderness. However, if more than one site was involved or if tenderness persisted over time, then this was more likely to represent true enthesitis. This was felt to be a conservative and best available definition without the use of ultrasound, which would be impractical to use to routinely assess 33 sites at each visit.

Instruments:

We used two validated instruments to measure health-related quality of life (HRQoL) in our study, the Juvenile Arthritis Quality of life Questionnaire (JAQQ) and the Quality of My Life questionnaire (QoML) (20, 42, 43). The JAQQ is a JIA-specific non-preference-based questionnaire which includes 74 items in four domains: gross motor, fine motor, psychosocial, and systemic symptoms. Items are scored from 1 (indicating no difficulty with a given activity) to 7 (indicating difficulty 100% of the time in the preceding 2 weeks). The mean of the 5 highest-scoring items within a domain comprise each domain score and the mean of the 4 domain scores comprises the total score (39). The QoML questionnaire is not specific to JIA. It is a preference-based visual analogue scale (VAS) with two scales from 0 (worst) to 10 (best). The first scale is for overall quality of life and the second scale (HRQoML) is for HRQoL (40).

Functional ability was assessed with the Childhood Health Assessment Questionnaire disability index (CHAQ). This is a JIA-specific instrument that measures difficulty in daily living activities in children with this disease (41). Scores can go from 0 = no difficulty with any activity, to 3 = unable to do some activities. Average pain attributed to arthritis in the last week was assessed with a 10 cm horizontal VAS (0 indicating no pain and 10 indicating very severe pain) (39).

Parents completed the forms for children 9 years of age or younger. Older children completed their own questionnaires. Data from all completed questionnaires were entered into the analyses, without differentiation between parent and child responders.

Statistical Analyses:

All statistical analyses were performed using STATA 13 software (50). The characteristics of children with enthesitis were compared to the characteristics of children without enthesitis using t-tests and chi square analyses.

Mean PRO scores were compared over time for those with, versus without, enthesitis using linear mixed models for longitudinal data to account for the repeated measures and variable timing of visits for each child. Mean PRO scores were adjusted for the following covariates: sex, age of onset of JIA, JIA category, upper joint arthritis, lower joint arthritis, SI joint arthritis, polyarticular involvement, psoriasis, uveitis, ANA positivity, and presence of HLA-B27. These covariates were felt to be the most clinically relevant by our study team. Next, ANCOVA was used to compare the last available PRO scores in follow-up of those with enthesitis to that of those without enthesitis, after adjusting for baseline values of the PRO and the covariates listed above.

3.4 Results

ReaCCh-Out recruited a total of 1497 children with JIA between 2005 and 2010. Of these, 5 were excluded due to unconfirmed JIA category and 86 because they only attended the enrolment visit. Of the remaining 1406 children, 1371 provided at least one PRO during a median follow-up of 35.3 months (IQR 21.1, 49.1). Characteristics of these patients are shown in Table 1.

Enthesitis was detected in 214 children (16% of the cohort). Children with enthesitis were older at the onset of their JIA and more often male (Table 1). The JIA category was ERA for 137 (64%) children and undifferentiated for 39 (18%). All JIA categories were represented, except for systemic arthritis. Of note, as per ILAR criteria, it is possible to have ERA without ever having enthesitis and this was the case for 59 of our patients (5% of the 'no enthesitis' group). Thus, there were 196 patients with ERA in our cohort.

Health-related Quality of Life (HRQoL):

The raw mean JAQQ score across all visits in children with enthesitis (ever) was 2.71 compared to 2.16 in children without enthesitis. The adjusted mean difference was 0.41 higher (worse) in children with enthesitis ($p<0.001$) (Table 2). When considering whether enthesitis was present at a given visit or not, the adjusted mean JAQQ was 0.49 higher in those with enthesitis present than in those with no enthesitis present ($p<0.001$).

The last JAQQ of those with enthesitis was, on average, 0.37 higher than those without enthesitis after adjusting for baseline JAQQ (and other covariates) over the follow-up period ($p=0.002$).

The mean JAQQ tended to decrease over time in both groups, roughly in parallel to each other (Figure 1).

The raw mean HRQoML score across all visits in children with enthesitis (ever) was 7.02 compared to 8.23 in children without enthesitis. The adjusted mean HRQoML of those with enthesitis was 0.80 lower (worse) than that of those without enthesitis ($p<0.001$) (Table 2). When considering whether enthesitis was present at a given visit or not, the adjusted mean HRQoML was 0.76 lower in those with enthesitis present than in those with no enthesitis present ($p<0.001$).

The last HRQoML score of those with enthesitis was, on average, 0.64 lower than that of those without enthesitis, after adjusting for baseline HRQoML score (and other covariates) over the follow-up period ($p=0.008$). The mean HRQoML score tended to increase over time in both groups, roughly in parallel to each other. The scores for the enthesitis group remained lower than those of the no enthesitis group throughout the follow-up period (Figure 1).

Functional Assessment:

The raw mean CHAQ across all visits in children with enthesitis (ever) was 0.47 compared to 0.31 in children without enthesitis. The adjusted mean CHAQ of those with enthesitis was 0.14 higher (worse) than that of those without enthesitis ($p<0.001$) (Table 2). When considering whether enthesitis was present at a given visit or not, the adjusted mean CHAQ was 0.16 higher in those with enthesitis present than in those with no enthesitis present ($p<0.001$).

The last CHAQ of those with enthesitis was, on average, 0.08 higher than that of those without enthesitis, after adjusting for baseline CHAQ (and other covariates) over the follow-up period ($p=0.04$). The mean CHAQ tended to decrease over time until 36 months and then slightly increased for both groups. The mean CHAQ scores for those with enthesitis were consistently higher than for those without enthesitis over the follow-up period (Figure 1).

Pain:

The raw mean pain VAS score across all visits in children with enthesitis (ever) was 3.01 compared to 1.68 in children without enthesitis. The adjusted mean pain VAS score of those with enthesitis was 0.94 higher (worse) than that of those without enthesitis ($p<0.001$) (Table 2). When considering whether enthesitis was present at a given visit or not, the adjusted mean pain VAS score was 1.57 higher in those with enthesitis present than in those with no enthesitis present ($p<0.001$).

The last pain VAS score of those with enthesitis was, on average, 0.57 higher than that of those without enthesitis, after adjusting for baseline pain VAS score (and other covariates) over the follow-up period ($p=0.02$). The mean pain VAS score tended to decrease over the follow-up period in both groups, but was consistently higher in the group with enthesitis (Figure 1).

Missing Data:

PROs were collected at the main 8 study visits. Out of the 7125 main study visits attended by our cohort, the following were missing PROs: JAQQ 21%, HRQoML 23%, Pain VAS 20%, CHAQ 21%. The missing data was dealt with in two ways. First, linear mixed models were

used in the analysis, which inherently account for missing data. Second, we did sensitivity analyses for each of the PROs, filling forward the previous scores into missing visits and then filling backward the remaining missing scores. This did not significantly change the results (see APPENDIX 2) obtained.

3.5 Discussion

Enthesitis was a frequent occurrence in this inception cohort of children with JIA, and was seen in all JIA categories except systemic arthritis. Two thirds of the patients who developed enthesitis during follow-up were classified as having ERA by their 6-month visit. Children with enthesitis had worse health-related quality of life (on both domain-based and preference-based scales), poorer function, and worse pain, throughout the course of follow-up than children without enthesitis, after adjusting for JIA category and other covariates.

Weiss et al. have shown in a cross-sectional study that children with ERA have higher pain intensity and poorer health status than children in other JIA categories (4). They used similar measures as the present study, including the pain VAS and the CHAQ, but JAQQ was not part of that study. Also, they were comparing patients with different ILAR categories, whereas our study looks at the impact of enthesitis (regardless of JIA category) on the various PROs. Only 4% of their patients had enthesitis at the time of assessment, while 16% of our patients had enthesitis when studied longitudinally (4).

In a single centre longitudinal study, Taxter et al. compared PROs across JIA categories and showed that children with ERA and Undifferentiated JIA had more pain, worse QoL, and poorer function than children with other JIA categories. They used an ordinal numerical rating scale (NRS) for pain assessment, the Pediatric Rheumatology Quality of Life scale (PRQL), for QoL assessment, and the CHAQ to assess function. In their models limited to ERA, female sex and tender enthesis count were significant predictors of decreased function (21).

Strengths and Limitations:

The main strengths of our study are the longitudinal structured assessment of entheseal tenderness at 33 anatomic sites across all Canadian pediatric rheumatology centres over up to 5 years and the use of validated scales to assess PROs. There are 4 potential limitations. First, the assessment of entheseal tenderness is subjective. However, this is likely as accurate as it can be without the aid of diagnostic imaging, which would be very time-consuming and impractical in a busy clinical setting.

Second, patient and parent reported measures were analyzed together, regardless of who completed the questionnaires. Since young children may not fully understand some of the concepts that are being asked and may not be physically able to complete the forms, proxy assessments are unavoidable. However, for older children, there may be discrepancies between what they and their parents perceive. Children older than 9 years were encouraged to fill out the forms whenever possible, but we have no measure of how often that was done or to what extent the parents consulted with their children while filling out forms for them.

Third, the majority of children missed at least one PRO assessment. However, we used linear mixed models, which account for the missing data. Furthermore, we did sensitivity analyses (described in Results) and found that this did not significantly change the results obtained.

Lastly, PRO values after 3 years of diagnosis should be interpreted with caution due to the relatively low numbers of assessments at that time.

Conclusion:

Patient-reported outcomes (PROs) are the children and families' way of telling physicians how they are doing and what matters most to them (61). It has been shown that these measures do not correlate well with how physicians think that their patients are doing (36, 37, 55, 56). This study shows that patients with enthesitis, regardless of their JIA category, report they are doing worse in multiple patient reported measures than those without enthesitis. This has two important implications. First, because enthesitis has a clear measurable impact on patient well-being, physicians should ascertain its presence in every patient with JIA and make it a treatment target, if present. Second, enthesitis should be strongly considered for inclusion in future criteria used to classify JIA and criteria to assess response to treatment. None of the major currently available standardized response criteria [American College of Rheumatology (ACR) Pedi improvement criteria (e.g. ACR Pedi 20) (62), the Wallace criteria for clinically inactive disease (63), and the Juvenile Arthritis Disease Activity Score (JADAS) (64)] include enthesitis. A newer scale for patients with juvenile spondyloarthroarthritis, the Juvenile Spondyloarthritis Disease Activity Index (JSpADAI), does include enthesitis. However, this index has yet to be validated in a prospective cohort of patients and it remains to be seen if it will be a useful tool on a larger scale (65).

3.6 Tables and Figures

Table 3-1: Characteristics of Children with JIA, With and Without Enthesitis*

Characteristic	Children with Enthesitis	Children without Enthesitis	p-value for comparison
Number of Patients	214 (16%)	1157 (84%)	-
Mean age of onset of JIA in years (SD)	10.8 (3.1)[1]	7.5 (4.4)[1]	$p < 0.001$
Male Sex	121 (57%)[1]	358 (31%)[1]	$p < 0.001$
ANA Positive**	51 (24%)[1]	549 (47%)[1]	$p < 0.001$
HLA-B27 Present***	69 (32%)[1]	72 (6%)[1]	$p < 0.001$
JIA Category (At 6 month visit)	-	-	-
-ERA	137 (64%)[1]	59 (5%)[1]	$p < 0.00001$
-Oligoarticular	12 (6%)[1]	538 (47%)[1]	$p < 0.00001$
-Polyarticular RF –ve	17 (8%)[1]	250 (22%)[1]	$p < 0.00001$
-Polyarticular RF +ve	4 (2%)	50 (4%)	$p = 0.09$
-Systemic	0	84 (7%)	X
-Psoriatic	5 (2%)[2]	78 (7%)[2]	$p = 0.013$
-Undifferentiated	39 (18%)[1]	98 (8%)[1]	$p = 0.00001$
Uveitis (ever)	21 (10%)[1]	195 (17%)[1]	$p = 0.009$
Sacroiliitis (ever)	65 (30%)[1]	41 (4%)[1]	$p < 0.001$
Psoriasis (ever)	18 (8%)	68 (6%)	$p = 0.16$
Polyarticular involvement (ever)	123 (57%)[1]	475 (41%)[1]	$p < 0.001$
Lower Limb Involvement (ever)	174 (81%)	933 (81%)	$p = 0.82$
Upper Limb Involvement (ever)	118 (55%)	592 (51%)	$p = 0.29$
Medication (at baseline)[3]	-	-	-
-Any treatment	147 (69%)	828 (72%)	$p = 0.39$
-Systemic steroids	18 (8%)	93 (8%)	$p = 0.85$
-NSAIDs	132 (62%)	747 (65%)	$p = 0.42$
-DMARDs	36 (17%)	186 (16%)	$p = 0.79$
-Biologics	2 (1%)	3 (0.3%)	$p = 0.13$

*Modified with permission from Table 1 in Rumsey DG, et al. Characteristics and Course of Enthesitis in a Juvenile Idiopathic Arthritis Inception Cohort. Arthritis Care Res (Hoboken) 2018; Feb;70(2):303-308. doi: 10.1002/acr.23256. (47).

**ANA status unknown in 11.9% of the enthesitis group and 8.4% of the no enthesitis group

***HLA-B27 status unknown in 26.5% of the enthesitis group and 56.0% of the no enthesitis group

[1]Significantly different at $p<0.01$

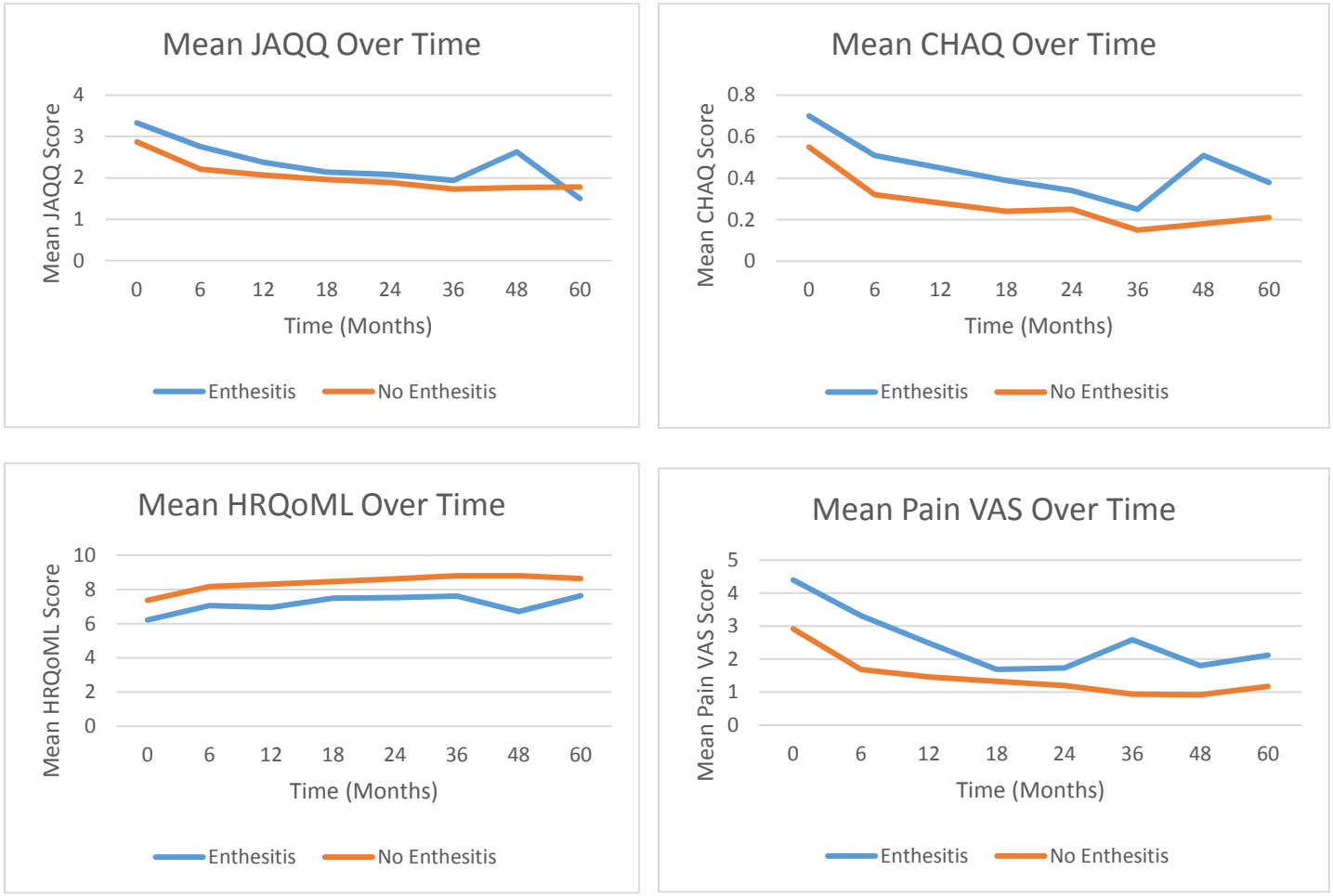
[2]Significantly different at $p<0.05$

[3]These are the medications that the patients were taking at the time of enrollment. Several more patients had previous medication (especially NSAIDs) that were stopped prior to enrollment.

Table 3-2: Mean Scores of Patient Reported Outcomes (PROs) in Children With and Without Enthesitis

Patient reported outcome	Mean score in patients with enthesitis (SD)	Mean score in patients with no enthesitis (SD)	Mean difference	Adjusted mean difference (95% CI)
JAQQ (1=best, 7=worst)	-	-	-	-
Across all visits	2.71 (1.33)	2.16 (1.23)	0.55	0.41 (0.22,0.59)
First available	3.33 (1.35)	2.80 (1.39)	0.53	0.08 (-0.21,0.37)
At last follow-up	2.44 (1.37)	1.97 (1.15)	0.47	0.37 (0.14,0.59)
Enthesitis present at that visit (y/n)	2.96 (1.29)	2.13 (1.21)	0.83	0.49 (0.33,0.65)
HRQoML (0=worst, 10=best)	-	-	-	-
Across all visits	7.02 (2.44)	8.23 (2.10)	-1.21	-0.80 (-1.09,-0.51)
First available	6.34 (2.60)	7.51 (2.43)	-1.17	-0.33 (-0.84,0.19)
At last follow-up	7.28 (2.44)	8.47 (1.91)	-1.19	-0.64 (-1.11,-0.16)
Enthesitis present at that visit (y/n)	6.63 (2.33)	8.25 (2.07)	-1.62	-0.76 (-1.06,-0.45)
CHAQ (0=best, 3=worst)	-	-	-	-
Across all visits	0.47 (0.54)	0.31 (0.49)	0.16	0.14 (0.07,0.22)
First available	0.67 (0.62)	0.51 (0.59)	0.16	0.13 (0.02,0.25)
At last follow-up	0.39 (0.54)	0.25 (0.43)	0.14	0.08 (0.002,0.16)
Enthesitis present at that visit (y/n)	0.59 (0.54)	0.34 (0.51)	0.25	0.16 (0.10,0.23)
Pain VAS (0=best, 10=worst)	-	-	-	-
Across all visits	3.01 (2.79)	1.68 (2.34)	1.33	0.94 (0.64,1.25)
First available	4.19 (2.76)	2.75 (2.71)	1.44	0.31 (-0.28,0.90)
At last follow-up	2.67 (2.87)	1.41 (2.17)	1.26	0.57 (0.08,1.07)
Enthesitis present at that visit (y/n)	4.00 (2.7)	1.61 (2.31)	2.39	1.57 (1.23,1.92)

Figure 3-1: Mean JAQQ, HRQoML, CHAQ, and Pain VAS in Children With Versus Without Enthesitis



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CHAPTER 4 – SUMMARY

4.1 Summary of Research

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood, but is under-recognized and poorly understood not only by the general public, but also by many medical practitioners. This disease causes joint swelling, pain, and stiffness and can affect various other parts of the musculoskeletal (MSK) system, as well as other organ systems (eyes, gastrointestinal tract, heart, lungs) (1, 22, 66). One manifestation of JIA that has not yet been described in detail is enthesitis or inflammation at sites of attachment of tendon, ligament, joint capsule, or fascia into bone. The characteristics of enthesitis and its impact on the quality of life, function, and pain of children with JIA are of interest and were the foci of this research program.

The objectives of this thesis were, therefore, to: (1) describe the prevalence, associated characteristics, and course of enthesitis over time across children with all categories of JIA, and its relationship to active joint counts (arthritis) in these children, and (66) to estimate the impact of enthesitis, irrespective of JIA category, on various patient reported outcomes (PROs), i.e. measures of health-related quality of life, function, and pain in children with JIA. Prospectively collected information from close to 1500 Canadian children newly diagnosed with JIA in the ReACCh-Out cohort was used to address these objectives (45-47).

We found that enthesitis was frequently detected by rheumatologists in patients with JIA and was present in children with all categories of JIA except for systemic JIA. Two thirds of the children with enthesitis were classified as having enthesitis-related arthritis (ERA), the category of JIA classically associated with this manifestation. Classic descriptions of patients with this

manifestation are that they have oligoarticular arthritis (i.e. arthritis involving 4 or less joints) (33, 34). However, in the ReACCh-Out cohort, we found that most children with enthesitis (57%) had polyarticular involvement (arthritis in 5 or more joints). Other interesting findings were that the number of tender entheseal sites decreased over time, in parallel with active joint count (arthritis). Further, the decrease in mean active joint count over time was similar in those children with and without enthesitis. Our cohort was similar to previous cohorts of patients with ERA in that the children with enthesitis were predominantly adolescent boys in whom sacroilitis (arthritis of the sacroiliac joint(s) in the lower back) and HLA-B27 positivity (a genetic marker associated with this 'family' of arthritis, including adult ankylosing spondylitis) were both more common than in the children without enthesitis (4, 21, 32). A key difference between our study and previous literature in this area is that we studied all children who developed the clinical manifestation of enthesitis (irrespective of JIA category) and compared them to children without enthesitis, whereas previous studies compared children with ERA (regardless of whether they had enthesitis or not) and compared them to children with other categories of JIA.

In terms of patient reported outcomes, we found that children with enthesitis had worse scores in all the PROs that we examined. They reported worse quality of life (higher JAQQ scores and lower HRQoML scores), worse function (higher CHAQ scores), and more pain (higher pain VAS scores) than the children without enthesitis, after controlling for category of JIA and various other covariates, including sex, age of onset of JIA, upper joint arthritis, lower joint arthritis, SI joint arthritis, polyarticular involvement, psoriasis, uveitis, ANA positivity, and presence of HLA-B27. These differences persisted up to 5 years after diagnosis.

It had previously been found in a cross-sectional study (4) that children with the ERA category of JIA report more pain and poorer health status than children with other categories of JIA. They used some of the same measures as in our study, including the pain VAS and CHAQ, but the JAQQ was not part of that study. Their study was cross-sectional, whereas our study is longitudinal. Further, only 4% of their patients had enthesitis at the time of assessment, while 16% of our patients had enthesitis when studied longitudinally (4).

In a single centre longitudinal study (21), children with ERA and Undifferentiated JIA reported more pain, worse QoL, and poorer function than children with other categories of JIA. In models limited to ERA, female sex and tender enthesis count were significant predictors of decreased function. These findings were in keeping with the findings of our work. Again, however, they did not examine the effects of enthesitis across categories of JIA and their study was conducted at a single centre in the U.S., i.e. the Children's Hospital of Philadelphia (CHOP) as compared to our study, which involved 16 different Canadian centres (21).

PROs are children and families' way of telling physicians how they are doing and what matters most to them (21, 36-43). Our research shows that children with JIA and enthesitis, regardless of their JIA category, report they are doing worse in multiple areas (including measures of quality of life, pain, and function) than those without enthesitis.

4.2 Strengths and Potential Biases/Limitations

This program of research has several strengths. First, in terms of the study population, the ReACCh-Out cohort is the largest cohort of children with JIA in which the characteristics

associated with enthesitis have been described. It included patients from all the major pediatric rheumatology centers in Canada, following prospectively over a period of up to 5 years.

A second strength is that enthesitis in this cohort was evaluated systematically by highly trained pediatric rheumatologists, making it as accurate as clinically possible. Our study provides new information about the frequency, pattern of involvement, course, and association with other clinical characteristics of enthesitis in children with JIA. This has not been done previously.

Further strengths of this research are the longitudinal structured assessment of these children with JIA and the use of validated scales to assess patient-reported outcomes (PROs) over time.

Potential Biases:

Selection Bias:

The patients in the ReACCh-Out Cohort were a convenience sample of children presenting to pediatric rheumatology clinics across Canada. This had the advantage of being closer to real life practice, in that there were no strict exclusion criteria. Most patients with JIA were, in fact enrolled, in most centres. However, this did introduce the possibility of sampling bias. It was up to the discretion of the treating physician whether or not to approach a given patient to be in the study. Thus, there is the possibility that patients felt to be 'difficult' or 'non-adherent' or who had more or less severe disease or any number of other factors could have been excluded.
The fact that there were 1500 children with JIA across 16 centres who were invited to participate by many different physicians, however, likely helped to protect against this.

Measurement Bias:

There are a few sources of measurement bias related to the exposure(s) in this study. One such potential source of measurement bias that is not specific to this study *per se* is the use of the ILAR classification system for JIA. Some of our patients with ERA developed psoriatic rashes over the course of their disease (which is an exclusionary criterion for ERA), and many children with enthesitis were categorized as undifferentiated because of a family history of psoriasis. We hope our data inform current discussions to modify the ILAR criteria.

Another source is the fact that the presence of enthesitis was subjectively determined on clinical exam by the treating rheumatologists had the potential to introduce measurement bias. There may be variation on what would be called enthesitis by the different physicians. However, the fact that the assessors were all highly trained pediatric rheumatologists and that there were many of them across Canada likely helped to reduce this variation.

Still, the assessment of entheseal tenderness is subjective and Kehl et al have reported that enthesitis was underdiagnosed by physical examination relative to ultrasound (29). This is, nonetheless, likely as accurate as it can be without the aid of diagnostic imaging, which would be very time-consuming, cost prohibitive, and impractical in a busy clinical setting. Despite instructions to perform an assessment of entheseal sites in all children, it is possible that children diagnosed with ERA were more thoroughly assessed for enthesitis than those in other JIA categories. This may have resulted in underestimation of the prevalence of enthesitis in non-ERA categories. We could not control for how closely these instructions were followed.

Yes another potential source of measurement bias related to the exposure(s) in our study was from the fact that sacroiliitis was defined clinically. A patient was said to have sacroiliitis if the pediatric rheumatologist determined this to be so, based on history and physical examination. A recent study reported low predictive values of clinical examination to predict MRI findings (54). Prospective MRI ascertainment of sacroiliitis would have been ideal, but impractical in our study.

There are also several potential sources of measurement bias related to the outcome(s) of the study. First, patient and parent reported measures were analyzed together, regardless of who completed the questionnaires. Since young children may not fully understand some of the concepts that are being asked and may not be physically able to complete the forms, proxy assessments are unavoidable. However, for older children, there may be discrepancies between what they and their parents perceive. Children older than 9 years were encouraged to fill out the forms whenever possible, but we have no measure of how often that was done or to what extent the parents consulted with their children while filling out forms for them.

A further potential measurement bias related to the outcome(s) is that the majority of children missed at least one PRO assessment. We used linear mixed models which allowed us to fully utilize all available data and minimize the impact of missing data. We acknowledge, however, that no method can fully account for the missing data. Furthermore, we did sensitivity analyses around the missing data and found that this did not significantly change the results obtained adding to the robustness of our main findings.

Lastly, PRO values after 3 years of diagnosis should be interpreted with caution due to the relatively low numbers of assessments at that time.

Confounding:

There is always the possibility that some factor(s) other than the independent variable [i.e. a confounder(s)] resulted in the effects seen. In this study, there is question of whether it was truly the presence of enthesitis that was associated with worse PROs (i.e. more pain, worse quality of life, and worse function). To address this, we used mixed models and adjusted for all the major (measured) factors that we thought reasonable. For example, it could have been that since males are more likely than females to develop enthesitis, that being male (rather than having enthesitis) was associated with worse PROs. However, after controlling for sex, we found this not to be the case. We acknowledge that other factors which were not measured or considered important in the disease could be confounding our results. It is important to consider, however, that controlled trials, randomized or otherwise, would not be possible in the evaluation of PROs in enthesitis, as as the occurrence of enthesitis is not a factor that can be controlled by investigators.

4.3 Implications for Future Research

Our descriptions of the characteristics of enthesitis in children with JIA will help researchers better define the role of this clinical manifestation in the classification of children with JIA. In recent years, there has been a move in pediatric rheumatology toward developing a new, more comprehensive, biologic-based classification system for JIA. In fact, a partnership between pediatric rheumatologists in Canada and The Netherlands called Understanding Childhood Arthritis Network – Canadian Dutch (UCAN-CANDU) was recently successful in securing a

multi-million-dollar research grant, funded by the Canadian Institutes of Health Research (CIHR) and a similar Dutch organization. The main goal of UCAN-CANDU over the next several years is to determine the biologic basis of JIA, which will help inform a personalized approach to treatment (when to start therapy, what to start, and when to stop) for these children (67). Thus, the time is ripe for any information that can help inform this new classification system, which will consider multiple clinical and biological factors. Our studies on enthesitis in JIA will contribute to this larger research program.

Enthesitis should be strongly considered for inclusion in future criteria used to classify JIA and criteria to assess response to treatment. None of the major currently available standardized response criteria used in JIA include enthesitis. A newer scale for patients with juvenile spondyloarthroarthritis, the Juvenile Spondyloarthritis Disease Activity Index (JSpADAI), does include enthesitis (65). However, this index has yet to be validated in a prospective cohort of patients and it remains to be seen if it will be a useful tool on a larger scale.

There is suggestion in the adult literature that the 'family' of diseases associated with the development of enthesitis (i.e. the spondyloarthritides), which are known to involve the IL-23-IL-17 immune axis, may be better treated with medications which specifically target this axis, rather than the medications currently used to treat rheumatoid arthritis (in adults) and JIA (68). One such medication, sekukinumab, a human monoclonal antibody that targets IL-17a, is currently being used to treat psoriasis, ankylosing spondylitis, and psoriatic arthritis in adults (68. 69). Another, ustekinumab, a human monoclonal antibody targeting IL-12 and IL-23, is used to

treat psoriasis and psoriatic arthritis in adults (68, 70, 71). These medications have not yet been approved for use in children, but this is an area which should be explored in the coming years.

Finally, the role of imaging (ultrasound, MRI) in the assessment of enthesitis is an area that should be further explored. A key component of this research will be the feasibility of implementation in routine clinical practice, in terms of time and cost to the health care system (24-28). I am interested in all these areas of research and plan to be actively involved in this area of clinical investigation in the coming years.

4.4 Implications for Clinical Practice

Our research will help clinicians to better understand enthesitis and its impact on children with JIA. This will allow them to tailor treatment toward this manifestation of disease and will give them further insight into what their patients with enthesitis are likely experiencing. It will equip the physicians with better information with which to counsel their patients. In particular, physicians can let children with enthesitis know that other children with this manifestation often report more pain, worse function, and worse quality of life than those without it, but that it generally improves or resolves over time, with current treatment.

Because enthesitis has a clear measurable impact on patient well-being, physicians should ascertain its presence in every patient with JIA and make it a treatment target, if present. Based on our findings, it is advisable that physicians who see children with JIA develop a routine of checking the most common areas of entheseal involvement (as outlined in Chapter 1 of this thesis) in patients with all categories of JIA (with the possible exception of systemic JIA). It

would be useful for physicians to document the response of enthesitis to treatment by recording accurate enthesitis counts (with specific areas noted) at each visit, similar to the way that physicians document joint counts at present. In the future, ultrasound documentation of enthesitis at each visit may become a part of routine practice. However, we are not there yet.

4.5 References

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APPENDIX 1 – Patient-Reported Outcome (PRO) Measures Used in Our Study

1. Juvenile Arthritis Quality of Life Questionnaire (JAQQ)
2. Childhood Health Assessment Questionnaire (CHAQ) and Pain Visual Analogue Scale (VAS)
3. Quality of My Life (QoML) - Health-Related Quality of My Life (HRQoML)

Study Identification Number: | | | | Site Identification Number: | | | Date: Y Y Y Y - M M - D D

Visit Month: ☐ 0 ☐ 6 ☐ 12 ☐ 18 ☐ 24

Juvenile Arthritis Quality of Life Questionnaire (JAQQ)
Section 1 - Motor Function

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 1-10 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child	
1 = None of the time	- NEVER
2 = Hardly any of the time	- 10% of the time
3 = Some of the time	- 25% of the time
4 = Half of the time	- 50% of the time
5 = Most of the time	- 75% of the time
6 = Almost all of the time	- 90% of the time
7 = All the time	- ALWAYS

		NEVER							ALWAYS
1	Getting out of bed upon awakening	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
2	Stepping in and out of the shower or bath	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
3	Washing, combing, or brushing hair	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
4	Putting on underwear, skirt, or pants	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
5	Pulling on sweater or coat	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
6	Walking on a flat surface for 1/2 block or walking up a slight incline	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
7	Walking up or down a flight of 10 stairs	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
8	Running 2 blocks	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
9	Riding a bicycle (or tricycle)	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

10	Playing a favourite sport (Which one?_____)	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 1 - Motor Function - continued

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 11-17 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child
1 = None of the time - NEVER
2 = Hardly any of the time - 10% of the time
3 = Some of the time - 25% of the time
4 = Half of the time - 50% of the time
5 = Most of the time - 75% of the time
6 = Almost all of the time - 90% of the time
7 = All the time - ALWAYS

		NEVER							ALWAYS
11	Participating in physical education class	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
12	Bending and lifting an object from the floor	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
13	Kneeling or sitting on heels for several minutes	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
14	Sitting for 1/2 hour	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
15	Turning to look over your shoulder	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
16	Chewing or swallowing food	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
17	Standing for 1/2 hour	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

B. From the above list of 17 items, please select up to 5 items that are the biggest problem for you/your child and write the item number(s) in a box. If you cannot identify 5, select as many as are relevant up to a maximum of 5.

☐ ☐ ☐ ☐ ☐

Section 1 - Motor Function - continued

C. If you/your child have any difficulties with any other similar physical activity that has not been mentioned, please describe it below and score the degree of difficulty using the same scale as above.

	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 2 - Fine Motor Function

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 1-6 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child	
1 = None of the time	- NEVER
2 = Hardly any of the time	- 10% of the time
3 = Some of the time	- 25% of the time
4 = Half of the time	- 50% of the time
5 = Most of the time	- 75% of the time
6 = Almost all of the time	- 90% of the time
7 = All the time	- ALWAYS

		NEVER						ALWAYS
1	Turning the faucets (taps) on and off	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
2	Brushing teeth	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
3	Pulling on socks	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
4	Putting on shoes	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
5	Tying shoe laces	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
6	Putting on shirt/blouse	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 2 - Fine Motor Function – continued

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 7-16 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child	
1 = None of the time	- NEVER
2 = Hardly any of the time	- 10% of the time
3 = Some of the time	- 25% of the time
4 = Half of the time	- 50% of the time
5 = Most of the time	- 75% of the time
6 = Almost all of the time	- 90% of the time
7 = All the time	- ALWAYS

		NEVER							ALWAYS
7	Fastening shirt or coat buttons	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
8	Putting on gloves	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
9	Turning the handle to open the door	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
10	Opening a soft drink can	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
11	Twisting off a bottle/jar top (previously opened)	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
12	Lifting a cup and drinking from it	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
13	Using a spoon, knife, or fork	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
14	Writing, drawing, or colouring with a pencil/pen/crayon or painting with a small paintbrush	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
15	Using an eraser	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
16	Cutting paper with scissors	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 2 - Fine Motor Function - continued

B. From the above list of 16 items, please select up to 5 items that are the biggest problem for you/your child and write the item number(s) in a box. If you cannot identify 5, select as many as are relevant up to a maximum of 5.

☐ ☐ ☐ ☐ ☐

C. If you/your child have any difficulties with any other similar fine motor physical activity that has not been mentioned, please describe it below and score the degree of difficulty using the same scale as above.

	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 3 - Psychosocial Function

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 1-4 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child
1 = None of the time - NEVER
2 = Hardly any of the time - 10% of the time
3 = Some of the time - 25% of the time
4 = Half of the time - 50% of the time
5 = Most of the time - 75% of the time
6 = Almost all of the time - 90% of the time
7 = All the time - ALWAYS

		NEVER							ALWAYS
1	Disobeyed or interacted poorly with parents	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
2	Interacted poorly with brothers or sisters	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
3	Interacted poorly with other children	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
4	Was mean to others	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 3 - Psychosocial Function - continued

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 5-14 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child
1 = None of the time - NEVER
2 = Hardly any of the time - 10% of the time
3 = Some of the time - 25% of the time
4 = Half of the time - 50% of the time
5 = Most of the time - 75% of the time
6 = Almost all of the time - 90% of the time
7 = All the time - ALWAYS

		NEVER							ALWAYS
5	Hung around others who get into trouble	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
6	Argued a lot	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
7	Demanded a lot of attention	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
8	Got teased a lot	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
9	Cried a lot for no apparent reason	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
10	Was easily jealous	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
11	Complained of loneliness	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
12	Felt unloved	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
13	Felt frustrated	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
14	Felt depressed	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 3 - Psychosocial Function - continued

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 15-22 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child
1 = None of the time - NEVER
2 = Hardly any of the time - 10% of the time
3 = Some of the time - 25% of the time
4 = Half of the time - 50% of the time
5 = Most of the time - 75% of the time
6 = Almost all of the time - 90% of the time
7 = All the time - ALWAYS

		NEVER							ALWAYS
15	Felt worthless or inferior	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
16	Felt sad	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
17	Missed school (other than for appointments)	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
18	Disturbed the class at school	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
19	Couldn't pay attention for long	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
20	Disobeyed teachers	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
21	Did poorly in school	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
22	Failed to finish things already started	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 3 - Psychosocial Function – continued

B. From the above list of 22 items, please select up to 5 items that are the biggest problem for you/your child and write the item number(s) in a box. If you cannot identify 5, select as many as are relevant up to a maximum of 5.

☐ ☐ ☐ ☐ ☐

C. If you/your child have any difficulties with any other similar physical activity that has not been mentioned, please describe it below and score the degree of difficulty using the same scale as above.

	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 4 - Systemic Symptoms

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 1-4 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child
1 = None of the time - NEVER
2 = Hardly any of the time - 10% of the time
3 = Some of the time - 25% of the time
4 = Half of the time - 50% of the time
5 = Most of the time - 75% of the time
6 = Almost all of the time - 90% of the time
7 = All the time - ALWAYS

		NEVER							ALWAYS
1	Poor appetite	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
2	Mouth sores	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
3	Nausea/vomiting	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
4	Abdominal pain	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 4 - Systemic Symptoms - continued

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 5-14 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child
1 = None of the time - NEVER
2 = Hardly any of the time - 10% of the time
3 = Some of the time - 25% of the time
4 = Half of the time - 50% of the time
5 = Most of the time - 75% of the time
6 = Almost all of the time - 90% of the time
7 = All the time - ALWAYS

		NEVER							ALWAYS
5	Heartburn	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
6	Diarrhea	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
7	Constipation	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
8	Blood on stool (Blood with bowel movement)	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
9	Sore, painful, red eyes	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
10	Skin rash	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
11	Pain or discomfort passing urine	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
12	Dark or blood stained urine	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
13	Headache	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
14	Fever	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 4 - Systemic Symptoms - continued

A. How often have you/your child, over the past **2 WEEKS**, had difficulty with the following activities **AS A RESULT OF ARTHRITIS OR ITS TREATMENT**? Please score all items, numbered 15-19 below, in accordance with the following scale. Mark the box from 1-7 to the right of the item which corresponds with how often you/your child has had difficulty with this particular item.
If you/your child is unable to perform a particular activity because you/he/she is too young or would not be expected to perform this activity for any other reason, **please mark N/A - does not apply**.

SCORING SCALE

N/A = Does not apply to me/my child
1 = None of the time - NEVER
2 = Hardly any of the time - 10% of the time
3 = Some of the time - 25% of the time
4 = Half of the time - 50% of the time
5 = Most of the time - 75% of the time
6 = Almost all of the time - 90% of the time
7 = All the time - ALWAYS

		NEVER							ALWAYS
15	Decreased or limited strength	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
16	Stiffness	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
17	Tires easily	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
18	Joint swelling	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
19	Joint tenderness or pain	☐ N/A	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

B. From the above list of 19 items, please select up to 5 items that are the biggest problem for you/your child and write the item number(s) in a box. If you cannot identify 5, select as many as are relevant up to a maximum of 5.

☐ ☐ ☐ ☐ ☐

C. If you/your child have any difficulties with any other similar physical activity that has not been mentioned, please describe it below and score the degree of difficulty using the same scale as above.

	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Section 5 - Systemic Symptoms

1. **Patient/Parent's impression of patient's pain:**

a) Mark an X on the line at a point corresponding to your degree of pain overall in the past week (0 = no pain; 10 = worst pain imaginable)

cm

☐ ☐ 0 ☐ ☐ 10 ☐

b) Which of these phrases would you use to describe your child's (your) pain (overall in the past week)? Please mark the appropriate box.

no pain	slight pain	moderate pain	severe pain	extreme pain

c) If your child is 10 years or younger, please ask your child to select the picture which best corresponds with his/her degree of pain (overall in the past week):

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

1 2 3 4 5

2. **Patient/Parent global assessment:** Relative to the last assessment do you feel your child is:

Y Y Y Y M M D D

Much better	Better	Same	Worse	Much worse

Date:	Completed by: Parent/Guardian Patient

Study Identification Number: Site Identification Number: Date:

Study Identification Number: Site Identification Number: Date: Visit Month:

YYYY-MM-DD ☐ 0 ☐ 6 ☐ 12 ☐ 18 ☐ 24

Child Health Assessment Questionnaire

In this section, we are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the extra page provided at the end of this questionnaire package. In the following questions, please mark an X in the box corresponding to the one response which best describes your child's usual activities (averaged over an entire day) **OVER THE PAST WEEK**. **ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS.** If most children at your child's age are not expected to do a certain activity, please mark as "Not Applicable". For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but NOT because he/she is RESTRICTED BY ILLNESS, please mark as "Not Applicable".

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To DO	Not Applicable
DRESSING and GROOMING					
Is your child able to: - Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐	☐
- Shampoo his/her hair?	☐	☐	☐	☐	☐
- Remove socks?	☐	☐	☐	☐	☐
- Cut fingernails?	☐	☐	☐	☐	☐
ARISING					
Is your child able to: - Stand up from a low chair or floor?	☐	☐	☐	☐	☐
- Get in and out of bed or stand up in a crib?	☐	☐	☐	☐	☐
EATING					
Is your child able to: - Cut his/her own meat?	☐	☐	☐	☐	☐
- Lift a cup or glass to mouth?	☐	☐	☐	☐	☐
- Open a new cereal box?	☐	☐	☐	☐	☐
WALKING					
Is your child able to: - Walk outdoors on flat ground?	☐	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐	☐

Please mark any AIDS or DEVICES that your child usually uses for any of the above activities:

☐ Cane ☐ Walker ☐ Crutches Wheelchair

Devices used for dressing (button hooks, zipper pull, long handled shoehorn, etc.)

Built up or special utensils

Special or built up chair

Other (specify below) _____

Please mark any categories for which your child usually needs help from another person **BECAUSE OF ILLNESS**:

Dressing and Grooming Arising Eating Walking

YYYY MM DD

Child Health Assessment Questionnaire – continued

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To DO	Not Applicable
HYGIENE					
Is your child able to: - Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a tub bath (get in and out of tub)?	☐	☐	☐	☐	☐
- Get on and off toilet or potty chair?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb/brush hair?	☐	☐	☐	☐	☐
REACH					
Is your child able to: - Reach and get down a heavy object such as a large game or book from just above his/her head?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor	☐	☐	☐	☐	☐
- Pull on a sweater over his/her head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
Is your child able to: - Write or scribble with pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐	☐
- Push open a door when he/she has to turn a door knob?	☐	☐	☐	☐	☐
ACTIVITIES					
Is your child able to: - Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bicycle or tricycle?	☐	☐	☐	☐	☐
- Do household chores (for example, wash dishes, take out trash, vacuuming, yardwork, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐

Child Health Assessment Questionnaire – continued

Please mark any AIDS or DEVICES that your child usually uses for any of the above activities (page 3):

- ☐ Raised toilet seat
- ☐ Bathtub seat
- ☐ Jar opener (for jars previously opened)
- ☐ Bathtub bar
- ☐ Longhandled appliance for reach
- ☐ Longhandled appliance for bathroom

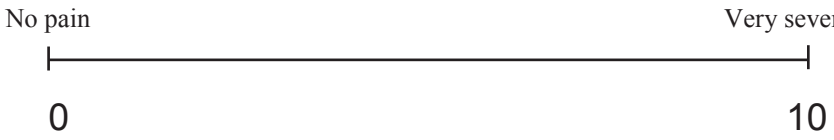
Please mark any categories for which your child usually needs help from another person **BECAUSE OF ILLNESS**:

- ☐ Hygiene
- ☐ Reach
- ☐ Gripping and opening things
- ☐ Errands and chores

We are also interested in learning whether or not your child has been affected by pain because of his or her illness.

How much pain do you think your child has had because of his or her illness IN THE PAST WEEK?

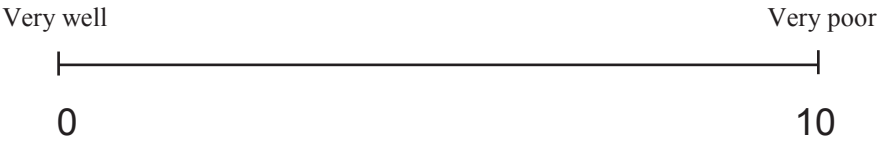
Place a mark on the line below to indicate the severity of the pain.



cm

HEALTH STATUS

1. Considering all the ways that arthritis affects your child, rate how your child is doing on the following scale by placing a mark on the line.



cm

2. Is your child stiff in the morning? ☐ Yes ☐ No

If YES, about how long does the stiffness usually last (in the past week)? ☐ Hours ☐ Minutes

Date: Y Y Y Y M M D D

Completed by: ☐ Parent/Guardian ☐ Patient

Study Identification Number: | | | |

Site Identification Number: | | |

Date: Y|Y|Y|Y - M M - D D

Visit Month: ☐ 0 ☐ 6 ☐ 12 ☐ 18 ☐ 24

Quality of My Life

Some of the children who come to see us feel that their life is not that great, while others think that their life is O.K.

How about you?

OVERALL, my life is...

The **WORST** ☹ 0 ———————————— 10 ☺ The **BEST**

☐☐.☐ **cm**

Considering my HEALTH, my life is...

The **WORST** ☹ 0 ———————————— 10 ☺ The **BEST**

☐☐.☐ **cm**

Since the last time I was here my life is...

☐ This is my **FIRST** visit

☐ Much **WORSE**

☐ A Little **WORSE**

☐ The **SAME**

☐ A Little **BETTER**

☐ Much **BETTER**

Check one or both boxes.
This form was filled out by

☐ Me:

☐ My parents:

☐ Other:
(please explain) ____________________

APPENDIX 2 - Sensitivity Analyses – Linear Mixed Models for Longitudinal Data

Patient-Reported Outcome	Without Imputed Values*	With Imputed Values*
JAQQ – Enth y/n	0.41 (0.22, 0.59)	0.36 (0.16, 0.55)
QoML – Enth y/n	-0.80 (-1.09, -0.51)	-0.78 (-1.09, -0.47)
CHAQ – Enth y/n	0.14 (0.07, 0.22)	0.12 (0.05, 0.20)
Pain VAS – Enth y/n	0.94 (0.64, 1.25)	0.90 (0.57, 1.24)

*Imputed Values – Fill down, followed by fill up; all study visits attended by each patient (described further in text)