

Juvenile Idiopathic Arthritis and Pain — More Than Simple Nociception



Pain is a very common and sometimes limiting symptom in patients with juvenile idiopathic arthritis (JIA). Nonetheless, there remain many unanswered questions regarding pain perception in JIA and the neurobiology of pain in this disease. In this edition of *The Journal*, Leegaard, *et al*¹ report their findings of lowered pain threshold in patients with JIA that add to our understanding of a fundamental aspect of this disease manifestation in JIA.

The disease pattern for JIA tends to follow a course of quiescent periods with disease activity flares superimposed. Some children have unrelenting disease activity that may be resistant to therapeutic interventions. Treatment of JIA is often complex and relies on medications, allied health interventions, and multidisciplinary expertise, ideally delivered in a coordinated manner in a predominantly ambulatory setting.

JIA may have a profound influence on children's lives and their experience of pain may be central to this^{2,3}. Studies have found that reduced quality of life and functional outcome (social, emotional, and physical), lowered mood, and poor sleep are all associated with higher levels of pain perception in JIA^{4,5,6}.

Pain in JIA has historically been underreported, under-recognized, and underresearched, with clinical and research focus on inflammation, damage, and function. There are few specific or multidimensional and reliable pain assessment tools⁷, which has limited clinical research. Thus, the evidence base for pain management has traditionally relied upon extrapolation from adult medicine⁸. By enriching our understanding of the neurobiology of pain pathways in JIA, the predictive factors for those young people most vulnerable to pain, in conjunction with a focus on developing effective treatments, we will make inroads into one of the most significant symptoms for our patients with JIA.

What is known regarding the pain experience in JIA?

While there are many studies outlining the pain experience

in adults with chronic arthritis, there has been until recently a paucity of information regarding the pain experienced by children and adolescents with JIA. Only 30 years ago, researchers suggested that children with JIA experience less pain than adults with comparable disease processes such as rheumatoid arthritis⁸. These findings were based on the pain measurement tools available at that time, which have since been refined, and this may have hindered the understanding of the pain experience in JIA, which is more prevalent than initially appreciated.

Children and adolescents with JIA experience pain commonly. Studies in JIA reveal a prevalence of pain between 50% and 86%, with many children having continuing pain over the course of their illness (50% at 1 year postdiagnosis and 40% at 5 years postdiagnosis)^{9,10}. Pain is the most common symptom at presentation and at followup clinic visits, occurring > 85% of the time^{2,11}. Even in the age of biologic disease-modifying antirheumatic drugs, pain remains the most common symptom for patients with JIA, with 76% of children reporting pain on > 60% of days despite treatment with methotrexate, tumor necrosis factor blockers, or combination therapy¹².

The character of the pain tends to be in the mild to moderate range of intensity. However, up to 25% of children feel pain at a higher intensity than this¹¹. Several studies over recent decades have attempted to describe the character of the pain experienced in JIA^{9,10,13}. The most common descriptors are of a background, constant pain with a superimposed sharp component, as well as movement-induced incident pain¹⁵. A recent study reported 65% of young people with JIA have marked within-day differences in pain intensity (≥ 10 units on a 0–100 visual analog scale) and this affects quality of life¹⁴.

The cause of pain in JIA is somatic; however, there are other important pathogenic influences on a young person's pain. These include psychological, genetic, psychosocial, familial models of pain, developmental stage, and chrono-

See Decreased pain threshold in JIA, page 1212

logical age, along with past experiences of pain^{7,8,16,17}. These will all influence the pain experience for an individual young person. This biopsychosocial model of pain used more broadly within pediatric pain medicine is also very relevant in the context of JIA pain.

Additionally, in this era of advanced pharmacological therapies that have significantly influenced the disease course of JIA, there is now the potential effect of repeated soft-tissue needling that is often required for drug delivery. This results in repeated stimulation of nociceptors on a background of often daily persistent pain. Many also undergo repeated procedures such as venipunctures, magnetic resonance imaging scans with injectable contrast, and intraarticular injections. It is therefore important to optimize procedural pain management to minimize distress and prevent further central sensitization of the nervous system.

Pain neurobiology and predictors of pain in JIA

Several research studies have reported reduced pain thresholds in patients with JIA (with both active or quiescent joint disease) as well as evidence from the laboratory using cold pressor-induced pain that JIA patients have reduced pain tolerance^{17,18}. Of interest, the lower pain threshold and tolerance correlated with increased pain report, possibly reflecting central sensitization and nociceptive pathway plasticity in the face of prolonged painful stimuli. Leegaard, *et al*¹ report that children with JIA had a substantially lower pain threshold even in areas unaffected by arthritis. The researchers used a novel method: a digital pressure algometer on both articular and nonarticular anatomical locations. One particularly interesting finding was that the decreased pain threshold occurred without correlation to disease duration. That is, neurobiological changes were detected early after disease onset, reflecting possibly both physiological early central sensitization and psychological effects of persisting and fluctuating pain. These results add to knowledge of pain neurobiology in JIA and in particular how pain perception may be altered and pain threshold decreased. Further studies are needed to determine the mechanisms as well as predictive and risk factors, with the goal of improving identification of the most vulnerable patients and providing effective treatments.

A number of demographic and psychosocial factors may play a role in the pain experienced in JIA¹⁶. Sex may be important, although the evidence has been inconclusive^{2,16}. Of note, several studies found females reported more pain than males, and those with polyarticular disease were at particular risk^{12,19}. The age of the child or adolescent often has a role in the level of pain-reporting; this likely reflects the developmental stages and cognitive maturity regarding pain in the pediatric population. As children develop they are more able to localize the pain of a site such as a joint and to interpret it in the context of an ongoing illness such as

JIA. However, the data are conflicting and a number of other studies have not shown age or sex to be a predictor of pain in patients with JIA^{12,16}. A wide range of psychosocial variables have been studied and those found to influence the pain experience in JIA include emotional distress, daily stress, and mood changes^{7,20}. Additionally, familial pain history, parental pain history, and how children with JIA cope with their pain (with catastrophizing a key factor) have all been shown to affect the pain experience in JIA^{6,20}.

The presumption has been that disease activity in JIA should correlate well with the severity of the pain experienced. However, a number of studies found that disease activity predicted only a small to medium proportion of the pain experience in JIA^{7,16}. Disease severity was recently found to be a significant predictor of higher intensity pain variability¹⁴.

Traditionally, the approach to JIA pain management has been to treat the active disease component of JIA, with the view that pain will cease or dramatically diminish thereafter. However, there is more to JIA pain management than merely suppression of synovitis. In the past decade we have seen an increased research base regarding the change in neurobiology for young people with JIA, and an increased understanding of persisting sensitivity to altered pain sensation beyond that of the period of active synovitis. Interventions have been extrapolated from other pediatric pain management and adult arthritis pain management approaches. There have been no clinical drug trials researching pain and JIA⁷. Thus, there are no evidence-based clinical guidelines for JIA pain management. Pain management predominantly involves a multimodal approach, ideally involving a multidisciplinary strategy from medical, nursing, and allied health professionals.

Multiple aspects of JIA pain neurobiology and clinical expression remain poorly understood. Reliable multidimensional pain assessment tools are under development. The study by Leegaard, *et al*¹ clarifies several aspects of lowered pain threshold and the neurobiology and pain experience for young people with JIA. This interesting work assists in guiding our clinical practice and clinical research to look beyond pure JIA disease activity into the complex puzzle of the neurobiology, psychology, and social aspects that form the pain experience for each of our patients.

JANE MUNRO, MBBS, FRACP, MPH,

Department of Rheumatology,
Royal Children's Hospital,
Melbourne, Victoria;

DAVINDER SINGH-GREWAL, MBBS, FRACP, MMedSci, PhD,

Department of Rheumatology,
The Children's Hospital at Westmead,
Locked Bag 4001 Westmead,
Sydney, New South Wales 2145,
Australia

Address correspondence to Dr. Singh-Grewal;

E-mail: davinder.singhgrewal@health.nsw.gov.au

REFERENCES

1. Leegaard A, Lomholt JJ, Thastum M, Herlin T. Decreased pain threshold in juvenile idiopathic arthritis: a cross-sectional study. *J Rheumatol* 2013;40:1212-8.
2. Anthony KK, Schanberg LE. Pain in children with arthritis: a review of the current literature. *Arthritis Rheum* 2003;49:272-9.
3. Tong A, Jones J, Craig JC, Singh-Grewal D. Children's experiences of living with juvenile idiopathic arthritis: a thematic synthesis of qualitative studies. *Arthritis Care Res* 2012;64:1392-404.
4. Margetic B, Aukst-Margetic B, Bilic E, Jelusic M, Tambic Bukovac L. Depression, anxiety and pain in children with juvenile idiopathic arthritis (JIA). *Eur Psychiatry* 2005;20:274-6.
5. Butbul Aviel Y, Stremmler R, Benseler SM, Cameron B, Laxer RM, Ota S, et al. Sleep and fatigue and the relationship to pain, disease activity and quality of life in juvenile idiopathic arthritis and juvenile dermatomyositis. *Rheumatology* 2011;50:2051-60.
6. Sawyer MG, Whitham JN, Robertson DM, Taplin JE, Varni JW, Baghurst PA. The relationship between health-related quality of life, pain and coping strategies in juvenile idiopathic arthritis. *Rheumatology* 2004;43:325-30.
7. Stinson JN, Luca NJ, Jibb LA. Assessment and management of pain in juvenile idiopathic arthritis. *Pain Res Manag* 2012;17:391-6.
8. Anthony KK, Schanberg LE. Pediatric pain syndromes and management of pain in children and adolescents with rheumatic disease. *Pediatr Clin North Am* 2005;52:611-39, vii.
9. Sherry DD, Bohnsack J, Salmonson K, Wallace CA, Mellins E. Painless juvenile rheumatoid arthritis. *J Pediatr* 1990;116:921-3.
10. Lovell DJ, Walco GA. Pain associated with juvenile rheumatoid arthritis. *Pediatr Clin North Am* 1989;36:1015-27.
11. Schanberg LE, Lefebvre JC, Keefe FJ, Kredich DW, Gil KM. Pain coping and the pain experience in children with juvenile chronic arthritis. *Pain* 1997;73:181-9.
12. Schanberg LE, Anthony KK, Gil KM, Maurin EC. Daily pain and symptoms in children with polyarticular arthritis. *Arthritis Rheum* 2003;48:1390-7.
13. Thompson KL, Varni JW, Hanson V. Comprehensive assessment of pain in juvenile rheumatoid arthritis: an empirical model. *J Pediatr Psychol* 1987;12:241-55.
14. Tupper SM, Rosenberg AM, Pahwa P, Stinson JN. Pain intensity variability and its relationship with quality of life in youths with juvenile idiopathic arthritis. *Arthritis Care Res* 2013;65:563-70.
15. Abu-Saad HH, Uiterwijk M. Pain in children with juvenile rheumatoid arthritis: a descriptive study. *Pediatr Res* 1995;38:194-7.
16. Malleson PN, Oen K, Cabral DA, Petty RE, Rosenberg AM, Cheang M. Predictors of pain in children with established juvenile rheumatoid arthritis. *Arthritis Rheum* 2004;51:222-7.
17. Thastum M, Zachariae R, Herlin T. Pain experience and pain coping strategies in children with juvenile idiopathic arthritis. *J Rheumatol* 2001;28:1091-8.
18. Hogeweg JA, Kuis W, Huygen AC, de Jong-de vos van Steenwijk C, Bernards AT, Oostendorp RA, et al. The pain threshold in juvenile chronic arthritis. *Br J Rheumatol* 1995;34:61-7.
19. Benestad B, Vinje O, Veierod MB, Vandvik IH. Quantitative and qualitative assessments of pain in children with juvenile chronic arthritis based on the Norwegian version of the Pediatric Pain Questionnaire. *Scand J Rheumatol* 1996;25:293-9.
20. Schanberg LE, Anthony KK, Gil KM, Lefebvre JC, Kredich DW, Macharoni LM. Family pain history predicts child health status in children with chronic rheumatic disease. *Pediatrics* 2001;108:E47.

J Rheumatol 2013;40:1037-9; doi:10.3899/jrheum.130557