Calcitonin Gene–Related Peptide for Identifying Pediatric Bacterial Musculoskeletal Infections

A Prospective, Multicenter Study

Caroline G. Kahane, MD, Lise E. Nigrovic, MD, MPH,* Daping Yang, PhD,† Joseph A. Majzoub, MD,‡ Mark D. Kellogg, PhD,§ Ron L. Kaplan, MD,‖ Andrea T. Cruz, MD, MPH,¶ Isaac M. Chiu, PhD,# and Todd W. Lyons, MD, MPH**

Objectives: Bacterial musculoskeletal infections (MSKIs) can be challenging to diagnose. We compared the accuracy of calcitonin gene–related peptide (CGRP), a neuropeptide which is transcribed from the same gene as procalcitonin, to procalcitonin for the diagnosis of a MSKI in children.

Methods: We conducted a prospective cohort study of patients 21 years old or younger who underwent evaluation for MSKIs at one of 3 emergency departments. Our primary outcome was a MSKI, defined as septic arthritis, osteomyelitis, or pyomyositis. We used a Spearman correlation coefficient to measure the association between serum CGRP and procalcitonin and compared the diagnostic accuracy using area under the receiver operating characteristic curve (AUC) analysis.

Results: Of the 200 enrolled patients, 33 (17%) had a MSKI. Overall, median serum CGRP level did not differ between patients with and without a MSKI (13.5 pg/mL MSKI vs 10.9 pg/mL no MSKI; difference: 2.6, 95% CI: −0.6, 5.8), while PCT was higher in patients with a MSKI (0.12 ng/mL MSKIs vs 0.04 ng/mL no MSKI; difference: 0.08, 95% CI: 0.03 to 0.13). CGRP and PCT levels were not correlated (Spearman rank coefficient: −0.01, 95% CI: −0.15 to 0.13). CGRP had a lower AUC than procalcitonin [0.57, 95% CI: 0.47 to 0.66 CGRP vs 0.78, 95% CI: 0.69 to 0.87 PCT, $P < 0.01$].

Conclusions: Although biochemically related, CGRP was not correlated with procalcitonin in children undergoing evaluation for a MSKI. Our exploratory pilot highlights the ongoing need for novel biomarkers for the accurate and timely identification of children with a MSKI.

Key Words: biomarker, osteomyelitis, septic arthritis, pyomyositis, procalcitonin, calcitonin generelated peptide

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It can be challenging for the emergency department (ED) clinician to identify children with bacterial musculoskeletal infections (MSKIs) such as osteomyelitis, septic arthritis, or pyomyositis given the clinical and laboratory overlap with other inflammatory and infectious conditions (ie, clinical mimics).[1] Both traditional and newer biomarkers such as procalcitonin (PCT) and clinical decision tools provide risk stratification, but do not accurately identify all children with MSKIs.[1,2] Therefore, novel biomarkers are needed to risk-stratify children with suspected MSKIs.

Calcitonin gene–related peptide (CGRP), a neuropeptide produced by alternative processing of the calcitonin gene (same superfamily as PCT), is a potent vasodilator and a neurotransmitter in the peripheral and central nervous system, with roles in pain and cardiovascular regulation.[3,4] CGRP is elevated in mouse models of gut, brain, and skin infections,[5–7] and in human studies has been found to play a role in COVID-19[8] and pediatric bacterial pneumonia,[9] as well as in painful conditions, including migraine headaches,[10] postoperative pain[11] and osteoarthritis.[12] However, its role in pediatric MSKIs has not been established.

Because of the shared clinical features that MSKIs have with these previously studied conditions, including an infectious etiology and often high levels of reported pain, we hypothesized that CGRP levels may be elevated in children with MSKIs and could potentially be used clinically as a novel biomarker of these difficult to diagnose conditions. This hypothesis was further supported by emerging data demonstrating potential utility for PCT—which is transcribed from the same pro-gene as CGRP—in the diagnosis of bacterial MSKIs.[1,2,13] To this end, we sought to measure the ability of CGRP to identify children with a MSKI and to compare CGRP to PCT as a diagnostic biomarker.

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From the *Division of Emergency Medicine, Boston Children's Hospital and Harvard Medical School, Boston, MA; †Institute of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai, China; ‡Division of Endocrinology, Boston Children's Hospital and Harvard Medical School; §Department of Laboratory Medicine, Boston Children's Hospital and Department of Pathology, Harvard Medical School, Boston, MA; ‖Department of Pediatrics, Seattle Children's Hospital and University of Washington School of Medicine, Seattle, WA; ¶Department of Pediatrics, Baylor College of Medicine, Houston, TX; and #Department of Immunology, Harvard Medical School.

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Reprints: Caroline G. Kahane, MD, Division of Emergency Medicine, Boston Children's Hospital, 300 Longwood Avenue, BCH3066, Boston, MA 02115 (e-mail: caroline.kahane@childrens.harvard.edu).

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METHODS

Study Population

We conducted a prospective cohort study of patients 21 years old or younger undergoing evaluation for bacterial MSKIs at one of 3 EDs: Boston Children's Hospital (Boston, MA), Seattle Children's Hospital (Seattle, WA), and Texas Children's Hospital (Houston, TX) between January 2020 and April 2023. We included patients 21 years of age or younger to reflect the age spectrum commonly seeking care in our study centers.[14] Study research teams identified potentially eligible patients in real-time using chief complaint, triage note, and the diagnostic testing ordered, and confirmed eligibility with the patient's treating providers. Patients with primary or secondary immunodeficiency or congenital musculoskeletal disorders were excluded. The study was approved by the institutional review board at each participating site with permission for data sharing.

Data Collection

At enrollment, treating clinicians captured patient demographics, history, and physical examination findings using REDCap data collection tools hosted by Harvard University.[15] Research blood biosamples were collected after obtaining clinical samples. Study samples were frozen at -80 °C after initial processing and then batch shipped to the central biobank housed at Boston Children's Hospital. One month after enrollment, study staff reviewed medical records to abstract laboratory, microbiology, and radiology test results, and performed a structured telephone follow-up using a standardized script to assess for potentially missed MSKI diagnoses.

Research Testing

Research biomarkers (PCT and CGRP) were measured from previously stored biosamples. We measured PCT levels in the clinical laboratory at Boston Children's Hospital using the Food and Drug Administration–approved Elecsys BRAHMS PCT electrochemiluminescent immunoassay (Roche Diagnostics) on a Cobas e601analyzed[1] and CGRP levels in a research laboratory (Chiu Laboratory at Harvard Medical School; Boston, MA) using an Enzyme Immunoassay (EIA) technique in duplicate using a commercially available kit (MyBioSource Inc, MBS267126, San Diego, CA) following the manufacturer's instructions.[8,16] To determine appropriate sample dilution (1:25 in manufacturer-provided dilution reagent), we used research samples from 3 patients with osteomyelitis and 2 control cases from the PrecisionLink Biobank for Health Discovery at Boston Children's. Optical density at 450 nm was fitted versus a calibration curve prepared with CGRP standard (range: 0 to 1000 pg/mL), as suggested by the manufacturer. For study samples, serum samples were prioritized (93% of samples); however, plasma was utilized when adequate serum was unavailable (7% of samples).

Outcome Measure

Our primary outcome was a bacterial MSKI (septic arthritis, osteomyelitis, and/or pyomyositis).[1] We defined septic arthritis as the growth of pathogenic bacteria in synovial fluid or positive blood culture plus synovial fluid pleocytosis [$\geq$ 50,000 white blood cell/mm^3]. As *Kingella kingae* (*K. kingae*) does not always grow well in routine bacterial culture, we included positive polymerase chain reaction tests of synovial fluid in our septic arthritis case definition.[17] We classified bacterial pathogens not associated with human infection in immunocompetent hosts as contaminants [eg, non-aureus staphylococci (except for recently instrumented joints), viridans streptococci]. We defined osteomyelitis and pyomyositis based on bone scan or magnetic resonance imaging findings consistent with these diagnoses, as interpreted by the attending radiologist. We did not require identification of a bacterial pathogen to diagnose either osteomyelitis or pyomyositis as blood cultures can be falsely negative and few patients had a diagnostic bone or muscle biopsy performed.[18] Patients with Lyme arthritis were included in the comparator group as *Borrelia burgdorferi* does not produce the same kind of inflammatory response as other pyogenic infections and because Lyme arthritis treatment urgency differs.[19,20] We defined Lyme arthritis with a positive modified or standard 2-tier Lyme disease serology test interpreted using standardized criteria.[21,22] All other patients were classified as having other inflammatory arthritis (eg, transient synovitis, reactive arthritis, juvenile idiopathic arthritis) and were included in the comparator group.

Statistical Analysis

We described our patient population using medians and their associated interquartile ranges for continuous variables and counts with proportions for categorical variables. We averaged duplicate CGRP results and used this number for subsequent analyses. We measured the average coefficient of variation between duplicates for CGRP levels.[23,24] We compared median blood CGRP and PCT levels between patients with and without bacterial MSKIs using Wilcoxon rank-sum tests. We constructed receiver operating characteristics (ROC) curves for CGRP and PCT to measure test performance and compared the area under the ROC curve (AUC) using the DeLong method.[25] We measured the correlation between CGRP and PCT levels using Spearman rank coefficient.

We performed all statistical analyses using SAS version 9.4 software, copyright 2012 SAS Institute Inc. (Cary, NC).

RESULTS

Of the 262 eligible patients undergoing evaluation for bacterial MSKIs, 200 (76%) had adequate biosample to measure both CGRP and PCT levels (Table 1). Median patient age was 7 years [interquartile range (IQR): 4 to 11 y] and 126 (63.0%) were male. The majority had lower limb or pelvis pain or swelling. A minority of patients had received antibiotics in the preceding 72 hours. Patients with a MSKI were more likely to present with fever.

Thirty-three patients (17% of enrolled) had a MSKI: 10/33 (30.3%) septic arthritis alone, 15/33 (45.5%) osteomyelitis alone, 2/33 (6.1%) pyomyositis alone, 4/33 (12.1%) osteomyelitis and pyomyositis, 2/33 (6.1%) septic arthritis and osteomyelitis. There were no missed MSKIs identified by the 1-month follow-up phone call. We identified the following 23 bacterial pathogens: 17/23 (73.9%) *Staphylococcus aureus*, 2/23 (8.7%) *Streptococcus pneumoniae*, 2/23 (8.7%) *Staphylococcus epidermidis* (both in patients with recently instrumented joints), 1/23 (4.3%) *Streptococcus pyogenes*, and 1/23 (4.3%) *K. kingae*. Among the 60 patients 4 years of age or younger included in the study, 12 underwent arthrocentesis, and 2 (16.7%) of these patients had PCR testing for *K. kingae* performed, of which both had

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TABLE 1. Baseline Characteristics of Enrolled Patients With and Without a Bacterial Musculoskeletal Infection

Characteristics	Patients With a Bacterial MSKI;N = 33	Patients Without a Bacterial MSKI (Comparator Group);N = 167
Demographics		
Age, y *	10 (5.5, 14)	6 (4, 10)
Male, n (%) †	20 (60.6)	106 (64.2)
Clinical features		
Affected body part, n (%)		
Upper extremity	2 (6.1)	13 (7.8)
Lower extremity ‡	31 (93.9)	146 (87.4)
Spine	0	1 (0.6)
Multiple	0	7 (4.2)
Antibiotic pretreatment in 72 h, n (%)	4 (12.1)	18 (10.8)
Presence of fever, n (%) §	16 (51.6)	40 (24.5)
Duration of fever, y *	1.5 (1, 3.8)	1 (1, 3)

*Median, interquartile range.
†Missing for 2 children (2 patients without bacterial MSKI).
‡Includes pelvis and lower limb.
§Missing for 6 children (2 patients with a bacterial MSKI; 4 patients without a bacterial MSKI).

negative results. One child had a synovial fluid bacterial culture, which grew *K. kingae*. Of the 167 patients without a MSKI, 26/167 (15.6%) had Lyme arthritis and 141/167 (84.4%) had other inflammatory arthritis. No child with a MSKI also had Lyme arthritis.

The average coefficient of variation between duplicate CGRP samples was 11.1%. Patients with a MSKI versus no MSKI had a higher median PCT level (0.12 ng/mL MSKIs vs 0.04 ng/mL no MSKI; difference: 0.08 ng/mL, 95% CI: 0.03 to 0.13 ng/mL) but a similar median CGRP level (13.5 pg/mL MSKIs vs 10.9 pg/mL no MSKI; difference: 2.6 pg/mL, 95% CI: −0.6, 5.8 pg/mL). PCT had better discriminative ability than CGRP (PCT AUC: 0.78, 95% CI: 0.69 to 0.87 vs CGRP AUC: 0.57, 95% CI: 0.47 to 0.66 vs $P = 0.004$; Fig. 1). We found no correlation between CGRP and PCT levels in samples collected simultaneously from the same child (Spearman rank coefficient: −0.01, CI: −0.15 to 0.13; Fig. 2).

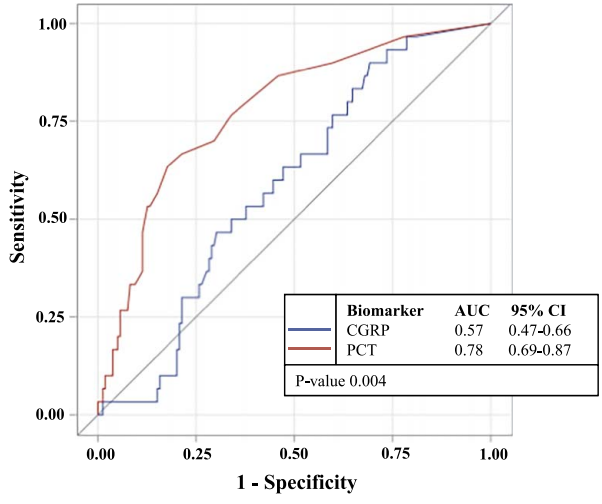

FIGURE 1. Receiver operating characteristics curve analysis of calcitonin gene–related peptide (CGRP) and procalcitonin (PCT) in patients with and without a bacterial MSKI.

DISCUSSION

In our pilot study, CGRP did not accurately discriminate between children with and without a pyogenic MSKI. Although PCT is transcribed from the same gene as CGRP, blood levels of CGRP and PCT did not correlate in our population of children being evaluated for a MSKI. While CGRP levels have been correlated with multiple other inflammatory and infectious conditions, our pilot work suggests its blood levels may not accurately stratify a child's risk of a bacterial MSKI.

CGRP is elevated in other infections including mouse models of *Streptococcus pyogenes* soft tissue infections[3] and bacterial meningitis,[6] and in in vitro studies of human immunodeficiency virus infections.[26] Using the same assay platform, CGRP has been positively correlated with the need for hospitalization, pulmonary deterioration, and increased morbidity in adults with COVID-19 infection.[8] In a recent study, CGRP distinguished between bacterial and viral pneumonia in pediatric patients (AUC: 0.96, 95% CI: 0.93 to 1.0).[9] Furthermore, CGRP has been recognized as a critical player in migraine pathophysiology,[10] as well as other painful conditions including postoperative pain[11] and osteoarthritis.[12] Our study was the first to evaluate CGRP as a biomarker for pyogenic MSKIs in children. Although further study will be needed, one potential explanation for our failure to detect a difference may be that included children with a MSKI had a more localized inflammatory processes without substantial systemic symptoms. CGRP could be elevated in localized tissue samples (ie, bone and muscle biopsy).

Furthermore, while CGRP and PCT are transcribed from the same pro-gene, we found no significant correlation between patients' levels of CGRP and their PCT levels. This lack of correlation has been previously described in a study evaluating CGRP and PCT levels in postoperative pain.[11] The lack of correlation and the lower discriminative ability may reflect the very short half-life for CGRP (ranging from

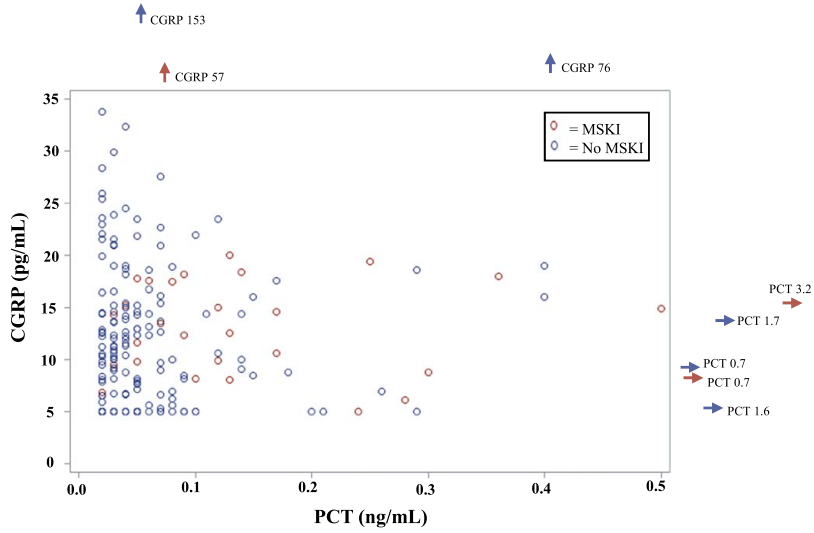

FIGURE 2. Scatter plot depicting each subject's procalcitonin (PCT; *x*-axis) versus calcitonin gene–related peptide (CGRP; *y*-axis).

7 to 27 min),[27] compared with the substantially longer half-life for PCT (~24 h).[28] Given that many children with bacterial MSKIs do not present hyper acutely and have had symptoms for multiple days,[29,30] one hypothesis is that CGRP levels have already peaked and subsequently decreased at the time of sample collection and diagnosis, as symptoms of MSKIs can often be sub-acute and children may not present acutely.[29] Another possibility is due to tissue-specific sources and alternative splicing of the *CALCA* gene: thyroid C cells favor retention of exon 4 to generate procalcitonin, while sensory neurons skip exon 4 to produce CGRP.[31] Thus, thyroid C cells may contribute to circulating PCT during infection, while neuronal CGRP may remain largely localized close to nerve terminals in the tissues, with limited spillover into serum.

Recent data have shown that PCT may have utility in the evaluation of bacterial MSKIs, especially when interpreted in conjunction with other biomarkers such as CRP. One prospective study examined 258 children being evaluated for a bacterial MSKI and found PCT >0.1 ng/mL independently predicted bacterial MSKI in 85% of cases, outperforming white blood cell (WBC) count, CRP, and absolute neutrophil count (ANC).[13] Another prospective study of 735 children being evaluated for MSKI in Lyme-disease endemic regions, found serum PCT level >0.50 ng/mL was one of 3 independent predictors of MSKI (sensitivity: 100%, 95% CI: 91.0% to 100%; specificity: 74.2%, 95% CI: 70.5% to 77.6%),[2] adding to the growing literature surrounding the utility of PCT in the evaluation of pediatric MSKIs.[1,32]

Our study must be interpreted in the context of its limitations. First, the CGRP assay we utilized is labeled for research use only and was not validated in an accredited clinical laboratory. However, all research assays were performed by trained personnel using manufacturer-approved procedures. Second, most tests were run on serum samples, although a minority were run on plasma due to limited serum sample availability. Given the small pilot sample, we were unable to compare the performance of CGRP in serum to plasma. However, the CGRP EIA assay utilized is approved for both serum and plasma samples. Third, the average coefficient of variation between duplicate CGRP samples was slightly higher than the commonly accepted 10% variance.[33] Fourth, a minority of children had received antibiotic pretreatment before enrollment. We were unable to evaluate the impact this had on CGRP or PCT levels. Fifth, as diagnostic testing was left to the treating clinician's discretion, many children were not evaluated for *K. kingae* infection. Although patients with *K. kingae* MSKIs could have been misclassified due to incomplete testing, we performed 1-month follow-up to limit missed MSKI diagnoses. Sixth, given the short half-life of CGRP, this protein might have degraded while frozen;[34] future studies should consider using fresh samples or frozen samples prepared with a protease inhibitor buffer. Last, our study was an exploratory pilot, and we may have been underpowered to detect small differences in biomarker levels. Even in our multicenter, multi-year cohort, MSKIs were uncommon, limiting the precision of our estimates of diagnostic accuracy, and our ability to analyze biomarker performance. This underscores the need for larger studies investigating multiple diagnostic biomarkers for a MSKI in children.

CONCLUSIONS

CGRP did not accurately discriminate between children with and without a pyogenic MSKI. Furthermore, CGRP levels were not correlated with blood PCT levels, which had higher discriminatory ability for these infections. Given the exploratory nature of this study, further work is needed to better understand CGRPs' role as a diagnostic biomarker for pediatric infections.

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