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Original Article

Retrospective Analysis of Children with Chronic Non-bacterial Osteomyelitis

Kronik Non-bakteriyel Osteomiyelitli Çocukların Retrospektif Analizi

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ABSTRACT

Objective: Chronic non-bacterial osteomyelitis (CNO) is a rare autoinflammatory bone disorder which mainly affects children and young adolescents. In this study, we report our single-center experience with pediatric CNO patients.

Method: Children diagnosed with CNO at the Department of Pediatric Rheumatology of Hacettepe University between November 2006 and July 2021 were retrospectively reviewed. The demographics, clinical features, laboratory findings, imaging modalities, concomitant diseases, and treatments were recorded. Diagnostic delay was defined as the time interval from symptom onset to diagnosis.

Results: A total of 48 patients (52.1% male) with a median age of 13.7 (minimum-maximum: 3.3-20.4) years were included. Local bone pain was the most frequent symptom (72.9%), followed by arthralgia (52.1%), limping or difficulty in walking (43.8%), and back pain (33.3%). Elevated erythrocyte sedimentation rate (52.1%) and high C-reactive protein levels (43.8%) were the most frequently observed laboratory abnormalities. Magnetic resonance imaging (MRI) (regional MRI in 87.5% and whole-body MRI in 66.7% of patients) was widely used in the diagnosis. Non-steroidal anti-inflammatory drugs (NSAIDs) were used in all patients and six patients (12.5%) achieved complete clinical remission with NSAIDs alone. Methotrexate (MTX) (80.9%), biological agents (7.1%), and pamidronate (11.9%) were used as the second-line treatment. Also, 26.4% of patients achieved clinical remission with MTX. Biological treatment was required in a total of 27 patients (56.2%).

Conclusion: Local bone pain is a warning sign for CNO diagnosis. Complete clinical remission can be achieved in CNO patients with an escalating anti-inflammatory treatment, having NSAIDs in one end, and biological drugs and bisphosphonates on the other end of the spectrum.

Keywords: Chronic non-bacterial osteomyelitis, children, autoinflammatory bone disease

ÖZ

Amaç: Kronik nonbakteriyel osteomiyelit (KNO) nadir görülen bir otoenflamatuvar kemik hastalığıdır ve esas olarak çocukları ve genç adolesanları etkiler. Bu çalışmada pediatrik KNO hastalarına ait tek merkez deneyimimizi sunmayı amaçladık.

Yöntem: Hacettepe Üniversitesi Çocuk Romatoloji Anabilim Dalı'nda Kasım 2006-Temmuz 2021 tarihleri arasında KNO tanısı alan çocuklar geriye dönük olarak değerlendirildi.

Bulgular: Çalışmaya ortanca yaşı 13,7 (min-maks: 3,3-20,4) yıl olan toplam 48 hasta (%52,1 erkek) dahil edildi. Lokal kemik ağrısı en sık görülen semptomdu (%72,9), bunu artralji (%52,1), topallama veya yürüme güçlüğü (%43,8) ve bel ağrısı (%33,3) izledi. Artmış eritrosit sedimantasyon hızı (%52,1) ve yüksek C-reaktif protein seviyeleri (%43,8) en sık gözlenen laboratuvar anormallikleriydi. Tanıda manyetik rezonans görüntüleme (MRG) (hastaların %87,5'inde bölgesel MRG ve %66,7'sinde tüm vücut MRG) yaygın olarak kullanılmıştır. Tedavide tüm hastalara nonsteroid anti-enflamatuvar ilaçlar (NSAİİ) verildi ve altı hasta (%12,5) sadece NSAİİ tedavisi ile tam klinik remisyon sağladı. İkinci basamak tedavi olarak metotreksat (MTX) (%80,9), biyolojik ajanlar (%7,1) ve pamidronat (%11,9) kullanıldı. Hastaların %26,4'ü MTX ile klinik remisyona ulaştı. Toplam 27 hastada (%56,2) biyolojik ajan tedavisi gerekti.

Sonuç: Lokal kemik ağrısı, KNO tanısı için uyarıcı bir işarettir. Spektrumun bir ucunda NSAİİ'lerin diğer ucunda ise biyolojik ilaçlar ve bifosfonatların bulunduğu artan anti-enflamatuvar tedavi planı ile KNO hastalarında tam klinik remisyon elde edilebilir.

Anahtar kelimeler: Kronik non-bakteriyel osteomiyelit, çocuk, otoenflamatuvar kemik hastalığı

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INTRODUCTION

Chronic non-bacterial osteomyelitis (CNO) is an autoinflammatory disorder characterized by sterile bone inflammation[1]. It was defined as "chronic recurrent multifocal osteomyelitis", since the first described cases were characterized by subacute and chronic symmetric multifocal bone lesions. However, considering that the disease is not always multifocal and recurrent, the term CNO is commonly used as an umbrella term for all presentations[2,3]. Although the annual incidence is estimated to be 0.4 per 100,000 children, the true incidence of CNO in childhood is still unclear[4]. The number of new cases has been increasing, as awareness raises[5]. The co-occurrence of inflammatory bowel disease (IBD), palmoplantar pustulosis, psoriasis, acne fulminans, and ankylosing spondylitis with CNO has also been reported[6-9]. Altered expression of cytokine and chemokine is considered to play a central role in the pathogenesis of CNO. Reduced interleukin-10 (IL-10) levels, high levels of pro-inflammatory cytokines [IL-1β, IL-6, tumor necrosis factor-alpha (TNF-α)] and chemokines, increased inflammasome assembly, and osteoclast differentiation and activation are involved in the pathogenesis[10,11].

The most common clinical manifestation is bone pain which is a common symptom in childhood[12]. CNO osteomyelitis may be difficult to diagnose due to the non-specific symptoms and clinical findings. Possible infective and malignant causes should be ruled out in the differential diagnosis. The fact that acute phase reactants may be normal in laboratory evaluation and no pathology can be detected in radiographs, particularly in the early stage of the disease, makes the diagnosis even more difficult. Magnetic resonance imaging (MRI) has a high sensitivity in detecting CNO lesions. In the treatment, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs including sulfasalazine and methotrexate (MTX), biological treatments (anti-TNF agents), and bisphosphonates are widely used.

In the present study, we aimed to report our single-center experience in pediatric patients with CNO.

MATERIALS and METHODS

This single-center, retrospective study was conducted at Department of Pediatric Rheumatology of Hacettepe University a tertiary care center between November 2006 and July 2021. Patients diagnosed with CNO were included. The demographics, clinical features, laboratory findings, imaging modalities, concomitant diseases, and treatments were recorded. Diagnostic delay was defined as the time interval from symptom onset to diagnosis. Since the lack of validated and accepted diagnostic criteria, the diagnosis was based on expert opinion and the exclusion of other bone pathologies such as malignancies and infections. In the presence of CNO-related symptoms, typical findings on bone imaging were helpful for diagnosis. Laboratory tests at the time of diagnosis were also noted.

The study was approved by the Hacettepe University Non-invasive Clinical Research Ethics Committee (decision no: 2022/10-04, date: 07.06.2022) and conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in median [minimum (min) - maximum (max)] or number and frequency. The normality of distribution of the variables was checked using the visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test).

RESULTS

Patient Characteristics

A total of 48 patients, 25 boys (52.1%), with a median age of 13.7 (min-max: 3.3-20.4) years were enrolled in the study. The demographics and clinical findings of the patients at the time of diagnosis are summarized in Table 1. The median age at diagnosis was 9.9 (min-max: 2.9-16.8) years and the median follow-up time was 2.3 (min-max: 0-12.9) years. The median diagnostic delay time was 1.0 (min-max: 0-6.3) year. The most common symptom observed in almost three-quarters of patients was local bone pain and most of them presented with leg pain. Other common signs and symptoms included arthralgia (52.1%), limping or difficulty in walking (43.8%), and back pain (33.3%). In addition, CNO was accompanied by psoriasis in three (6.3%), IBD in four (8.3%), and severe papulopustular lesions in one patient (2.1%). Two patients met the International League of Associations for Rheumatology classification criteria for enthesitis-related arthritis.

Parental consanguinity was present in 14.6% of patients and five patients had a family history of rheumatic disease including rheumatoid arthritis,

ankylosing spondylitis, and psoriatic arthritis. Physical examination revealed tenderness on palpation of the affected area in 28 (58.3%), swelling of the affected area in seven (14.6%), and redness in one patient (2.1%). The modified Schober's test was positive in 13 of 35 patients (37.1%).

Laboratory Features and Diagnostic Tests of Patients

In the laboratory examination, elevated erythrocyte sedimentation rate (ESR), high C-reactive protein (CRP) levels, thrombocytosis, anemia, and leukocytosis were found in decreasing order of frequency (52.1%, 43.8%, 39.6%, 27.1%, and 2.1%, respectively) (Table 2). Human leukocyte antigen-B27 positivity was detected in four of 15 patients (26.6%). During the diagnosis, regional MRI was performed in 42 (87.5%), whole-body MRI in 32 (66.7%), plain radiography in 25 (52%), and bone scintigraphy in eight patients (16.7%). Bone marrow aspiration was performed in 18 patients (37.5%) and bone biopsy in 19 patients (39.6%) to exclude malignancy. Pathological fractures were detected in seven patients (14.5%) in the imaging findings.

Table 1. Demographic and clinical features of patients with chronic non-bacterial osteitis

Median (minimum-maksimum) or n (%)	Patient number (n=48)
Gender, male	25 (52.1)
Age at study, years	13.7 (3.3-20.4)
Age at disease onset, years	8.5 (0.1-13.4)
Age at diagnosis, years	9.9 (2.9-16.8)
Diagnostic delay, years	1 (0-6.3)
Follow-up time, years	2.3 (0-12.9)
Fever	11 (22.9)
Fatigue	11 (22.9)
Weight loss	1 (2.1)
Local bone pain	35 (72.9)
Diffuse bone pain	4 (8.3)
Leg pain	33 (68.8)
Back pain	16 (33.3)
Arthritis	7 (14.6)
Arthralgia	25 (52.1)
Walking with a limp or difficulty in walking	21 (43.8)
Concomitant diseases	
Inflammatory bowel disease	4 (8.3)
Psoriasis	3 (6.3)
Severe papulopustular lesions	1 (2.1)
PFAPA syndrome	1 (2.1)
Parental consanguinity	7 (14.6)
Family history of rheumatic diseases	5 (10.4)
Swelling of affected area	7 (14.6)
Tenderness on palpation of the affected area	28 (58.3)
Redness of the affected area	1 (2.1)
Schober's test <5 cm	13/35 (37.1)

PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, and adenitis

Treatments

The flowchart of treatment in our cohort is shown in Figure 1. All patients received NSAIDs in the first-line treatment, until the definitive diagnosis was made. Six patients (12.5%) achieved remission with only NSAIDs. Subsequent medical treatment was MTX in 34 patients (80.9%), biological agents in three patients (7.1%), and pamidronate in five patients (11.9%). Pamidronate was mostly preferred in patients with spinal lesions. Short courses of glucocorticoid regimen were given to nine patients (19.7%). In the MTX-treated patients, remission was achieved in nine (26.4%). The median duration of treatment was 8.1 (min-max: 2.0-10.9) months for MTX. Three patients were given pamidronate due to flares,

Table 2. Laboratory findings at diagnosis and the summary of diagnostic imaging tests in patients with chronic non-bacterial osteitis

	Patient number (n=48)
Anemia, n (%)	13 (27.1)
Hemoglobin (g/dL), median (min-max)	12.2 (9.1-15.1)
Leukocytosis, n (%)	1 (2.1)
Leukocyte count (10^9/L), median (min-max)	7.5 (4.6-19.1)
Thrombocytosis, n (%)	19 (39.6)
Platelet count (10^9/L), median (min-max)	360 (185-857)
High level of CRP, n (%)	21 (43.8)
CRP (mg/dL), median (min-max)	0.6 (0.1-16.9)
Elevated ESR, n (%)	25 (52.1)
ESR (mm/h), median (min-max)	22 (2-120)
HLA-B27 positivity, n (%)	4/15 (26.6)
Type of imaging test at diagnosis	
Plain radiography, n (%)	25 (52.0)
Regional MRI, n (%)	42 (87.5)
Whole body MRI, n (%)	32 (66.7)
Bone scintigraphy, n (%)	8 (16.7)

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, HLA: Human leukocyte antigen, MRI: Magnetic resonance imaging, min: Minimum, max: Maximum

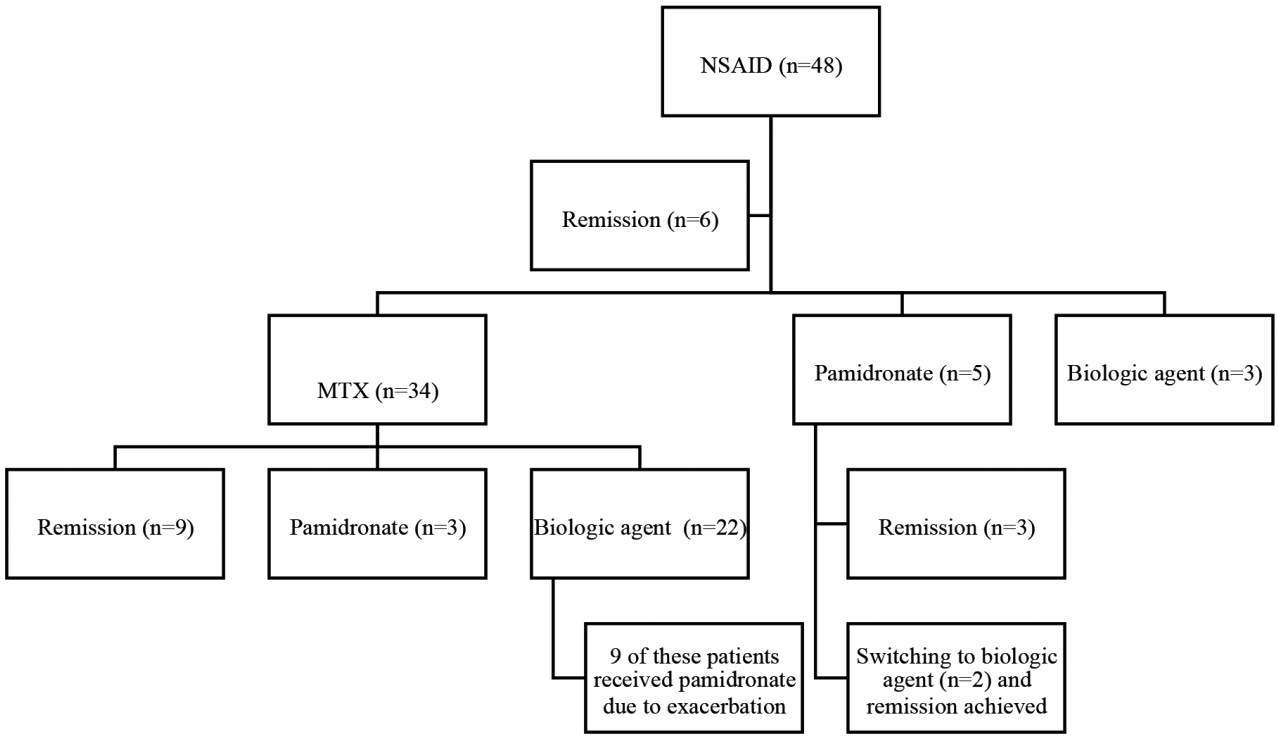

Figure 1. Flow chart of the treatment scheme in our patients with chronic non-bacterial osteitis

NSAID: Non-steroidal anti-inflammatory drugs, MTX: Methotrexate

while treatment was switched to a biological agent in 22 patients who did not respond to MTX. Nine of these patients with biological treatment also received pamidronate due to flares during the course of the disease.

Treatment with Biological Agents

A total of 27 patients (56.2%) used biological agents for refractory disease or as second-line therapy. The median duration of treatment was 8.0 months (min-max: 5.0-39.0) months for biological agents. Etanercept (ETN) was the first-choice biological in all patients, except for one with IBD who was administered adalimumab at the time of diagnosis. In four patients, ETN was switched to adalimumab due to psoriasis or IBD during follow-up. Two patients had refractory disease, despite MTX and ETN and/or pamidronate treatments. One of them achieved remission with the adalimumab treatment, while adalimumab, infliximab, and tocilizumab treatments were used in the other patient to control disease activity. In addition, ETN was restarted due to disease activity in one patient whose ETN treatment was discontinued due to long-term disease control.

DISCUSSION

In the present study, we evaluated the characteristics of children with CNO, a rare disease in children, in a large cohort in a tertiary referral center. Fifty-two percent of patients were male in our cohort. Female predominance was reported in two large CNO cohort, one was a series of 486 cases (64% female) from the Eurofever international registry and the other was the German national pediatric rheumatology database, the largest cohort of the CNO patients (n=774, 62.8% female)[13,14]. The increased awareness and increasing number of CNO patients are helpful to understand whether sex distribution is different or affects the disease occurrence. The median age at the time of diagnosis in the present study was similar to other previous reports[5,15-18]. However, the diagnostic delay time indicates a wide variety ranging from 3 to 21 months in the literature which was one year in our study group[15,19-21]. This can be attributed to varying levels of awareness and diagnostic difficulties. The data of 15 patients diagnosed with CNO between January 2008 and January 2017 in our center were published previously[22]. Between January 2017 and July 2021, 32 patients were newly diagnosed with CNO, while only one patient was diagnosed between November 2006

and January 2008. Over the years, a significant increase in the rate of CNO diagnosis was noted.

The most common symptom in our patients was local bone pain consistent with the literature, mostly presented as leg pain[23,24]. Diagnosing CNO in patients presenting with the complaint of leg pain, which is a common symptom in children, may be challenging. The lack of internationally accepted diagnostic criteria and specific laboratory markers for CNO makes the diagnosis more difficult. Normal laboratory values can be detected in some patients at diagnosis[5,25]. The rate of increased acute phase reactants in our study group was similar to the Eurofever cohort (59% vs 52.1% for ESR, 49% vs 43.8% for CRP)[14]. Thrombocytosis was also reported in approximately 30% of CNO patients, as we detected in 39.6% of patients[26]. As for the use of diagnostic imaging modalities for CNO patients, a survey was conducted by members of the Childhood Arthritis and Rheumatology Research Alliance. The frequency of use of imaging modalities among physicians was listed as plain radiographs (89%), regional MRI (78%), bone scintigraphy (43%), and whole-body MRI (36%). In the analysis of Eurofever registry, the whole-body MRI was reported to use in 34% of patients which was lower compared to our cohort (66.7%)[14]. The whole-body MRI is the most sensitive method to detect bone lesions[27]. The widespread use of whole-body MRI may ease and fasten the diagnostic process. However, it is not accessible in all centers and it may not be cost-effective to apply whole-body MRI to all patients.

To exclude malignancy and infection for patients with particularly unifocal lesions in our cohort, bone biopsy was performed in 19 patients (39.6%). In the analysis of the German National Pediatric Rheumatology database, the frequency of bone biopsy was reported as 69.1%, 49.4%, and 54.8% for the 2009-2012, 2013-2015, and 2016-2018 time periods, respectively[13]. Decreased biopsy rates over time were noted. Along the same lines, a bone biopsy was reported to conduct in 60% of CNO patients in the Eurofever registry analysis[14]. The lower rate of bone biopsy in our study group can be attributed to the widespread use of whole-body MRI over time. The chance of detecting multifocal bone lesions and/or typical sites involvement such as clavicula with the imaging may have reduced the need for biopsy.

Currently, NSAIDs are frequently used as the first-line treatment. These agents provide symptomatic relief and are effective in controlling inflammation in a limited group of patients. In our study, only 12.5% of the patients achieved remission with NSAID treatment alone. Along the same lines, in the analysis of the Irish national cohort with CNO, 13.6% of patients achieved remission with NSAIDs[28]. In general, MTX, biological agents, and pamidronate are the second-line treatment agents used in the CNO treatment. Borzutzky et al.[29] found the remission rate with MTX in their CNO cohort to be 20%. Similar to our findings (remission rate with MTX: 26.4%), it was effective in achieving remission only in a limited subset of patients. Although there are case reports and case series indicating that anti-TNF and pamidronate are effective in CNO, there are no clinical studies or treatment guidelines[30,31].

Study Limitations

Nonetheless, this study has some limitations. It is a single-center, retrospective study. Also, the possibility of spontaneous regression in CNO might have affected our results while evaluating treatment response and outcome. On the other hand, we believe that our study provides additional contribution to the literature to increase awareness of CNO and gain a better understanding of this rare disease.

CONCLUSION

In conclusion, delay in diagnosis is frequently observed in CNO. It is essential to increase awareness of this disease to prevent missing the diagnosis. The more widespread use of whole-body MRI in diagnosis can be helpful to diagnose CNO earlier. Further large-scale, prospective studies are needed to draw more reliable conclusions on this subject.

Ethics

Ethics Committee Approval: The study was approved by the Hacettepe University Non-invasive Clinical Research Ethics Committee (decision no: 2022/10-04, date: 07.06.2022) and conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer reviewed.

Author Contributions

Concept: Ü.K.A., Y.Bi., Design: Ü.K.A., Y.B., Y.Bi., Data Collection or Processing: Ü.K.A., Y.B., Y.Bi., Analysis or Interpretation: Ü.K.A., Y.B., Y.Bi., Literature Search: Ü.K.A., Y.B., Y.Bi., Writing: Ü.K.A., Y.Bi.

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