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Original Article

Diagnostic Conundrum: Fever and Pyuria Preceding Diagnosis of Kawasaki Disease in Children

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ABSTRACT

Purpose: Children with incomplete Kawasaki disease (KD) and pyuria may be misdiagnosed with urinary tract infection (UTI) during the early phase of the prodrome. We investigated the percentage of UTI diagnoses preceding a KD diagnosis.
Methods: Using the National Health Insurance data of South Korea, we assessed differences in UTI diagnoses made during the week preceding a KD diagnosis, according to demographic and geographic factors from November 2007–October 2019.
Results: A total of 53,822 KD cases were identified, including 304 patients (0.56%) diagnosed with a UTI during the week preceding a KD diagnosis. The younger age group (0–11 months) showed the highest percentage of preceding UTI diagnoses (0.95%), with higher odds than 4-year-old children (3.12; 95% confidence interval, 2.05–4.77).
Conclusions: These findings suggest a potentially misleading presentation of incomplete KD, a clinical conundrum requiring further investigation and validation, particularly in infants.

Keywords: Kawasaki disease; Pyuria; Diagnosis; Urinary tract infections

INTRODUCTION

Kawasaki disease (KD) is an acute febrile illness of autoimmune origin primarily affecting children younger than 5 years.[1] Clinical signs include fever, rash, swelling of the hands and feet, irritation and redness of the whites of the eyes, swollen lymph glands in the neck, and irritation and inflammation of the mouth, lips, and throat. KD is the leading cause of acquired heart disease in pediatric patients in most high-income countries.[2]

Early diagnosis and prompt initiation of treatment with intravenous immunoglobulin (IVIG) are paramount in KD management.[3] However, diagnosing KD can be challenging because the established diagnostic criteria may not encompass all cases, especially in infants.[4] In such cases, the diagnosis of incomplete KD, also known as atypical KD, relies on compatible echocardiographic or laboratory findings in a child whose clinical presentation strongly suggests KD but does not meet the complete criteria.

Pyuria is observed in up to 80% of children during the initial stages of KD and serves as a valuable indicator when assessing suspected cases of incomplete KD.[5] However, this may

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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present a diagnostic challenge and potentially lead to a misdiagnosis of KD as a urinary tract infection (UTI), especially in febrile children lacking typical KD features but exhibiting pyuria and elevated C-reactive protein levels. In such cases, delayed treatment of KD due to misdiagnosis of UTI may increase the risk of additional complications associated with KD.

In the current study, our objective was to identify the prevalence and risk factors for misdiagnosis of UTI preceding cases of KD in Korean children aged <5 years.

MATERIALS AND METHODS

In South Korea, the National Health Insurance System (NHIS) is a public, single-payer system for over 99% of all citizens and residents nationwide. Upon utilization of medical services, the provider sends reimbursement claims for expenses incurred to the Health Insurance Review and Assessment Service (HIRA), which reviews the claims, assesses the quality of care, and reviews the adequacy of provided services. Therefore, all medical services covered by the NHIS can be tracked using the HIRA database.[6] To construct a national KD cohort, we retrieved HIRA data of children aged 0–4 years associated with the KD code (M30.3) from the 10th revision of the International Classification of Diseases (ICD-10), from November 2007–October 2019. Our analysis was restricted to patients who received IVIG therapy. Furthermore, after restricting the study to the first episode in each child, the sample population numbered 53,840 children. We used the ICD-10 codes for UTI (N10, N12, N136, N151, N159, N300, N308, N309, N34, and N390) to define UTIs. All children diagnosed with a UTI during the week preceding IVIG administration were identified. We then excluded from the population those who had been diagnosed with UTIs between 1 and 2 weeks before IVIG treatment.

The incidence of UTI diagnoses during the week preceding KD diagnoses in each stratum of variables was calculated and tested for differences using the χ^2 test. The Mantel-Haenszel χ^2 test was used to test for a linear trend in the annual incidence. We applied logistic regression models with and without covariates to compute the odds ratios (ORs) for UTI diagnoses. The covariates included age, sex, region, season, and year of KD diagnosis. All statistical analyses were conducted using R version 4.0.2 (R Core Team 2020; R Foundation, Vienna, Austria).

This study was reviewed by the Korea University Anam Hospital Institutional Review Board (IRB No. 2021AN0486).

RESULTS

Among the 53,840 KD patients aged 0–4 years diagnosed in Korea from 2007–2019, a preceding UTI diagnosis was made in 370 (0.7%) children. Most patients (89.5%, n=331) were diagnosed with cystitis (**Table 1**). The mean interval between the UTI diagnosis and IVIG administration was 2.1±1.4 days. The annual incidence rate of UTIs ranged from 0.5–0.9%, without a significant linear trend. After reaching the highest incidence in those aged <1 year (1.2%), the proportion of UTIs decreased linearly with age (*P* for trend <0.001).

Table 2 shows the risk estimates for UTI diagnoses made during the week preceding KD diagnosis. The adjusted OR (aOR) was higher in patients aged <1 year (aOR, 3.12; 95% confidence interval [CI], 2.05–4.77) and 2 years (aOR, 1.78; 95% CI, 1.14–2.78), than that

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Table 1. Characteristics of children diagnosed with urinary tract infection during the week preceding a Kawasaki disease diagnosis

Variables	Frequency (%)	*P* for difference*
Age (yr)		<0.001
<1	161 (1.2)	
1 to <2	86 (0.7)	
2 to <3	56 (0.5)	
3 to <4	42 (0.4)	
4	25 (0.4)	
Sex		0.313
Male	225 (0.7)	
Female	145 (0.6)	
Region		0.001
Seoul capital area†	202 (0.8)	
Non-Seoul capital area	168 (0.6)	
Season		0.024
Spring (Mar–May)	70 (0.5)	
Summer (Jun–Aug)	109 (0.8)	
Fall (Sep–Nov)	78 (0.6)	
Winter (Dec–Feb)	113 (0.8)	

Data are based on National Health Insurance Service of South Korea claims from 2007–2019 (n=53,840).
*Calculated using the χ^2 test; †Includes Seoul, Gyeonggi Province, and Incheon.

Table 2. Risk estimates for urinary tract infection diagnoses made during the week preceding a Kawasaki disease diagnosis

Variables	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Age (yr)		
<1	3.16 (2.07–4.82)	3.12 (2.05–4.77)
1 to <2	1.79 (1.14–2.79)	1.78 (1.14–2.78)
2 to <3	1.28 (0.80–2.05)	1.27 (0.79–2.04)
3 to <4	1.17 (0.71–1.92)	1.16 (0.71–1.91)
4	1.00 (reference)	1.00 (reference)
Sex		
Male	1.11 (0.90–1.97)	1.07 (0.87–1.32)
Female	1.00 (reference)	1.00 (reference)
Region		
Seoul capital area	1.00 (reference)	1.00 (reference)
Non-Seoul capital area	1.39 (1.13–1.71)	1.41 (1.15–1.73)
Season		
Spring (Mar–May)	1.00 (reference)	1.43 (1.06–1.93)
Summer (Jun–Aug)	1.49 (1.10–2.01)	1.17 (0.84–1.61)
Fall (Sep–Nov)	1.19 (0.86–1.64)	1.44 (1.07–1.95)
Winter (Dec–Feb)	1.48 (1.10–2.00)	1.00 (reference)

Data are based on National Health Insurance Service of South Korea claims from 2007–2019 (n=53,840).
Abbreviations: OR, odds ratio; CI, confidence interval.
*Adjusted for age, sex, region, season, and year of Kawasaki disease diagnosis.

in children aged 4 years. Sex differences in the ORs for UTI diagnosis were not evident. Living outside the capital area was associated with a higher OR (1.41; 95% CI, 1.15–1.73). KD diagnoses made in the spring (1.43; 95% CI, 1.06–1.93) and fall (1.44; 95% CI, 1.07–1.95) were associated with higher probabilities of preceding UTI diagnoses than those made in winter.

DISCUSSION

In this study, we found that a preceding diagnosis of UTI in South Korea occurred in 1.2% of infants with KD aged <1 year. This is consistent with the findings of previous observational studies suggesting diagnostic challenges in infants presenting with fever and pyuria. A

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clinical observation from Suzhou, China, suggested laboratory values for differentiation of infantile KD and UTI.[7] A retrospective review from a tertiary hospital in South Korea showed that elevated liver enzymes were more specific to KD than to UTI, whereas a positive nitrite test result was more specific to UTI than to KD in infants.[8] Another study from South Korea suggested that persistent fever, elevated erythrocyte sedimentation rate, and negative urine nitrite test results could serve as early clues for suspecting KD in febrile infants with pyuria.[9] Limited data are available regarding the clinical presentation of KD in infants. Diagnosing KD in infants younger than one year of age can be particularly challenging because of the atypical clinical presentations, predominance of incomplete forms, and scarcity of typical clinical signs. It is well established that infants with KD are at a higher risk of experiencing cardiac involvement than older children.[10,11] Our findings highlight the clinical importance of suspecting KD in infants with UTIs to avoid any misdiagnoses. It also underscores the challenges associated with recognizing incomplete forms of the condition when guidelines are followed, particularly in infants.[12] Despite the reported clinical clues for differentiating between KD and UTI, pyuria in patients with KD poses challenges for prompt differential diagnosis on many occasions, and our findings support that the risk is higher in infants than in older children.[13]

We observed variations in the diagnosis of UTI in the week leading up to a KD, with a greater prevalence in Seoul as opposed to the non-Seoul capital area (0.8% vs. 0.6%, with a significant *P*-value of 0.001). Additionally, the incidence of UTI was higher in the summer and winter compared to the spring and fall (0.8% vs. 0.5–0.6%, with a *P*-value of 0.024). One study aimed to analyze the spatiotemporal patterns of KD in Korea revealed that KD cases showed seasonal variations and exhibited spatial clustering, with differences between males and females.[14] Another study investigated the relationship between KD respiratory viruses in Korea. The findings indicate a significant correlation between KD outbreaks and respiratory infections caused by rhinovirus, respiratory syncytial virus, and varicella occurring 1 to 3 months before KD outbreaks.[15] In light of these results, our findings strongly imply that KD is probably the result of a complex interplay of factors, encompassing infectious, genetic, and environmental elements, and that this interplay may exhibit gender-related variations, thereby impacting the proportion of children diagnosed with UTI before the onset of KD.

This study had several limitations. First, we used claims data that did not include information on treatment outcomes or diagnostic evaluation details. Second, because the study cohort was retrospective and relied on the National Health Insurance database, it had insufficient or lacked altogether clinical information, including comorbidities and their severity, clinical events occurring beyond the follow-up period, and clinical characteristics such as fever, rash, lymphadenitis, and changes in these conditions over time. While some of this information could be extracted from ICD codes in insurance claims, an inherent risk of significant over- or under-diagnosis existed because the diagnoses relied on ICD codes from the database. Additionally, inaccuracies in the KD and UTI diagnoses may have existed. However, it is worth noting that the diagnoses of KD and UTI were based on ICD codes for admission, which are known to have fewer errors than those in outpatient settings. In future studies, the utilization of clinical data containing information lacking in the claims data including symptoms, comorbidities, and treatment outcomes, would help address the current limitations.

Our analyses indicate that KD is infrequently associated with a preceding UTI diagnosis. These findings suggest a potentially misleading presentation of incomplete KD, a clinical conundrum requiring further investigation and validation. Pyuria combined with non-

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specific clinical symptoms constitutes the sole manifestation, making it a perplexing diagnosis in infants. In cases of pyuria, particularly in young infants, pediatricians could include KD as a differential diagnosis because incomplete forms of the condition are more common in this age group.

REFERENCES

1. Brogan PA, Bose A, Burgner D, Shingadia D, Tulloh R, Michie C, et al. Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. Arch Dis Child 2002;86:286-90.
PUBMED | CROSSREF
2. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927-99.
PUBMED | CROSSREF
3. Golshevsky D, Cheung M, Burgner D. Kawasaki disease--the importance of prompt recognition and early referral. Aust Fam Physician 2013;42:473-6.
PUBMED
4. Manlhiot C, Christie E, McCrindle BW, Rosenberg H, Chahal N, Yeung RS. Complete and incomplete Kawasaki disease: two sides of the same coin. Eur J Pediatr 2012;171:657-62.
PUBMED | CROSSREF
5. Shike H, Kanegaye JT, Best BM, Pancheri J, Burns JC. Pyuria associated with acute Kawasaki disease and fever from other causes. Pediatr Infect Dis J 2009;28:440-3.
PUBMED | CROSSREF
6. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. J Korean Med Sci 2017;32:718-28.
PUBMED | CROSSREF
7. Tang Y, Li X, Cao L, Chen Y, Yan W, Xu Q, et al. Characteristics and indications of Kawasaki disease among infants under 6 months. Front Pediatr 2020;8:470.
PUBMED | CROSSREF
8. Han SB, Lee SY. Differentiating Kawasaki disease from urinary tract infection in febrile children with pyuria and C-reactive protein elevation. Ital J Pediatr 2018;44:137.
PUBMED | CROSSREF
9. Yoon SH, Kim DS, Ahn JG. Early features of Kawasaki disease with pyuria in febrile infants younger than 6 months. BMC Pediatr 2018;18:389.
PUBMED | CROSSREF
10. Salgado AP, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, et al. High risk of coronary artery aneurysms in infants younger than 6 months of age with Kawasaki disease. J Pediatr 2017;185:112-116.e1.
PUBMED | CROSSREF
11. Satoh K, Wakejima Y, Gau M, Kiguchi T, Matsuda N, Takasawa R, et al. Risk of coronary artery lesions in young infants with Kawasaki disease: need for a new diagnostic method. Int J Rheum Dis 2018;21:746-54.
PUBMED | CROSSREF
12. Mori M, Matsubara T. Overview of guidelines for the medical treatment of acute Kawasaki disease in Japan (2020 revised version) and positioning of plasma exchange therapy in the acute phase. Pediatr Infect Dis J 2023;42:e328-32.
PUBMED | CROSSREF
13. Watanabe T. Pyuria in patients with Kawasaki disease. World J Clin Pediatr 2015;4:25-9.
PUBMED | CROSSREF
14. Kim J, Hong K, Yoo D, Chun BC. Spatiotemporal clusters of Kawasaki disease in South Korea from 2008 to 2017: a municipal-level ecological study. Front Pediatr 2023;10:1054985.
PUBMED | CROSSREF
15. Kang JM, Jung J, Kim YE, Huh K, Hong J, Kim DW, et al. Temporal correlation between Kawasaki disease and infectious diseases in South Korea. JAMA Netw Open 2022;5:e2147363.
PUBMED | CROSSREF

요약

농뇨는 가와사키병 환아의 약 30–60%에 동반되는 소견으로, 임상적 증후가 다 나타나지 않은 초기의 가와사키병 또는 불완전 가와사키병에서 요로감염으로 오인할 수 있으나, 불완전 가와사키병 진단에 중요한 검사실 소견 중 하나일 수 있다. 본 연구에서는 한국의 5세 미만 영유아에서 가와사키병 진단 전 요로감염으로 선행 진단 사례의 유병률과 역학적 위험인자를 평가하고자 한다. 건강보험심사평가원에서 제공하고 있는 보건의료 빅데이터 개방시스템 자료를 바탕으로 2007년 11월부터 2019년 10월까지 가와사키병과 요로감염으로 진료, 청구된 대상자에 대해 후향적 단면연구를 시행하였다. 가와사키병 확정 진단 전 1주일 이내의 요로감염 선행 진단된 환아의 발생률을 계산하였고, 카이제곱 (χ^2 test) 검정을 실시하였다. 연령, 성별, 지역, 계절별 발생률에 대한 요로감염 선행 진단 여부에 대해 로지스틱 분석 (logistic regression)을 수행하였다. 연구 결과, 총 53,822명의 가와사키병 환자가 포함되었으며 그 중 304명 (0.56%)이 선행 요로감염 진단이 있었다. 12개월 미만에서의 요로감염 선행 진단률이 가장 높았으며 (0.95%), 4세와 비교했을 때 요로감염 선행진단의 오즈비는 3.12 (2.05–4.77) 였다. 발열을 동반한 농뇨가 있는 영아의 일부에서는 불완전 가와사키병의 감별진단이 필요할 수 있다.

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